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WHAT IS THE OPTIMUM ARTIFICIAL TREATMENT FOR DRY EYE?

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Summary:

Dry eye disease is a common clinical condition whose aetiology and management challenges clinicians and researchers alike. Practitioners have a number of dry eye tests available to clinically assess dry eye disease, in order to treat their patients effectively and successfully.

This thesis set out to determine the most relevant and successful key tests for dry eye disease diagnosis/ management. There has been very little research on determining the most effective treatment options for these patients; therefore a randomised controlled study was conducted in order to see how different artificial treatments perform compared to each other, whether the preferred treatment could have been predicted from their ocular clinical assessment, and if the preferred treatment subjectively related to the greatest improvement in ocular physiology and tear film stability.

This research has found:

1. From the plethora of ocular the tear tests available to utilise in clinical practice, the tear stability tests as measured by the non-invasive tear break (NITBUT) up time and invasive tear break up time (NaFL TBUT) are strongly correlated. The tear volume tests are also related as measured by the phenol red thread (PRT) and tear meniscus height (TMH). Lid Parallel Conjunctival Folds (LIPCOF) and conjunctival staining are significantly correlated to one another. Symptomology and osmolarity were also found to be important tests in order to assess for dry eye.
2. Artificial tear supplements do work for ocular comfort, as well as the ocular surface as observed by conjunctival staining and the reduction LIPCOF. There is no strong evidence of one type of artificial tear supplement being more effective than others, and the data suggest that these improvements are more due to the time than the specific drops.
3. When trying to predict patient preference for artificial tears from baseline measurements, the individual category of artificial tear supplements appeared to have an improvement in at least 1 tear metric. Undoubtedly, from the study the patients preferred artificial tear supplements' were rated much higher than the other three drops used in the study and their subjective responses were statistically significant than the signs.
4. Patients are also willing to pay for a community dry eye service in their area of £17.

In conclusion, the dry eye tests conducted in the study correlate with one another and with the symptoms reported by the patient. Artificial tears do make a difference objectively as well as subjectively. There is no optimum artificial treatment for dry eye, however regular consistent use of artificial eye drops will improve the ocular surface.

Key words: Artificial tear supplements; Dry Eye; LIPCOF; NIBUT; Osmolarity

Dedication

This doctorate is dedicated to my parents, who I am lucky to have and without their support and encouragement I would not be able to have achieved all I have so far in life.

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The TearLab was kindly loaned to the author by TearLab Ltd.

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Abbreviations

ADDE	Aqueous tear deficient dry eye
ARDE	Age related dry eye
AT	Artificial tears
BAK	Benzalkonium Chloride
BUT	Break up time
CCGS	Clinical Commissioning Groups
CIEs	Corneal inflammatory events
CLDEQ	Contact Lens Dry Eye Questionnaire
CMC	Carboxymethylcellulose
DED	Dry eye disease
DEEP	Dry eye epidemiology projects
DEQ	Dry Eye Questionnaire
DEWS	Dry eye workshop
Dia	Diameter
DOH	Department of Health
EDE	Evaporative dry eye
Evap	Tear film evaporation rate
FBUT	Fluorescein break up time
FDA	Federal Drug Administration
FPR	False positive rate
GP	General practitioner
GSL	General sales list
HA	Hyaluronic acid
HEC	Hydroxyethylcellulose
HEFCE	Higher Education Funding Council for England
HPMC	Hypromellose
KCS	Keratoconjunctivitis Sicca
Lacto	Lactoferrin assay
LCD	Liquid Crystal Display
LG	Lissamine green
LIPCOF	Lid parallel conjunctival folds
LLG	Lipid layer grade
LLT	Lipid layer thickness
LOSCU	Local Optical Committee Support Unit
MC	Methylcellulose
MGD	Meibomian gland dysfunction

NaFL TBUT	Fluorescein Break Up Time
NEI-VFQ	National Eye Institute Visual Function Questionnaire
NHS	National Health Service
NIBUT	Non-invasive tear break up time
NITBUT	Non-invasive tearscope break up time
NNSDE	Non- Sjögren syndrome dry eye
OA	Overall Accuracy
OSD	Ocular surface disease
OSDI	Ocular Surface Disease Index
OTC	Over-the-counter
P	Pharmacy
PEG	Polyethylene glycol
PHS	Physicians health study
PPV	Positive predictive value
PRT	Phenol red thread
PVA	Polyvinyl alcohol
PVP	Polyvinylpyrrolidone
RB	Rose Bengal
SS	Sjögrens Syndrome
SSDE	Sjögren syndrome dry eye
SUC	Single unit container
TBUT	Tear Break Up Time
TMH	Tear meniscus height
TMS-BUT	Tear break up time measured with the topographic modelling system
TP-RPT	Tear Film Pre-Rupture Phase Time
TTR	Tear turnover rate
TTT	Tear thinning time
WHS	Women's health study

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CHAPTER 1

Introduction

1.0 Introduction

Dry eye disease is a common condition reported by many patients in clinical practice. Patients may attend the practice mentioning that they suffer from gritty, burning, irritated, eyes. Other symptoms include, foreign body sensation, blurred vision and photophobia, or uncomfortable feeling eyes particularly in the evening (Begley et al., 2003). The aetiology and management of dry eye disease has challenged clinicians and researchers alike. An understanding of dry eye disease has been made over the past decade in areas of epidemiology, pathogenesis, clinical appearance, and potential treatment (DEWS, 2007).

Dry eye has been defined by the Dry Eye Workshop (DEWS) as:

'a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.' (Lemp, 2007)

It has been found that 52% of contact lens wearers, 7% of emmetropes and 23% of spectacle wearers report dry eyes in clinical practice (Nichols et al., 2005). These findings are not unusual for contact lens wearers; however it is novel for spectacle wearers. The possible reasons for these findings is that spectacle wearers require more frequent eye tests care for their refractive error (unlike the emmetropes). Spectacle wearers may also have more of an awareness of their ocular health than an individual not requiring refractive correction. In addition, those wearing spectacles may have had a previous diagnosis of dry eye disease, which may have influenced their self-reported dry eye status (Nichols et al., 2005). An increase in age, a female gender, connective tissue disease, various medications and refractive surgery are a few factors which affect dry eyes (Lemp, 2007).

There are a number of tests available to the practitioner to evaluate both the quality and quantity of tears, in order to provide the appropriate treatment for their dry eye condition. The tests normally performed in practice include the non-invasive tear break up time (NIBUT), invasive or fluorescein break up time (NaFL TBUT), conjunctival and corneal staining, tear meniscus height measurement (TMH), phenol red test (PRT) and numerous questionnaires (Marci et al., 2000; Doughty et al., 2002,2005,2007; Santodomingo-Rubido, 2006). In recent years the diagnostic ability of metrics such as

lid parallel conjunctival folds (LIPCOF) has been endorsed (Höh et al., 1995, Pult et al., 2000).

A survey conducted by Korb et al., (2000) determined the preferred tests for dry eye diagnosis of a number of eye care practitioners with an interest in the tear film. If given only one test, 28% chose a dry eye questionnaire, followed by fluorescein break up time (19%), then fluorescein staining (13%) and lastly rose bengal (10%). On the other hand, a study by Smith et al., (2008) found that symptom assessment with questionnaires was preferred alongside tear break up time, corneal staining, tear film assessment, conjunctival staining and Schirmer test. The majority of practitioners used multiple tests (mean number 6). Doughty (2010) recommended just a logical approach as to what tests might be used, suggesting it makes sense to be selective and consistent in the tests undertaken.

1.2 The Tear Film

1.2.1 The tear apparatus

The tear system consists of various components; these are the secretory, distribution and excretory components.

1.2.1.1 The Secretory component includes the conjunctival goblet cells, and lacrimal epithelial cells which are responsible for secreting mucin. The glands of Krause present in the fornices and the glands of Wolfring present in the upper and lower tarsal boarder; these glands are responsible for secreting aqueous. The thin superficial lipid layer is produced by secreting meibomian glands and glands of Zeiss and Moll. All of these make up the secretory component of the tear apparatus (Snell and Lemp, 1998).

1.2.1.2 The Distributary component consists of the lids that mix the tear components in order to provide one of the main functions of the tear film by providing a smooth optical surface over the cornea. These tears reform after every blink action. There are small accumulations of the tears at the lid margins forming the tear 'lake' (Saude, 1993).

1.2.1.3 The Excretory component comprises of the superior and inferior lacrimal canaliculi, their puncta, the lacrimal sac and the naso lacrimal duct. In 60% of eyes the puncta are found to be round, however they tend to gradually get more oval in shape and more slit like with age (Patel et al., 2006).

The tears help protect the corneal surface by maintaining epithelial hydration and act as a lubricant to prevent the eyelids from rubbing against the cornea on blinking (Saude, 1993).

1.2.2 Tear film structure

The classic composition of the tear layer is made of three distinct layers:

1.2.2.1 Lipid Layer is produced by the meibomian glands (or tarsal glands) and is responsible for coating the aqueous layer and provides a hydrophobic layer that evaporates and prevents tears from dropping on to the cheek (Greiner et. al., 1996). These glands are found among the tarsal plates. Therefore the tear fluid deposits between the eye ball and oil barriers of the lids (Mishima et al., 1961). Rapid and forceful blinking has been shown to increase the thickness of the lipid layer (Korb et al., 1994).

1.2.2.2 Aqueous Layer water produced by the lacrimal gland acini and the soluble mucins secreted by the goblet cells which promotes spreading of the tear film (Walcott et al., 1994), the control of infectious agents (Lal and Khurana, 1994, Flanagan and Wilcox, 2009), providing a smooth refracting surface to the cornea (Montes-Mico, 2007) and osmotic regulation. The sebum consisting of polar lipids spread over the aqueous surface and apolar lipids spread over the polar lipids (Holly, 1980).

1.2.2.3 Mucus Layer comprises of immunoglobulins, salts, urea, glucose, leukocytes, tissue debris, and enzymes such as betalysin, peroxidase and lysozyme (Holly and Lemp, 1977). Mucins are produced in the goblet cells of the conjunctiva and secreted from them to become the gel forming component in the mucus layer of the tear film (Nichols et al., 1985). Mucins from various sources have similar structures (Silberberg et al., 1982; Allan, 1983). They are Glycoproteins containing 50 to 80 % carbohydrate. They are large, elongated molecules ($2-15 \times 10^6$ Daltons) with a protein back bone to which oligosaccharides are fixed in a bottle-brush configuration. Cross linking of these molecules through disulphide bridges forms polymers of high molecular weight, which bind to similar polymers by weak, interactions of their carbohydrate chains to form a gel.

Mucin produced by the conjunctival goblet cells and coats the cornea providing a hydrophilic layer allowing even distribution of the tear film covering the cornea. It helps it adhere to the epithelium and the lipid layer on the top and protects it from rapid evaporation. This layer is the innermost layer and is in contact with the microvilli of the

corneal epithelium in order to aid wetting of the epithelium and spread the tears over the hydrophobic corneal tissue (Hirji and Patel, 2010).

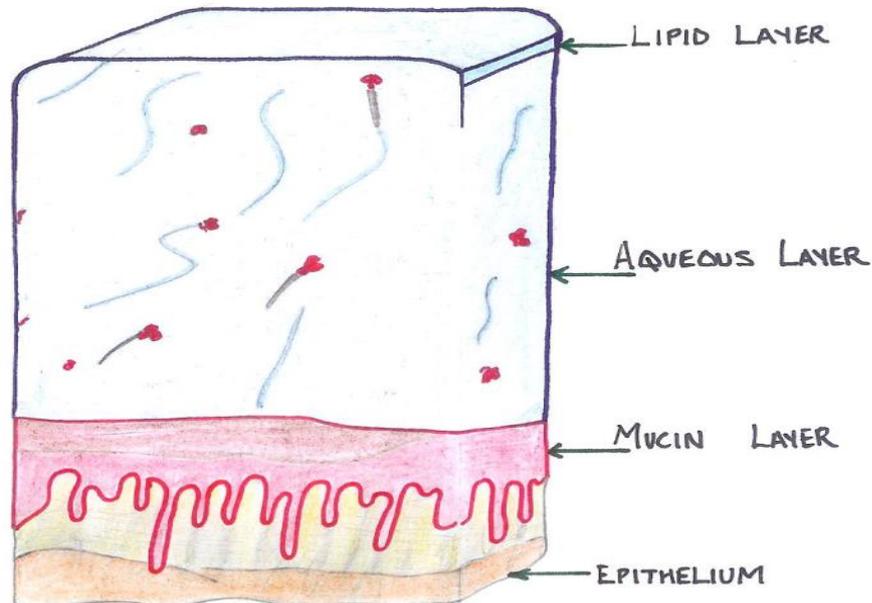


Figure 1.1: Composition of the tear layer. The outer lipid layer protects the tear film from evaporation. The middle aqueous layer of the tear film is produced by the lacrimal glands. The inner mucin layer underneath helps it to adhere to the corneal epithelium.

However, a revised view of the tear layer is that it is an aqueous-mucin gel with sulphated glycoaminoglycans on the microvilli of the corneal epithelium. The gel-forming mucins and the soluble mucins are distributed in a concentration gradient that reduces towards the surface lipid (Pflugfelder et al., 2000), see figure 1.2.

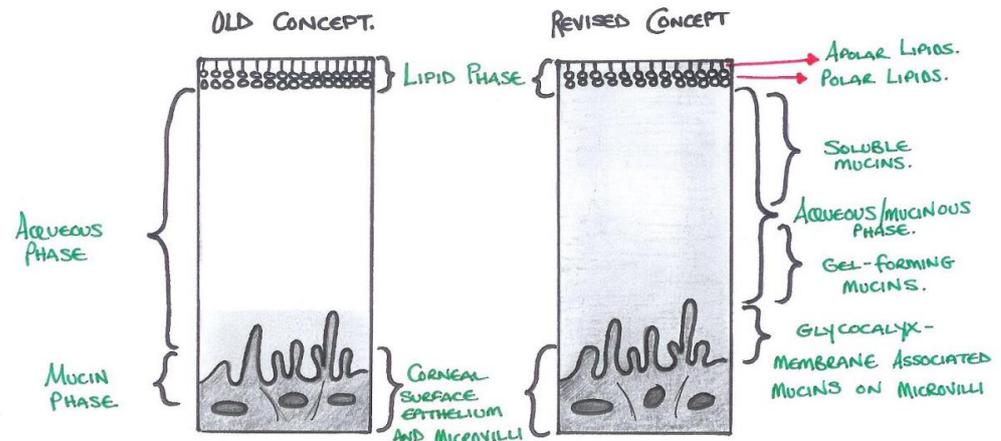


Figure 1.2: A schematic representation of the tears. The aqueous-mucin gel with glycocalyx (sulphated glycoaminoglycans) on the microvilli of the corneal epithelium, whilst the gel-forming mucins and soluble mucins are distributed in a concentration gradient that decreases towards the surface lipid layer. (Adapted from Hirji and Patel, 2010)

1.2.3 Properties of the tear layer

The tear layer is by most techniques is 7-10µm thick (DEWS, 2007), and secretes at a rate of 1-2µl/min (Ehlers, 1965) an undisturbed resident volume of approximately 6-8 ml (Mishima et al., 1966) and a surface tension of 42-46 dyn/cm (Nagyova et al., 1999). The pH of the tears is 7.5 ± 0.1 (Fischer et al., 1982) and osmolarity of 310-334 mOsm/kg (Benjamin et al., 1983).

The normal estimated tear volume tear volume is 6-10µl, (Mishima et al., 1966; Franklin et al., 1973; Port et al., 1990). There are two types of aqueous production: basic rate production and reflex production (Jones, 1966). Therefore tear volume assessment should ideally be carried out without stimulating reflex tears in order to assess tear volume in its most natural state.

The tears are important in providing protection and nourishment for the cornea and conjunctiva. The tears also play an important role in transporting the atmospheric oxygen in to the avascular cornea; it also supplies the cornea with glucose, salts, and minerals and removes cellular debris and metabolic waste. The tears maintain a constant pH whilst maintaining a smooth and transparent optical surface for the best refraction through the cornea. The tears also lubricate the cornea and the eyelids

preventing dehydration and enabling smooth movement of the eyelids over the cornea thus maintaining ocular comfort. In addition the tears trap foreign particles and flush them from the eye. They also defend against microbial attack through action of anti-bacterial enzymes such as lysozyme (DEWS, 2007).

An instable tear film can cause patients to have dry eye syndrome. These patients would complain of irritation, burning, grittiness, foreign body sensation, blurred vision, photophobia or discomfort. There are two main types of dry eyes. Secretive dry eye where there is inadequate tear production. Many of these patients have inflammation in the tear gland together with the presence of inflammatory mediators in the tears and within the conjunctiva (Jones et al., 1994) and inflammation elsewhere in the body like Rheumatoid arthritis or Sjögren's syndrome.

Evaporative dry eye is where there is adequate tear production but excess evaporation. The commonest causes of increased evaporation of the tears are due to meibomian gland disease in which the oil glands of the eyelids fail to coat the surface of the tears with a healthy layer of oil (DEWS, 2007). An abnormal tear film lipid layer can be caused by various forms of blepharitis which affect the changes in the meibomian gland secretions (McCulley et.al., 1982). There are generally lower levels of phosphatidyl ethanolamine and sphingomyelin in meibum of patients with blepharitis who suffer from dry eye symptoms (Shine et al., 1998).

Therefore, when evaluating the tears, it is important to note that an alteration or anything that affects the secretory, distributary or excretory components of the lacrimal system will have an effect on the effectiveness of the quantity and quality of the tears on the eye.

1.3 Dry Eye Disease

Dry eye has been recognised as an inefficiency of the lacrimal glands, ocular surface including the cornea conjunctiva and meibomian glands and the lids, including the sensory and motor nerves that connect them (Stern et al., 1998). Dry eye is a disorder of the tear film due to deficiency or excessive evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort (Lemp, 1995). Dry eye disease is a common yet under recognised clinical condition whose management challenges optometrists and other medical professionals alike. There have been great advances in the understanding of dry eye disease in the last decade with regards to epidemiology, pathogenesis, clinical representation and potential treatment.

The Dry Eye Work Shop (DEWS) report developed a new definition of dry eye based on current understanding of the disease and recommended a three part classification system. The first part is etiopathogenic and illustrates the numerous causes of dry eye. The second is mechanistic and shows each cause of dry eye may act through a frequent pathway. The third and final part is based on the severity of the dry eye disease which is expected to provide a rational basis for treatment. The DEWS definition of dry eye was enhanced from previous definitions in the light of new information gathered with regards to the roles of tear hyperosmolarity and ocular surface inflammation in dry eyes as well as the effects on visual function.

The DEWS definition is – ‘Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, (Begley et al., 2003; Adatia et al., 2004; Vitale et al, 2004) visual disturbance, (Rieger 1992; Liu et al., 1999; Goto et al., 2002) and tear film instability (Holly et al., 1973; Bron, 2001; Goto et al., 2003) with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film (Farris et al., 1986; Gilbard, 1994; Murube, 2006; Tomlinson et al., 2006) and inflammation of the ocular surface’ (Pflugfelder et al., 1999; Tsubota et al., 1998).

Figure 1.3 Summarises the DEWS definitions and classification of Dry eye. Dry eye is classified in to two major groups: the aqueous deficient dry eye and the evaporative dry eye. Aqueous-deficient dry eye has two major divisions, Sjögren syndrome dry eye and non-Sjögren syndrome dry eye. Evaporative dry eye is either intrinsic, where the regulation of evaporative loss from the tear film is directly affected, e.g., by meibomian lipid deficiency, poor lid congruity and lid dynamics, low blink rate, and the effects of drug action. In contrast, extrinsic evaporative dry eye occurs where there is an increase in evaporation by their pathological effects on the ocular surface. The causes of this include: vitamin A deficiency, the action of toxic topical agents such as preservatives, contact lens wear and a range of ocular surface diseases, including allergic eye disease.

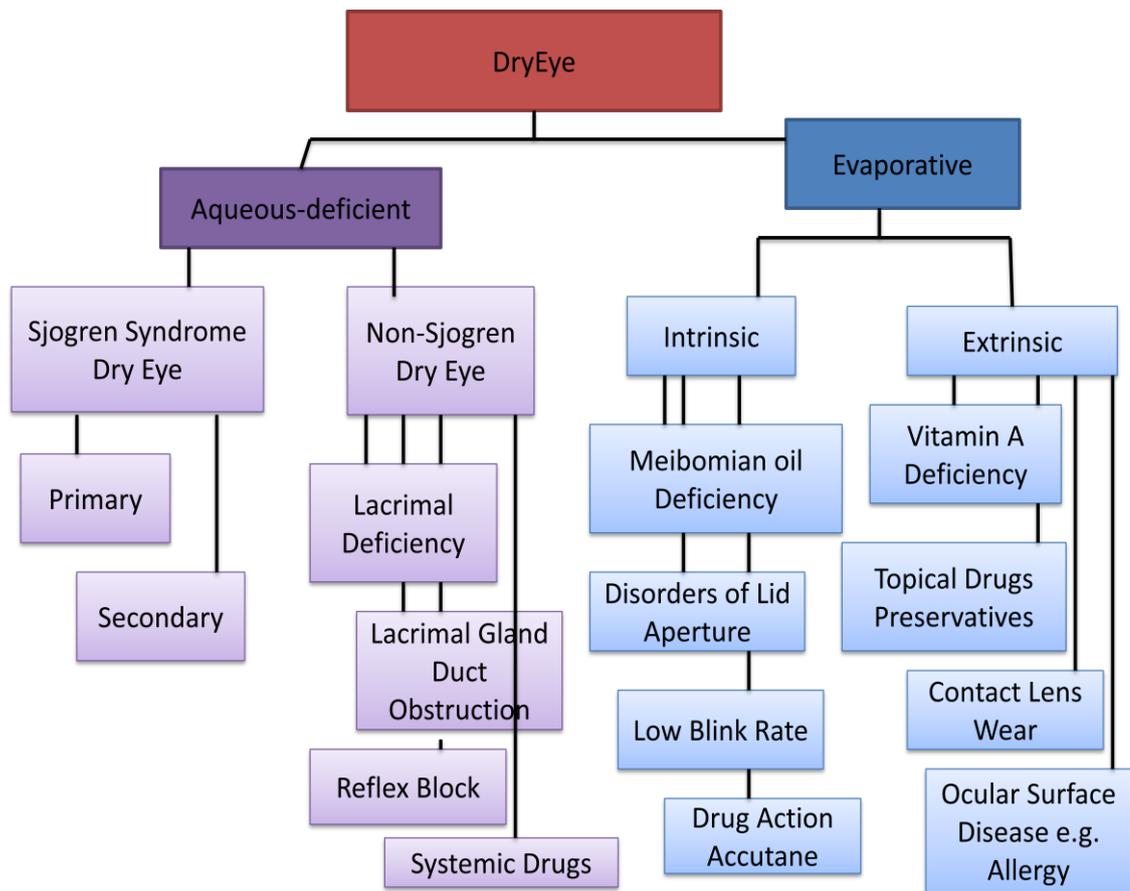


Figure 1.3: Illustrating the Major etiological causes of dry eye disease. (Adapted from DEWS report 2007)

Evidence supports a role of sex hormones in the aetiology of dry eye (Sullivan, 2004) with a consensus that low levels of androgens and high oestrogen levels are risk factors for dry eye. Lacrimal and meibomian gland function is promoted by androgens and a deficiency is associated with dry eye (Sullivan, 2004).

Physiological changes associated with aging are pre disposed to dry eye including reduced tear volume and flow, an increase in osmolarity, (Mathers et al., 1996) reduced tear film stability, (Patel et al., 1989) and alterations in the composition of the meibomian lipids (Sullivan et al., 2006).

The 1995 National Eye Institute (NEI) / Industry Dry Eye Workshop classifications of dry eye are still held. Firstly there is aqueous tear deficient dry eye which refers mainly to a failure of lacrimal secretion and a failure of water secretion by the conjunctiva may also contribute to this. Secondly, evaporative dry eye which is dependent on intrinsic conditions of the lids and ocular surface.

The major classes and sub classes of dry eye are described below:

1.3.1 Aqueous tear deficient dry eye (ADDE)

ADDE is due to a failure of lacrimal tear secretion. Dryness results from a reduced lacrimal secretion as well as volume (Mishima et al 1966.; Scherz et al., 1975). A dysfunction in the lacrimal tear secretion causes tear hyperosmolarity due to a reduced aqueous tear pool. The tear film hyperosmolarity causes hyperosmolarity of the ocular surface epithelial cells which stimulate a series of inflammatory events (Li et al., 2004; Luo et al., 2005). There is an uncertainty in ADDE whether evaporation is increased (Tsubota et al.; 1992, Mathers, 1996) or if evaporation is reduced. Studies have suggested that the reservoir of lid oil is greater in non-Sjögren syndrome dry eye (Yokoi et al., 1999) and the tear film lipid layer is thicker (Yokoi et al., 1996). However, studies of the tear film lipid layer in ADDE have shown that spreading of the lipid layer is delayed in the inter blink interval (Owens et al., 2002, Goto et al., 2003)

ADDE has two classes' Sjögren syndrome dry eye (SSDE) and non-Sjögren syndrome eye (NSSDE).

1.3.1.1 Sjögren syndrome dry eye (SSDE)

SSDE is when the lacrimal and salivary glands are targeted by an autoimmune process and other organs are also affected. The lacrimal glands are penetrated by activated T-cells, which results in acinar and ductular cell death and hypo secretion of the tears. The dryness of the ocular surface is due to this hypo secretion and inflammation of the lacrimal gland, in conjunction with the existence of inflammatory mediators in the tears and within the conjunctival tissue (Jones et al., 1994).

1.3.1.2 Non-Sjögren syndrome (NSSDE)

NSSDE is due to lacrimal dysfunction where the systemic auto immune features which are characteristic of the SSDE have been excluded. Age related dry eye is the most common form of NSSDE. Different forms of NSSDE are listed in table 1.1.

Primary Lacrimal Gland Deficiencies	Age Related Dry Eye Congenital Alacrima Familial Dysautonomia
Secondary lacrimal gland deficiencies	Lacrimal Gland infiltration Sarcoidosis Lymphoma Aids Graft Vs Host disease Lacrimal gland ablation Lacrimal gland denervation
Obstruction of the lacrimal gland ducts	Trachoma Cicatricial pemphigoid and mucous

	membrane pemphigoid Erythema multiforme Chemical and thermal burns.
Reflex Hypo secretion	Reflex sensory block – contact lens wear, diabetes, neurotrophic keratitis Reflex motor block – VII cranial nerve damage, Multiple neuromatosis, Exposure to systemic drugs.

Table 1.1: Conditions associated with non-Sjögren syndrome dry eye. (Adapted from DEWS, 2007)

1.3.1.2.1 Age related dry eye (ARDE) - is a primary disease and there is some uncertainties as to whether tear dynamics are affected by age in the normal population (Tomlinson et al., 2005). A significant age related correlation for tear evaporation flow osmolarity and volume has been shown (Mathers, 1996). However, studies conducted by Craig and Tomlinson (Craig et al., 1998) have shown that there is no such relationship. Likewise for tear turnover (Sahlin et al., 1996) tear evaporation (Rolando et al., 1983, Tomlinson et al., 1993) and the lipid layer (Norn et al., 1979) no age relationship has been found.

1.4 Evaporative dry eye (EDE)

EDE is due to excessive water loss from the ocular surface in the presence of normal lacrimal secretion. Evaporative dry eye causes have been described as intrinsic disease affecting structures or the dynamics of the eye, or extrinsic where the ocular surface disease to some external exposure (DEWS, 2007).

1.4.1 Intrinsic causes of EDE

1.4.1.1 Meibomian Gland Dysfunction (MGD) - is the most common cause of EDE (Bron, 2004). If present to a sufficient extent it is associated with a reduced tear lipid layer, an increase in tear evaporation and evaporative dry eye (Knape et al., 2011).

1.4.1.2 Disorders of lid aperture or lid globe congruity- proptosed eyes will encounter an increased evaporation of the tear film (Gilbard et al., 1983). An increased palpebral fissure is associated with tear hyperosmolarity and ocular surface drying (Gilbard et al., 1983). Having an upward gaze position is also known to affect ocular surface drying as it causes an increased ocular surface exposure (Tsubota et al., 1995). An increased palpebral fissure correlates well with an increase in tear film evaporation (Rolando et al., 1985).

1.4.1.3 Low blink rate - drying of the ocular surface will be affected when the period between blinks increases (Abelson et al., 2002). This can occur as a physiological

phenomenon through particular visual tasks e.g. working at a display screen (Nakamori et al., 1997). It is also known to be a characteristic of Parkinson's disease (Lawrence et al., 1991).

1.4.2 Extrinsic causes of EDE

1.4.2.1 Ocular surface disorders– a condition affecting the ocular surface will lead to poor surface wettability thus causing a short tear break up time of the tear film and hyperosmolarity which leads to a dry eye. The main causes of ocular surface disorder include a deficiency in Vitamin A and the effects of topical anaesthetics and preservatives.

1.4.2.1.1 Vitamin A- is crucial for goblet cell production and glycocalyx formation (Tei et al., 2000). Vitamin A deficiency causes lacrimal acinar damage as well; hence patients with xerophthalmia will result in having aqueous tear deficient dry eye (Sommer et al., 1982).

1.4.2.1.2 Topical drugs and preservatives- preservatives such as benzalkonium chloride (BAK) can cause a toxic response of the epithelium of the cornea causing reduced surface wettability. Hence non-preserved tear preparations are preferable to preserved ones (Pisella et al., 2002). Topical anaesthesia reduces lacrimal secretion by inhibiting the sensory innervation to the lacrimal gland and reduces the blink rate. The chronic use of anaesthesia causes a neurotrophic keratitis which can lead to corneal perforation (Pharmakakis et al., 2001, Chen et al., 2004).

1.4.2.2 Contact lens wearers– are 12 times more likely than an emmetrope and 5 times more likely than spectacle wearers to state dry eye symptoms (Nichols et al., 2004). Females report more dry eye symptoms than males, with 40% of males and 62% of females classified as having dry eye in one study in the USA ($p < 0.0001$; Nichols et al., 2006).

1.4.3 Ocular Surface Disease

Evidence suggests that various forms of chronic ocular surface disease result in disruption of the tear film and add a dry eye component to the ocular surface disease. A well-studied example is allergic eye disease (Abelson et al., 2003). Similarly any form of dry eye, whatever its origins, may cause at least a loss of goblet cell numbers, so that an ocular surface element is added (Ralph, 1975).

1.4.4 Allergic Conjunctivitis

Allergic conjunctivitis includes seasonal allergic conjunctivitis, vernal keratoconjunctivitis, and atopic keratoconjunctivitis. There is stimulation of goblet cell secretion and loss of surface membrane mucins (Kunert et al., 2001). Surface epithelial cell death occurs, affecting conjunctival and corneal epithelium (punctate keratoconjunctivitis). Surface damage and the release of inflammatory mediators' leads to allergic symptoms and to reflex stimulation of the normal lacrimal gland.

The Beaver Dam study, noted that ocular allergy was a risk factor for dry eye, although the concomitant use of systemic medications, such as antihistamines, was recognized as a potential contributor (Moss et al., 2004).

1.5 The core mechanisms of Dry Eye

The tear hyperosmolarity and tear film instability can change dry eye over time. The interactions of various aetiologies with these fundamental processes are summarised in figure 1.3.

1.5.1 Tear Hyperosmolarity

In the early stages of dry eye, it is considered that ocular surface damage is caused by osmotic, inflammatory or mechanical pressure, resulting in reflex stimulation of the lacrimal gland. Trigeminal nerve activity is responsible for an increase in blink rate and increased lacrimal secretion. This may help to reduce the degree of tear hyperosmolarity. However, tear flow in these patients may be greater than average, which show reduced tear breakup time and increased ocular surface staining (Shimazaki et al., 1998).

Tear hyperosmolarity is deemed as the fundamental mechanism causing ocular surface inflammation, damage and symptoms in dry eye. It arises as a result of water evaporation from the exposed ocular surface. It occurs in circumstances of a low aqueous tear flow, or a consequence of excessive evaporation, or a mixture of these events (DEWS, 2007). There appears to be wide variation of tear film thinning rates in normal subjects, and therefore, it is reasonable to conclude that, for a given initial film thickness, subjects with the fastest thinning rates would experience a greater tear film osmolarity than those with the slowest rates as demonstrated by Nichols et al., (2004).

Osmolarity is higher in the tear film itself than in the adjacent menisci. This is due to the ratio of area to volume which is higher in the film than the menisci (Bron et al., 2002). Hyperosmolarity stimulates a series of inflammatory events in the epithelial surface

cells, involving MAP kinases and NF κ B pathways (Li et al., 2004) and the group of inflammatory cytokines (IL-1 α ; -1 β ; TNF- α) and MMPs (principally MMP9), (De Paiva et al., 2006), which stimulate inflammatory cells at the ocular surface (Baudouin, 2007). Hyperosmolarity stimulates inflammatory events in epithelial surface cells and the production of inflammatory cytokines and matrix metallo-proteinases (Li et al., 2004; Tsubota and Yamada, 1992). These inflammatory events lead to the death of surface epithelial cells, including goblet cells (Yeh et al., 2003). A trait of every form of a dry eye is a loss of goblet cells (Zhao et al., 2001). A decline in goblet cells will result in reduced mucin production (Argüeso et al., 2002) and therefore a reduction in tear film stability (DEWS Report 2007). A diminished goblet cell density has been shown to correlate with decreased levels of MUC 5AC in dry eye patients by Argüeso and colleagues (2002). The effects of chronic inflammation may be directly associated with goblet cell loss (Brignole et al., 2000; Kunert et al., 2002).

Inflammatory mediators such as tumour necrosis factor A and interleukin-1 result from a hyperosmolar state and severely affects the nerve supply to the cornea (Acosta et al., 2007) causing a reduction in tear flow (Figure 1.4). This will support the pre-existing reduced tear flow in ADDE and may well reduce tear volume in a previous high volume EDE. Hence patients with ADDE and hyperosmolar tears may have a reduction in goblet cell density and secondary increased tear film evaporation - EDE. On the other hand a patient with primary EDE, e.g. secondary to MGD, will encounter reduced corneal sensitivity and a consequently a reduction in tear production resulting in a form of ADE (Mathers et al., 1996; Tomlinson et al., 2005). Therefore, for this reason differentiating between ADDE and EDE in a clinical setting is challenging.



Illustration removed for copyright restrictions

Figure 1.4: Aetiology of dry eye disease (Taken from DEWS 2007). The core mechanisms of dry eye are driven by tear hyperosmolarity and tear film instability. The cycle of events is shown on the right of the figure. Tear hyperosmolarity causes damage to the surface epithelium by activating a cascade of inflammatory events at the ocular surface and a release of inflammatory mediators into the tears. Epithelial damage involves cell death by apoptosis, a loss of goblet cells and disturbance of mucin expression, leading to tear film instability. This instability exacerbates ocular surface hyperosmolarity and completes the vicious circle. Tear film instability can be initiated, without the prior occurrence of tear hyperosmolarity, by several aetiologies, including xerophthalmia, ocular allergy, topical preservative use, and contact lens wear (DEWS, 2007).

The epithelial injury caused by dry eye stimulates corneal nerve endings, leading to symptoms of discomfort, increased blinking and, potentially compensatory reflex lacrimal tear secretion. Loss of normal mucins at the ocular surface contributes to symptoms by increasing frictional resistance between the lids and globe. During this period, the high reflex input has been suggested as the basis of a neurogenic inflammation within the gland (DEWS, 2007).

1.5.2 Tear Film Instability

Tear film instability may be the initiating factor in some categories of dry eye. It is generally accepted that a TBUT < 10 seconds is abnormal (Lemp, 1995). Once break-up occurs within the blink interval, hyperosmolarity of the tears will result with all of the sequelae discussed in the previous sections (Figure 1.4) and further disrupt the tear film.

Tear film variability is increased with a low TBUT due to local drying and hyperosmolarity, surface epithelial damage, and disturbance of glycocalyx and goblet cell mucins. The tear film instability is thought to be due to a disturbance of ocular surface mucins (Sommer et al., 1982). The early loss of tear stability in vitamin A deficiency results from a decreased amount of mucins at the ocular surface and a loss of goblet cells (Sommer et al., 1982). Other examples include the actions of topical agents, in particular, preservatives such as BAK. These excite the expression of inflammatory cell markers at the ocular surface, causing epithelial cell damage, cell death by apoptosis, and a decrease in goblet cell density (Ronaldo et al., 1991). Tear film evaporation is inhibited by the presence of the tear film lipid layer (Mishima et al., 1961). The lipid layer comprises of an inner polar layer, interfacing with the aqueous phase, and a thicker outer non-polar layer (Bron et al., 2004). The tear film lipid layer stabilises the tear film by reducing the surface tension by 25% and aqueous evaporation by 90-95% (Lozato et al., 2001).

1.6 Clinical Tear Film Tests

There are multiple clinical tests to evaluate the tear film:

1.6.1 Non Invasive Break up Time (NIBUT)

NIBUT is a means of measuring the stability of the tear film without a staining agent. NIBUT is typically measured by observing a grid pattern, Purkinje image I or keratometer mires projected onto the corneal surface. This can be achieved by using a slit lamp, Tearscope (Keeler Inc., Windsor, Berkshire, UK), (Guillon et al., 1994, 1997, 1998a) or a keratometer, (Patel et al., 1985). Although the tearscope is no longer available there is a new product named Polaris on the market (www.bon.de).

Various acronyms have been used to define these non-invasive measurements of tear stability-tear thinning time (TTT), measured using the Bausch & Lomb keratometer (Patel et al., 1985); tear film pre-rupture phase time (TP-RPT), measured using a modified grid on a Bausch & Lomb keratometer (Hirji et al., 1989); and NIBUT using instruments that project a grid pattern image that covers about 70 to 80% of the corneal surface (Mengher et al., 1985; Young et al., 1991; Cho et al., 1993).

1.6.2 Tear Meniscus Height (TMH) and Regularity

The volume of aqueous tears contained within the upper and lower tear meniscus is approximately 75-90 per cent of the total volume of the aqueous component (Mainstone et al., 1996). Therefore a reasonable assessment for the tear volume can be made by observing the height and width of this tear meniscus.

The height of the tear meniscus can be measured with a slit lamp graticule, directly below the pupil centre, adjusting the beam height or by capturing an image and quantifying with digital callipers. The TMH can be observed with or without fluorescein. An increased height indicates poor tear drainage due to an obstructed punctum or an excessive aqueous layer giving a watery tear film. On the other hand a reduced tear meniscus height suggests a reduced tear volume. The TMH is classified as follows:

- Good: >0.2mm
- Normal: =0.2mm
- Poor <0.2mm (Kawai et al., 2007).

If the prism height is regular along the lid margins it indicates the potential for the tears to wet the eye consistently. This is said to reduce with age (Gasson & Morris, 1998).

Numerous studies demonstrate a good correlation between TMH and symptoms of dryness (Mainstone et al., 1996; Golding et al., 1997; Glasson et al., 2003).

A normal TMH has been stated to be between 0.2 and 0.3 mm (Kulkarni et al., 1997) or 0.5 mm (Marquardt, 1986), therefore suggesting that any value of <0.2 mm could be indicative of lacrimal deficiency. The TMH values of <0.1 mm (Herrerias et al., 1992), 0.1–0.2 mm (Basinger et al., 1994) are suggestive of a marginal dry eye, and TMH of ≤ 0.3 mm is abnormal (Lithgow, 1996; Kinney, 1998), or that <0.3 mm was diagnostic for dry eye (Terry, 1984). Liao et al., (2000), suggested that a TMH of ≥ 0.2 mm as a high value and indicative of ocular irritation, possibly applying to the elderly patients.

1.6.3 The Schirmer Test

The Schirmer test was introduced at the turn of the last century for assessing aqueous production/volume (Schirmer, 1903). The Schirmer strip is a filter paper, measuring 5mm in width and 35mm in length and is folded 5mm from one end. The folded end is inserted nearly one third from the temporal canthus amid the lower eyelid and the ocular surface (Farrell, 2010).

The Schirmer test (I), is performed without anaesthesia, and perhaps the most frequently used of the Schirmer tests in clinical practice (Farrell, 2010). The strip is left in position for 5 minutes while the patient is instructed to keep their eyes open and blink normally. In normals the average result is approximately 17mm wetting in five minutes (Wright et al., 1962; Loran et al., 1987). A wetting value of 5mm or less in five minutes is considered abnormal (severe deficiency), while 5-10mm in five minutes is moderately deficient (Farrell, 2010). However, when the test is performed without anaesthetic, the invasive nature of the test may stimulate reflex lacrimation, therefore, under these conditions tears quantified may combine both basal and reflex production (Doughman, 1973). Hence, the use of anaesthetic is aimed at preventing reflex secretion to allow for isolated basal measurement (Jones, 1966). The difference between the result with and without anaesthetic has been suggested as a measure of reflex production (Kanski, 1989).

There is wide intra subject, day-to-day, and visit-to-visit variation, but the variation and the absolute value decrease in aqueous-deficient dry eye, probably because of the decreased reflex response with lacrimal failure (DEWS, 2007). The diagnostic cut off used in the past was ≤ 5.5 mm in 5 minutes, (Van Bijsterveld, 1969; Mackie et al., 1981). Pflugfelder et al., (1997 and 1998) and Vitali et al., (2002) have made a case for using ≤ 5 mm. By lowering the cut-off will decrease the sensitivity (i.e. the detection

rate), but will increase the specificity of the test. DEWS (2007) have recommended conducting the Schirmer test using a cut-off of ≤ 5 mm in 5 minutes.

1.6.4 Phenol Red Thread (PRT) (ZONE QUICK)

The Phenol Red Test (PRT) consists of cotton, treated with a pH indicator phenol red (phenolsilfonphthalein) (Contact lens manual). The thread is pH sensitive and changes from yellow to a light red colour as it comes in to contact with the tears (Hamano et al., 1987). The PRT measures the tear volume.

The PRTs characteristics is that it is easy to handle, has a rapid testing time of only 15 seconds for each eye and the discomfort associated with the Schirmer tear test is minimised. As the Schirmer test may stimulate reflex lacrimation may combine both basal and reflex tear production, the PRT measures the tears in the lower tear meniscus without causing this stimulating reflex. The advantages of the PRT test, is that it does not require any anaesthesia and it may also be performed whilst patients are wearing contact lenses. However, it is very difficult to purchase PRT in the UK, and the PRT used for this study were purchased from the Netherlands.



Figure 1.5: Picture showing the PRT.



Fig 1.6: Photograph showing the PRT in situ.

The PRT test has been shown to be repeatable and the interpretation of the results are: (Little and Bruce, 1994a)

- < 11 mm wet suggests low tear secretion
- 11-16 mm wet suggests borderline secretion
- >21 mm wet suggests normal tear flow

1.6.5 Sodium Fluorescein Tear Break up Time (NaFL TBUT)

The application of a standard volume of fluorescein, illuminated by a blue light source and the use of a yellow barrier filter can enhance the visibility of the breakup of the tear film. The established NaFL TBUT cut-off for dry eye diagnosis, as with NIBUT, has been < 10 seconds (Lemp and Hamill, 1973). Abelson et al., (2002), suggested that the diagnostic cut-off falls to < 5 seconds when small volumes of fluorescein are instilled. At present, sensitivity and specificity data to support this choice have not been provided, and the population in that study was not defined. Selecting a cut off below <10 seconds will tend to decrease the sensitivity of the test and increase its specificity. It has been suggested by various authors that the introduction of fluorescein may affect the TBUT by disrupting the stability of the aqueous layer of the tear film, increasing the volume of the tear film, and affecting the surface tension of the tear film (Holly, 1978; Mengher et al., 1985; Norn, 1986). Some researchers have stressed that the volume and concentration of fluorescein could disrupt the tear film (Norn, 1969; 1974; Lemp, 1973; Mengher et al., 1985; Patel et al., 1985; Guillon et al., 1988; Sorbara et al., 1988; Jaanus, 1990) and is therefore been criticised if these are not controlled (Johnson et

al., 2005; Peterson et al., 2006). Therefore many researches use a micropipette in order to control the volume of fluorescein however; this is not practical in clinical practice. Korb et al., (2001) developed the Dry Eye Test (DET) which is a 5 times smaller fluorescein strip, in order to enable a controlled amount of fluorescein. The DET (Amcon Laboratories, Inc., USA) is not CE labelled and unfortunately cannot be used in Europe. Therefore Pult et al., (2012) modified a standard fluorescein strip, by folding over the top 1mm of the strip in order to define a standard area for fluorescein instillation, and concluded that the modified fluorescein strip was better in the repeatability of fluorescein instillation than the use of a standard fluorescein strip.

1.6.6 Corneal Staining

The corneal or conjunctival surfaces and/or the intracellular surfaces become compromised (Korb, 2002) in dry eye patients and staining agents allow these changes to be observed. Sodium Fluorescein is the most frequently utilised stain in optometric practice.

Sodium fluorescein is a pH-dependent indicator dye which derives its functionality from its fluorescent properties (Morgan and Moldonado-Codina, 2009). At the normal ocular surface pH (6.5-8.0), the colour of fluorescence remains a constant green (Wang et al., 2002), and once exposed to light of a wavelength of 495nm, maximum excitation of fluorescein is achieved. A blue filter is placed in the illumination system; which blocks the wavelengths that don't stimulate fluorescein molecules, allowing only beneficial light to be shone on to the eye. A yellow filter, such as a Kodak Wratten 12, in the viewing system will absorb the unwanted reflected light and transmit only the longer wavelengths emitted by the fluorescein, when stimulated by the blue light. A moistened flouret shaken to remove excess saline provides a peak intensity of fluorescence after about 1 minute (Peterson et al., 2006). An increase in corneal staining has been shown to occur with successive doses of fluorescein, however the reasons why are poorly understood (Korb and Herman, 1979).

Corneal staining is observed when fluorescein enters damaged epithelial cells (Wilson et al., 1995); however, evidence also suggests that fluorescein can diffuse into adjoining cells (Kanno and Loewenstein, 1964). McNamara and colleagues (1998) demonstrated that low levels of fluorescein can enter healthy corneal epithelium through tight cell junctions, but at insufficient levels to be detected with a slit lamp. Dundas and colleagues (2001) found up to 79% of healthy corneas have some degree of staining.



Figure 1.7: Flouret of 1mg fluorescein sodium.

A drop of sodium fluorescein is instilled in to the eye and a blue light is used to observe the pre corneal tear film after a few blinks. This is to ensure that the fluorescein is completely mixed in to the tear film. The patient is asked to stare ahead whilst the blue beam of light is focused on to the cornea. Observation is made as to any damage that may appear on the corneal surface. Various grading scales to score fluorescein staining have been devised, such as:

- Van Bijsterveld system, (Van Bijsterveld, 1969)
- Oxford system, (Bron et al., 2003)
- Standardized version of the NEI/Industry Workshop system, (Lemp, 1995)
- Efron (Efron, 1999)
- CCLRU (CCLRU, 1997)

The Oxford system uses a wider range of scores than the Van Bijsterveld system, allowing for the detection of smaller steps of change in a clinical trial. A study conducted by Efron et al., (2000), evaluated the validation of grading scales for contact lens complications comparing two artist-rendered scales 'Efron' (Efron, 1999), 'Annunziato' (Annunziato et al., circa 1992), and two photographic grading scales 'CCLRU' (CCLRU, 1997) and 'Vistakon' (Andersen et al., 1996). It was concluded from their study all four grading systems are valid for clinical use and practitioners can expect to use these systems with average 95% confidence limits of +1.2 grading scale units (observer range +0.7 to + 2.5 grading scale units). However, in view of the significant differences revealed in this study in both precision and reliability between

systems, observers and conditions, their advice was to consistently use the same grading system.

1.6.7 Lissamine Green Conjunctival Staining

Lissamine green (LG) is a vital stain which is primarily a conjunctival dye which stains membrane dead and degenerate cells (Feenstra et al.,1992) and areas of the conjunctiva not protected by mucus. It is now replacing the use of rose bengal as the preferred dye for conjunctival staining due to better availability and causing less discomfort (Machado et al., 2009).

It is instilled using impregnated paper strips containing 1.5mg of the dye. A drop of sterile saline is added to the strip before it is placed into the lower fornix of the eye. When lissamine green is used it is important to instil a relatively large volume (10-20 μ l) in order to allow adequate staining (Matheson, 2007). At least a minute and no more than four minutes, shows optimum staining (Foulks et al., 2003).

A Wratten 25 filter (or equivalent red filter) has been advocated by some to enhance the staining contrast against the sclera. Conjunctival staining with LG could show up prior to corneal staining with fluorescein in patients with early dry eye (Uchiyama et al., 2007).



Figure 1.8: Lissamine Green Strips.

1.6.8 Lid Parallel Conjunctival Folds (LIPCOF)

LIPCOF are subclinical folds in the lower conjunctiva parallel to the lower lid margin (Höh et al., 1995; Pult et al., 2000; Schirra et al., 1998), which have been shown to be predictive of dry eye symptoms in contact lens wearers (Pult et al., 2000).

There are several hypothesised causes of bulbar conjunctival folds. The conjunctiva 'looseness' as a result of inflammatory processes, (Meller et al., 1998; Zhang et al., 2004; Di Pascuale et. al., 2004), aging (Meller et al., 1998; Hirotsu et. al., 2003), a reduction of elastic fibres (Meller et al., 1998; Zhang et al., 2004), or lymphatic dilation by mechanical forces between the lower lid and conjunctiva that progressively interferes with lymphatic flow (Watanabe et al., 2004). An increase in friction in blinking may follow from insufficient mucins, or transformed composition of the mucins at the ocular surface (Pult, 2008; Berry et al., 2008; Pult et al., 2008).

They are typically evaluated, without the instillation of fluorescein, using a 2-3 mm wide vertical slit located along the temporal limbus at an angle between the observation and illumination system of 20-30 degrees, viewed at 25 times magnification. The slit lamp beam ought to run from the temporal limbus to the inferior bulbar conjunctiva just above the lower lid margin. Höh et al., (1995) examined the relationship between the degree of severity of the dry eye disease (DED) and the presence of the LIPCOF. They classification LIPCOF developing a grading scale based on the height of the normal tear meniscus and the number of individual folds contained in the LIPCOF (Table 1.2). The 'normal' TMH for this study was set at 0.15mm.

Degree of intensity of LIPCOF	Description of the finding of the conjunctival fold in primary position.	Interpretation/intensity of the dry eye syndrome.
Degree 0	No permanently present fold.	No dry eye.
Degree 1	Single small fold; smaller than the normal tear meniscus.	Mild intensity of dry eye.
Degree 2	Fold of up to the height of the normal tear meniscus multiple folds.	Moderate intensity of dry eye.
Degree 3	Fold being higher than the normal tear meniscus multiple folds.	Severe intensity of dry eye.

Table 1.2: LIPCOF grading scale (Höh et al., 1995). The different degrees of LIPCOF, description of the finding of the conjunctival fold in primary position and Interpretation / intensity of the dry eye syndrome are noted.



LIPCOF Degree 3

Fold being higher than the normal tear meniscus, multiple folds

Figure 1.9: Schematic diagram of LIPCOF degrees (from Höh et al., 1995). These small folds are illustrated at the temporal lid margin.

LIPCOF can also be graded by 'optimized LIPCOF grading scale' where by the conjunctival folds are just counted. The four point scale is represented in table 1.3. Pult et al., (2008), provided evidence that LIPCOF graded \geq grade 2 is likely to be associated with dry eye symptoms.



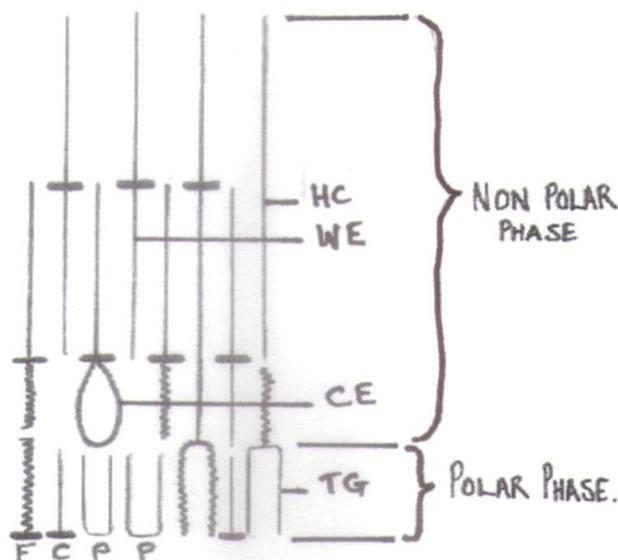
Table 1.3: Optimised LIPCOF grading scale (Pult and Sickenberger, 2000).



Fig 1.10: LIPCOF grade 3. It can be observed that there are several folds. (The image was kindly provided by Dr Heiko Pult).

1.6.9 Lipid Analysis

The lipid layer of the tears is created by the meibomian glands located in the tarsal plates of the eyelids. The function of the lipid layer is to reduce tear film evaporation and enhance tear film stability (Mishima et al., 1961). The secretion from the meibomian glands is known as meibum and consists of polar and non-polar lipids. The polar component of the meibomian layer is comprised mainly of phospholipids, hence acting like a surfactant allowing spreading over the aqueous layer. The non-polar component of the meibomian layer lies at the air-lipid interface (Greiner et al., 1996; Figure 1.11). Mishima et al., (1961) showed that the absence of a lipid layer in rabbits increased tear film evaporation by a factor of 10; therefore an increase in tear film evaporation will result in tear film hyperosmolarity. A rapid and forceful blinking has been shown to increase the thickness of the lipid layer (Korb et al., 1994).



Composition of the Lipid Layer

HC: Hydrocarbon

CE: Cholesterol Ester

WE: Wax Ester

TG: Triglyceride (Mono & Doimsaturated)

F: Fatty Acid

— Carboxyl or Ester Group

C: Cerebroside

~~~ Unsaturated

P: Phospholipid

\_\_\_ Saturated

**Fig 1.11:** Composition of the lipid layer (Adapted from McCulley and Shine, 1997).

The varied lipid layer thickness has been estimated by observation of interference patterns, to measure between 0.06-0.18 microns in the open human eye (Korb, 1998) and it spreads from the opening of the meibomian glands to cover the tear film (Table 1.4). The lipid layer can be considered independent from other features of the tear film as it does not flow from lateral to medial canthi; neither does it enter the conjunctival sac (Ruskell and Bergmanson, 2007).

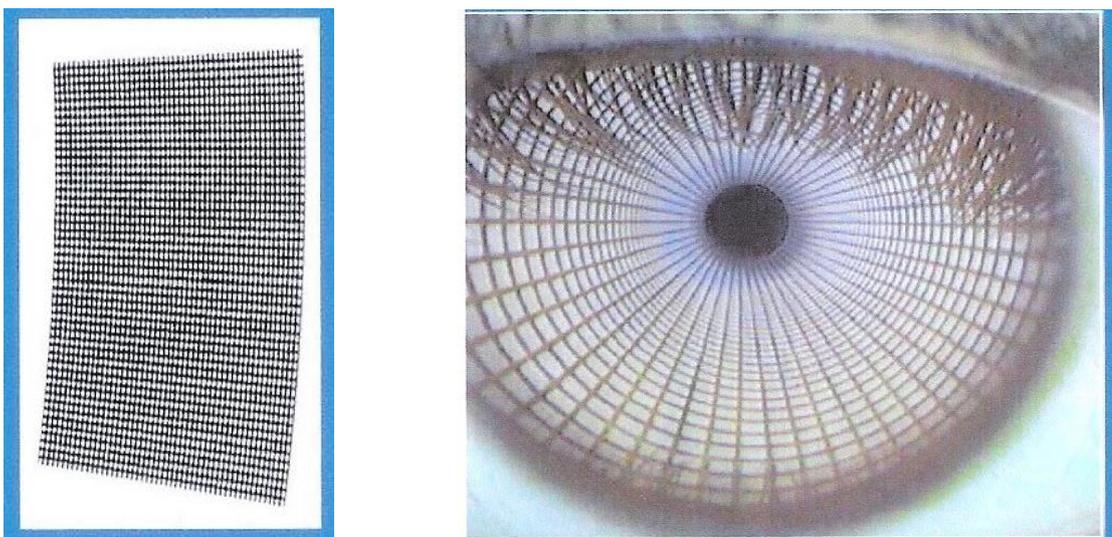
The observation of the pre-ocular tear film can be observed by using the Keeler Tearscope Plus. The Tearscope (Keeler) developed by Guillon in 1986, comprises a 90mm hemispherical cup and handle with a central 15mm diameter observation hole (Figure 1. 12). The inner cup surface is illuminated by a cold cathode ring light source, which was specifically designed to prevent any artificial drying of the tear film during an

examination. The light emitted is diffuse, therefore, does not need to be in focus to observe the tear film. It is designed to be used in conjunction with various inserts (Guillon, 1997).

The advantage of the Tearscope Plus is that the illuminated source consisting of a double concentric cold cathode light is positioned away from the corneal surface, avoiding increased tear film evaporation.

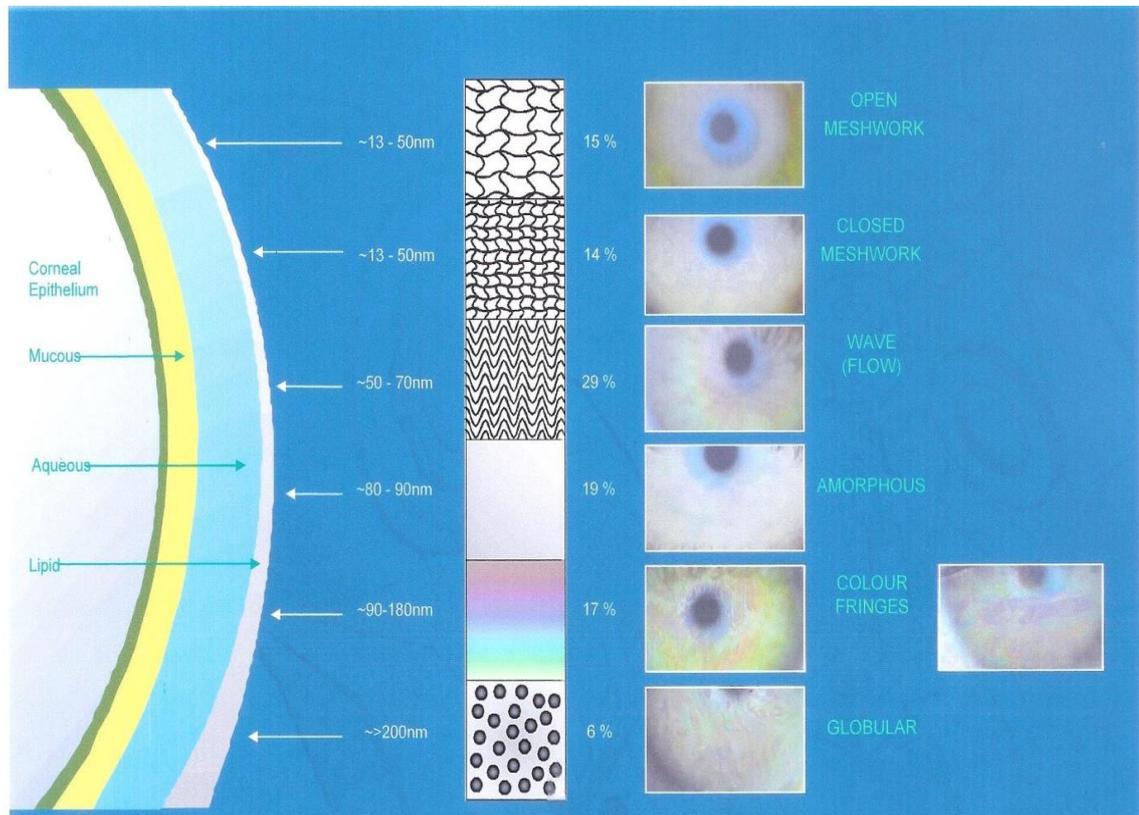


**Figure 1.12:** Tearscope Plus by Keeler. (Keeler Inc., Windsor, Berkshire, UK). (Permission granted by Keeler to reproduce the image).



**Fig: 1.13:** Fine grid patterns as used with the Tearscope. (Permission granted by Keeler to reproduce the image).

The lipid layer is visible by specular reflection. As the lipid layer becomes thicker, a pattern of flowing lipids appears. With an increase in thickness of the lipid layer, an amorphous pattern becomes apparent. The ideal observation appears when no coloured patterns are seen, which are due to interference and relate to abnormal clumps and irregularity in the thickness of the tear lipid layer. Figure 1.14 displays the patterns typically seen in the normal population.



**Figure 1.14:** Pre Ocular Tear Film Lipid Patterns. (Permission granted by Keeler to reproduce the image). The various lipid layer thickness, incidence (%) and lipid layer pattern are illustrated.

Patients with lipid observation of closed meshwork marmoreal, flow and normal coloured fringes are all possible candidates for contact lens wear; however they may experience having some lipid deposits on their contact lenses. Contact lens wear is contraindicated for patients with lipid observation of abnormal coloured fringes and open meshwork marmoreal observation would cause some drying problems. Patients with an amorphous lipid layer observation are excellent candidates for contact lenses. Table 1.4 below, highlights the description and approximate thickness of the tear lipid layer.

| Lipid Layer Pattern              | Appearance                                                                                            | Clinical                                                                                      | Estimated Thickness (nm) | Incidence (%) | Code   | Grade Used For This Study |
|----------------------------------|-------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------|---------------|--------|---------------------------|
| <b>Absent</b>                    | No lipid layer visible                                                                                |                                                                                               | <10                      |               | Abs    | 0                         |
| <b>Open Meshwork marmoreal</b>   | Indistinct, grey, marble-like pattern, frequently visible, only by post blink movement                | Contact lens drying problems                                                                  | 10-20                    | 21            | M(o)   | 1                         |
| <b>Closed Meshwork marmoreal</b> | Well defined grey, marble like pattern with a tight meshwork                                          | Stable tear film. Possible contact lens candidate. Possible excess lipid deposition           | 20-40                    | 10            | M(c)   | 2                         |
| <b>Flow</b>                      | Constantly changing, wavelike pattern                                                                 | Generally stable tear film. Possible contact lens candidate. Possible excess lipid deposition | 30-90                    | 23            | F      | 3                         |
| <b>Amorphous</b>                 | Blue-whitish appearance with no discernible features                                                  | Highly stable tear film. Excellent contact lens candidate. Occasional greasing problems       | 80-90                    | 24            | A      | 4                         |
| <b>Normal coloured fringes</b>   | Appearance of coloured interference fringes                                                           | Contact lens wear possible but excessive lipid deposition likely                              | >100                     | 15            | CF(n)  | 5                         |
| <b>Abnormal coloured fringes</b> | Discrete areas of highly variable coloured fringes. These change rapidly in colour over a small area. | Contact lens wear contraindicated                                                             | variable                 | 7             | CF(ab) | 6                         |

**Table 1.4:** The appearance and approximate thickness of the lipid layer patterns, observed by specular reflection with the Tearscope (Adapted from Craig, 1997 and Guillon, 1986). The grade used for this study can be seen in the far right column.

The Keeler Tearscope plus has been used traditionally to measure and observe the lipid layer of the tears, there are currently new more objective devices available to

observe and measure the lipid layer of the tears, namely the Keratograph 5M and LipiView®.

The LipiView® Ocular Surface Interferometer (Tear Science, Inc., Morrisville, NC) is a device that illuminates the tear film and is capable of delivering quantitative values of the tear-film lipid layer thickness (LLT) (Finis et al., 2013; 2014). The assessment of the LLT may possibly be a suitable screening test for identifying meibomian gland dysfunction (Finis et al., 2013). The LipiView® Ocular Surface Interferometer measures the tear film objectively. It records and measures the interference pattern of the reflected light. This “interferogram” is captured and analysed by software included with the device, allowing lipid layer thickness to be determined with nanometre accuracy. If the lipid layer is too thin or the tear film composition abnormal, then the associated LipiFlow® Thermal Pulsation System treatment may be advised, provided the meibomian glands remain expressible (McDonald, 2012).

The Keratograph 5M (OCULUS Optikgeräte GmbH, Wetzlar, Germany) combines a placido disc topographer with objective NITBUT, lipid layer observation, infrared meibography, blue light fluorescein viewing, bulbar hyperaemia grading and tear film particle tracking (Figure 1.14). The tear layer with the Keratograph 5M is observed subjectively by the examiner. While earlier versions have shown promise although the average objective NITBUT is much lower than subjective observation (Best et al. 2012; Hong et al., 2013; 2014), the 5M version is yet to be evaluated in the academic literature.



**Figure 1.15:** Keratograph 5M. (Photograph kindly provided by OCULUS Optikgeräte GmbH).

#### **1.6.10 Tear Osmolarity**

An increase in osmolarity occurs when water is lost from the aqueous phase of the tear film, thus leaving behind the metal ions. These left over solutes then draws the moisture out of the cornea in an effort to re-establish stability, causing dryness. This event causes a reduction in mucous production, steering in to further tear loss. Therefore a greater tear osmolarity has been shown to cause ocular surface inflammation (Gilbard, 2005; Luo et al., 2005) which results in signs and symptoms of ocular discomfort. Patients with dry eyes generally have a higher tear osmolarity than normal patients (Gilbard, 1986). This hyperosmolarity is said to be a primary reason causing inflammation seen in dry eye patients resulting in ocular discomfort and surface damage (Farris et al., 1983; Gilbard et al., 1978). Hyperosmolarity can trigger an inflammatory response, resulting in the production of inflammatory cytokines (Li et al., 2004) which can lead to increased apoptosis of corneal and conjunctival epithelial cells and conjunctival goblet cells. A decrease in goblet cells would result in reduced mucin production (Argueso et al., 2002) and increase in tear film instability (DEWS, 2007). The tear osmolarity has great value as it assesses a parameter that is directly involved in the mechanism of dry eye. Tear hyperosmolarity may reasonably be regarded as the signature feature that characterizes the condition of “ocular surface dryness” (DEWS, 2007). Tear osmolarity is said to be a single biophysical measurement that can provide significant information about the balance between tear

production, retention and elimination (Tomlinson et al., 2006). Tear osmolarity has been offered as a “gold standard” in dry eye diagnosis in the past (Farris et al., 1981). Traditionally Tear osmolarity has been measured by researchers based in laboratories. Collecting these tear samples were a very complicated and longwinded process due to the calibration of the device. Tear Osmolarity has been traditionally measured by observing the alteration in the freezing point of tear samples (Gilbard and Farris, 1979; Farris et al., 1983). These traditional methods required approximately 0.2 microliters of tears, a high level of user training, continuous maintenance of the equipment and errors may well occur owing to tear sample evaporation (Nelson and Wright, 1986; Tomlinson et al., 2006). Tear osmolarity can also be measured by method of electrical conductivity of the tear film by placing a sensor on the ocular surface (Ogasawara et al., 1996), unfortunately may well trigger reflex tearing.

The feasibility of this objective test is greatly enhanced by the availability of the TearLab (Sullivan, 2004; Buchholz et al., 2006). The TearLab (TearLab Ltd, San Diego, CA, USA) is a relatively new device available for practitioners to determine the tear osmolarity (i.e. the amount of total solute concentrate in patients' tears). The advantages of the TearLab Osmolarity System are fast and accurate results are collected in seconds using 50 nanoliters (nL) of tear film to diagnose dry eye disease (Sullivan et al., 2010), with a recommended cut-off value of 316 mOsms/L (Tomlinson et al.,2006).



A. TearLab Osmolarity System Reader



B. TearLab Osmolarity System Pen



C. TearLab Osmolarity Test Cards



D. TearLab Electronic Check Cards



E. TearLab Control Solutions

**Figure 1.16:** TearLab System. (TearLab Ltd, San Diego, CA, USA). (Permission granted by TearLab to use the images).

### 1.6.11 Symptomology

Numerous questionnaires have been developed for use in dry eye diagnosis, over time. These questionnaires explore different aspects of dry eye disease in changing complexity, ranging from diagnosis alone, to the identification of triggering factors and impact on quality of life. The time taken to administer a questionnaire may affect the choice of questionnaire for general clinical use. The number of questions administered in various questionnaires is listed in Table 1.5.

| Authors/Report       | Instrument Title/Description/Reference                                                                                                                     | Questionnaire Summary | Description/Use                                           |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|-----------------------------------------------------------|
| McMonnies, 1986      | McMonnies<br>Key questions in a dry eye history (McMonnies)                                                                                                | 15 Questions          | Screening questionnaire-used in a clinic population       |
| Nichols et al., 2004 | McMonnies<br>Reliability and validity of McMonnies Dry Eye Index (Nicholos et al.,)                                                                        | Previously Described  | Screening questionnaire Dry eye clinic population         |
| Doughty et al., 1997 | *CANDEES<br>A patient questionnaire approach to estimating the prevalence of dry eye symptoms in patients presenting to optometric practices across Canada | 13 questions          | Epidemiology of dry eye symptoms in a large random sample |

|                            | (CANDEES)                                                                                                                                                        |                                                                                                    |                                                                                                                                                                                                       |
|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Schiffman et al., 2000     | OSDI<br>The Ocular Surface Disease Index                                                                                                                         | 12 item questionnaire                                                                              | Measures the severity of dry eye disease; end points in clinical trials, symptoms, functional problems and environmental triggers queried for the past week                                           |
| Vitale et al., 2004        | OSDI and NEW-VFQ comparison.                                                                                                                                     | Comparison of existing questionnaires                                                              | Tested in Sjögren Syndrome population                                                                                                                                                                 |
| Rajagopalan et al., 2005   | IDEEL Comparing the discriminative validity of two generic and one disease-specific health-related quality of life measures in a sample of patients with dry eye | 3 modules (57 questions):<br>1. Daily Activities<br>2. Treatment satisfaction<br>3. Symptom bother | Epidemiologic and clinical studies                                                                                                                                                                    |
| Schein et al., 1997        | Salisbury Eye Evaluation Relation between signs and symptoms of dry eye in the elderly                                                                           | Standardized 6-question Questionnaires*                                                            | Population – based prevalence survey for clinical and subjective evidence of dry eye                                                                                                                  |
| Bandein-Roche et al., 1997 | Salisbury Eye Evaluation Self-reported assessment of dry eye in a population-based setting                                                                       | Standardized 6-question Questionnaires*                                                            | Population-based prevalence survey for clinical and subjective evidence of dry eye                                                                                                                    |
| Oden et al., 1998          | Dry Eye Epidemiology Projects (DEEP) Sensitivity and specificity of a screening questionnaire for dry eye                                                        | 19 questions                                                                                       | Screening                                                                                                                                                                                             |
| Schaumberg et al., 2003    | Women's Health Study Questionnaire Prevalence of dry eye syndrome among US women                                                                                 | 3 items from 14 item original questionnaire                                                        | Women's Health Study/Epidemiologic studies                                                                                                                                                            |
| Mangione et al., 1998      | National Eye Institute Visual Function Questionnaire (NEI-VFQ)                                                                                                   | 25 item questionnaire; 2 ocular pain subscale questions                                            | Useful tool for group-level comparisons of vision-targeted, health-related QOL in clinical research; not influenced by severity of underlying eye disease, suggesting use for multiple eye conditions |
| Begley et al., 2003        | Dry Eye Questionnaire (DEQ) Habitual patient-reported symptoms and clinical signs among patients with dry eye of varying severity                                | 21 items on prevalence, frequency, diurnal severity and intrusiveness of sx                        | Epidemiologic and clinical studies                                                                                                                                                                    |
| Begley et al., 2000        | Dry Eye Questionnaire (DEQ) Use of the dry eye questionnaire to measure                                                                                          | As Above                                                                                           | As Above                                                                                                                                                                                              |

|                        |                                                                                                                                         |                                                                                                                |                                                                                          |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
|                        | symptoms of ocular irritation in patients with aqueous tear deficient dry eye                                                           |                                                                                                                |                                                                                          |
| Begley et al., 2000    | Contact Lens DEQ<br>Responses of contact lens wearers to a dry eye survey                                                               | 13 Questions                                                                                                   | Screening questionnaire for dry eye symptoms in contact lens wear                        |
| McCarty et al., 1998   | Melbourne Visual Impairment Project<br>The epidemiology of dry in Melbourne, Australia                                                  | Self-reported symptoms elicited by interviewer-administered questionnaire                                      | Epidemiologic studies                                                                    |
| Hays et al., 2003      | National Eye Institute 42-Item refractive Error Questionnaire                                                                           | 42-Item questionnaire: 4 related questions: ocular pain or discomfort, dryness, tearing, soreness or tiredness | QoL due to refractive error                                                              |
| Bowman et al., 2003    | Sicca/SS questionnaire<br>Validation of the Sicca symptoms inventory for clinical studies of Sjögrens Syndrome                          | Inventory of both symptoms and signs of Sjögren Syndrome                                                       | Epidemiologic studies for Sjögren syndrome                                               |
| Bjerrum, 2000          | Bjerrum questionnaire<br>Study Design and Study Populations                                                                             | 3-part questionnaire which includes an ocular part with 14 questions                                           | QOL due to SS dry eye, diagnosis of dry eye, epidemiology of SS                          |
| Bjerrum, 2000          | Bjerrum questionnaire<br>Dry eye symptoms in patients and normal                                                                        | As Above                                                                                                       | Screening questions                                                                      |
| Bjerrum, 1996          | Bjerrum questionnaire<br>Test and symptoms in keratoconjunctivitis sicca and their correlation                                          | Dry eye tests<br>Ocular symptoms questionnaire (14 questions)                                                  | Examine correlation between dry eye test and ocular symptoms questionnaire responses     |
| Schiffman et al., 2003 | Utility assessment questionnaire<br>Utility assessment among pts with dry eye disease                                                   | Utility assessment                                                                                             | Utility assessment                                                                       |
| Shimmura et al., 1999  | Japanese dry eye awareness study<br>Results of a population-based questionnaire on the symptoms and lifestyles associated with dry eyes | 30 questions relating to symptoms and knowledge of dry eye                                                     | Population-based, self-diagnosis study to asses public awareness and symptoms of dry eye |
| Jensen et al., 1999    | Sicca/SLE questionnaire<br>Oral and ocular sicca symptoms and findings are prevalent in systemic lupus erythematosus                    | 6 question symptom questionnaire                                                                               | Screening for dry eye symptoms in SLE patients                                           |
| Vitali et al., 2002    | American-European Consensus Group<br>Classification criteria for Sjörgen's syndrome: a                                                  | 6 areas of questions: Ocular symptoms; oral                                                                    | Clarification of classification of primary and secondary Sjörgren                        |

|               |                                                                                            |                                                                     |                                      |
|---------------|--------------------------------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------|
|               | revised version of the European criteria proposed by the American-European Consensus Group | symptoms; ocular signs; histopathology; oral signs; auto-antibodies | syndrome, and of exclusion criteria. |
| Ellwein, 1994 | The Eye Care Technology Forum Impacting Eye Care                                           | Issues: Standardizing clinical evaluation                           | Decree for change                    |

**Table 1.5:** Symptom questionnaires in current use (Adapted from DEWS 2007). The instrument title / description, questionnaire summary and the use of these tests are summarised.

These questionnaires have been validated to differing extents, and they differ in the degree to which the dry eye symptoms assessed correlate with dry eye signs. The Diagnostic Methodology Subcommittee concluded that the administration of a structured questionnaire to patients presenting to a clinic provides a great opportunity for screening patients with potential dry eye disease (DEWS, 2007). Clinic time can be used most efficiently by utilizing trained support staff to administer the questionnaires. Symptomatology questionnaires should be used in combination with objective clinical measures of dry eye status. Questionnaires are employed in clinical practice in order to screen for the diagnosis of dry eye disease, the effects of the treatment and to grade the severity of the disease. Begley et al., (2002) and Nichols et al., (2004) advocate that the use of dry eye questionnaires is valuable in evaluating the following with regards to DED: for determining the severity of the condition; evaluating the success of the treatment or otherwise; identifying the environmental triggers; and assessing the end points in clinical trials.

### 1.7 Treatment of Dry Eyes

Currently treatment goals for dry eye disease are directed towards either 'tear replacement' or 'tear retention', and are aimed primarily at relieving the subjective symptoms associated with this condition (Farrell, 2010). The treatment of dry eyes by means of artificial tears have been labelled and marketed over the years, those responsible for labelling and marketing simple tear replacement therapy or ocular lubricants (Doughty, 2010). Artificial tears can be considered as 'simple' or 'complex', in order to re wet a 'dry' ocular surface (Doughty, 2010).

Simple artificial tears are mostly to be created on saline (0.9% sodium chloride) with a single polymer in order to assist ocular surface lubrication. Whilst complex artificial tears contain two or more polymers and true ocular lubricants contain the highest concentration of polymers or special polymers or an ointment vehicle base rather than saline (Doughty, 2010).

A cure for dry eye disease has still to be found. The aims of treating dry eye can be broken down to improving the patient symptoms and improve the ocular surface health. There are multiple treatments available which include artificial tears to improve tear volume and the quantity of the mucus layer; lid hygiene and hot compresses to improve the tear lipid layer; punctal plugs to reduce tear drainage; ointments to reduce tear evaporation; anti histamines or steroids to reduce inflammation. The main route for treating dry eye are tear supplements with little evidence as to their effectiveness and whether some work better for some patients than others.

Numerous formulations have been introduced over the years. These formulations with and active ingredients can be classified as aqueous artificial tears, ocular lubricants and viscoelastics (Farrell, 2010). These will be discussed later on in this chapter in detail.

Unfortunately, it is very apparent that dry eye suffers self-prescribe artificial supplements in order to alleviate their symptoms and is usually based on trial and error. However, the treatment goals for dry eye will always be aimed at appropriate ocular healing, and the re-establishment of a normal ocular surface (Göbbels et al., 1992). In order to choose the most suitable treatment option the cause and severity of the dry eye should be established, and the management strategy selected to successfully target the nature of the condition.

The ultimate tear supplement requires the following fundamental features:

- Provide immediate discomfort relief
- Give prolonged residency of the tear film, for long lasting relief
- Is non-toxic to the ocular surface
- Is simple to instil
- Does not blur vision after instillation (Atkins, 2008).

The model delivery system for these tear supplements requires the following important features:

- Easy/simple to use/instil
- Small (measured) droplet size to avoid blurring/washing away the tear film
- Helps maintain solution sterility between usage (with or without preservatives)
- Should be affordable (Atkins, 2008).

Regrettably, all of these requirements cannot be met in a single preparation, and at best a single product is a compromise. The pharmaceutical industry is constantly developing new products and many artificial tears can be purchased in pharmacies and opticians. Several over-the-counter topical lubricants are available based on two treatment methods, which are:

- Designed to lubricate the ocular surface allowing uninhibited movement of the lids without causing epithelial damage;
- Designed to mimic the natural tear fluid as closely as possible, with properties similar to its natural counterpart pH, tonicity and electrolyte balance (Nichols et al., 2004).

The perfect tear substitute should be comfortable on instillation and last for a long period. As a result, there are several artificial tears that vary in property which explains why a number of patients benefit from a particular type while others benefit from another.

Artificial lubricants contain buffers, sodium salts, preservatives, electrolytes and a viscosity enhancing agent. The importance of electrolytes is to maintain corneal thickness, increasing goblet cell density and corneal glycogen contents. The electrolyte bicarbonate is used in artificial eye drops as it preserves the mucin layer as well as promotes the regeneration of an impaired corneal epithelium. Table 1.6 summarises the various artificial tear supplements that are available.

|                                 | Active Ingredient               | Product brand name                                                                            |
|---------------------------------|---------------------------------|-----------------------------------------------------------------------------------------------|
| <b>Aqueous artificial tears</b> | Hypromellose                    | Tears Naturale<br>Isopto Plain<br><i>Artelac SDU</i>                                          |
|                                 | Carboxymethylcellulose          | Optive<br>Theratears                                                                          |
|                                 | Polyvinyl alcohol               | Sno Tears<br>Liquifilm Tears<br>Hypotears<br><i>Liquifilm</i>                                 |
|                                 | Polyvinyl alcohol with povidone | Refresh<br>Clinitas Ultra<br><i>Ocutect (povidone)</i>                                        |
| <b>Liposomes</b>                | Liposome Spray                  | <i>Tears Again</i><br>Optrex Actimist Eye<br>Spray<br><i>Dry Eye Mist</i><br><i>Tear Mist</i> |

|                                                                |                                                  |                                                                                                                   |
|----------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| <b>Viscoelastics</b>                                           | Sodium hyaluronate                               | Optrex Dry Eye Drops<br>Blink Revitalising Drops<br>Sainsbury's Dry Eye Drops<br><i>Clinitas Soothe</i><br>Hyabak |
|                                                                | Carbomer 940                                     | Geltears*                                                                                                         |
|                                                                | Carbomer 980                                     | Viscotears*<br>Liposic*<br>Clinitas Hydrate<br><i>Viscotears</i>                                                  |
|                                                                | Hydroxypropyl guar                               | Systane                                                                                                           |
|                                                                | Tamarind seed polysaccharide and hyaluronic acid | Rohto Dry Eye Relief<br><i>Rohto daily dose</i>                                                                   |
| <b>Ocular lubricants</b>                                       | Liquid paraffin                                  | Lacri-Lube                                                                                                        |
|                                                                | White soft paraffin                              | Lubri-Tears                                                                                                       |
|                                                                | Yellow soft paraffin                             | Simple Eye Ointment<br>Lubrifiilm                                                                                 |
| <b>Lipid Emulsion</b>                                          |                                                  | Refresh Dry Eye Therapy<br>Soothe                                                                                 |
| <b>Sodium Chloride 0.9% (Similar to that of natural tears)</b> |                                                  |                                                                                                                   |

**Table 1.6:** Artificial Tears available in the UK (2013) (Adapted from McGinnigle et al., 2011). All the solutions listed are preserved with Benzalkonium chloride with the exception of those highlighted with an asterisk (\*), which use Certrimide. Italics indicate single unpreserved preparations.

The pH of tears is comparable to that of blood plasma at approximately 7.4-7.5; therefore a pH value of 7.4 is typically elected for artificial tear supplements (Farrell, 2010). It is very important to adjust the pH of artificial tears in order to reduce ocular irritation; as the tears would be have to neutralise the pH of the solution on contact with the ocular surface. The appropriate isotonic solution helps maintain a normal corneal thickness and reduce visual disturbance. The use of a hypotonic solution aids the cornea to successfully transport essential nutrients into the corneal stroma, in severe dry eye.

In order to provide the suitable conditions for lubricating the ocular surface and retaining the artificial tear drops the viscosity of the solution is extremely important. Therefore an artificial tear supplement with low viscosity would decrease the surface tension and increase spreading across the cornea, increase the aqueous evaporation rate and reduce the retention time. On the other hand, a high viscosity lubricant would significantly decrease evaporation and increase the retention time, but may increase the surface tension and cause reduced vision (Farrell, 2010).

Numerous artificial eye drops have been introduced over the years with varying active ingredients and formulations with varying success; these can be classified as aqueous artificial tears, ocular lubricants and viscoelastics (Table 1.7).

| <b>Tear replacement – Classification</b>                                                                                                          | <b>Active ingredient (polymer)</b>                                                                                                                                                                                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Aqueous artificial tears (low viscosity)</b><br><br><b>Flowing liquid that replaces/ replenishes the tear aqueous element.</b>                 | Cellulose derivatives:<br>-methylcellulose (MC)<br>-hydroxymethylcellulose (HEC)<br>-carboxymethylcellulose (CMC)<br>-hydroxypropylmethylcellulose (HPMC)<br>Polyvinyl alcohol (PVA)<br>Polyvinylpyrrolidone (PVP) |
| <b>Ocular Lubricants (high viscosity)</b><br><br><b>Ointments – resistant to flowing and reduce friction between palpebral and ocular surface</b> | White soft paraffin<br>Liquid paraffin<br>Lanolin alcohol                                                                                                                                                          |
| <b>Viscoelastics (thixotropic)</b><br><br><b>Exhibit both liquid and gel properties</b>                                                           | Polyacrylic acid (Carbomer 940)<br>Sodium hyaluronate                                                                                                                                                              |

**Table 1.7:** Common polymers in use in tear replacement classification (Adapted from Farrell, 2010).

### 1.7.1 Aqueous artificial tears

The natural aqueous tear film in tear-deficient dry eyes has been treated typically by varying formularies by means of topical ‘artificial tears’ (Holly, 1991; Bernal et al., 1993). These include cellulose derivatives, mucomimetics, polyvinyl alcohol and providone.

Cellulose derivatives can be prepared in a variety of viscosities and are water-soluble polymers. Various cellulose organic compounds have been used to enhance the viscosity of artificial eye drops; these include the following: carboxymethylcellulose (CMC or carmellose sodium), hydroxyethylcellulose (HEC), hydroxypropylmethylcellulose (HPMC) and methylcellulose (MC). The advantage of these chemically inert polymers enables them to be suitable for the use as artificial tear drops, is that they have a similar refractive index to that of natural tears ( $n=1.336$ ) and have a stable pH. A disadvantage of these cellulose derivatives is that they are watery in substance requiring frequent instillation of the artificial tear drops (Gilbard et al., 1979). Due to their low molecular weight, these cellulose derivatives are absorbed easily by the corneal epithelium, therefore reducing the retention time of the drops being used and ideally for use in mild cases of aqueous deficiency. Marquardt (1986), recommended that artificial tears ‘must have a long retention time’, which is not the case for these cellulose derivatives especially MC. They are used in combination with tear gels in moderate aqueous deficiency due to their low surface tension which

increases in distribution which helps maintain a moist corneal epithelium and therefore reduce further tissue damage.

Mucomimetics contain the cellulose derivatives in a greater viscous preparation and molecular structure. The cellulose derivatives used in mucomimetics are HPMC CMC. An advantage of mucomimetics are that they improve retention time on the ocular surface, as they act as muco adhesives (mimicking the action of tear mucus glycoprotein) in order to improve tear stability. As the preparation is more viscous tear evaporation reduces as the surface tension of the tears increases. The viscous nature may increase surface tension to the point where the surface activity of the preparation is reduced in severe dry eye cases (Lemp, 1972). An increase in viscosity may also result in matting of eyelashes and temporary blurring of vision, which should be considered cautiously for patients who may be driving or operating machinery.

Polyvinyl alcohol (PVA) is a hydrophilic polymer which reduces surface tension. It is used as a viscosity enhancer and chiefly as a wetting agent, due to its outstanding lubricating function, in artificial tears. PVA is less viscous than mucomimetics and offers better aqueous lubrication to the epithelial tissues, in moderate and severe aqueous deficiency, particularly in patients where the natural mucin is diminished (Farrell, 2010).

PVA has been shown to extend tear break-up time as a measure of tear stability (Nelson et al., 1988). In aqueous deficiency the tear film is frequently in a condition of hyperosmolarity (Edwards et al., 1993; Smith, 2002), hence the hydrophilic properties of PVA, in conjunction with decreased osmolarity, may help to re-establish tonicity. PVA has the property to decrease surface tension without affecting the vision (Marquardt, 1986). PVA has a considerably greater retention period than a viscosity-increasing agent acting on its own and continues to maintain its moistening properties in low concentrations (Hardberger et al., 1975). PVA is very unstable in alkaline solutions and has an ideal effective pH value of between 5 and 6 (Gilbard et al., 1979; Lenton et al., 1998). Therefore the tear film is required to neutralise the slightly acidic pH following instillation which may cause the dry eye patient minor discomfort for several minutes.

Polyvinylpyrrolidone (PVP) is a hydrophilic polymer with a related structure and lubricating properties to PVA. The molecular weight of the polymer can be varied for several uses; such as dispersing and suspending agents as well as a vehicle for pharmaceuticals. PVP is ideal as a lubricating agent for artificial tears due to its

consistent rate of dissolution. PVP also helps to improve the solubility of artificial tear preparations, as it increases their retention rate and be able to sweep across the ocular surface. Unfortunately, the preservation of artificial tear drops on the eye is poor and there is no improvement with frequent usage and may increase patient symptoms (Farris, 1991). The natural tears would dilute and wash away essential antibodies and anti-bacterial agents, by frequent use of eye drops. Benzalkonium chloride (0.01%) which is frequently used in artificial tears is toxic to ocular tissues and the adverse effects are increased with frequent use of preserved eye drops (Holly, 1978; Bernal et al., 1991). Benzalkonium chloride is known to reduce the corneal epithelial barrier, disrupt the tear film and decrease the tear break-up time. Unpreserved saline or hydroxyethylcellulose are available in single dose Minims form for the patients who develop solution toxicity. The pharmaceutical industry has increasingly introducing various formulations in single-dose preservative-free options.

### **1.7.2 Ocular lubricants**

For patients suffering from severe lacrimal deficiency, ocular lubricants containing various concentrations of white soft paraffin, liquid paraffin and/or lanolin alcohol as a base, have been developed, in order to increase the retention time on the ocular surface (Farrell, 2010). Ocular lubricants are high viscosity ointments, with a similar formulation to E45 cream, which help to reduce the friction created between the palpebral conjunctiva and ocular surface during blinking (Farrell, 2010). They have a high molecular structure, which aids an increase in the retention time of the lubricant on the ocular surface and is unable to penetrate the tear-cornea barrier with a decreased evaporation rate compared with conventional aqueous solutions. It is traditionally promoted in cases of severe aqueous disorders for overnight (Farrell, 2010). Unfortunately, these ointments cause blurring of vision (Rieger, 1990), therefore, limiting their daytime use, especially for driving. Ointments can also disrupt the tear film to a condition that increased evaporation of the depleted underlying aqueous may follow (Holly, 1978). Some patients may also have a hypersensitive response to lanolin (Farrell, 2010).

### **1.7.3 Viscoelastics**

Viscoelastics predominantly gel polymers that display thixotropic properties (they have the ability to become fluid when agitated and set again when left at rest). These gel polymers are referred to as 'non-Newtonian' (pseudoplastic) by demonstrating an increased viscosity when stationary and during blinking their viscosity decreases considerably to that similar of water which is believed to simulate the function of the tear glycoprotein. Therefore, this characteristic permits the combined gel-fluid and

natural tear film to distribute more successfully during blinking, aiding the formation of a more stable tear film between blinks. When compared with aqueous tear supplements the retention time of viscoelastics is significantly increased. The main viscoelastics used by the pharmaceutical industry in artificial tears are carbomer and sodium hyaluronate (Farrell, 2010).

Carbomers are high molecular weight polymers of polyacrylic acid, which linger in the conjunctival sac for numerous hours and dissolve gradually. Carbomers have an increased retention time of approximately sixteen minutes, in comparison to PVA which is two minutes (Brodwall et al., 1997). This increase in retention time offers a more sustained symptomatic relief as well as reduced frequency of application for patients suffering from moderate and severe aqueous deficiency. Gambaro and colleagues (1990) noted that carbomer gel increased the stability of the tear film as well as improvement in the corneal and conjunctival epithelium in patients with KCS. An increase in the occurrence of 'sticky eyelids' has been reported (Brodwall et al., 1997), due to the high viscosity and increased ocular retention time of carbomers. If carbomers are administered in large doses or too frequently, ocular irritation and blurred vision have been reported (Lebowitz et al., 1984). Therefore, on these grounds, the use of carbomers overnight is preferred and the use of a less viscous drop used during the daytime to treat dry eye patients.

The viscoelastic Sodium Hyaluronate is a biologically occurring polymer, responsible for the jelly-like consistency of the vitreous humour. Sodium hyaluronate is a pharmacologically inert polymer making it non-toxic. It protects the eye due to its physicochemical and rheological properties and has an effective water binding property which decreases evaporation and assists retention. The spreading of Sodium hyaluronate during blinking is enhanced as it increases its elasticity (Farrell, 2010), which enhances the aqueous lubrication of the epithelial tissues on the ocular surface. Sand et al., (1989), reported reduced rose Bengal staining after KCS patients used sodium hyaluronate. Sodium hyaluronate increases in viscosity aiding to stabilise the tear film hence increasing the measured tear break-up time (Mengher et al 1986, Limbreg et al., 1987). Sodium hyaluronate has also been shown to act as a mucoadhesive (Saettone et al., 1989) and may therefore mimic the action of tear mucus glycoprotein to further enhance tear film stability. When Sodium hyaluronate is applied instead of hypromellose, patient symptoms of 'burning' and 'grittiness', are considerably relieved (Bron et al., 1991). There are no reports available in literature of any significant drawbacks of the use of sodium hyaluronate in KCS patients apart from minor initial blurring following instillation.

#### **1.7.4 Lipid Emulsion**

It has been reported by researchers that there is a significant decrease in tear evaporation and improvement in lipid layer thickness with the use of topical lipid emulsion eye drops containing neutral oils and castor oil (Scaffadi et al., 2007; Di Pascuale et al., 2004; Goto et al., 2002; Khanal et al., 2007).

An emulsion-based lubricant eye drop has been conducted in normal subjects and patients with aqueous-deficient dry eye, with or without MGD (Di Pascuale et al., 2004; Solomon et al., 2005) and the results showed that the eyes treated with the emulsion showed a swift rearrangement of the tear film lipid layer in comparison to the control eyes.

A study conducted by Scaffadi et al., (2007) concluded that the use of lipid emulsion eye drops would increase the tear film lipid layer thickness and therefore benefit patients with deficient lipid layers who suffer from dry eye symptoms. They used two different products and concluded from their study that the lipid based eye drop Soothe effectively doubled the lipid layer thickness with a mean increase in the lipid layer 2.5 times greater than the Refresh Dry Eye Therapy. Emulsion eye drops also produces significant changes in the tear film of normal and dry eye patients (Di Pascuale et al., 2004).

A small double-masked, placebo-controlled crossover clinical study conducted by Goto et al., (2002); in patients with non-inflamed obstructive MGD, with and without aqueous deficient dry eye. The patients used homogenised 2% castor oil eye drops, six times per day. The results showed that patients' subjective symptoms tear interference image grade, tear evaporation rates, rose bengal staining scores, tear film breakup time and meibomian gland expressibility grades after using these eye drops showed significant improvement compared with the results after the placebo period. It was concluded that castor oil eye drops are safe and effective in the treatment of MGD. The advantage of this kind of treatment would improve tear stability as a result of lipid spreading, prevent tear evaporation and ease meibum expression. Castor oil emulsion (1.25%) has been proven to be more effective than hypromellose in reducing tear evaporation than hypromellose, which signifies the potential of castor oil emulsion being used in the management of evaporative dry eye (Khanal et al., 2007).

### **1.7.5 Liposomal Sprays**

The lipid layer of the tears plays an important role in reducing tear film evaporation (Craig et al., 2010). Meibomian gland dysfunction results in an abnormal tear lipid layer and has been identified as one of the main causes of ocular discomfort and ocular surface damage (Paulsen et al., 2010; Bischoff et al., 2011; Singh et al., 2011).

Phospholipids have been identified to be significant components within the natural tear film and are imperative to the surface mono-layer formation as well as surfactant properties. The polar lipids of the tear lipid layer consist of 70% phospholipids, with phosphatidylcholine being the most prevalent (38%). A deficit of these phospholipids prevents formation of a stable, uninterrupted lipid layer, which, causes an increased evaporation rate (Craig et al., 1997; McCulley et al., 2003).

Liposomes are minute spherical vesicles, which form when hydrated phospholipids become organised with harmonious head-tail formation into circular sheets (Ebrahim et al., 2005). These sheets unite to form a phospholipid bi-layer membrane, which captures the aqueous-soluble material within aqueous to produce a phospholipid sphere. Liposomes remain stable in aqueous solvents so long as the liposomes are held together by hydrophobic connections (Lee et al., 2004). Phospholipid based sprays aim to improve the tear lipid polar layer by improving lipid dispersion over the tear film. The spray is applied to the closed eyelids and supplements phospholipid liposomes to the eye lid margins where they blend the lipid reservoir at the lid margin from. The lipid reservoir disperses over the tear film and reforms the tear film lipid layer. Various authors have reported improvements in symptomatology, visual acuity, lipid layer thickness, tear film stability, eyelid margin inflammation, tear production and lid parallel conjunctival folds with use of liposomal sprays in dry eye patients (Lee et al., 2004; Dausch et al., 2006; Craig et al., 2010; Khairuddin et al., 2010; Bischoff et al., 2011) in contact lens wear (Künzel, 2008); and following cataract surgery (Reich et al., 2008).

Various studies have been conducted over recent years with phospholipid liposomal sprays as a potential therapy for evaporative dry eye. Dausch et al., (2006) concluded that liposomal eye spray (Tears Again) shows statistically significant clinical advantages over triglyceride-containing eye gel. The patients' subjective direct comparisons of the two preparations revealed a clear preference for the liposomal eye spray regarding its application onto the closed eye as well as for its effectiveness and tolerability. A direct comparison disclosed that the phospholipid-liposome therapy is advantageous and distinctly superior to conventional standard therapy. A significant

improvement in tear film stability and lipid layer thickness can be achieved in normal eyes between 60 and 90 minutes following a single application of a phospholipid liposomal spray (Tears Again) (Craig et al. 2010). However, a limitation of this study was the absence of significant dry eye signs and symptoms in the subject group. Pult et al., (2012), concluded that the liposomal spray ActiMist (Tears Again; liposome phosphatidylcholine) significantly enhanced ocular comfort and tear film stability while TearMist and DryEyesMist worsened these metrics. It was concluded that TearMist and DryEyesMist may not be effective clinically in dry eye treatment due to either too little or inappropriate type of liposomal ingredients (liposome isoflavonoids).

### **1.8 Defining Dry Eye Treatment Success**

While the primary principle of successful dry eye treatment is to improve the ocular surface and prevent damage to the cornea, it is also important to try to provide relief of symptoms and so offer the patient some degree of satisfaction (Asbell et al., 2010). The final point for relief and/or provision of satisfaction is, however, likely to vary between patients and the practitioners managing the patient. A patient with a dry eye is likely to suffer from some symptoms, and successful treatment may just be that the frequency of symptoms has subsided. Patient satisfaction with treatment may also be linked to the cost, i.e. relief from use of an inexpensive product may be considered adequate in comparison to gaining slightly more relief from use of a more expensive product. Most tear supplements act as lubricants; other actions may include replacement of deficient tear constituents, dilution of pro inflammatory substances, reduction of tear osmolarity (Asbell, 2006; DEWS, 2007), and protection against osmotic strain (DEWS, 2007; McDonald, 2007).

A wide variety of over-the-counter (OTC) artificial tear products are available. These products differ with respect to a number of variables which include electrolyte composition, osmolarity, viscosity, the presence or absence of preservatives, (Asbell, 2006) and the presence or absence of compatible solutes (McDonald, 2007).

- **Electrolyte composition** - Products that mimic the electrolyte composition of natural tears are available. Potassium and bicarbonate appear to be the most important, of the electrolytes (Asbell, 2006).
- **Osmolarity** - DED patients have greater than normal tear film osmolarity. Although some studies suggest that artificial tears ideally should mimic the osmolarity of normal tears, others suggest that hypo-osmolar artificial tears are

optimal (DEWS, 2007). Products with varying degrees of hypo-osmolarity have been developed (DEWS, 2007).

If the use of a dry eye product produces even mild undesirable sensations or adverse effects, then a patient is less likely to be compliant. As the primary goal of dry eye treatment is to improve the ocular surface, then this provides the only real means of assessing product efficacy and so also allowing for comparison between products or different product types (Doughty, 2010). This contrasts to what is being termed a surrogate marker, i.e. changes in tear film osmolarity (Lemp, 2008).

Rose Bengal has been used traditionally in order to assess the ocular surface in order to diagnose for dry eye disease as well as to provide follow-up on treatment efficacy (Doughty et al., 2009). The severity of rose bengal staining was introduced in the 1960s by Van Bijsterveld (Van Bijsterveld, 1969). A score of between 0 and 3 is delegated for the nasal, temporal conjunctiva and corneal surface.

Therefore, the worse the rose bengal staining, the worse the condition and the more intensive the treatment that is required. At the follow up appointment by assessing the staining, a change in the rose bengal score can be evaluated in absolute terms (e.g. the Van Bijsterveld score go down from 7 to 5) or in relative terms (e.g. if the score changed from 7 to 5, could be regarded as a 29% reduction or a 40% improvement in ocular surface staining). It is also worth noting whether the patient's symptoms have reduced with treatment.

Hence from this viewpoint, it is suitable to consider whether dry eye treatments have improved over the past twenty five years, where the percentage improvement in rose bengal staining is given as the treatment efficacy as represented in figure 1.17. The upward trend shown in fig 1.17 shows that over the last twenty five year period, the efficacy of dry eye treatments has improved. Equally, it could also suggest that practitioners are getting better at managing dry eye, especially in terms of maintaining compliance with treatments (Doughty, 2010).



**Figure 1.17:** Assessment of the overall efficacy of dry eye treatments over a 25-year period as assessed by improvement in rose bengal staining of the ocular surface following one-month tear of replacement therapy. The line is that generated by a step-wise Lowess regression (Taken from Doughty, 2010).

Even the best treatments only produce less than 100% effect, with very few published data available on whether there is much further improvement. There is a high likelihood that moderate dry eye patients will often swap treatments, probably because of a perceived lack of efficacy of the product type or regimen. Asbell et al., (2010) indicated that almost half (47.4%) of those with mild dry eye used two products over a year and a similar proportion of those with moderate dry eye used three different treatments.

Published articles over a twenty five year period have also been used to try to assess the average improvement after one month of treatment (Doughty et al., 2009). The treatments included traditional artificial tears versus the viscous eye drops or HA based eye drops. The viscous eye drops were likely to be multi-dose, while the HA products preservative-free preparations. The frequency of use with the gels was usually twice a day, and those for preservative-free product use at least four times per day if not more frequent. The overall outcome of any of these treatments, over one month, is shown in Figure 1.18. There appears to be an improved change of most rose bengal scores after one month of treatment. There is approximately 25% improvement overall indicating that suitable artificial tear drops can maintain and protect the ocular surface (Doughty, 2010).



**Figure 1.18:** Responses of dry eyes to one month of tear replacement therapies, as assessed by rose bengal staining. The data is from 30 different published studies with the red bars showing the rose bengal scores prior to treatment (baseline) and the grey hatched bars the scores after being treated. (Taken from Doughty, 2010).

The effects of treatment with different types of tear replacement therapy can also be analysed, however the apparent outcome depends on the calculations used (Doughty et al., 2009).

Unfortunately, there is no published data for equivalent rose bengal staining data does for the efficacy of ointments. Carbomer-based products show an equivalent effect to traditional artificial tears when assessing the absolute reduction in rose bengal scores after one month of treatment (Doughty and Galvin, 2009). There was a greater reduction in rose bengal scores with HA-based products and when the rose bengal score is analysed in terms of the percentage improvement, the use of carbomer products appears to provide a superior outcome to traditional artificial tears, and the HA-based products provide a similar efficacy to the gels (Doughty and Galvin, 2009).

### **1.9 Relative effectiveness of dry eye treatments**

Dry eye remains the commonest complaint encountered in clinical practice. The constant discomfort leads to a high level of nuisance that only the patients can fully appreciate and unfortunately, many practitioners continue to rely on ad hoc use of eye drops as a solution, thus this strategy usually provides little more than temporary relief.

There are various papers showing how well each individual drops and eye sprays perform (Lee et al., 2004; Matheson, 2006; Rahman et al., 2012). However, very few seem to compare various drops and sprays perform against each other (Table 1.8)

| Authors                     | Type of study                                                                         | Tests Used                                                                                                                                                                                                                                               | Drops Used                                                   | How many subjects | Results/Conclusions                                                                                                                                                                                                                                                  |
|-----------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Forest-Larsen et al., 1978. | Randomised, double blind crossover trial                                              | Schirmer Test, BUT                                                                                                                                                                                                                                       | Bromhexine 24 mg and 48 mg Vs Placebo                        | 29                | In the Sjögren's patients BUT increased after bromhexine with a dose effect.                                                                                                                                                                                         |
| Meghner et al., 1986.       |                                                                                       | NIBUT                                                                                                                                                                                                                                                    | Sodium Hyaluronate (0.1%)                                    | 10                | Tear film stability was significantly increased, and symptoms of grittiness and burning were also significantly alleviated in eyes treated with sodium hyaluronate.                                                                                                  |
| Tsubota et al., 1999.       | Controlled double-masked                                                              |                                                                                                                                                                                                                                                          | Calcium Carbonate (10%) Vs Control                           | 18                | Subjective symptoms significantly improved, as well as fluorescein, rose bengal scores, and blink rate. Tear evaporation also significantly decreased. BUT did not improve.                                                                                          |
| Stevenson et al., 2000.     | Multi-centre, randomised, double-masked, parallel-group, 6 month, vehicle controlled. | Corneal and inter palpebral staining, Schirmer test, TBUT, OSDI, facial expression, patients subjective rating scale, symptoms of dry eye, investigators evaluation of global response to treatment, treatment success and daily use of artificial tears | Cyclosporine A (CsA 0.05% and 0.1% ophthalmic emulsions)     | 877               | Improvement in corneal staining and Schirmer values, blurred vision, need to concomitant artificial tears, and the physicians' evaluation of global response treatment.                                                                                              |
| Nepp et al., 2001.          | Randomised, double-blind study                                                        | TBUT, Schirmer test, lipid-layer thickness and fluorescein staining.                                                                                                                                                                                     | Sodium hyaluronate (0.4% and 0.25%)<br>Chondroitin sulphate. | 28                | Sodium chloride solutions may be a useful short term alternative to other tear formulations.                                                                                                                                                                         |
| Albietz et al., 2001.       |                                                                                       | McMonnies survey TBUT, nucleo-cytoplasmic (N/C), goblet cell density (GCD) and expression of monoclonal antibodies HLA DR and CD23                                                                                                                       | Preserved and Non-preserved dry eye treatments               | 134               | No significant differences were found between the group perceiving non-preserved dry eye treatments and untreated dry eye group. The group receiving the preserved treatments had a reduced GCD and an increased expression of HLA DR and CD23 compared to the group |

|                           |                                                         |                                                                                                                                                          |                                                                                                                                              |                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|---------------------------|---------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                           |                                                         |                                                                                                                                                          |                                                                                                                                              |                                             | receiving non-preserved treatments.                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Dogru et al., 2002.       | Single – centre, 3-visit, prospective, open-label study | Measurements of corneal sensitivity, Schirmer test, TBUT fluorescein staining.                                                                           | Olopatadine hydrochloride 0.1%                                                                                                               | 58                                          | Patients mean corneal sensitivity improved, BUT values improved, goblet cell density improved                                                                                                                                                                                                                                                                                                                                                                        |
| Aragona et al., 2002.     | Blind Study                                             | Subjective symptoms, TBUT, fluorescein, rose bengal staining, Schirmer I test, conjunctival impression cytology                                          | Hypotonic (150 mOsm/l) 0.4% hyaluronate eye drops, isotonic 0.4% hyaluronate eye drops.                                                      | 40                                          | Symptoms significantly improved. An improvement of BUT, fluorescein, and rose bengal score. Improved conjunctival impression cytology Hyaluronate eye drops are useful for treating severe dry eye in Sjögren's syndrome patients.                                                                                                                                                                                                                                   |
| Aragona et al., 2002.     | Randomised double blind study                           | Rose bengal, fluorescein staining, TBUT, Schirmer test                                                                                                   | Preservative free sodium hyaluronate or saline                                                                                               | 86                                          | Sodium Hyaluronate improved impression of cytology score Sodium hyaluronate may effectively improve ocular surface damage associated with dry eye syndrome.                                                                                                                                                                                                                                                                                                          |
| Shimmura et al., 2003.    |                                                         | The effects of albumin on the viability of serum deprived conjunctival cell were observed in vitro. Rose Bengal, fluorescein, TBUT, subjective symptoms. | 5% or 10% solutions of human albumin. 0.3% sodium hyaluronate.                                                                               | 40 Japanese white rabbits. 9 human subjects | Corneal erosions in rabbits healed significantly faster in eyes treated with albumin compared with control and sodium hyaluronate. Patients with Sjögren's syndrome used albumin drops showed improvement in fluorescein and rose bengal scores, but not in TBUT and subjective symptoms. The use of albumin as a protein supplement in artificial tear solutions is a viable approach in the treatment of ocular surface disorders associated with tear deficiency. |
| Di Pascuale et al., 2004. | Design comparative, non-randomised interventional study | Symptom score, TBUT, dye staining and fluorescein clearance test.                                                                                        | Single dose of emulsion eye drop (EED) and non-preserved saline.                                                                             | 15                                          | Emulsion eye drops produces significant changes in the tear film or normal and dry eye patients.                                                                                                                                                                                                                                                                                                                                                                     |
| Nakamura et al., 2004.    |                                                         | Non-invasive specular reflection video recording system, appearance of a tear break up area and tears film images.                                       | 1ppm hypochloric acid (HOCL) sodium hyaluronate (SH), hydropropylmethylcellulose (HPMC), hydroxyethylcellulose (HEC) or chondroitin sulphate |                                             | Ocular surface bathing with artificial tear preparations composed of suitable viscosity agents could be useful in managing tear film instability.                                                                                                                                                                                                                                                                                                                    |

|                           |                                                                                  |                                                                                                       |                                                                         |     |                                                                                                                                                                                                               |
|---------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                           |                                                                                  |                                                                                                       | (CS)                                                                    |     |                                                                                                                                                                                                               |
| Chag et al., 2005.        | Randomly divided into two groups.                                                | Schirmer Test, Rose bengal fluorescein test, TBUT, questionnaires                                     | Chi-Ju-Di-Huang-Wan                                                     | 80  | Chi-Ju-Di-Huang-Wan is an effective stabiliser of tear film and decrease the abnormality of corneal epithelium. It provides an alternative choice for dry eye treatment.                                      |
| Johnson et al., 2006.     | Randomised, double-masked.                                                       | Symptom intensity and NIBUT                                                                           | Sodium hyaluronate 0.1% and 0.3% (SH)                                   | 13  | Sodium hyaluronate of 0.1% and 0.3% reduces symptoms of ocular irritation and lengthens NIBUT in subjects with moderate dry eye more effectively than saline, in terms of peak effect and duration of action. |
| Moon et al., 2007.        |                                                                                  | Schirmer Test, TBUT, conjunctival impression cytology                                                 | Topical 0.05% cyclosporine, 0.08% chondroitin, 0.06% sodium hyaluronate | 36  | While both CS-HA and 0.05% CsA eye drops improve ocular surfaces, topical CsA may have a better effect on enhancing tear film stability and goblet cell density.                                              |
| Prabhasawat et al., 2007. | Randomised, double blind, controlled, exploratory study                          | NIBUT                                                                                                 | Isotonic 0.3% hydropropyl-methylcellulose (HPMC) 0.1% dextran           | 10  | Treatment with sodium hyaluronate and HPMC/dextran eye drops is useful for treating patients with dry eye. Sodium hyaluronate caused a significantly greater increase in NIBUT values than HPMC/dextran.      |
| Durrie et al., 2008.      | Randomised, double-masked, single centre, placebo controlled contralateral study | TBUT, visual acuity, corneal and conjunctival staining and treatment related adverse events           | Systane Lubricant eye drops                                             | 30  | Systane Lubricant Eye Drops are safe for use following LASIK surgery to relieve the discomfort symptoms of dry eye associated with the procedure.                                                             |
| Kim et al., 2009.         | Randomised, controlled, parallel group study.                                    | Fluorescein staining, Schirmer tear test, TBUT, dry eye symptoms, and impression cytological analysis | Vitamin A (retinol palmitate) and cyclosporine A 0.05% eye drops.       | 150 | Both vitamin A eye drops and topical cyclosporine A treatments are effective for the treatment of dry eye disorder.                                                                                           |
| Gupta et al., 2009.       | Retrospective observational case series                                          | Fluorescein staining, TBUT, Schirmer test                                                             | Cyclosporine 0.05%                                                      | 539 | Majority of patients has improvement in their symptoms.                                                                                                                                                       |
| Benelli et al., 2010.     | Randomised, investigator –                                                       | Schirmer test, TBUT, visual acuity, fluorescein staining,                                             | Carboxymethylcellulose sodium (CMC) 0.5%,                               | 60  | The results found that polyethylene glycol 400, 0.25% and sodium hyaluronate significantly                                                                                                                    |

|                                |                                                  |                                                                                                                                       |                                                                                                |                   |                                                                                                                                                                                                                                                                                                                               |
|--------------------------------|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                | masked evaluation.                               | tear osmolarity and wave front aberrometry.                                                                                           | polyethylene glycol 400 2.5%, sodium hyaluronate and HP Guar 18%                               |                   | improved tear osmolarity compared with carboxymethylcellulose sodium (CMC), 0.5% and HP Guar 0.18% after instillation.                                                                                                                                                                                                        |
| Sanchez et al., 2010.          | Prospective, interventional, single-centre study | Corneal and conjunctival staining with fluorescein and lissamine green, TBUT, Schirmer test with anaesthesia, tear clearance and OSDI | Hydroxypropyl HP-Guar                                                                          | 48                | The addition of HP-Guar to regular treatment after cataract surgery reduces ocular surface inflammation and dry eye signs and symptoms.                                                                                                                                                                                       |
| Zhivov et al., 2010.           | Randomised double-blind clinical trial           | Subjective discomfort, slit-lamp biomicroscopy, TBUT and Schirmer test.                                                               | 0.01% Benzalkonium Chloride (BAC) solution and a placebo.                                      | 20                | The return of Langerhans Cells (LC) counts toward (or even below) baseline levels just four weeks after the end of BAK administration demonstrates the rapid normalization of the inflammatory environment.                                                                                                                   |
| Rodriguez-Torres et al., 2010. |                                                  | Height of lacrimal meniscus, Schirmer II test (with anaesthetic), break up time BUT, and lissamine green staining.                    | Carboxymethylcellulose, hydroxypropylmethylcellulose, polyethyleneglycol, cyclosporine A 0.05% | 56                | Conjunctival lissamine green staining is a useful guideline that could be routinely used to confirm diagnosis in subjective evaluations and patient follow-up. Patients with dry eye show a decrease in OSDI after being treated with the appropriate medication prescribed for each particular group, depending on severity. |
| Shafaa et al., 2011.           |                                                  | Schirmer test and TBUT.                                                                                                               | Atropine sulphate eye drops 1%, tetracycline                                                   | 24 albino rabbits | There was a significant improvement in the group treated with tetracycline alone and empty liposome. The use of liposome encapsulated tetracycline significantly improved Schirmer test results and TBUT values as well as reverse surface ocular pathology.                                                                  |
| Evangelista et al., 2011.      | Randomised                                       | NIBUT and Ocular Protection Index (OPI)                                                                                               | Benzalkonium chloride-containing lubricant – Carnidrop, Optive and Blu Sal                     |                   | The instillation of compounds that improve the quality and stability of the tear film, which are impaired in dry eye syndrome, could be effective in the treatment of this condition.                                                                                                                                         |
| Opitz et al., 2011.            | Open Label study.                                | TBUT, corneal and conjunctival staining, Schirmer test scores with anaesthetic, meibomian                                             | Azithromycin 1.0%                                                                              | 33                | Azithromycin 1% ophthalmic solutions offer viable option for the treatment of posterior blepharitis.                                                                                                                                                                                                                          |

|                               |                                                                            |                                                                                                                |                                                     |     |                                                                                                                                                                                                                                                                                                                                                                      |
|-------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                               |                                                                            | gland score, patients symptom scores and OSDI score                                                            |                                                     |     |                                                                                                                                                                                                                                                                                                                                                                      |
| Lemp et al., 2011.            | Prospective, observational case.                                           | Bilateral tear osmolarity, TBUT, corneal and conjunctival staining, Schirmer test and meibomian gland grading. |                                                     | 314 | Tear osmolarity is the best single metric both to diagnose and classify dry eye disease. Inter eye variability is a characteristic of dry eye not seen in normal subjects.                                                                                                                                                                                           |
| Byun et al., 2012.            |                                                                            | Symptom scores, TBUT, Schirmer test, corneal and conjunctival staining.                                        | Cyclosporine 0.05% (tCsA) and 1% Methylprednisolone | 21  | Treatment with tCsA appears to be safe and effective in moderate-to-severe chronic dry eye. Additional short-term use of a topical steroid had the benefit of providing faster symptom relief and improvement of ocular sign without serious complications.                                                                                                          |
| Kinoshita et al., 2012.       | Randomised, double-masked, multicentre, placebo, controlled phase II study | Fluorescein corneal staining, lissamine green conjunctival staining, TBUT and Schirmer test                    | 1% & 2% Rebamipide                                  | 308 | The incidence of ocular abnormalities was similar across the rebamipide and placebo groups. Rebamipide was effective in treating both objective signs and subjective symptoms of dry eye and were well tolerated in this 4-week study. Although 1% and 2% rebamipide were both efficacious, 2% Rebamipide may be more effective than 1% Rebamipide in some measures. |
| Stanković-Babić et al., 2012. |                                                                            | Ocular discomfort, Schirmer test, TBUT and Rose Bengal staining.                                               |                                                     | 50  | The use of autologous serum in dry eye therapy should provide benefit to the patients, relieve symptoms and improve objective parameters for the evaluation of dry eye.                                                                                                                                                                                              |
| Kamiya et al 2012.            | A prospective, randomised, multicentre study                               | Tear volume, TBUT, fluorescein and rose Bengal staining, subjective symptoms and adverse events                | Diquafosol tetrasodium and sodium hyaluronate 0.1%  | 32  | In dry eyes where sodium hyaluronate monotherapy was insufficient, diquafosol tetrasodium was effective in improving objective and subjective symptoms, suggesting its viability as an option for the additive treatment of such eyes.                                                                                                                               |
| Liu et al., 2012.             |                                                                            | OSDI, TBUT, Schirmer test, ocular surface staining (OSS) and conjunctival HLA-DR                               | Pranoprofen 0.1% sodium hyaluronate 0.1%            | 60  | Topical pranoprofen 0.1% has a beneficial effect in reducing the ocular signs and symptoms of dry eyes and decreasing                                                                                                                                                                                                                                                |

|                         |                                                                                   |                                                                                                                                                 |                                                       |     |                                                                                                                                                                                                                                                                                                                     |
|-------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                         |                                                                                   | expression.                                                                                                                                     |                                                       |     | inflammatory marks on conjunctival epithelial cells.                                                                                                                                                                                                                                                                |
| Matsumoto et al., 2012. | Randomised, double masked, multicentre, parallel-group, placebo controlled trial. | Fluorescein corneal staining, rose bengal corneal and conjunctival staining scores, tear break up time (BUT) and subjective symptom assessment. | 1% or 3% diquafosol                                   | 286 | Both 1% and 3% diquafosol ophthalmic solutions are considered effective and safe for the treatment of dry eye syndrome.                                                                                                                                                                                             |
| Çómez et al., 2013.     | Single-institution, single masked, randomised, pilot study                        | OSDI                                                                                                                                            | Systane, Eystil, Tears Naturale II and Refresh tears. | 43  | All four artificial tear formulations were effective in relieving dry eye signs and symptoms. Although the greatest improvement in two of the objective tests was achieved by Eystil, the drug with the lowest osmolarity, differences among the four artificial tear eye drops were not statistically significant. |
| Chung et al., 2013.     |                                                                                   | Schirmer test I, TBUT, corneal temperature and dry eye symptom questionnaire.                                                                   | Cyclosporine 0.05% and saline 0.9%                    | 32  | The dry eye symptom score was significantly reduced in the cyclosporine 0.05% group. Cyclosporine 0.05% can also be an effective treatment for dry eye after cataract surgery.                                                                                                                                      |
| Saeed et al., 2013.     | Multi-centre, open label, uncontrolled study                                      | TBUT, Schirmer test, corneal staining                                                                                                           | Sodium hyaluronate eye gel                            | 250 | Sodium Hyaluronate can provide a suitable alternate in the treatment of dry eye disease due to its reported efficacy on foreign body sensation, itching, burning, watering, photophobia and feeling of dryness.                                                                                                     |
| Tomić et al., 2013.     |                                                                                   | Intraocular pressure (IOP), TBUT and OSDI                                                                                                       | BAK-preserved travoprost 0.004%                       | 40  | This study showed that BAK-preserved travoprost 0.004% is an effective medication in newly diagnosed POAG patients, but its long-term use may negatively influence ocular surface health by disrupting the tear film stability.                                                                                     |
| Guo et al., 2013.       | Randomised controlled study.                                                      | Eye symptom score, Schirmer I test, TBUT, corneal fluorescein staining (CFS) and visual analogue scale (VAS)                                    |                                                       | 47  | Both electro acupuncture and ordinary acupuncture in improving eye symptom and Schirmer score.                                                                                                                                                                                                                      |
| Koh et al.,             |                                                                                   | Subjective dry eye                                                                                                                              | Diquafosol                                            |     | Prolonged use of diquafosol ophthalmic                                                                                                                                                                                                                                                                              |

|                         |                                                        |                                                                                                                                                      |                                                                                          |     |                                                                                                                                                                                                                              |
|-------------------------|--------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2013.                   |                                                        | symptoms, corneal and conjunctival staining with fluorescein, TBUT, lower TMH, optical coherence tomography, Schirmer testing and adverse reactions. |                                                                                          |     | solution for 6 months produced significant improvement both subjectively (dry eye symptom score) and objectively (ocular staining score and tear function tests) for aqueous-deficient dry eye.                              |
| Celebi et al., 2014. .  | Prospective double-blind randomised crossover study    | OSDI, TBUT, Schirmer test and oxford scale.                                                                                                          | 20% diluted Autologous serum (AS) eye drops vs Preservative free artificial tears (PFAT) | 20  | AS eye drops were more effective than conventional eye drops for improving tear film stability and subjective comfort in patients with severe DES.                                                                           |
| Zhang et al., 2014.     | Single factor experiments                              | TBUT and fluorescein staining                                                                                                                        | Nanoscale-dispersed eye ointment (NDEO), petrolatum, lanoline and triglycerides (MCT)    |     | Histological evaluation demonstrated that the NDEO restored the normal corneal and conjunctival morphology and is safe for ophthalmic application.                                                                           |
| Ueta et al., 2014.      |                                                        | TBUT                                                                                                                                                 | Rebamipide                                                                               | 4   | Rebamipide eye drops might attenuate giant papillae in patients with allergic conjunctival diseases and that these eye drops may be useful for the treatment of not only dry eye but also of allergic conjunctival diseases. |
| Kaercher et al., 2014.  | A prospective, multi-centre, non-interventional study. | Dry eye severity, TBUT, Schirmer test, OSDI and patient assessment of symptoms.                                                                      | Optive Plus                                                                              |     | Optive plus was well tolerated and effective in reducing the signs and symptoms of all types of dry eye but is recommended for lipid-deficient dry eye patients.                                                             |
| Lee et al., 2013.       | Randomised controlled trial.                           | OSDI, TBUT), Schirmer test fluorescein staining, tear osmolarity and adverse events.                                                                 | 0.1% sodium hyaluronate                                                                  | 95  | No differences were found between the two groups in measures other than the OSDI. Adverse events were mild and transient. Thermal massage was effective in improving dry eye syndrome both subjectively and objectively.     |
| Kinoshita et al., 2014. | Multi centre, open-label study                         | Fluorescein corneal staining, lissamine green conjunctival staining, TBUT and subjective symptoms                                                    | 2% rebamipide ophthalmic suspension                                                      | 154 | 2% rebamipide is effective in improving both the objective signs and subjective symptoms of dry eye patients for at least 52 weeks. In addition, 2% rebamipide treatment was generally well tolerated.                       |
| Toda et al.,            | Prospective                                            | Subjective dry eye                                                                                                                                   | Diquafosol tetrasodium and                                                               | 105 | Hyaluronate and diquafosol combination                                                                                                                                                                                       |

|       |                               |                                                                                                                                                                             |                    |  |                                                                                                                                             |
|-------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--|---------------------------------------------------------------------------------------------------------------------------------------------|
| 2014. | randomised comparative trial. | symptoms, uncorrected and corrected visual acuity, functional visual acuity, manifest refraction, TBUT, fluorescein corneal staining, Schirmer test and corneal sensitivity | Sodium Hyaluronate |  | therapy is beneficial for early stabilization of visual performance and improvement of subjective dry eye symptoms in patients after LASIK. |
|-------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--|---------------------------------------------------------------------------------------------------------------------------------------------|

**Table 1.8:** A summary of numerous studies investigating the effectiveness of various artificial eye drops. The studies represented in the table have been conducted from 1978 to 2014; the type of study conducted; tests and drops used; the number of subjects in each study and the results and conclusion of the studies.

### **1.9.1 Predictability**

At present there is a plethora of literature which evaluates individual artificial eye drops or compares various different artificial eye drops in order to assess the effective treatment of dry eye. However, there is a lack of evidence on the actual predictability of which artificial eye drops will work best on the signs and symptoms of individual dry eye patients.

A review on the outcomes-based on treatment options for patients with dry eye secondary to Sjögren's syndrome was (SS) conducted by Akpek et al., (2011). They used a search strategy to identify prospective, interventional studies of treatments for SS-associated dry eye from electronic databases. Eligible references were restricted to English-language articles published after 1975. These sources were augmented by hand searches of reference lists from accessed articles. Study selection, data extraction, and grading of evidence were completed independently by 4 review authors. They assessed 245 full-text papers, 62 of which were relevant for inclusion in the review. Akpek et al., (2011) concluded that current literature on SS-associated dry eye, there is a lack of rigorous clinical trials to support therapy recommendations. However, the recommended treatments including topical lubricants, topical anti-inflammatory therapy, and tear-conserving strategies appear to improve symptoms. The efficacy of oral secretagogues seems greater in the treatment of oral dryness than ocular dryness. Although oral hydroxychloroquine is commonly prescribed to patients with SS to alleviate fatigue and arthralgia, the literature lacks strong evidence for the efficacy of this treatment for dry eye. No peer reviewed publications have attempted to determine which artificial tear formulation will work best for a patient based on baseline parameters.

Demonstrating clinical efficacy of therapeutic agents for dry eye has proven to be challenging because therapeutic effects must overcome environmentally induced day-to-day and seasonal fluctuations of eye discomfort symptoms and ocular surface signs. Alex et al., (2013), conducted a study to identify factors predicting the ocular surface response to experimental desiccating stress. The results of their study showed that corneal and conjunctival staining significantly increased in all subjects following 90-minute exposure to an adverse environment and the degree of change was similar in normal and dry eye subjects, except superior cornea which stained more in dry eye patients. Irritation severity in the desiccating environment was associated with baseline dye staining, baseline tear meniscus height and blink rate after 45 minutes.

### **1.10 Correlation of tests**

The goals of the Diagnostic Methodology Subcommittee (DEWS, 2007) were to identify tests used to screen, diagnose, and monitor dry eye disease, as well as establish criteria of test efficacy and to consider their practical use in a clinical setting. They reviewed a number of tests used to diagnose and monitor dry eye disease.

Dry eye tests are used for a variety of reasons, as listed below:

1. To diagnose dry eye in everyday clinical practice.
2. To assess eligibility in a clinical trial. These tests used in recruitment, could also be used as primary, secondary, or tertiary end points in a trial.
3. To follow quantitative changes over the period of a clinical trial. These tests may differ from those employed in recruitment.
4. To characterize dry eye as part of a clinical syndrome, e.g., as in the regularised classification criteria of Sjögren syndrome (Vitali et al., 2002).
5. To follow the natural history of the disorder. However this opportunity is limited for dry eye, because treatment is so widespread in the population.

There are a few shortcomings of tests for dry eye which include selection and spectrum bias.

#### **1.10.1 Selection Bias**

Unfortunately, there is no “gold standard” for the diagnosis of dry eye. Thus, when a test, is being evaluated for effectiveness, the test population may have been classified as affected or non-affected based on those identical tests. Likewise, the implementation of any “new” test may be compromised when the test is evaluated in a population of dry eye patients who have been diagnosed using un-established criteria.

Furthermore, because of the multi-factorial nature of dry eye, inconsistent test efficacy is likely to occur from study to study.

#### **1.10.2 Spectrum Bias**

Spectrum bias is when the study sample consists of subjects with either very mild or very severe disease. The results are therefore compromised because the severity of the disease in the sample studied has been highly selected. The bias is due to differences in the features of different populations e.g., sex ratios, age, severity of disease, which influences the sensitivity and/or specificity of a test.

Certain ground rules were proposed for appraising the performance of tests for dry eye diagnosis reported in the literature (Table 1.9).





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**Table 1.9:** Characteristics and current tests for dry eye. The table shows the effectiveness of a range of tests, used singly or in combination, for the diagnosis of dry eye. The tests included in the table are those for which values of sensitivity and specificity are available in the literature. The predictive values of these tests (positive, negative and overall accuracy) are calculated for a 15% prevalence of dry eye in the study population. The data shown here is susceptible to bias; selection bias applies to those studies shown in **bold**, in these, the test measure was part of the original criteria defining the dry eye sample group and spectrum bias applied to those studies (shown in light shading) where the study population contained a large proportion of severe cases. Both of these forms of bias can lead to an artificially increased test sensitivity and specificity. In most of the studies listed above the efficacy of the test was shown for the data from the sample on which the cut off or referent value for diagnosis was derived (indicated by a \*), again this can lead to increased sensitivity and specificity in diagnosis. Ideally test effectiveness should be obtained on an independent sample of patients, such data is shown in studies indicate by the symbol \*\* (Taken from DEWS, 2007).

### 1.10.3 Appraisal of tests used for screening for dry eye

A screening test should be simple, effective, appropriate to a specific population, and economical. However, diagnosis is of little interest without a targeted treatment.

#### 1.10.3.1 Recommended screening and diagnostic tests for dry eye

The recommended diagnostic and screening tests by the diagnostic methodology subcommittee (DEWS, 2007) are listed below. It was advised that when a sequence of tests is performed, they should be performed in the sequence that best preserves their integrity (Table 1.10). However, these tests would take too long to conduct on each patient in everyday clinical practice, so information on their relative usefulness is much needed.





**Table 1.10:** A sequence of tests used in dry eye assessment (DEWS, 2007). Test invasiveness increases from A to L. Intervals should be left between tests. Tests selected depend on facilities, feasibility and operational factors (Foulks et al., 2003).

### 1.11 Literature review summary

Irrespective of all the research performed to aid in the screening for dry eye and understanding the mechanism for developing dry eye, none or very little work has been done on determining the most effective treatment for an individual at diagnosis. There appears to be some overlap in determining the clinical tests that provide useful independent information on the ocular surface (chapter 2). However, there is a need for randomised controlled trials of artificial tear treatments on a relevant population to see how the treatments perform relevant to each other (chapter 3), and whether the preferred treatment could have been predicted (chapter 4). If the preferred treatment could not have been predicted, then is the preferred treatment subjectively related to the greatest improvement in ocular physiology and tear film performance (chapter 4).

## CHAPTER 2

### **150 Subjects: Correlation of Dry Eye Tests in Optometric Practice**

#### **2.0 Introduction**

Dry eye disease is typified by patient symptoms, ocular surface damage, diminished tear film stability, tear hyperosmolarity as well as inflammatory components (Bron, 2001). This condition can be classified as evaporative dry eye; in which the cause is excessive evaporation, or tear deficient, in which there is a deficiency of aqueous tear secretion (Lemp, 1995). The inflammatory factor has become increasingly apparent, which causes patient symptoms, and the disease process itself. Symptoms are the most important characteristic of their dry eye condition. However in order to diagnose dry eye disease, it is important for the practitioner to assess for tear film instability and ocular surface damage, as well as the patient symptoms (Bron, 2001). Tear film instability appears to be an important element of all forms of dry eye disease, where, tear hyperosmolarity is an important mechanism for causing ocular surface damage (Gilbard and Farris, 1979). Each form of dry eye has some universal characteristics in common, which include the following:

- A set of characteristic patient symptoms
- Ocular surface damage
- Reduced tear film stability
- Tear hyperosmolarity (Bron, 2001).

The prevalence of dry eye has been reported as 9% of patients over 40 years of age, increasing to 15% of those over 65 years (Schein et al., 1997; McCarty et al., 1998). A large survey (n = 893), conducted by Nichols et al., (2005), reported that on average 52.3% of contact lens wearers, 23.9% of spectacle wearers and 7.1% of clinical emmetropes self-report dry eye in optometric practice. In optometric practice, dry eye remains the primary reason for reduced wearing times and for contact lens failure with studies reporting approximately 50% prevalence of self-reported dry eye in contact lens wearers compared with 20% in non-contact lens wearers (Nichols et al., 2005).

An increase in age, female gender, medication, connective tissue disease, radiation therapy and refractive excimer laser surgery are proven factors for causing dry eye (Lemp et al., 2007). It has also been reported that environmental stresses at the workplace such as prolonged VDU use or during recreational activities can also initiate or exacerbate dry eye (Miljanovic et al., 2007). Allergic and inflammatory ocular surface

conditions disrupt the tear film (Fujishima et al., 1996) and smoking interferes with the lipid layer (Altinors et al., 2006).

Dry eye signs and symptoms often do not correlate well (Nelson, 1988; Nelson et al., 1992; Schein et al., 1997); however, both these factors are believed to be important in the diagnosis and management of dry eye, with the patient's history and symptoms playing a significant role (Smith et al., 2008). Patients attending optometric practice may report ocular irritation, grittiness, burning, foreign body sensation, blurred vision, photophobia or possibly overall discomfort, predominantly in the evening (Begley et al., 2003). Doughty (2010) has suggested that it can be useful, especially for borderline cases, to confirm the patient's perception of their condition, i.e. do they think they have 'dry eye' or not, or maybe they are not sure. Therefore the nature of a patient's symptoms i.e. how do they describe them and how frequent these symptoms bother a patient should be made e.g. sometimes, often, always (Doughty, 2002). The symptoms that patients present with can be ocular or visual or both and they can also experience a transient degradation of vision associated with their symptoms (Doughty, 2010). However, clinical assessment of the patient's ocular surface and tear integrity is important too.

Experience over many years from a collection of practitioners, has taught that clinicians cannot expect a logical agreement between the external eye appearance and the symptoms that a dry eye patient is reporting (Nichols et al., 2004; Johnson, 2009). Hence, a logical approach is needed as to what tests might be used in order to diagnose dry eye and clinicians should be selective and consistent in the tests that have been selected in order to do so (Doughty, 2010).

The overall features of dry eye disease can be identified by the following types of diagnostic tests:

1. Symptom questionnaires,
2. Tear break up time to assess tear instability or quality
3. Staining to identify ocular surface damage,
4. Osmolarity, (Bron, 2001).

The two most popular validated questionnaires dry eye questionnaires are the McMonnies Dry eye Questionnaire (McMonnies, 1986; McMonnies et al., 1998) and the Ocular Surface Disease Index (OSDI) ©Allergan Inc. (Schiffman et al., 2000).

In order to assess the tear film quality, non-invasive stability tests can be conducted without touching either the tear film or ocular surface. This is because they are more validated than 'traditional' tests, since fluorescein has the potential to disrupt the tear film and reduce the measured tear break up time (Patel et al., 1985). In non-invasive tear tests the mires are reflected from the tear film (Hirji et al., 1989). The Bausch & Lomb keratometer and Tearscope Plus™ with grid insert can be used to measure non-invasive break up tear time. The tear film stability measurements are variable therefore an average of at least three values was recorded for each eye. Overall, non-invasive stability values are longer than those measured with fluorescein. The cut-off for a healthy vs. dry eye is usually considered to be >20 seconds with non-invasive tear test, compared with >10 seconds with the fluorescein tear break-up test (Guillon et al., 2004).

Invasive tear break up time measured with fluorescein disrupts the tear film and shortens the normal tear break up time (Mengher et al., 1985). It has been suggested that in order to reduce its provocative nature, the instillation of fluorescein sodium must be minimised and volumes of 1µl does not cause the same destabilisation of the tear film that occurs with larger volumes (Craig et al., 2002).

The tear lipid quality can be assessed with the aid of a wide-angle lighting system with a cold-cathode light source. The Tearscope Plus™ was used in conjunction with non-illuminated slit lamp bio microscope in order to assess the tear lipid layer thickness and quality.

The tear volume can be assessed by simply observing the heights of the lower tear menisci with the slit-lamp bio microscope. Heights of less than 0.2mm (which can be estimated using the calibrated slit beam height adjuster on the slit lamp) indicate reduced tear volume. The Phenol Red Thread (PRT) tear can also be used in order to assess the tear volume. The use of the PRT test is where thin cotton thread, impregnated with phenol red dye is hooked over the lateral third of the lower eyelid. The wetted length is measured after 15 seconds, where values less than 10mm thread wetting are indicative of aqueous insufficiency. Even though this is an invasive test, an advantage is that most patients are ever aware of the thread be in in situ.

In order to assess the health of the ocular surface, Lid parallel conjunctival folds (LIPCOF), bordering the posterior lid margin in the primary direction of gaze, can be observed in dry eye patients. Lissamine green observed in white light, produces a staining pattern similar to rose bengal, (i.e. staining is best seen over the white of the

sclera and on the cornea, over a dark iris) (Norn, 1973). Lissamine green highlights epithelial surfaces that have been deprived of mucin protection or which have exposed epithelial cell membranes.

There is significant evidence suggesting that tear hyper osmolarity is a principle mechanism for ocular surface damage in all forms of dry eye (Gilbard and Farris, 1979; 1983). In the rabbit, deficiency of the aqueous or lipid layer of the tear film, in rabbit studies showed a rise in tear osmolarity and associated squamous metaplasia and loss of goblet cells (Gilbard et al., 1988; 1989). In clinical practice the Tear film osmolarity can be measured with the TearLab. The disposable probe was touched onto the lower tear meniscus at the lid margin, where a nanolitre sample of tears was collected, analysed within seconds and provided a reading.

The diagnosis and management of dry eye patients greatly depends on the results of a number of the above tests, which ideally could be performed at a single clinic visit. It is therefore very important to perform these dry eye tests in an appropriate sequence, in order to avoid one test interfering with another. Bron, (2001), suggested a suitable order of diagnostic tests. It is advisable that after all non-invasive and minimally invasive tests have been performed, should staining agents be utilised as there is no formal data to validate a particular sequence of tests or the intervals between them (Table 2.1) suggests a suitable order of diagnostic tests.

|                                                                  |                                                                                                                                      |
|------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| <b>Symptomology</b>                                              | OSDI Questionnaire                                                                                                                   |
| <b>Non-invasive tests</b>                                        | Non-invasive tear break-up test (to assess tear stability)<br>Tear Volume test (TMH)<br><br>Tear Lipid Observation                   |
| <b>Minimally invasive tests</b>                                  | Tear break-up test (to assess tear stability)<br><br>Staining of the bulbar conjunctiva and cornea (to assess ocular surface damage) |
| <b><i>A 5-minute gap is recommended before the next test</i></b> |                                                                                                                                      |
| <b>Tests of tear volume or secretion</b>                         | Phenol red thread test (to assess tear volume)                                                                                       |
| <b><i>A 5-minute gap is recommended before the next test</i></b> |                                                                                                                                      |
| <b>Tear Osmolarity</b>                                           | TearLab                                                                                                                              |
| <b>Additional dye tests</b>                                      | Lissamine green staining (to assess ocular surface damage)                                                                           |

**Table 2.1:** Suggested sequence of tests for the diagnosis of dry eye disease. (Adapted from Bron, 2001).

Although numerous studies have investigated the correlations between dry eye tests in different populations, no one study has used a comprehensive suite of currently recognised clinical dry eye tests, and in general the population sizes examined in these past studies have been limited. Some studies concluded that there was no correlation between the dry eye tests and patient symptoms (Fuentes-Paez et al., 2011; De AF Gomes et al., 2012); on the other hand, some studies concluded that there was a correlation between symptoms and the dry eye tests (Pult et al., 2011; Cuevas et al., 2012). Studies investigating these correlations have been summarised in table 2.2.

| Author                    | Study Population                                                        | Subjects | Age Range                                        | Meniscus Height | Hyperaemia | Hyperaemia | LIPCOF | PRT Test | Schirmer | FBUT | Corneal Staining | Rose Bengal | LWE | Symptom | NIBUT | Comments                                                                                                                                |
|---------------------------|-------------------------------------------------------------------------|----------|--------------------------------------------------|-----------------|------------|------------|--------|----------|----------|------|------------------|-------------|-----|---------|-------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Korb et al., 2005         | 100 patients divided into those with and those without dry eye symptoms | N=100    | mean age 44.3 (symptomatic), 42.8 (asymptomatic) |                 |            |            |        |          |          |      |                  |             | ✓   | ✓       |       | 76% of symptomatic patients had lid wiper staining, 12% of the asymptomatic patients had staining of the lid wiper                      |
| Pult et al., 2009         | New contact lens wearer                                                 | N=33     | median age 30.5 (range 19 to 44)                 | ✓               | ✓          | ✓          | ✓      | ✓        |          |      | ✓                | ✓           | ✓   |         | ✓     | LIPCOF, NIBUT and OSDI are significant discriminators of contact lens induced dry eye                                                   |
| Fuentes-Paez et al., 2011 | Patients > 50 years                                                     | N=270    | average age 64.5                                 |                 |            |            |        |          | ✓        | ✓    | ✓                | ✓           |     | ✓       |       | No correlation between screening questionnaire and objective tests                                                                      |
| Pult et al., 2011         | Non-contact lens wearers                                                | N=47     | median age 45 (range 19-70)                      | ✓               | ✓          | ✓          | ✓      |          |          | ✓    | ✓                | ✓           | ✓   | ✓       | ✓     | NIBUT, TMH, Phenol red, LIPCOF and LWE We're related to OSDI scores. The strongest relationship appeared by combining NIBUT with LIPCOF |
| Cuevas                    | Subjects                                                                | N=21     |                                                  | ✓               |            |            |        |          |          | ✓    | ✓                | ✓           |     | ✓       |       | Correlation                                                                                                                             |

|                          |                                                               |      |  |  |  |  |  |  |   |   |  |   |  |   |  |                                                                                   |
|--------------------------|---------------------------------------------------------------|------|--|--|--|--|--|--|---|---|--|---|--|---|--|-----------------------------------------------------------------------------------|
| et al., 2012             | with evaporative dry eye secondary to meibomian gland disease |      |  |  |  |  |  |  |   |   |  |   |  |   |  | between symptoms and some clinical tests (TBUT, conj hyperaemia, TMH, conj stain) |
| De AF Gomes et al., 2012 | Patients with systemic sclerosis n=45,                        | N=45 |  |  |  |  |  |  | ✓ | ✓ |  | ✓ |  | ✓ |  | No statistically significant correlations                                         |

**Table 2.2:** A summary of several studies investigating the correlation between several of dry eye tests in different populations. The study population, number of subjects in an individual study and the age range are noted. The 'ticks' indicate the dry eye tests that were performed in each individual study with any comments related to the correlation of the tests performed.

Based on their uses over the years, the commonest clinical tests include the Schirmer test, the phenol red thread test (PRT), tear meniscus height (TMH), and fluorescein-based tear break up time (NaFL TBUT) (Doughty et al., 2002; 2005; 2007; Miller et al., 2004; Macri et al., 2000; Santodomingo et al., 2006). Dry eye induced damage of the ocular surface has been observed with staining induced by fluorescein, rose bengal or lissamine green dyes (Bron et al., 2003).

A combination of two or three objective tests have been suggested in order to obtain reasonable correlations between symptoms and signs (Klaassen-Broekema et al., 1992; Bron et al., 2001; Viso et al., 2006). It has been suggested by Doughty (2010), that it is very difficult to differentiate between a preference for a test based on convenience or practitioners chair time against a choice made because the outcome of the tests might provide definitive answers.

Therefore, the practitioner is justified on relying on their own experience in the diagnostic tests that they choose to perform on a routine basis, as it is difficult to differentiate between a patient having dry eye disease (DED) or not (Doughty, 2010). Hence, from this point of view, the practitioner might choose to adopt certain cut-off values to assist them in coming to a diagnosis for a dry eye condition (Table 2.3). However, this approach lacks evidence basis and researchers must support clinicians by identifying a group of dry eye tests that are most informative of patient outcomes, but can be rapidly conducted within everyday clinical practice. It should be noted that some tests are prone to reflex tearing and/or the impact of use of any recent treatments, which may hinder the interpretation of results and impact on the order in which a group of tests should be performed (Doughty, 2010).



**Table 2.3:** Some typical outcomes for dry eye tests (Taken from DEWS, 2007). The dry eye tests included are Schirmer test (without anaesthesia, Phenol Red Thread test (PRT), Tear meniscus height (TMH), Tear break up time with fluorescein (NaFI TBUT), Fluorescein staining, Rose Bengal

staining and Lissamine green staining, with values for normal eyes and the outcome for true dry eye patients.

Therefore, the purpose of this study is to utilise a wide range of clinical tests and a large patient cohort to better understand the independent contribution of each of these clinical dry eye tests prior to later chapters which will examine how well they predict dry eye management.

## **2.1 Methods**

One hundred and fifty subjects (average age 56.33 years, range 19 to 91 years; 96 females and 54 males) were recruited from the patients of a community optometric practice in the North West of England, over a four month period. To be eligible, patients reported a 'dry eye' and were then asked to complete the OSDI questionnaire in routine practice (no cut of value was set for the OSDI questionnaire). A convenient appointment was offered to the patients between 9am to 5pm from Monday through to Saturday. Unfortunately the TearLab 'chips' did not arrive into the practice in time for when the study commenced, so a further convenient appointment was offered to the patients between 9am to 5pm from Monday through to Saturday. Patients were advised of this minor setback at the initial appointment and were advised that they would have to return for the TearLab test. The patients were happy to return to the practice in order to have their tear osmolarity tested. Ethics approval was granted by the Aston University Ethics Committee and the research conformed to the tenets of the Declaration of Helsinki. Subjects gave their written consent following an explanation of the study procedures and potential risks. A copy of the ethics application form can be seen in Appendix A. The approval letter from the ethics committee can be seen in Appendix B.

### **2.1.1 Clinical Evaluation**

Given the complex nature of the tear film and the existence of several different types of dry eye, it is apparent that a single clinical method will not detect all tear abnormalities resulting from lacrimal, meibomian, or conjunctival disturbances.

Essentially, the hallmark of dry eye damage to the corneal and conjunctival surfaces, associated with an array of symptoms of varying severity that include, photophobia, foreign body sensation, ocular discomfort and itching (Foulks, 2003; Nichols et al., 1999). Therefore an assessment of the tear film must include a plethora of tests for assessing tear volume, stability and quality, in order to differentiate the normal from the dry eye (Farrell, 2010). Although none of these tests used to diagnose dry eye are highly sensitive or specific (Heath, 2004), and tests for one category of dry eye may be

positive and yet yield a negative result for another category of dry eye, despite the fact that both may lead to ocular surface disease (Heath, 2004). Most forms of dry eye have symptoms associated with the condition and some form of symptom screening will offer valuable information for diagnosis (McMonnies et al., 1987).

Tear film 'stability' was assessed by Non-invasive mire break-up time (NIBUT), Non-invasive Tearscope break up time (NITBUT) and Fluorescein break up time (NaFL BUT). Tear film 'volume' tests were measured by means of Tear meniscus height (TMH) and Phenol red thread (PRT). The relationship to ocular surface damage was assessed by observing the corneal and conjunctival staining, lid-parallel conjunctival folds (LIPCOF) and lipid interference pattern. Patient symptoms were measured by using the Ocular Surface Disease Index (OSDI). The tear film osmolarity was also measured.

It has been recommended, that when a battery of tests is performed, they should be performed in an arrangement that best preserves their reliability (DEWS, 2007), and intervals should be left between the tests (Bron, 2001; Foulks and Bron, 2003). The tear film metrics were assessed in the following order due to the invasive nature of some tests. The right eye was observed followed by the left eye for every patient. These dry eye metrics:

- **Symptoms** – were assessed using the OSDI questionnaire (Appendix C). The OSDI was selected from the range of possible questionnaires for assessing dry eye symptoms (see Table 1.5 for a summary) due to its validity in the chosen population and extensive use in the academic literature. The OSDI consists of 12 questions arranged on a scale of 0-4 designed to assess the level of discomfort as well as how dry eye interferes with daily living activities. The questions are broken down further in to:
  1. Three of the twelve questions relate to ocular symptoms
  2. Six of the twelve to visual function
  3. Three of the twelve to environmental triggers

The frequency is with 1 week recall period. The answers to the questions are:

- None of the time,
- Some of the time,
- Half of the time,
- Most of the time,

- All of the time [0-4]

The scoring algorithm published:

- 100 = complete disability;
- 0 = no disability.

The OSDI score was calculated by multiplying the total score by 25 and dividing by the total number of questions answered generating a result between 0 and 100.

- **Non-invasive break-up time (NIBUT)** – was measured by observing a keratometer mire projected onto the front of the corneal surface achieved by using a keratometer (Patel et al., 1985). The one position Bausch and Lomb keratometer with circular mires was used to measure the NIBUT in this study. Subjects were instructed to blink normally and then keep their eyes open for as long as possible. The NIBUT was recorded with a stop watch, when distortion is first seen in any part of the mire pattern. This was repeated 3 times in total and was averaged to give a mean NIBUT value.
- **Tear meniscus height (TMH)** - was measured using a slit lamp bio-microscope (25 times magnification). The slit beam was rotated to align parallel to the lower eyelid margin, and the height of the slit beam was adjusted to correspond to the tear meniscus located directly below the pupil while the patient was looking in primary gaze. The TMH was expressed as the gap between the lower eyelid margin and the upper limit of the reflected zone of the tear meniscus (Farrell et al., 2003). The TMH was recorded from the built in, calibrated, slit beam width scale. This process was repeated 3 times in total and was averaged to give a mean TMH value.
- **Lid Parallel Conjunctival Folds (LIPCOF)** - are folds in the lower conjunctiva, parallel to the lower lid margin (Pult and Sickenberger, 2000). They were observed using a 2-3 mm wide vertical slit beam located along the temporal limbus, to the inferior bulbar conjunctiva just above the lower lid margin. The angle between the observation and illumination system was between 20-30 degrees and the LIPCOF viewed at 25 times magnification. The number of folds were counted and graded. This table can be seen in table1.2 (Höh et al., 1995).

- **Non-invasive Tearscope break up time (NITBUT)** - was measured using the Tearscope Plus (Keeler Ltd, Windsor, UK) in conjunction with a fine grid pattern insert mounted on a slit lamp bio-microscope to produce an image of the fine grid pattern over the entire cornea via specular reflection. Subjects were instructed to blink normally and then keep their eyes open for as long as possible. The NITBUT was defined as the time period between the last complete blink and the appearance of a break or distortion in the fine grid pattern (Guillon, 1998), measured using a digital stop-clock. This was repeated 3 times in total and was averaged to give a mean NITBUT value.
- **Lipid pattern as observed by the Tearscope** - was measured using the Tearscope Plus (Keeler Ltd, Windsor, UK) on a slit lamp bio-microscope. With the patient's head positioned on the slit-lamp chin rest, the slit-lamp source was positioned nasally and switched off, as alternative illumination is provided by the Tearscope itself. The Tearscope was held as close to the eye as possible and positioned to allow observation through the sight hole via one of the bio microscope objectives. The light reflected from the tear film was observed as a white circular area, 10-12mm in diameter. Magnification was set at 10 times to examine the interference patterns after blinking, via specular reflection. Subjects were instructed to blink normally and then keep their eyes open for as long as possible. The observation patterns were compared with the pictures as provided by Keeler, as shown in figure 1.14. Tear lipid observation was graded from zero to 6, according to the lipid observation; where absent lipid layer pattern =0, open meshwork marmoreal =1, closed meshwork marmoreal =2, wave flow =3, amorphous =4, normal coloured fringes =5 and abnormal coloured fringes =6 (table 1.4). This is a categorisation scale related to thickness rather than a range from good to bad; hence correlation is against apparent thickness rather than severity of a sign.
- **Fluorescein break up time (NaFL TBUT)** - was measured with the slit lamp bio-microscope (magnification 10 times) with a diffuse cobalt blue light at maximum brightness. A single drop of sterile saline was applied to a fluorescein sodium impregnated paper strip (Fluorets, 1mg fluorescein sodium, Chauvin Pharmaceuticals, Essex, UK) and the excess shaken off before applying it to the patients' eye. The lower lid of both eyes was lowered and the moistened strip was swiftly, but gently applied to the lower tarsal conjunctiva. The subject was then instructed to blink normally after application to circulate the fluorescein. Subjects were then asked to look in primary gaze without blinking.

NaFL TBUT was defined as the interval of time between the last complete blink and the first appearance of a dry spot or disruption (black/dark blue area) in the tear film (Lemp et al., 1995) measured with a digital stop clock. A yellow filter (Kodak Wratten 12) was used to enhance contrast and improve visibility of breaks in the tear film (Bron et al., 2003). This was repeated 3 times in total and was averaged to give a mean NaFL TBUT value.

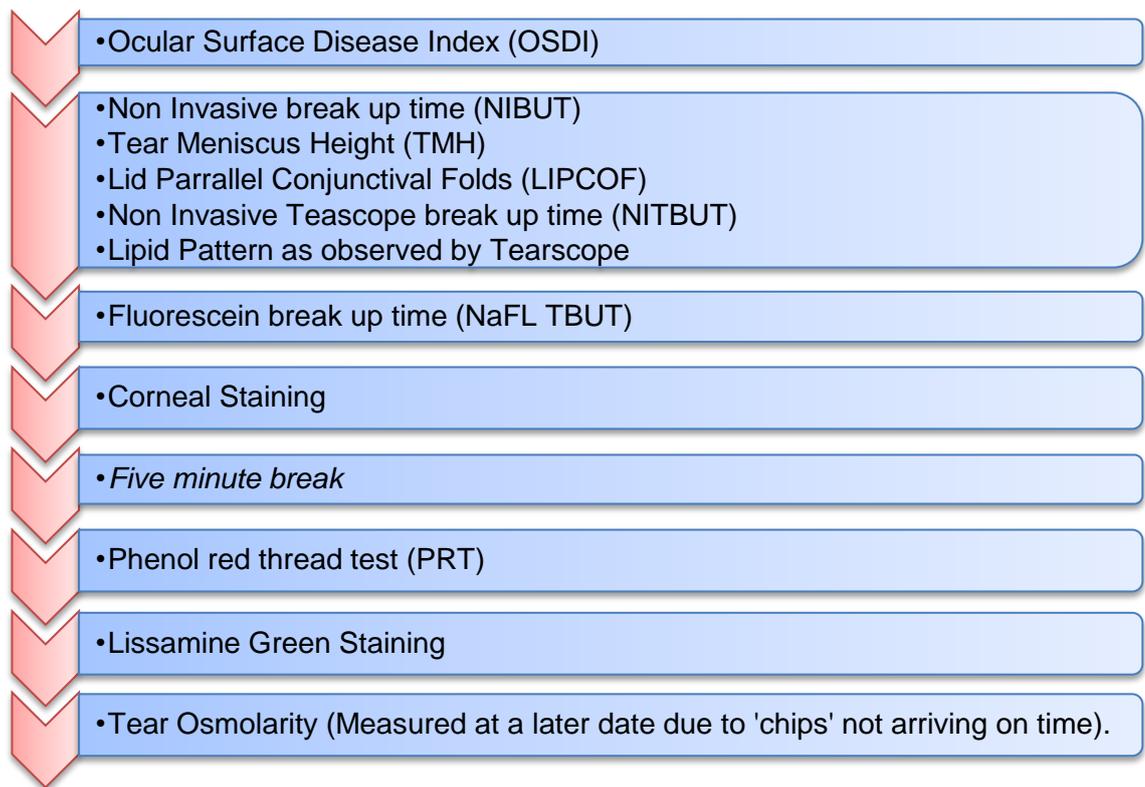
- **Corneal staining** - corneal staining was assessed using fluorescein sodium (Fluorets) impregnated paper strips. A single drop of sterile saline was applied to a fluorescein sodium impregnated paper strip and the excess shaken off before applying it to the patients' eye. The lower lid of both eyes was lowered and the moistened strip was swiftly and gently applied to the lower tarsal conjunctiva. The cornea of each eye was examined using a cobalt blue light source (10 times magnification), with contrast enhanced using a yellow filter. The presence of staining on the cornea of both eyes was recorded. The Efron grading scale used to denote the corneal staining (Efron, 2000). The Efron grading scale provides practitioners with a simple method of grading the ocular condition, enabling assessment of any ocular changes in the future. There are 16 sets of grading images which cover the key anterior ocular complications of contact lens wear. The conditions are illustrated in five stages of increasing severity from 0 to 4, with 'traffic light' colour banding from green (normal) to red (severe) (Efron, 2000). Once the corneal staining was noted via the Efron grading scale; for statistical analysis, no corneal staining was graded =0, the presence of corneal staining in one quadrant was graded =1, and if there was corneal staining in more than one quadrant was graded =2.

After a 5 minute break the following tests were performed as recommended by Bron, (2001).

- **Phenol red thread (PRT)** - was used to measure tear volume. A yellow phenol (phenolsulfonphthalein) impregnated thread with the top 3mm folded over, was inserted along the lower temporal eyelid margin of both eyes approximately 1/3 of the distance from the lateral canthus. The subject was instructed to blink normally while looking in primary gaze for 15 seconds, immediately after insertion (timed with a digital stop-clock). Following the 15 seconds, the thread was removed and the section of the thread transformed to a red colour from yellow was measured using a ruler to the nearest 0.5mm (Little & Bruce, 1994).

- **Conjunctival staining** – Lissamine Green (Green Glo, 1.5mg Lissamine Green, HUB Pharmaceuticals, USA) strips were used to evaluate the conjunctival integrity, where a single drop of sterile saline was applied to the strip. The wetted strip was quickly but gently applied to the lower tarsal conjunctiva after lowering the lower lid. The subject was then instructed to blink normally after application to distribute the lissamine green, before the conjunctiva of each eye was studied using a slit lamp bio-microscope (white light, 10 times magnification) (Feenstra et al.,1992). The presence of staining on the bulbar conjunctiva in both eyes was recorded (i.e. nasal, temporal, superior or inferior bulbar conjunctiva) and then graded by numbers with no staining =0, staining in one quadrant =1, and staining in more than 1 quadrant =2.
- **Osmolarity** – was measured by The TearLab (TearLab Ltd, San Diego, CA, USA). It requires only a very small volume of tears, therefore can be used in subjects with relatively dry ocular surfaces. The TearLab osmolarity test utilizes a temperature-corrected impedance measurement to provide an indirect assessment of osmolarity. After applying a lot-specific calibration curve, osmolarity is calculated and displayed as a quantitative numerical value. It was ensured that patients had not use medicinal eye drops at least 2 hours prior to testing. Tears were collected from the outer margin of the eye lid lacrimal lake without lid manipulation as pulling the lower lid away from the globe may reduce the tear meniscus height, affecting tear collection. The patient was seated with their head tilted back looking upwards. The tear collection pen was positioned parallel over the inner margin of the lower eye lid and moved downwards on the lid until an audible sound indicated that sufficient tears had been gathered. Both eyes were tested and the higher of the two numbers was taken as recommended by the manufacturer (<http://www.tearlab.com/products/doctors/productinfo.htm>; Tomlinson et al, 2006). The patients returned a couple of weeks after their first visit to have their tear osmolarity measured, this is due to the chips for the TearLab system not arriving in to the practice on time. Patients were happy returning to the store to have their tear osmolarity measured.

Further details on all of the above tests can be found in section 1.6. A summary of the tear film metrics assessed are represented in figure 2.1.



**Figure 2.1:** Summary of the tear film metrics, in the order represented due to the invasive nature of certain tests.

### 2.1.2 Data Analysis

The data of the three repeats of NIBUT, NITBUT, NaFL TBUT and TMH were averaged for analysis. Corneal and conjunctival staining were graded as 0 if none was observed, 1 if punctate staining occurred in one quadrant only and graded as 2 if punctate staining was evident in more than one quadrant. Tear lipid observation was graded from zero to 6, according to the lipid observation; where absent lipid layer pattern =0, open meshwork marmoreal =1, closed meshwork marmoreal =2, wave flow =3, amorphous =4, normal coloured fringes =5 and abnormal coloured fringes =6. One-Sample Kolmogorov-Smirnov Tests were used to test for a normal distribution, and where there was a deviation from this with a particular metric, non-parametric statistics were applied.

A cluster analysis technique was conducted in order to appreciate if there were groups with similar tear film metric results (SPSS v 20 software, IBM Corporation, New York, USA). A k-means cluster algorithm was utilised (where k is the number of clusters). The primary phase locates the k cluster centres by identifying cases that are well separated and treating these as initial cluster centres. The software then assigns cases to the cluster closest to them based on the distance from the cluster centre. After the

cases have been assigned, the cluster centres are recalculated and cases are reassigned using the new cluster centres. This procedure is repeated until no cluster centre changes significant in the number of iterations assigned. The number of clusters was selected based on whether the analysis failed to converge within 10 iterations or less than a certain percentage of these cases were within each cluster. The clusters were chosen to maximise the differences among cases between the clusters, hence, analysis of variance (ANOVA) statistical significance levels were used for the descriptive purposes only, (an increase in levels of significance indicate that it is more likely that a variable contributes to cluster separation).

## 2.2 Results

### 2.2.1 Comparison of the Eyes

Analysis using the one-Sample Kolmogorov-Smirnov Tests showed that only NITBUT ( $p = 0.085$ ) and osmolarity ( $p = 0.672$ ) were normally distributed whereas the OSDI ( $p < 0.001$ ), NaFL TBUT ( $p = 0.008$ ), TMH ( $p = 0.002$ ), PRT ( $p = 0.009$ ) and lipid pattern grade ( $p = 0.001$ ) were not normally distributed and non-parametric statistics were applied. The average results of the 150 subjects are presented in table 2.4. As expected the results from the two eyes were similar for all the tear film metrics except NaFL TBUT (where the difference of  $0.0 \pm 1.2\text{sec}$  could be considered clinically insignificant) – note for osmolarity, the manufacturer recommends measuring both eyes and selecting the higher value, hence although a comparison is made, the highest value was used for subsequent evaluation. As this was the case, all further analysis was conducted on the right eye data only (highest eye value for osmolarity), to prevent statistical bias.

|               | OSDI (%)     | NITBU T (sec) | NIBUT (sec)    | NaFL TBUT (sec) | TMH (mm)      | PRT (mm)       | Osmolary ty (mOsms/L) | Lipid Patter n Grade |
|---------------|--------------|---------------|----------------|-----------------|---------------|----------------|-----------------------|----------------------|
| Right Eye     | 22.7±<br>0.2 | 7.41±<br>2.32 | 13.04±<br>2.07 | 13.23±<br>2.28  | 0.12±<br>0.02 | 12.72±<br>3.58 | 306.7±<br>13.3        | 2.62±<br>1.10        |
| Left Eye      |              | 7.31±<br>2.23 | 13.08±<br>2.50 | 13.28±<br>2.69  | 0.12±<br>0.02 | 12.77±<br>3.48 | 302.5±<br>11.3        | 2.62±<br>1.09        |
| Significan ce |              | 0.737         | 0.777          | 0.023           | 0.677         | 0.221          | 0.001                 | <0.00<br>1           |

**Table 2.4:** Comparison of the two eyes of each subject (average + S.D) for non-invasive break-up time (NIBUT / NITBUT), fluorescein tear break-up

time (NaFL TBUT), tear meniscus height (TMH), phenol red test (PRT), osmolarity and lipid pattern grade (all analysed by related-samples Wilcoxon Signed Rank except NITBUT and osmolarity, evaluated with a t-test) tear film metrics of the right and left eyes. For completeness the Ocular Surface Disease Index (OSDI) data is also presented. N=150.

|                          | OSDI               | NIBUT               | NaFL<br>TBUT        | NI<br>TBUT        | TMH                 | PRT                 | Corneal<br>Staining | Conjunctival<br>Staining | LIPCOF              | Lipid             | Osmolarity          |
|--------------------------|--------------------|---------------------|---------------------|-------------------|---------------------|---------------------|---------------------|--------------------------|---------------------|-------------------|---------------------|
| Age                      | r=.284**<br>p<.001 | r=-.222**<br>p=.006 | r=-.217**<br>p=.008 | r=-.047<br>p=.748 | r=-.387**<br>p<.001 | r=-.236**<br>p=.004 | r=.161*<br>p=.049   | r=.264**<br>p=.001       | r=.276**<br>p=.001  | r=-.251<br>p=.079 | r=-.071<br>p=.624   |
| OSDI                     |                    | r=-.331**<br>p<.001 | r=-.293**<br>p<.001 | r=.111<br>p=.443  | r=-.463**<br>p<.001 | r=-.317**<br>p<.001 | r=.234**<br>p=.004  | r=.493**<br>p<.001       | r=.597**<br>p<.001  | r=-.041<br>p=.777 | r=-.075<br>p=.603   |
| NIBUT                    |                    |                     | r=.916**<br>p<.001  | r=.120<br>p=.405  | r=.466**<br>p<.001  | r=.531**<br>p<.001  | r=-.428**<br>p<.001 | r=-.331**<br>p<.001      | r=-.182*<br>p=.026  | r=-.018<br>p=.093 | r=.096<br>p=.508    |
| NaFLT<br>TBUT            |                    |                     |                     | r=.206<br>p=.151  | r=.457**<br>p<.001  | r=.497**<br>p<.001  | r=-.417**<br>p<.001 | r=-.316**<br>p<.001      | r=-.208*<br>p=.011  | r=.018<br>p=.901  | r=.034<br>p=.815    |
| NIT<br>TBUT              |                    |                     |                     |                   | r=.301*<br>p=.033   | r=.218<br>p=.128    | r=-.171<br>p=.235   | r=-.145<br>p=.315        | r=-.104<br>p=.473   | r=.149<br>p=.303  | r=-.053<br>p=.714   |
| TMH                      |                    |                     |                     |                   |                     | r=.576**<br>p<.001  | r=-.349**<br>p<.001 | r=-.445**<br>p<.001      | r=-.407**<br>p<.001 | r=-.089<br>p=.540 | r=-.117<br>p=.419   |
| PRT                      |                    |                     |                     |                   |                     |                     | r=-.377**<br>p<.001 | r=-.223**<br>p=.006      | r=-.187*<br>p=.002  | r=-.090<br>p=.535 | r=.012<br>p=.931    |
| Corneal<br>Staining      |                    |                     |                     |                   |                     |                     |                     | r=.358**<br>p<.001       | r=.254**<br>p=.002  | r=-.238<br>p=.097 | r=-.450**<br>p=.001 |
| Conjunctival<br>Staining |                    |                     |                     |                   |                     |                     |                     |                          | r=.601**<br>p<.001  | r=-.008<br>p=.958 | r=-.109<br>p=.452   |
| LIPCOF                   |                    |                     |                     |                   |                     |                     |                     |                          |                     | r=-.106<br>p=.464 | r=-.072<br>p=.620   |
| Lipid                    |                    |                     |                     |                   |                     |                     |                     |                          |                     |                   | r=.214<br>p=.136    |

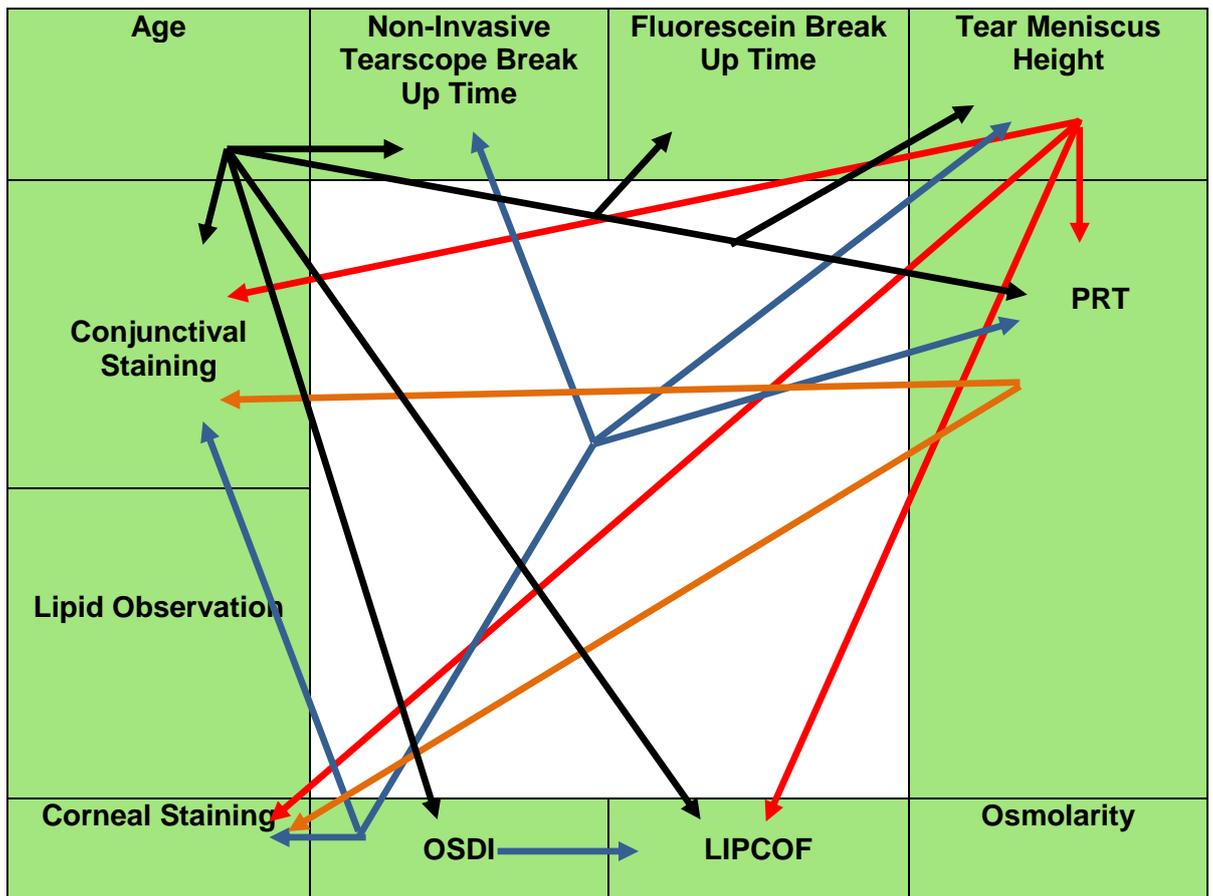
\*\* . Correlation is significant at the 0.01 level (2-tailed). \* . Correlation is significant at the 0.05 level (2-tailed).

**Table 2.5:** The average  $\pm$  S.D. for 150 patients for the right eye only, for tear film metrics. Non-invasive break-up time (NITBUT) and osmolarity (analysed by t-test) and fluorescein tear break-up time (NaFL TBUT), non-invasive break-up time (NIBUT), tear meniscus height (TMH), phenol red test (PRT), corneal and conjunctival staining grade, lid-parallel conjunctival folds (LIPCOF) and lipid pattern grade (all analysed by related-samples Wilcoxon Signed Rank) tear film metrics of the right eye. For completeness the Ocular Surface Disease Index (OSDI) data is also presented. \*\*. Correlation is significant at the 0.01 level (2-tailed) and \*. Correlation is significant at the 0.05 level (2-tailed).N=150, right eye only.

### 2.2.2 Comparison of Tear Film Tests

As only two of the tear film metrics was found to be normally distributed (NITBUT and osmolarity), and ocular surface tear film and damage metrics of lipid layer pattern, LIPCOF, corneal and conjunctival staining were graded, non-parametric correlations (Spearman's Rank) were performed on the 150 subjects for the following tests and demographics: age, OSDI score, NIBUT, NaFL TBUT, TMH, PRT, osmolarity, lipid pattern, LIPCOF, and corneal and conjunctival staining (Table 2.5). The link between the tests is presented visually in figure 2.2.

The correlation 'r' is mostly weak between the dry eye tests with some of the tests performing better in relation to symptomology (OSDI) than others. The following tests performed better in relation to the OSDI, LIPCOF; conjunctival staining; TMH; NIBUT; PRT; NaFL TBUT, with the least correlated being corneal staining. The tear stability tests (NIBUT and NaFL TBUT), were correlated to the tear volume tests (PRT and TMH), corneal and conjunctival staining and to a lesser extent LIPCOF. The TMH was correlated with PRT; conjunctival staining; LIPCOF and corneal staining. The dry eye tests correlated with LIPCOF were conjunctival staining; TMH and to a lesser extent NaFL TBUT followed by NIBUT and PRT. The only test correlating to the tear osmolarity was corneal staining.



**Figure 2.2:** A representation of the various tests which correlate with each other. Age correlates with Non Invasive Tearscope Break Up Time (NITBUT), Fluorescein break up time (NaFL TBUT), Tear meniscus height (TMH), Phenol red thread (PRT), Lid parallel conjunctival folds (LIPCOF), Ocular Surface Disease Index (OSDI) and Conjunctival staining. TMH is correlated with PRT, LIPCOF, Corneal staining and Conjunctival staining. PRT is correlated to conjunctival and corneal staining. Corneal staining is correlated to Conjunctival staining, LIPCOF and Osmolarity. OSDI is correlated to NITBUT, NaFL TBUT, TMH, PRT, LIPCOF, Corneal and Conjunctival staining.

Ocular Surface Disease Index (OSDI), non-invasive break-up time (NITBUT), fluorescein tear break-up time (NaFL TBUT), tear meniscus height (TMH), phenol red test (PRT), osmolarity and lipid pattern values were compared for patients with an absence or presence of lid-parallel conjunctival folds (LIPCOF), corneal staining and conjunctival staining ocular surface ‘damage’ for the right eye (Table 2.6). For corneal staining there were only two subjects with corneal staining and the rest with no staining; for conjunctival staining, nine subjects did not have staining and the rest did - hence no statistical comparison with lipid grade was possible.

|                                                | OSDI             | NITBUT (sec)     | NaFL TBUT (sec)  | TMH (mm)     | PRT (mm)         | Osmolarity (mOsm/L) | Lipid Pattern Grade |
|------------------------------------------------|------------------|------------------|------------------|--------------|------------------|---------------------|---------------------|
| <b>LIPCOF</b>                                  |                  |                  |                  |              |                  |                     |                     |
| <b>Absent</b>                                  | 11.47±9.34       | 13.65±1.58       | 13.69±1.59       | 0.12±0.02    | 13.33±2.63       | 314.0±15.2          | 2.67±1.37           |
| <b>Present</b>                                 | 30.14±18.33      | 12.60±2.25       | 12.60±2.47       | 0.10±0.02    | 12.30±4.06       | 310.3±18.0          | 2.61±1.08           |
| <b>P</b>                                       | <b>&lt;0.001</b> | <b>&lt;0.001</b> | <b>&lt;0.001</b> | <b>0.002</b> | <b>&lt;0.001</b> | 0.606               | 0.037               |
| <b>Corneal Staining (Fluorescein)</b>          |                  |                  |                  |              |                  |                     |                     |
| <b>Absent</b>                                  | 21.03±17.77      | 13.42±1.77       | 13.43±1.97       | 0.12±0.02    | 13.14±3.59       | 316.1±17.3          | 2.65±1.12           |
| <b>Present</b>                                 | 31.41±15.90      | 10.64±2.97       | 10.60±2.12       | 0.12±0.02    | 10.27±2.29       | 291.3±3.5           | 2.00±0.00           |
| <b>P</b>                                       | 0.962            | <b>&lt;0.001</b> | <b>&lt;0.001</b> | 0.258        | <b>&lt;0.001</b> | <b>&lt;0.001</b>    | <b>N/A</b>          |
| <b>Conjunctival Staining (Lissamine Green)</b> |                  |                  |                  |              |                  |                     |                     |
| <b>Absent</b>                                  | 14.20±12.95      | 13.79±1.59       | 13.83±1.68       | 0.12±0.02    | 13.38±3.13       | 315.8±19.4          | 2.62±1.00           |
| <b>Present</b>                                 | 29.76±18.31      | 12.78±1.89       | 12.87±2.16       | 0.11±0.02    | 11.88±3.58       | 309.8±17.3          | 2.54±1.12           |
| <b>P</b>                                       | <b>&lt;0.001</b> | <b>&lt;0.001</b> | <b>&lt;0.001</b> | 0.017        | 0.029            | 0.441               | <b>N/A</b>          |

**Table 2.6:** Findings and significance for dry eye tests; (p value for parametric or non-parametric test as appropriate) for Ocular Surface Disease Index (OSDI), non-invasive break-up time (NITBUT), fluorescein tear break-up time (NaFL TBUT), tear meniscus height (TMH), phenol red test (PRT), osmolarity and lipid pattern for the absence or presence of lid-parallel conjunctival folds (LIPCOF), corneal staining and conjunctival staining ocular surface 'damage' for the right eye. N=150. NA = not applicable.

### 2.2.3 Cluster analysis

Cluster analysis was carried out for 7, 6, 5, 4, 3 and 2 groups with the number of subjects in each cluster identified shown below in table 2.7.

| Cluster Number | Number of clusters and resulting subject split between these |    |    |    |    |    |
|----------------|--------------------------------------------------------------|----|----|----|----|----|
|                | 2                                                            | 3  | 4  | 5  | 6  | 7  |
| 1              | 53                                                           | 33 | 37 | 25 | 26 | 27 |
| 2              | 97                                                           | 77 | 31 | 28 | 21 | 14 |
| 3              |                                                              | 40 | 33 | 21 | 20 | 20 |
| 4              |                                                              |    | 49 | 39 | 25 | 24 |
| 5              |                                                              |    |    | 37 | 26 | 23 |
| 6              |                                                              |    |    |    | 32 | 24 |
| 7              |                                                              |    |    |    |    | 18 |

**Table 2.7:** The number of subjects in each cluster, when 2 to 7 way cluster analysis was completed. N=150.

Convergence was achieved when there was no significant change in cluster centres between iterations. Table 2.8 below shows the number of iterations performed for each cluster and the minimum distance between the initial cluster centres.

| Cluster | Iteration | Minimum distance between initial clusters |
|---------|-----------|-------------------------------------------|
| 7       | 5         | 24.44                                     |
| 6       | 6         | 24.76                                     |
| 5       | 4         | 30.26                                     |
| 4       | 7         | 38.90                                     |
| 3       | 4         | 60.78                                     |
| 2       | 5         | 75.03                                     |

**Table 2.8:** The distance between the initial cluster centres and iterations for the clusters.

None of the cluster analyses failed to converge. Once more than 3 clusters were established, the size of at least one of the clusters identified had less than 20% (n= 30) of the subjects (Table 2.9). To increase the number of clusters to consider, the percentage (in 5% steps) required for a cluster would have to be lowered to 10% (n = 15) of the subjects, in which case 5 clusters were identified (Table 2.10).

**A) Final Cluster Centres**

|                       | Cluster |        |        |
|-----------------------|---------|--------|--------|
|                       | 1       | 2      | 3      |
| Age                   | 49.55   | 70.83  | 33.08  |
| OSDI                  | .20     | .27    | .17    |
| NIBUT                 | 12.80   | 12.72  | 13.83  |
| NaFLTBUT              | 12.77   | 12.66  | 13.91  |
| NITBUT                | 6.28    | 7.34   | 8.12   |
| TMH                   | .12     | .11    | .13    |
| PRT                   | 12.85   | 12.47  | 13.05  |
| Corneal Staining      | .36     | .34    | .13    |
| Conjunctival Staining | .73     | 1.30   | .73    |
| LIPCOF                | .45     | 1.14   | .68    |
| Lipid                 | 3.25    | 2.42   | 3.10   |
| Osmolarity            | 334.75  | 307.03 | 305.60 |

**B) ANOVA**

|          | Cluster     |    | Error       |     | F       | Sig. |
|----------|-------------|----|-------------|-----|---------|------|
|          | Mean Square | Df | Mean Square | Df  |         |      |
| Age      | 19666.639   | 2  | 62.434      | 147 | 315.000 | .000 |
| OSDI     | .142        | 2  | .031        | 147 | 4.654   | .011 |
| NIBUT    | 17.367      | 2  | 4.105       | 147 | 4.231   | .016 |
| NaFLTBUT | 21.908      | 2  | 4.701       | 147 | 4.660   | .011 |
| NITBUT   | 5.174       | 2  | 5.410       | 47  | .956    | .392 |

|                       |          |   |         |     |        |      |
|-----------------------|----------|---|---------|-----|--------|------|
| TMH                   | .003     | 2 | .000    | 147 | 8.584  | .000 |
| PRT                   | 4.891    | 2 | 12.880  | 147 | .380   | .685 |
| Corneal Staining      | .721     | 2 | .444    | 147 | 1.624  | .201 |
| Conjunctival Staining | 6.145    | 2 | .902    | 147 | 6.810  | .001 |
| LIPCOF                | 6.474    | 2 | .628    | 147 | 10.301 | .000 |
| Lipid                 | 2.690    | 2 | 1.157   | 47  | 2.324  | .109 |
| Osmolarity            | 1453.899 | 2 | 111.832 | 47  | 13.001 | .000 |

The F tests should be used only for descriptive purposes because the clusters have been chosen to maximize the differences among cases in different clusters. The observed significance levels are not corrected for this and thus cannot be interpreted as tests of the hypothesis that the cluster means are equal.

**Table 2.9:** A) Final Cluster centres and B) Analysis of Variance (ANOVA) between cluster centres for Ocular Surface Disease Index (OSDI), non-invasive break-up time (NITBUT), fluorescein tear break-up time (NaFL TBUT), tear meniscus height (TMH), phenol red test (PRT), osmolarity and lipid pattern, lid-parallel conjunctival folds (LIPCOF), corneal staining and conjunctival staining for the right eye split into 3 clusters. N=150.

**A) Final Cluster Centres**

|                       | Cluster |        |        |        |        |
|-----------------------|---------|--------|--------|--------|--------|
|                       | 1       | 2      | 3      | 4      | 5      |
| Age                   | 40.56   | 77.82  | 25.67  | 54.51  | 69.03  |
| OSDI                  | .18     | .27    | .16    | .25    | .24    |
| NIBUT                 | 13.71   | 12.03  | 13.90  | 12.68  | 13.20  |
| NaFL TBUT             | 13.65   | 12.05  | 13.93  | 12.73  | 13.11  |
| NITBUT                | 7.60    | 7.38   | 6.62   | 8.12   | 6.91   |
| TMH                   | .13     | .11    | .13    | .12    | .11    |
| PRT                   | 13.28   | 10.93  | 12.86  | 13.64  | 12.59  |
| Corneal Staining      | .20     | .54    | .19    | .26    | .24    |
| Conjunctival Staining | .56     | 1.32   | .67    | 1.08   | 1.24   |
| LIPCOF                | .48     | 1.18   | .67    | .87    | 1.00   |
| Lipid                 | 3.00    | 2.00   | 2.40   | 2.94   | 2.65   |
| Osmolarity            | 358.00  | 294.00 | 312.40 | 305.33 | 316.82 |

**B) ANOVA**

|                  | Cluster     |    | Error       |     | F       | Sig. |
|------------------|-------------|----|-------------|-----|---------|------|
|                  | Mean Square | df | Mean Square | Df  |         |      |
| Age              | 11244.847   | 4  | 24.356      | 145 | 461.683 | .000 |
| OSDI             | .064        | 4  | .031        | 145 | 2.068   | .088 |
| NIBUT            | 15.372      | 4  | 3.977       | 145 | 3.865   | .005 |
| NaFLTBUT         | 14.423      | 4  | 4.670       | 145 | 3.088   | .018 |
| NITBUT           | 4.093       | 4  | 5.517       | 45  | .742    | .568 |
| TMH              | .002        | 4  | .000        | 145 | 5.585   | .000 |
| PRT              | 32.933      | 4  | 12.216      | 145 | 2.696   | .033 |
| Corneal Staining | .556        | 4  | .444        | 145 | 1.251   | .292 |

|                       |          |   |        |     |        |      |
|-----------------------|----------|---|--------|-----|--------|------|
| Conjunctival Staining | 3.107    | 4 | .914   | 145 | 3.399  | .011 |
| LIPCOF                | 1.990    | 4 | .672   | 145 | 2.964  | .022 |
| Lipid                 | 1.438    | 4 | 1.201  | 45  | 1.198  | .325 |
| Osmolarity            | 1441.562 | 4 | 53.282 | 45  | 27.056 | .000 |

The F tests should be used only for descriptive purposes because the clusters have been chosen to maximize the differences among cases in different clusters. The observed significance levels are not corrected for this and thus cannot be interpreted as tests of the hypothesis that the cluster means are equal.

**Table 2.10:** A) Final Cluster centres and B) Analysis of Variance (ANOVA) between cluster centres for Ocular Surface Disease Index (OSDI), non-invasive break-up time (NITBUT), fluorescein tear break-up time (NaFL TBUT), tear meniscus height (TMH), phenol red test (PRT), osmolarity and lipid pattern, lid-parallel conjunctival folds (LIPCOF), corneal staining and conjunctival staining for the right eye split into 5 clusters. N=150.

### 2.3 Discussion

There are batteries of tests which can be performed in optometric practice in order to evaluate the ocular surface and most importantly, to help diagnose and efficiently treat DED in practice. Despite the existence of all these dry eye tests, the clinical history of patients that has been regarded as a useful tool in uncovering this condition (O'Toole, 2005; Heath, 2007; Doughty, 2010). Both dry eye symptoms and ocular signs are often do not correlate well, but both are believed to be essential in the diagnosis and management of dry eye, with the patient's history and symptoms playing a crucial part (Smith et al., 2008). It is impractical to conduct every test on all dry eye patients, due to time restraints for both practitioner and patient. Therefore, it is important to justify if any of these tests are largely redundant in providing additional information compared to other tests and whether any have more diagnostic significance than others.

Unfortunately, most dry eye tests and symptoms often do not correlate, conflict with each other, and display considerable variation making classification difficult (Nichols et al., 2004; De Gomes et al., 2012). The dry eye tests included in this study could be categorised in the following way, in order to evaluate DED. The tear stability is assessed by break-up tests, i.e. NIBUT, NaFL TBUT and NITBUT. Tear volume can be assessed by means of the PRT, TMH. Corneal and conjunctival staining and LIPCOF are tests which provide an extent of the irritation and physiological status of the ocular surface. The balance of the tear film constituents can be assessed by assessing the osmolarity of the tears. Hence if the above mentioned groups are justifiable and the tests within a grouping are strongly correlated with one another, fewer tests would have to be performed.

Symptomology, assessed utilising the OSDI questionnaire, correlated with those tests investigating potential damage to the ocular surface i.e. LIPCOF; conjunctival and corneal staining as well as tests which assess both tear volume and stability as measured by the TMH and NIBUT. With age all these parameters were affected. Tear stability was significantly positively correlated with non-invasive and invasive tear break-up times. In this study, tear stability metrics were also correlated well with tear volume as measured by TMH and PRT, as well as corneal and conjunctival staining, and to a lesser degree LIPCOF. Both tear volume tests, as measured by the PRT and TMH, correlated well with corneal and conjunctival staining and LIPCOF; however the PRT test correlated less than the TMH for these tests. While several of the tear film metrics were statistically significant between those patients with and without LIPCOF, corneal and conjunctival staining (Table 2.6), it should be noted that some of the changes were small (such as 1 second difference in NITBUT) which are unlikely to be clinically significant. Tomlinson et al., (2001) reported a lack of correlation between TMH and the PRT, but their study had younger and fewer subjects than this one. Corneal staining was correlated to conjunctival staining, LIPCOF and osmolarity. Osmolarity was significantly positively correlated to corneal staining, unlike any of the other clinical tear film tests performed in the study. LIPCOF was significantly correlated to tear stability as well as conjunctival and corneal staining.

Cluster analysis was introduced for the first time in dry eye to try to establish whether it represents a group of distinct conditions (which may partly explain different preferences to dry eye treatments in subsequent chapters) or whether it is a single condition with a spectrum of severity as has been suggested for non-infectious and microbial keratitis, under the umbrella of corneal inflammatory events (CIEs) by Morgan and colleagues (2005). Although the research in this chapter demonstrated that statistically distinct clusters of dry eye metrics defining the disease could be established, there was no clear end point to the number of subgroups that could exist, with three or five potentially indicated for this cohort. This usefulness in explaining preference to dry eye treatments will be explored in chapter 3.

## **2.4 Conclusion**

Numerous dry eye tests have been applied to diagnose and monitor dry eye disease, either in a clinical setting or in clinical trials. However, there are a number of studies that have been subject to several forms of bias (section 1.10.1 and 1.10.2); therefore the cut-off values that they recommend may be unreliable. Another important factor to

consider is several tests available are expensive and may not be available routinely in optometric practice (e.g. TearLab, LipiView®, Keratograph 5M).

DEWS (2007), has suggested the following tests to diagnose dry eye disease in the series: symptomology; tear break-up time and ocular surface fluorescein staining; Schirmer test; lid and meibomian morphology and meibomian expression.

It has been reported that the following tests are the most commonly used diagnostic tests for the initial assessment of dry eye disease, tear break up time (93%), corneal staining (85%), and tear film assessment (76%), conjunctival staining (74%), and Schirmer test (54%)(Serin et al., 2007).

The use of questionnaires is used in order to ensure consistency in recording patients' symptoms. One of the most widely used questionnaires is The Ocular Surface Disease Index (OSDI), as it is deemed more (Schiffman et al., 2000). The OSDI questionnaire has been suggested to be more useful for monitoring disease progression, despite the difference in symptoms in meibomian gland dysfunction (Tomlinson et al., 2011), based on a recent validation of the survey (Miller et al., 2010). A number of studies have been conducted in order to ascertain the correlation of different dry eye tests or the predictive ability of a dry eye test. A large multicentre study involving 314 subjects, conducted by Lemp and colleagues (2011) measured bilateral tear osmolarity, tear film break-up time, corneal and conjunctival staining, Schirmer test, and meibomian gland grading. They reported 73% sensitivity and 92% specificity for tear hyperosmolarity with a cut off value chosen 312 mOsm/L. Tests displaying poor sensitivity were (corneal staining 54%; conjunctival staining 60%; meibomian gland grading 61%). The tests presenting with poor specificity were tear film break-up time 45% and Schirmer test 51%. They concluded that tear osmolarity is the best single metric in order to classify and diagnose dry eye disease. On the contrary it has also been reported that "tear osmolarity cannot be used as the sole indicator of dry eye disease" (Suzuki et al., 2010). Traditionally tear stability has been observed with the instillation of fluorescein, in order to measure the tear break up time, however the legitimacy of the results obtain have been scrutinised (Norn 1969, 1986; Lemp et al., 1973; Mengher et al., 1985). Several studies have reported that fluorescein tear break up time values are generally higher than non-invasive tear break up time (Mengher et al., 1985; Patel et al., 1985). The phenol red thread is less invasive than the Schirmer test which is used in order to assess the tear volume and has been described as an index of tear volume (Tomlinson et al., 2001). A study leaving the thread in place for 120 seconds differentiated between aqueous deficient and evaporative dry eye using a cut-off of 20 mm (sensitivity, 86%;

specificity, 83%) (Patel et al., 1998). No correlation has been found between phenol red thread test and tear meniscus height in dry eye, although the Schirmer I test has showed a significant correlation when both tests were performed for one minute (Yokoi et al., 2000). The tear lipid layer can be observed by looking at the images produced by specular reflection using the Tearscope (Keeler Ophthalmic Instruments). It has been reported that the tear lipid thickness and aqueous volume were interconnected after punctal occlusion (Goto et al., 2003). Corneal and conjunctival staining can be assessed by instilling dyes such as sodium fluorescein, rose bengal or lissamine green. However the repeatability of staining tests has been found to be poor (Nichols et al., 2004), as well as lacking discriminatory power in mild to moderate cases of dry eye (Sullivan et al., 2010). It has been reported that the strongest predictor of contact lens induced dry eye was a combination of nasal LIPCOF and non-invasive break-up time (Pult et al., 2011). The OCT has recently been used in a study to grade LIPCOF, which correlated well with slit lamp evaluation (Veres et al., 2011).

As the tear stability tests are strongly correlated, these results demonstrate that TBUT and NITBUT are both not necessary to perform in clinical practice. It would be more appropriate to observe the tear stability by performing NIBUT/NITBUT as fluorescein potentially disrupts the tear film structure (Mengher et al., 1985). The tear volume tests are also related and so any of the two can be used in clinical practice. It could be argued that conjunctival staining is linked to tear film stability and hence does to provide enough independent information to warrant the invasive and time consuming test. While lipid thickness lacks a severity rather than thickness grading scale, as some tear film supplements specifically target this layer and the lipid is so important for preventing evaporative loss (see section 1.6.9), lipid assessment should also be included in a dry eye test battery. Osmolarity and corneal staining provide similar information and the former, while more expensive to perform with the TearLab device, is linked to specific artificial tear treatments, and so could be preferred. Tear osmolarity has been reported to be the single best sign for dry eye disease (DEWS, 2007).

It can be seen from these results that there is no consistent relationship found between signs and symptoms of DED. However, each measurement offers distinct information about the condition of the ocular surface. Symptoms alone are insufficient to diagnose DED (DEWS, 2007), and more than one test has to be carried out in order to achieve the desired results with treatment. Therefore the key tests for DED diagnosis/management that are suggested from the results of this chapter are:

- Symptoms e.g. OSDI

- Stability e.g. NIBUT – which is linked with conjunctival staining.
- Volume e.g. TMH, as measured with slit lamp.
- Osmolarity e.g. TearLab – which is linked with corneal staining.
- Lipid e.g. as measured with the Tearscope, LipiView®, Keratograph 5M.

All these tests are easy to perform in optometric practice, but take some time and hence there is a necessity for specialist dry eye clinics conducting these specific tests for the diagnosis and monitoring of treatments of dry eye. This is considered to be a better alternative than practitioners 'diagnosing' and proposing inadequate treatments for DED on grounds of less relevant examinations carried out as a small subset of the full eye examination

## **CHAPTER 3**

### **Relative Effectiveness of Different Categories of Artificial Tear Supplements**

#### **3.0 Introduction**

Practitioners are experiencing an increasing number of patients complaining of symptoms associated with ocular dryness (Atkins, 2008) and symptoms. Dry eye is a common disorder, typically dry eye is classified as either aqueous-deficient or evaporative (DEWS, 2007); however these aetiologies are not mutually exclusive, and increased evaporation has been reported to be the more significant factor, contributing to dry eye signs and symptoms in as many as 78% of patients (Heiligenhaus et al., 1994, Lemp, 1995, Scaffidi et al., 2007).

Dry eye is one of the most common conditions faced in clinical practice. It is estimated that clinical dry eye affects as many as 21.6% of the patient population between 43 to 86 years of age (Moss et al., 2000). Based on data from studies by the Women's Health Study (WHS), the Physicians' Health Study (PHS) and other studies (Lemp et al., 1995; Miyawaki et al., 1995; Miljanovic et al., 2007; Schein et al., 1997; McCarty et al., 1998; Christen et al., 1998; Schein et al., 1999; Muñoz et al., 2000; Moss et al., 2000; Christen et al., 2000; Lee et al., 2002; Chia et al., 2003; Schaumberg 2003; Lin et al., 2003) it has been estimated that 3.23 million female and 1.68 million male, Americans 50 years and older have dry eye (Schaumberg et al., 2003; Miljanovic et al., 2007). Reddy et al., (2004), reported a prevalence of 11-17 per cent in the general population.

A comparison of age-specific data on the prevalence of dry eye from large epidemiological studies reveals a range of 5% (McCarty et al., 1998) to greater than 35% (Lin et al., 2003) at different ages. However, different definitions of dry eye were employed in these studies; hence caution is advised in interpreting direct comparisons of these studies. Even though, limited data exists on the possible effect of race or ethnicity on dry eye prevalence, data from the WHS imply that the prevalence of severe symptoms and/or clinical diagnosis of dry eye may be greater in Hispanic and Asian, as compared to Caucasian women (Schaumberg et al., 2003). The combined data from large population-based epidemiological studies indicates that the number of women affected with dry eye appears to surpass that of men (Schein et al., 1997; 1999; Christen et al., 1998; 2000; McCarty et al., 1998; Moss et al., 2000; Muñoz et al., 2000; Lee et al 2002; Chia et al., 2003; Lin et al., 2003; Schaumberg et al., 2003; Miljanovic et al., 2007).

The studies were conducted in different populations across the world, therefore, providing valuable information regarding potential differences in dry eye according to geographic location. Data from the two studies performed in Asia suggest the possibility of a higher prevalence of dry eye in those populations (McCarty et al., 1998; Lee et al., 2002). The weight of the evidence from large epidemiological studies indicates that female sex and older age increase the risk for dry eye; the Salisbury Eye Evaluation study is the most notable exception (Schein et al., 1997; Muñoz et al., 2000). An overall summary of data suggests that the prevalence of dry eye lies somewhere in the range of 5-30% in the population aged 50 years and older. The prevalence of dry eye, using varying definitions, was tabulated for each epidemiologic study and is listed in table 3.1, along with the corresponding estimates of population prevalence (DEWS, 2007).



**Table 3.1:** Summary of population-based epidemiologic studies of dry eye (Taken from DEWS, 2007). The number of patients in each study, age range,

dry eye assessments and the prevalence are summarised. The studies were carried out over different continents; USA, Australia and Asia.

Ocular complaints, such as burning, dryness, stinging, and grittiness, are often reported in epidemiologic studies of indoor environments, especially in offices where highly demanding visual and cognitive tasks are performed (Skyberg et al., 2003). Typical symptoms of dry eye sufferers include photophobia, burning, itching, foreign-body sensation, eye fatigue, and dryness (Ball, 1982). Ocular dryness may be due to increased tear evaporation and to low humidity, high room temperature and air velocity, decreased blink rate, or indoor pollution or poor air quality (Tsubota et al., 1993; Skyberg et al., 2003; Wolkoff et al., 2005; McCulley et al., 2006) and ultra-low humidity environments, such as aircraft cabins, have also been associated with dry eye symptoms (Lindgren et al., 2002; Sato et al., 2003). The symptoms of patients tends to be diurnal, with symptoms becoming worse as the day progresses, and they are frequently aggravated in dry, warm environments where tear evaporation is highest (Kanski, 1989).

The effect of contact lenses on exacerbating dry eye is indicted by the higher prevalent rate in this population (typically around 50%, DEWS, 2007). However, studies assessing contact lens wear in adverse environmental conditions such as dehydration (Fonn et al., 1999; Efron et al., 1999) and temperature / humidity (Morgan et al., 2004) have suggested contradictory effects on their impact on subjective comfort.

Unfortunately, there is no known cure for dry eye disease and so treatment can be seen as management in order to supplement, preserve or stimulate tears to minimise ocular discomfort. The fundamental treatment goals in the management of dry eye are suitable healing, epithelialisation and the re-establishment of normal ocular surface (Gobbles et al., 1992).

Even though dry eye disease in its milder form may react to treatments that lessen symptoms without altering the disease process, recent pharmacological approaches are directed toward reducing, stopping the disease process. Therefore tests are required to discriminate between dry eyes, quantify disease severity, and demonstrate the effect of disease on a patients' quality of life.



**Fig 3.1:** Schematic illustration of the relationship between dry eye and other forms of ocular surface disease. OSD = Ocular surface disease; MGD = Meibomian gland dysfunction. (Taken from DEWS, 2007)

The most widely used therapy for dry eye is by the use of topical artificial tears and lubricants (Calonge, 2001). There are numerous components used to formulate a vast number of commercially available preparations (table 1.6 and table 1.7). The main aim of using artificial tears is to improve the ocular lubrication (Calonge, 2001), 'tear

replacement' or 'tear retention' (Farrell, 2010) and are principally aimed at relieving the subjective symptoms of patients (Doughty, 2010; Farrell, 2010).

However, there various treatment options for dry eye, rather than just using artificial tears. They are discussed briefly below:

- **Blink exercises-** an incomplete blink will usually present as inferior punctate corneal epithelial staining (Heath, 2004). Blink modification exercise plan has been recommended by Schendowich (2003), for contact lens wearers with incomplete blinking.
- **Lid hygiene and warm compresses-** Blepharitis may be seborrheic, staphylococcal or a combination of both (Kanski, 1989). Blepharitis can be observed as oily secretions, 'dandruff' or collarettes around the eyelashes and missing or misdirected eyelashes. Patients may complain of photophobia, tearing, pain, redness, blurred vision and/or discharge. Warm compresses of the lid may reduce tear evaporation by temporarily thickening the lipid layer (Gilbard, 2005). Korb et al., (1994) reported that patients with MGD with a daily regimen of eyelid scrubbing and warm compresses, as well as meibomian gland expression resulted in less solid meibomian secretions and significantly increased lipid layer thickness and patients reported improved dry eye symptoms. Craig and colleagues (1995) also showed that manual expression of the meibomian glands increases lipid layer thickness and tear film stability in normal subjects.
- **Autologous serum tears-** are produced from the patient's serum and have been used in severe DED. Autologous serum tears have biochemical and mechanical properties similar, to those of normal aqueous tears (Geerling et al., 2004).
- **Punctal plugs-** are the most commonly used means of occlusion (Lemp, 2008). A number of clinical studies have evaluated the efficacy of punctal plugs (Tuberville et al., 1982; Willis et al., 1987; Gilbard et al., 1989; Balaram et al., 2001; Baxter et al., 2004) and their use has shown both objective and subjective improvement in patients with Sjögren and non-Sjögren aqueous tear deficient dry eye. It has been reported that, patients who are symptomatic of dry eyes, have a Schirmer test (with anaesthesia) result less than 5 mm at 5 minutes, and appear to have ocular surface staining would benefit from punctal

plugs (Baxter et al., 2004). The complications of punctal plugs are conjunctival irritation, epiphoria where 5% of patients request plug removal (Taban et al., 2006) and infection (DEWS, 2007).

- **Anti-inflammatory therapy-** Disease of the tear secretory glands results in an alteration of the tears leads to changes in the tears, such as hyperosmolarity, which stimulate the production of inflammatory mediators on the ocular surface (Luo et al., 2004; 2005), this inflammation may cause dysfunction of cells responsible for tear secretion and / or retention (Nieder Korn et al., 2006).
- **Essential fatty acids-** can be obtained from dietary sources (DEWS, 2007). Several clinical trials have shown a clinical benefit of the effect of fish oil omega-3 fatty acids on rheumatoid arthritis (James et al., 1997; Kremer, 2000). In a study conducted by Barabino et al., (2003) showed a significant improvement in ocular irritation symptoms and lissamine green staining.
- **Environmental strategies-** anything that may affect a reduction in tear production or increased tear evaporation e.g. Antihistamines or antidepressants, environmental factors such as air conditioning and low humidity should be reduced (Seedor et al., 1986; Mader et al., 1991; Moss et al., 2000). It has been advised that visual display units be lowered to below the eye level, in order to reduce the inter-palpebral aperture as well as patients taking regular breaks when working on a computer (Tsubota et al., 1993).

Even though there are numerous topical lubricants, with varying viscosity, that may improve patient symptoms and clinical findings, there is no evidence that any particular artificial tear treatment is superior to another (DEWS, 2007). Generally clinical trials involving topical artificial tears will report some improvement of subjective symptoms and improvement in some clinical signs (Nelson et al., 1992). Therefore this study aims to investigate if any one artificial tear used in the trial is superior to another.

### **3.0.1 The ideal artificial tear solution**

The ideal tear supplement can be said to require the following key features:

- Provide immediate discomfort relief
- Give prolonged residency of the tear film, for long lasting relief
- Is non-toxic to the ocular surface
- Is simple to instil

- Does not blur vision after instillation (Atkins, 2008).

The ideal delivery system for such a solution can be said to have the following key features:

- Easy/simple to use/instil
- Small (measured) droplet size to avoid blurring/washing away the tear film
- Helps maintain solution sterility between usage (with or without preservatives)
- Affordable (Atkins, 2008).

Currently there are multiple treatments available, however, the majority being tear supplements, but with little evidence as to their effectiveness and whether some work better for some patients than others. At present treatment goals are directed towards either 'tear replacement' or 'tear retention', and are aimed primarily at relieving the subjective symptoms associated with this condition (Farrell, 2010). Numerous formulations and active ingredients have been introduced over the years, with varying success, and these may broadly be classified as aqueous artificial tears, ocular lubricants and viscoelastics (Farrell, 2010).

Artificial tears can be viewed as 'simple' or 'complex', and those that re-wet a 'dry' eye will provide at least a transient lubricating action. More complex eye drops labelled as true ocular lubricants are more likely to provide more substantial lubricating action (Doughty, 2010). Simple artificial tears are likely to be based on a normal saline 0.9% and usually a single polymer to assist any lubricating action. Whereas the complex artificial tears may contain two or more polymers, and the true lubricants category is limited either to products containing the highest concentrations of the polymers or special polymers, or have an ointment vehicle base rather than saline (Doughty, 2010). The main active ingredients are usually carboxymethylcellulose (CMC), polyvinyl alcohol (PVA), hyaluronic acid (HA), polyethylene glycol (PEG) and Poly Vinyl-Pyrrolidone (PVP) (see section 1.7.1). Current artificial tears and ocular lubricants are presented in Table 1.6.

### **3.0.2 Preservatives**

Topical ophthalmic solutions sometimes may cause toxic or allergic reactions resulting in iatrogenic ocular disease (Wilson, 1979). Toxic reactions relate to the direct chemical irritation of tissue, whereas allergic reactions imply sensitization and induction of ocular inflammatory processes by the patient's immune system (Arffa, 1979). Bernal and colleagues (1991) concluded from their study that solutions containing preservatives

such as benzalkonium chloride, polyquad and thimersol caused corneal damage, whilst non preservative solution showed no damage to the cornea. Likewise, Berdy and colleagues (1992) conducted a study to evaluate the corneal epithelium of rabbit eyes after administration of two preservative-free ocular lubricants: Hypotears PF and Refresh, and 0.02% benzalkonium chloride, and used a scanning electron microscopy to assess the corneal epithelial damage they came to the conclusion that with frequent-dosage regimens, preservative-free artificial tear solutions used in the study were free of the toxic effects associated with preserved solutions.

These adverse external ocular effects of ophthalmic therapy are due to the topically applied drug, or the excipients present in the preparation. Preservatives are among the excipients currently used in ophthalmic preparations (Furrer et al., 2002). Furrer and colleagues (2002) reviewed the ocular cytotoxic effects caused by preservatives and focused on the validity of the use of preservatives in ophthalmic solutions and the risks associated with their use. They concluded that the use of preservatives is the easiest way to prevent microbial spoilage of ophthalmic solutions. However, constitute a necessary compromise between what is legally required and necessary, and what is microbiologically efficacious on the one hand and possibly toxic on the other (Kilp et al., 1984). In other words, preservatives are meant to destroy microorganisms across a broad spectrum and to protect the eye against possible secondary infection, but unfortunately their action is non-specific and they can damage ocular tissues (Lemp et al., 1988). Furrer and colleagues (2002) suggested that the use of preservatives in eye drops should be restricted to solutions that are used selectively during a short period of time and recommended that preservatives should be avoided, if possible, in cases where patients have chronic ocular surface disease (dry eye or allergy), because of the risk of worsening patient symptoms. In others cases, caution is urged in the use of preservative-containing topical ocular medications over an extended period in patients with extensive ocular surface diseases (Olson et al., 1990). The use of preservative-free tear substitutes should be promoted as they are as effective as preserved artificial tears, and avoid adverse ocular effects induced by preservatives (Brewitt et al., 1991; Grene et al., 1992).

Hence the future of artificial tears is likely to be preservative free therefore the solutions selected for this study were unpreserved. The aim of this chapter was to determine the relative effectiveness of the different categories of tear supplements as identified in the introduction (Chapter 1), namely two with different concentrations of hyaluronic acid, one marketed on its osmolarity balancing effects and the other being a liposomal spray.

## **3.1 Method**

### **3.1.1 Drops chosen for the study**

The drops chosen for the study were Clinitas Soothe, Hyabak, Tears Again and TheraTears. The reason for using these drops for the study as they all are preservative free causing no potential cytotoxic effect on the ocular surface and represented the different non-pharmaceutical eye drop options commercially available to manage dry eyes.

#### **3.1.1.1 Clinitas Soothe and Hyabak**

Clinitas Soothe is marketed as a rewetting/lubricating solution for dry eye patients and contact lens wearers containing 0.4 per cent Sodium Hyaluronate as a preservative free eye drops containing 0.5ml of solution. The container is an interesting development on the traditional single unit container (SUC) in that it incorporates a replaceable cap for leak-free disposal and breaking the seal of the vial leaves a smooth opening, unlike most conventional SUCs (Atkins, 2008). Hyabak uses the patented Abak preservative-free multi-dose eye drop dispenser. This uses a system of filters to ensure that each drop dispensed is preservative-free and calibrated to always be 30µl in size. The key lubricant is unpreserved 0.15% Sodium Hyaluronate. The ingredients and benefits of Hyabak can be seen in table 3.2.

Several studies have reported that sodium hyaluronate is able to improve both symptoms and signs in patients with dry eye (Gill et al., 1973; Polack et al., 1982; De Luise et al., 1984, Stuart et al., 1985; Shimmura et al., 1995; Papa et al., 2001). Aragona and colleagues (2002) explored the effect of sodium hyaluronate containing eye drops on the ocular surface of patients with dry eye during long term treatment, concluding that sodium hyaluronate seems to effectively improve ocular surface damage associated with dry eye syndrome. Likewise a study conducted by Brignole et al., (2005) evaluated the efficacy and safety of 0.18% sodium hyaluronate in patients with moderate dry eye syndrome and superficial keratitis. They concluded sodium hyaluronate was well tolerated and tended to show a faster efficacy than did the CMC-based formulation in patients with moderate dry eye and superficial keratitis. Sodium hyaluronate could therefore advantageously be prescribed from the early stages of dry eye disease. Mengher and colleagues, (1986) evaluated the effect of 0.1% sodium hyaluronate (unpreserved) in 10 patients with dry eyes. The pre-corneal tear film break-up time was assessed by non-invasive technique, and the severity of symptoms was recorded before and after treatment on a 0 to +3 scale. Tear film stability was significantly increased ( $p < 0.05$ ) in eyes treated with sodium hyaluronate. The

symptoms of grittiness and burning were also significantly alleviated in the treated eyes. Sand and colleagues, (1989) investigated the effect of Sodium hyaluronate in the treatment of keratoconjunctivitis sicca (KCS). They evaluated this in a double masked crossover trial, comparing the effect of a 0.1% solution, a 0.2% solution and placebo in 20 patients. The authors showed significantly decreased rose bengal staining and increased break-up time following 0.2% treatment compared to placebo. No significant difference was found in the Schirmer values and the cornea sensitivity. The patients significantly preferred sodium hyaluronate treatment over the placebo. Hence the consensus of studies is that hyaluronic acid based dry eye treatment should be effective, even in low concentrations.

### **3.1.1.2 TheraTears**

TheraTears was developed by Gilbard at the Schepens Eye Institute. TheraTears is a preservative free hypotonic solution in unit dose, with the active ingredient Carboxymethylcellulose (CMC 0.25 %). CMC is negatively charged and binds to the corneal epithelial surface well. CMC also has a cyto-protective function against the insult from the preservatives present in contact lens disinfecting solutions (Vehinge et al., 2003; Sulley, 2004). It has been claimed that TheraTears may have beneficial effects on conjunctival goblet cell density, especially in patients fitted with punctal plugs, due to its hypotonicity and may help corneal healing by reducing the effects from the upper eyelid on blinking (Gilbard, 1999).

TheraTears is designed to saturate dry eyes, and dilute down the high salt concentration that causes dry-eye irritation. Dry eye is a result of a loss of water from the tears on the eye surface that makes the tears hyper-osmotic. TheraTears has an osmolarity mean value of 181mmol/kg which is significantly lower than general ocular lubricants (Perrigin et al., 2004). The hypo-osmotic TheraTears help replace the lost water, lowering the high salt concentration, so that they not only wet but also rehydrate dry eyes, leading to an improvement in symptoms (Matheson, 2006). In addition the tears are an electrolyte solution specially designed to protect the eye surface. The ingredients and benefits of TheraTears can be seen in table 3.2.

The importance of electrolyte balance has been reported extensively (Gilbard et al., 2005, Schofield, 2004). The corneal epithelium derives its electrolytes and oxygen from the tear film (Matheson, 2006). Volker and colleagues, (2000) showed that unless an eye drop has an electrolyte balance that precisely matches that of the human tear film, there is a loss of conjunctival goblet cells (conjunctival goblet-cell density appears to be a sensitive indicator of ocular surface health, and goblet cells provide the natural

lubrication for the ocular surface). TheraTears has been shown to restore conjunctival goblet cells in dry eye seen after Lasik vision correction surgery (Lenton et al., 1998).

### **3.1.1.3 Tears Again**

The tear lipid layer has long been recognised to play an important role in preventing tear film evaporation (Mishima et al., 1961). The tear lipid layer is a complex structure with a thin, inner polar layer, interfacing with the aqueous phase and reducing surface tension, and a thicker, outer, non-polar layer which is believed to inhibit tear evaporation (Korb et al., 2002, Bron et al., 2004). Meibomian gland dysfunction results in abnormal lipid production and has been identified as one of the major causes of ocular discomfort and ocular surface abnormality (Shimazaki et al., 1998, McCulley et al., 2003, Foulks, 2003).

Traditionally, the focus of dry eye therapies has been to augment tear film volume to compensate for aqueous insufficiency but more recently, attention has been directed towards creating supplements that address deficiency in the tear film lipids. In the last decade, researchers have reported significant reductions in tear evaporation and improvements in lipid layer thickness with topical lipid emulsion eye drops containing neutral oils and castor oil (Goto et al., 2002; Di Pascuale et al., 2004; Khanal et al., 2007; Scaffidi et al., 2007).

Tears Again phospholipid liposomal spray is applied to the closed eyelids and the liposomes migrate, via the lid margins, into the tear film (Craig et al., 2010). An improvement in eyelid margin inflammation, symptomatology, tear production, visual acuity and lid parallel conjunctival folds have been documented with use of the lipid spray in patients with dry eye (Lee et al., 2004; Dausch et al., 2006; Khairuddin et al., 2010; Craig et al., 2010), as well as in contact lens wear (Kunzel, 2008) and following cataract surgery (Reich et al., 2008). The effect of significantly improving tear film stability and lipid layer thickness in normal and mildly symptomatic eyes appears to last for between 60 and 90 minutes following a single application of a phospholipid liposomal spray to the closed eye (Craig et al., 2010). The ingredients and benefits of Tears Again can be seen in table 3.2.

| Key Lubricant                                                                                                                                                                              | Size/Form                                                                | Other constituents                                                                                | Benefits                                                                                                                                                                                                                   | Manufacturer and Distributor                                                                                                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinitas Soothe</b>                                                                                                                                                                     |                                                                          |                                                                                                   |                                                                                                                                                                                                                            |                                                                                                                                                 |
| <p>Highest concentration of Sodium Hyaluronate 0.4%</p> <p>Molecular weight 1.2 million Daltons (Ds)</p>  | <p>20 Resealable droppers.</p> <p>0.5ml in each dropper (8-10 drops)</p> | <p>Monobasic sodium phosphate, dibasic sodium phosphate, sodium chloride, water for injection</p> | <p>No preservatives</p> <p>8 to 10 drops per dropper</p> <p>Each dropper is resealable for 12 hours</p> <p>Shelf life 2 years (Atkin 2008)</p> <p>Maximum expiry after opening : up to 2 years single use (Atkin 2008)</p> | <p>Manufacturer: Farmigea S.p.A., Pisa Italy.</p> <p>Distributed by: Altcor Ltd, Cambridge, UK</p>                                              |
| <b>Hyabak</b>                                                                                                                                                                              |                                                                          |                                                                                                   |                                                                                                                                                                                                                            |                                                                                                                                                 |
| <p>Sodium Hyaluronate 0.15%</p>                                                                         | <p>10ml Bottle</p>                                                       | <p>Sodium chloride, trometamol, hydrochloric acid, water for injection ad 100mL</p>               | <p>No Preservatives</p> <p>Dispenser contains around 300 drops</p>                                                                                                                                                         | <p>Manufactured by: Laboratoires Théa, Clermont-Ferrand, France.</p> <p>Distributed by: Spectrum Thea Pharmaceuticals Ltd, Macclesfield, UK</p> |
| <b>TheraTears</b>                                                                                                                                                                          |                                                                          |                                                                                                   |                                                                                                                                                                                                                            |                                                                                                                                                 |
| <p>Sodium Carboxymethylcellulose 0.25</p>                                                                                                                                                  | <p>32 single use containers per box</p>                                  | <p>Borate buffers, calcium chloride, Dequest®,</p>                                                | <p>No Preservative</p>                                                                                                                                                                                                     | <p>Manufacturer: Advanced Vision Research, Ann</p>                                                                                              |

|                                                                                                                   |                    |                                                                                                                                                  |                                                                                                                                               |                                                                                                                                                                                                                                  |
|-------------------------------------------------------------------------------------------------------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>%</p>                         |                    | <p>magnesium chloride, potassium chloride, purified water, sodium bicarbonate, sodium chloride, sodium perborate, and sodium phosphate</p>       | <p>es<br/>Patented so that each drop provides the special salt balance, the electrolyte balance, needed for the health of the eye surface</p> | <p>Arbar, MI, USA.<br/><br/>Distributor: Matheson Optometrists – 3 West St, Alresford, Hants, SO24 9AG</p>                                                                                                                       |
| <b>Tears Again</b>                                                                                                |                    |                                                                                                                                                  |                                                                                                                                               |                                                                                                                                                                                                                                  |
| <p>Phospho-lipid liposomes</p>  | <p>10ml Bottle</p> | <p>1ml contains 10mg soy lecithin, 8mg sodium chloride, 8mg ethanol, 5mg phenoxyethanol, 0.25mg vitamin A, 0.02mg vitamin E, aqua purificata</p> | <p>Apply to lids when closed<br/><br/>3 Year shelf life<br/><br/>Bottle contains 100 applications</p>                                         | <p>Manufacturer: Optima Pharmazeutische GmbH, D-85361, Moodburg/Wang, Germany.<br/><br/>Distributed by: Optrex, Damson Lane, Hull, HU8 7DS, UK. (<i>Optrex is an associate company of Reckitt Benckiser Healthcare Ltd.</i>)</p> |

**Table 3.2:** Listing the key lubricants, size/ form, other constituents, manufacturer and benefits of the drops chosen for the study. (Clinitas Soothe Hyabak, TheraTears and Tears Again).

### 3.1.2 Patients

Fifty patients (average age 60.8 years, range 26-82 years; 35 females and 15 males) were recruited from the patients of a community optometric practice in the north west of England. The study was approved by the ethical committee of Aston University and conformed to the tenets of the Declaration of Helsinki. Patients signed a consent form after an explanation of the study and its possible risks had been given.

The patients recruited, were advised of the purpose of the study which was to look more carefully at the signs and available treatments of dry eye and to be able to identify the best treatment for future patients with dry eye without the need to trial several possible treatments. Subjects were excluded if they had diabetes; Sjögren's Syndrome, recent ocular infection, hay fever, used any eye drops or ocular

medications, were currently on medications known to affect the eyes, wore contact lenses or were pregnant. Patients included in the study had subjective symptoms indicative of dry eye. The patients that met the inclusion and exclusion criteria and consented to take part in the research were advised that they would undergo clinical assessment of their tears and were then given artificial tears to use for one month. The patients were advised to continue without a 'wash out' period on the next set of tear supplements in order to ease ocular comfort, however, were asked not to use their artificial tear supplements on the day of the clinical observation. The same tests would be repeated in consecutive months. They were advised that there would be required to attend the practice a total of five times over a four month period and to use only the drops given to them at each visit.

Patients were asked to record how many drops they used on a daily basis. It was stressed to subjects that this was a single blinded study where the researcher was unaware of which drops were used and at which month, so total discretion with respect to this was required. In order for the researcher not to be involved with the actual handing over of the eye drops key staff members in the clinical practice were selected to distribute the drops out and facilitate the follow up appointments of the patients before they saw the researcher. The participants were free to discontinue with the trial at any time and were reassured that their information would be fully confidential. A copy of the consent form can be found in Appendix D.

### **3.1.3 Clinical evaluation**

It has been recommended, that when a battery of tests is performed, they should be performed in an arrangement that best preserves their reliability (DEWS, 2007), and intervals should be left between the tests (Bron, 2001; Foulks and Bron, 2003).

Therefore, on these recommendations, the tear film metrics for this study were assessed in the following order due to the invasive nature of some tests. These dry eye tests were conducted on the right eye of every patient at every visit.

- **Symptoms** – the OSDI questionnaire measures the severity of dry eye disease using 12 questions scored on a scale of 0-4. The OSDI score was calculated by multiplying the total score by 25 and dividing by the total number of questions answered generating a result between 0 and 100. Subjects were assigned normal ( $\leq 10$ ) or symptomatic ( $> 10$ ) status based upon the OSDI score. The OSDI is well validated and can differentiate dry eye severity with a limited time (Schiffman et al., 2000).

- **Non-invasive Break-up Time (NIBUT)** – was measured by observing the stability of the keratometer mire projected onto the front of the corneal surface (Patel et al., 1985). The one position Bausch and Lomb keratometer with circular mires was used to measure the NIBUT in this study. The portion of the image mire used in keratometry is not reflected from the exact centre of the cornea, but from two small areas on either side of the axis of the instrument, separated by about 3mm (Henson, 1983). Subjects were instructed to blink normally and then keep their eyes open for as long as possible. The NIBUT was recorded with a stop watch to the nearest second when distortion is first seen in any part of the mire pattern.
- **Tear Meniscus Height (TMH)** - the total volume of aqueous tears comprised within the upper and lower tear meniscus is approximately 75-90 per cent of the total volume of the aqueous component (Mainstone et al., 1996). The tear formation is controlled by the size and shape of the tear meniscus along the tear margin, (Holly et al., 1977). It has been reported that the height of the tear meniscus is reduced by half in the presence of KCS (Lim et al., 1991), as well as an irregular edge or intact temporal area of the lower tear meniscus being consistent with dry eye (Holly et al., 1977, Terry, 1984, Port et al., 1990). The method used to quantify TMH was to rotate the slit beam (under 25 times magnification) until it was horizontal and to adjust the width of the slit until it matched the height of the tear prism. The tear meniscus height (TMH) was measured directly below the pupil centre.
- **Lid Parallel Conjunctival Folds (LIPCOF)** - are folds in the lower conjunctiva parallel to the lower lid margin (Pult and Sickenberger, 2000). It is understood that friction between the upper eyelid and bulbar conjunctiva interferes with conjunctival lymphatic flow resulting in dilation and ultimately folds (Meller and Tsang, 1998). They were observed using a 2-3 mm wide vertical slit beam located along the temporal, viewed at 25 times magnification. The numbers of folds were counted and graded using the approach outlined in table 1.2 (Höh et al., 1995). LIPCOF graded  $\geq$  grade 2 is likely to be associated with dry eye symptoms (Pult et al., 2011).
- **Fluorescein Break up Time (NaFL TBUT)** - was measured with the slit lamp bio-microscope (magnification 10 times) with a diffuse cobalt blue light at maximum brightness. A single drop of sterile saline was applied to a fluorescein

sodium impregnated paper strip (Fluorets, 1mg fluorescein sodium, Chauvin Pharmaceuticals, Essex, UK) and the excess shaken off before applying it to the subjects' eye. The lower lid of the right eye was lowered and the moistened strip was swiftly but gently applied to the temporal lower tarsal conjunctiva. The subject was then instructed to blink normally after application to circulate the fluorescein. Subjects were then asked to look in primary gaze without blinking. NaFL TBUT was defined as the interval of time between the last complete blink and the first appearance of a dry spot or disruption (black/dark blue area) in the tear film (Lemp et al., 1995) measured with a digital stop clock. Three measurements were taken and averaged. A yellow filter (Kodak Wratten 12) was used to enhance contrast and improve the visibility of breaks in the tear film (Bron et al., 2003).

The established NaFL TBUT cut-off for dry eye diagnosis has been <10 seconds in Caucasian subjects (Lemp et al., 1973). Values between  $\leq 5$  and <10 seconds have been adopted, possibly based upon the report by Abelson et al (2002), which suggested that the diagnostic cut-off falls to <5 seconds when small volumes of fluorescein are instilled in the conduct of the test (e.g. clinical trials pipetting 5 $\mu$ l of 2.0% fluorescein dye). Selecting a cut off below <10 seconds will tend to decrease the sensitivity of the test and increase its specificity (Lemp et al., 1973).

- **Corneal Staining** - Corneal staining was assessed using fluorescein sodium (Fluorets) impregnated paper strips. A single drop of sterile saline was applied to a fluorescein sodium impregnated paper strip (Fluorets, 1mg fluorescein sodium, Chauvin Pharmaceuticals, Essex, UK) and the excess shaken off before applying it to the subjects' eye. The lower lid of the right eye was lowered and the moistened strip was swiftly but gently applied to the temporal lower tarsal conjunctiva. The subject was then instructed to blink normally after application to circulate the fluorescein. The cornea of each eye was examined use a cobalt blue light source (10 times magnification) with the excited fluorescein dye contrast enhanced using a yellow filter. The presence of staining on the cornea of both eyes was recorded.

After a 5 minute break the following tests were performed as recommended by Bron, (2001).

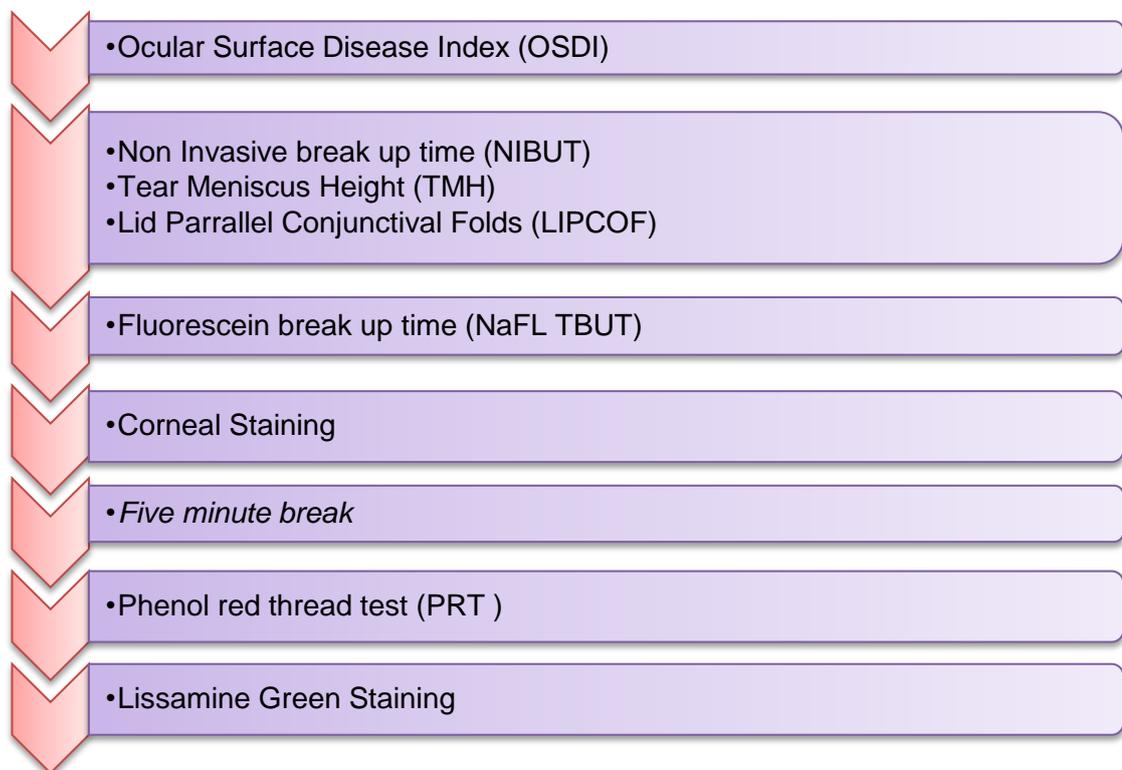
- **Phenol Red Thread (PRT)** – the use of cotton thread for absorbing the tears was originally advocated by Kurihashi (1975). In order to make the wetting observation easier, Hamano and colleagues (1982) impregnated the cotton thread with phenol red dye that acts as a pH indicator. On contact with the tear film, the thread changes colour from yellow to red in response to the pH of the tear fluid. The phenol red thread is very fine, and should not stimulate reflex tears. In theory the measurement should therefore represent basal tear production without interference from reflex tearing. It is an alternative to the well validated Schirmer strip, which is more invasive and hence is more likely to stimulate tearing.

Even though the thread is in contact with the ocular surface, although for a brief period, it may only be assessing the presence of tear volume in the lower conjunctival sac rather than overall tear production (Blades et al., 1996, Mainstone et al., 1996). In normal eyes, wetting values have been reported to be on average  $15.4 \pm 4.9$ mm while dry eyes average at 6.9 (no standard deviation reported; Cho et al., 1996; Mainstone et al., 1996). Whereas Little and Bruce (1994a) proposed that a PRT value of less than 11mm be used as the diagnostic criterion for low tear secretion and a value of less than 16mm for borderline cases. This diagnostic cut-off is affected by patient ethnicity. For example, Sakamoto and colleagues (1993) examined the results of the phenol red thread tear test in a cross-cultural comparison, and reported the mean wet length of the thread for patients in the United States was  $23.9 \pm 9.5$ mm whereas the mean for patients from Japan was  $18.8 \pm 8.6$ mm. There was a significant difference between the two countries ( $P < 0.05$ ). There were no overall differences between the right and left eye means for either country ( $P > 0.05$ ) as well as no differences between the eyes for any particular age group. Right and left results showed a moderate positive correlation for both countries (United States  $n=500$   $r=0.74$ ; Japan  $n=500$   $r=0.65$ ) and males subjects having a significantly longer wet length than females was noted ( $P < 0.05$ ).

The Zone-Quick (Showa Yakuhin Kako Co., Tokyo, Japan) version of the Phenol Red test was used which has a length of 70mm. A 3mm end of the thread was bent over and placed between the lower eyelid and the ocular surface approximately one fifth of the way in from the temporal canthus. The thread was left in position for 15 seconds while the patient is instructed to keep their eyes open and blink normally. After removal, the length of wetting was measured from the end of the thread in millimetres using a ruler.

- **Conjunctival Staining** – Lissamine green is primarily a conjunctival dye which does not stain healthy cells, but only dead and degenerate cells (Feenstra et al., 1992) and areas of the conjunctiva not protected by mucus. Uchiyama and colleagues suggested in 2007 that conjunctival staining with Lissamine Green could show up prior to corneal staining with fluorescein in patients with early dry eye. Lissamine Green (Green Glo, 1.5mg Lissamine Green, HUB Pharmaceuticals, USA) strips were used to evaluate the conjunctiva, where a single drop of sterile saline was applied to the strip. The wetted strip was quickly but gently applied to the lower tarsal conjunctiva after lowering the lower lid. The subject was then instructed to blink normally after application to distribute the Lissamine Green, before the conjunctiva of each eye was studied using a slit lamp bio-microscope (white light, 10 times magnification; Feenstra et al., 1992) and the presence of staining on conjunctiva in both eyes was recorded.

Further details on all of the above tests can be found in the section 1.6. Figure 3.2 represents the order in which the tear film metrics were assessed due to in the invasive nature of some tests.



**Figure 3.2:** Represents the order in which the tear film metrics were assessed due to in the invasive nature of some tests.

Unfortunately, the tear lipid layer of the participants could not be observed for the whole period of the trial, as the tearscope had to be returned to the university clinic. Slit lamp observation of the lipid layer utilising the slit lamp via specular reflection would not have given satisfying results. The tear osmolarity was also not measured for the length of the study as the TearLab was only loaned for collecting the baseline measurements.

Patients were also asked to rate the drops that they had just been trialling out of 10. They were also asked more specifically to rate the overall comfort, ease of insertion of the eye drops and the clarity of the vision after having instilled the eye drops.

### **3.1.4 Sample size and statistical analysis**

Sample size estimation was performed in order to obtain ethical clearance and to justify the number of subjects recruited. Conducting a sample size calculation is important in order to detect a real statistical difference and also having an ethically acceptable sample size and saves on resources and time for the practitioner. For repeated measures statistical comparisons such as ANOVA it is recommended that there are 15 or more degrees of freedom (Armstrong et al., 2000; 2010). Hence for this study four solutions were compared, so  $n-1$  degrees of freedom are equal to 3. Hence with 5 or more subjects this criterion is met. When comparing 2 groups, such as those who preferred one solution compared to the rest of the subjects, the typical mean value, the size of the difference one wants to detect and the standard deviation of the repeatability are required. Therefore, this information was inputted into a sample size calculator:

<https://www.dssresearch.com/knowledgecenter/toolkitcalculators/samplesizecalculator.s.aspx>).

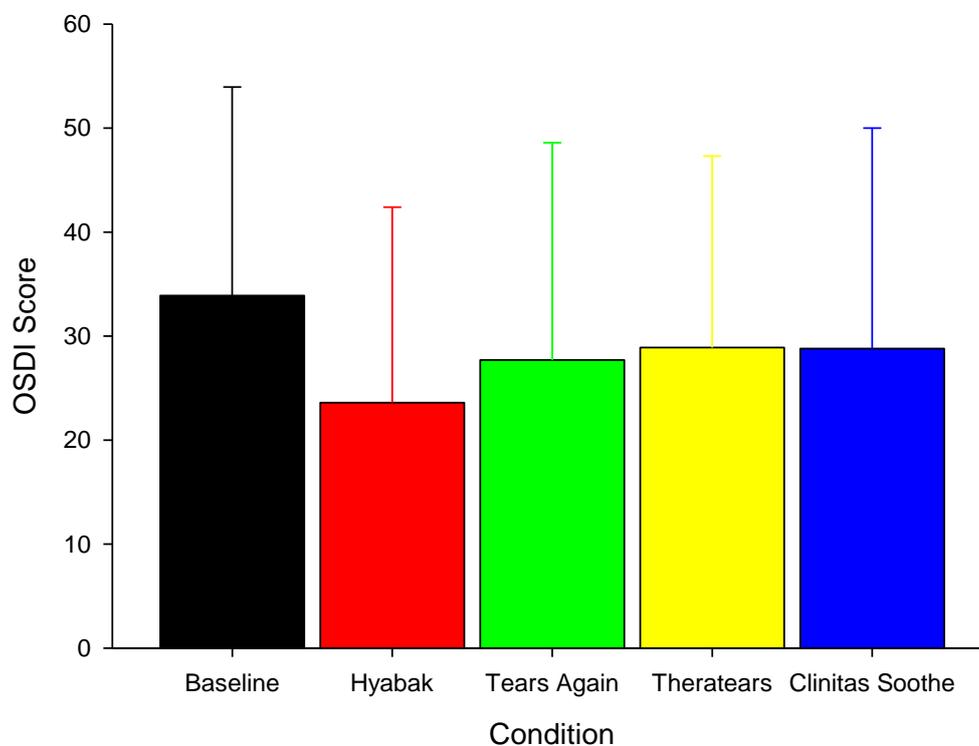
Assessment of normal distribution conducted in chapter 2 using one-Sample Kolmogorov-Smirnov Tests showed that only NITBUT of the metrics used in this study was normally distributed. Where data was normally distributed, the analysis of variance between tear metrics was evaluated using parametric analysis, with related-samples Friedman's two-way analysis of variance by ranks. The data were analysed using SPSS 20 software (IBM Corporation, New York, USA).

## 3.2 Results

### 3.2.1 Artificial Tear Comparison

#### 3.2.1.1 Ocular Comfort

OSDI was similar after treatment with each of the four artificial tear supplements (Hyabak:  $23.6 \pm 18.8$ ; Tears Again;  $27.7 \pm 20.9$ ; TheraTears:  $28.9 \pm 18.4$ ; Clinitas Soothe:  $28.8 \pm 21.2$ ;  $p = 0.521$ ), however, all of the treatments showed an improvement from baseline comfort ( $33.9 \pm 20.0$ ;  $p = 0.002$ ).



**Figure 3.3:** Ocular comfort as measured by the OSDI questionnaire with the four different artificial tears used. N= 50. Error bar = 1 S.D

#### 3.2.1.2 Non-invasive break-up time

The NIBUT was similar after treatment with each of the four artificial tear supplements (Hyabak:  $13.6 \pm 2.4$ s; Tears Again;  $13.2 \pm 2.2$ s; TheraTears:  $13.3 \pm 2.4$ s; Clinitas Soothe:  $13.3 \pm 2.6$ s;  $F = 1.315$ ,  $p = 0.272$ ) and did not improve from baseline ( $13.2 \pm 1.9$ s;  $F = 0.959$ ,  $p = 0.431$ ).

#### 3.2.1.3 Tear Meniscus Height

Tear meniscus height was similar after treatment with each of the four artificial tear supplements (Hyabak:  $0.11 \pm 0.02$ mm; Tears Again;  $0.11 \pm 0.01$ mm; TheraTears:  $0.11$

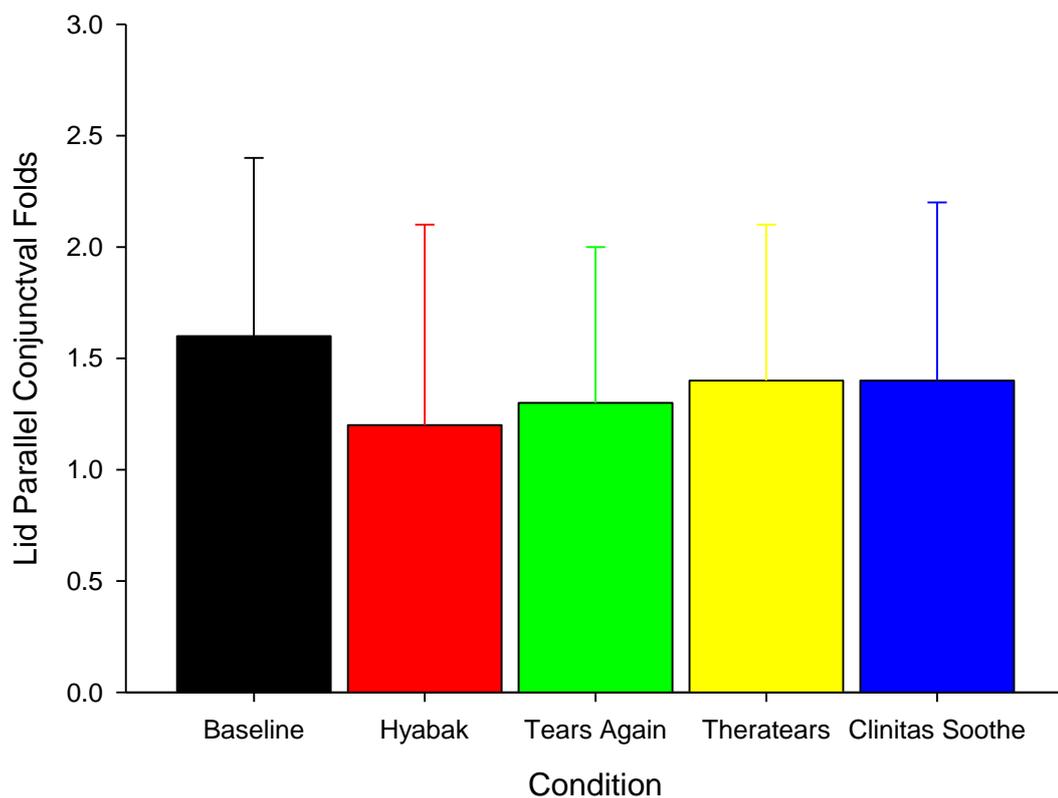
$\pm 0.01\text{mm}$ ; Clinitas Soothe:  $0.11 \pm 0.01\text{mm}$ ;  $p = 0.443$ ) and showed no improvement from baseline ( $0.11 \pm 0.02\text{mm}$ ;  $p = 0.184$ ).

### 3.2.1.4 Phenol Red Thread

Phenol red test tear volume was similar after treatment with each of the four artificial tear supplements (Hyabak:  $14.0 \pm 4.4\text{mm}$ ; Tears Again;  $14.0 \pm 4.2\text{mm}$ ; TheraTears:  $14.0 \pm 4.5\text{mm}$ ; Clinitas Soothe:  $14.1 \pm 4.6\text{mm}$ ;  $p = 0.724$ ) and showed no improvement from baseline ( $14.1 \pm 5.1\text{mm}$ ;  $p = 0.797$ ).

### 3.2.1.5 Lid Parallel Conjunctival Folds

The presence of LIPCOF was similar after treatment with each of the four artificial tear supplements (Hyabak:  $1.2 \pm 0.9$ ; Tears Again;  $1.3 \pm 0.7$ ; TheraTears:  $1.4 \pm 0.7$ ; Clinitas Soothe:  $1.4 \pm 0.8$ ;  $p = 0.688$ ) and while there was no improvement from baseline ( $1.6 \pm 0.8$ ;  $p = 0.055$ ), this approached statistical significance.



**Figure 3.4:** LIPCOF with the four different artificial tears used. N= 50. Error bars = 1 S.D.

### 3.2.1.6 Invasive Break-up Time

The NaFL TBUT was similar after treatment with each of the four artificial tear supplements (Hyabak:  $13.7 \pm 2.7\text{s}$ ; Tears Again;  $13.7 \pm 2.4\text{s}$ ; TheraTears:  $13.8 \pm 2.4\text{s}$ ;

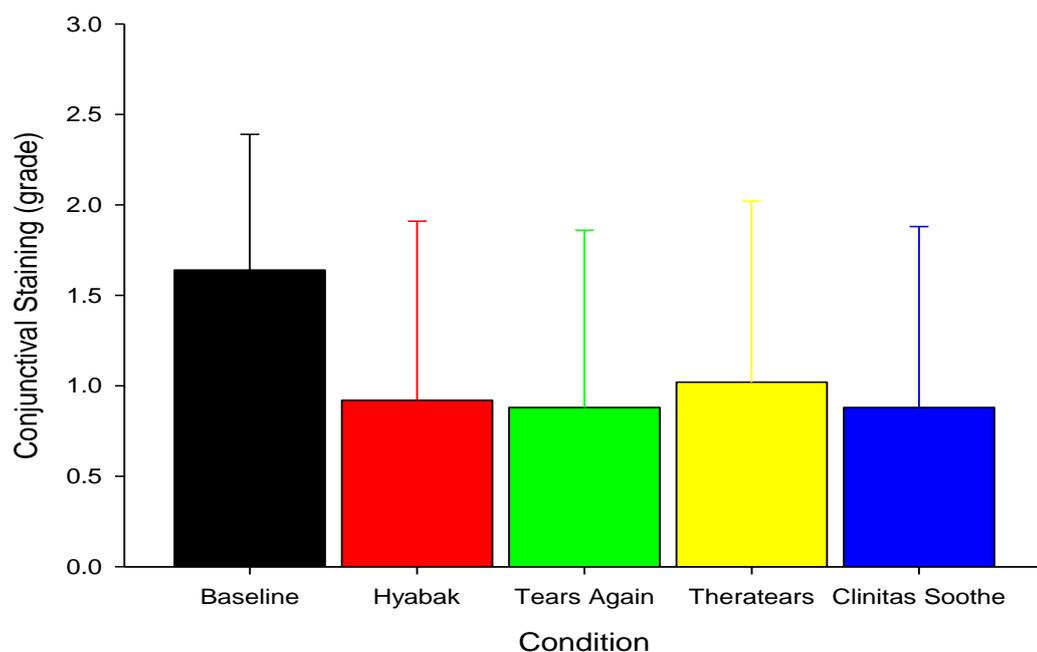
Clinitas Soothe:  $13.5 \pm 2.7s$ ;  $p = 0.225$ ) and showed no improvement from baseline ( $13.2 \pm 2.4s$ ;  $p = 0.588$ ).

### 3.2.1.7 Corneal Staining

The presence of corneal staining was similar after treatment with each of the four artificial tear supplements (Hyabak:  $0.08 \pm 0.40$ ; Tears Again;  $0.00 \pm 0.00$ ; TheraTears:  $0.12 \pm 0.44$ ; Clinitas Soothe:  $0.04 \pm 0.30$ ;  $p = 0.137$ ) and showed no improvement from baseline ( $0.08 \pm 0.27$ ;  $p = 0.218$ ).

### 3.2.1.8 Conjunctival Staining

The presence of conjunctival staining was similar after treatment with each of the four artificial tear supplements (Hyabak:  $0.92 \pm 0.99$ ; Tears Again;  $0.88 \pm 0.98$ ; TheraTears:  $1.02 \pm 1.00$ ; Clinitas Soothe:  $0.88 \pm 1.00$ ;  $p = 0.752$ ) however, all of the treatments showed an improvement from baseline ( $1.64 \pm 0.75$ ;  $p = 0.000$ ).



**Figure 3.5:** Conjunctival Staining with the four different artificial tears used. N= 50. Error bars = 1 S.D.

### 3.2.1.9 Overall Subjective Rating

#### 3.2.1.9.1 Overall Comfort comparing the drops preferred

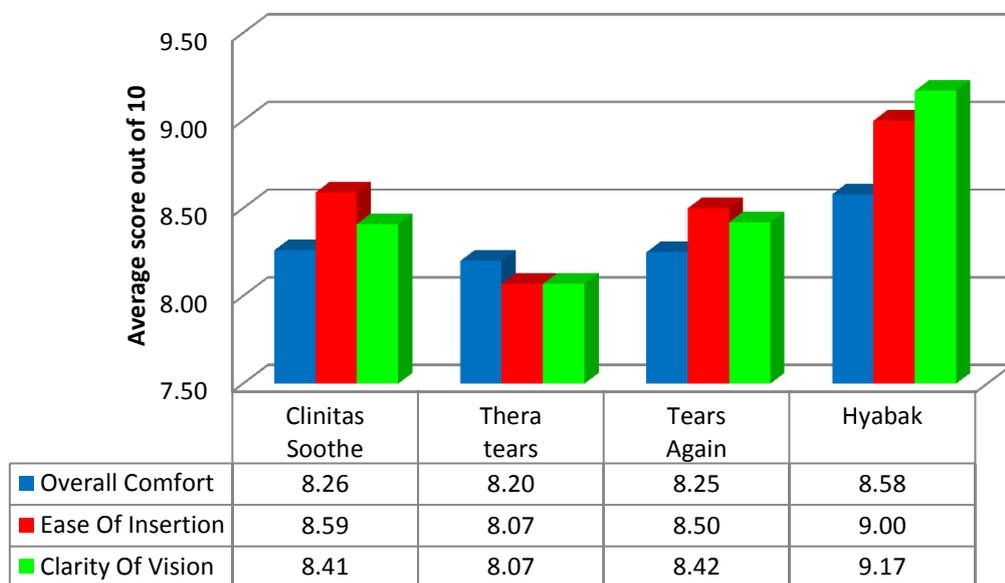
Each of the four artificial tear supplement treatments had similar results of overall comfort of the drops (Hyabak:  $8.6 \pm 1.0$ ; Tears Again;  $8.3 \pm 1.0$ ; TheraTears:  $8.2 \pm 1.5$ ; Clinitas Soothe:  $8.3 \pm 1.2$ ;  $p = 0.117$ ).

### 3.2.1.9.2 Overall Ease of Insertion the drops preferred

In totality the ease of insertion of the drops was comparable after treatment of each of the four artificial tear supplements (Hyabak:  $9.0 \pm 1.3$ ; Tears Again;  $8.5 \pm 1.1$ ; TheraTears:  $8.1 \pm 1.7$ ; Clinitas Soothe:  $8.6 \pm 1.1$ ;  $p = 0.233$ ).

### 3.2.1.9.3 Clarity of vision after use the drops preferred

The overall result of clarity of vision after instilling drops was similar upon treatment with each of the four artificial tear supplements (Hyabak:  $9.2 \pm 1.2$ ; Tears Again;  $8.4 \pm 1.1$ ; TheraTears:  $8.1 \pm 1.7$ ; Clinitas Soothe:  $8.4 \pm 1.5$ ;  $p = 0.091$ ).

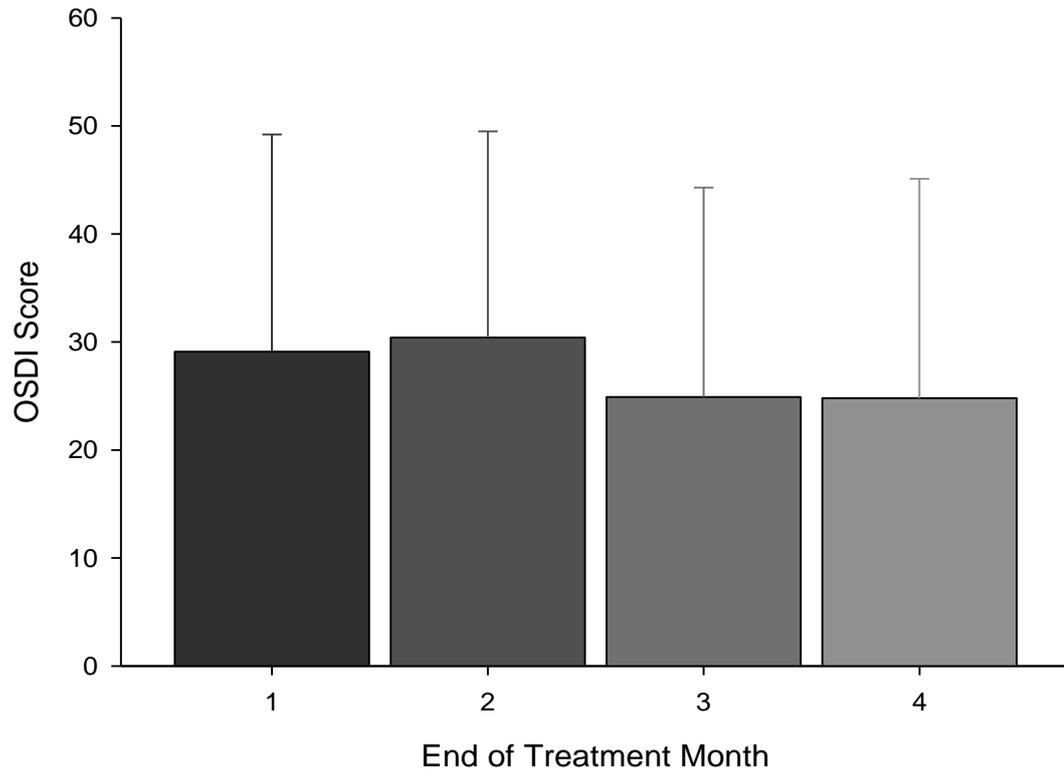


**Figure 3.6:** Average score out of 10 for the overall comfort, ease of insertion and clarity of vision, for the patients who preferred for Clinitas Soothe, TheraTears, Tears Again and Hyabak. N=50.

## 3.2.2 Treatment Effect with Time

### 3.2.2.1 Ocular Comfort

OSDI was showed a significant treatment effect with time ( $p = 0.041$ ) between the first 2 months (end of month 1:  $29.1 \pm 20.1$ ; end of month 2;  $30.4 \pm 19.1$ ) and second 2 months (end of third month:  $24.9 \pm 19.4$ ; end of fourth month:  $24.8 \pm 20.3$ ).



**Figure 3.7:** Ocular comfort as measured by the OSDI questionnaire over treatment months. N = 50. Error bars = 1 S.D.

### 3.2.2.2 Non-invasive break-up time

NIBUT showed no treatment effect with time (end of first month:  $13.2 \pm 2.4$ s; end of second month;  $13.3 \pm 2.3$ s; end of third month:  $13.4 \pm 2.5$ s; end of fourth month:  $13.6 \pm 2.4$ s;  $F = 1.584$ ,  $p = 0.196$ ).

### 3.2.2.3 Tear Meniscus Height

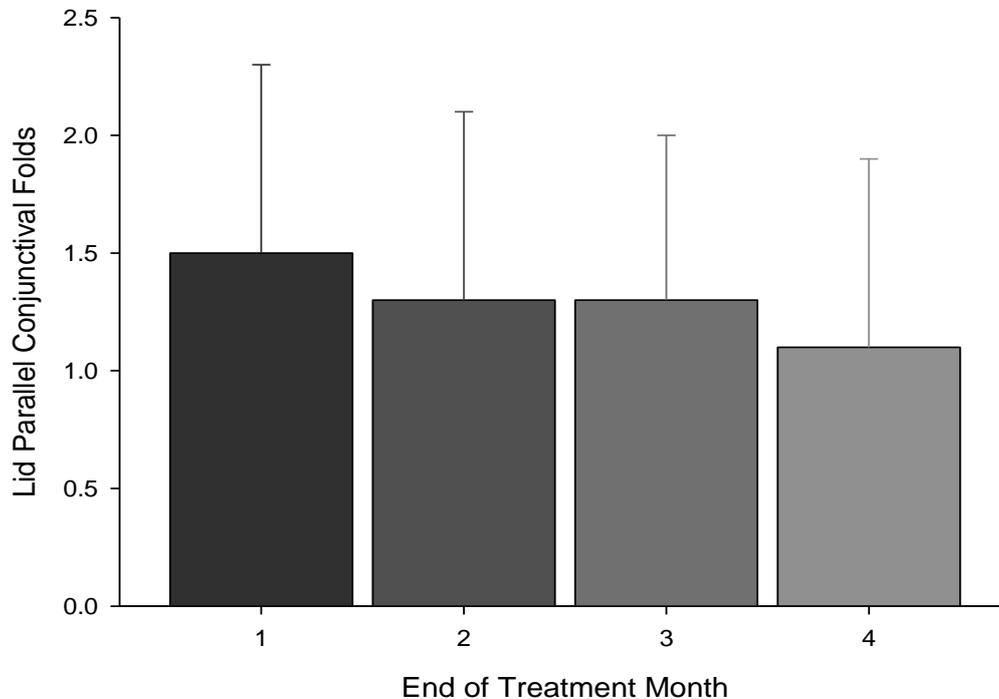
Tear meniscus height showed no treatment effect with time (end of first month:  $0.11 \pm 0.01$ mm; end of second month;  $0.11 \pm 0.01$ mm; end of third month:  $0.11 \pm 0.01$ mm; end of fourth month:  $0.11 \pm 0.01$ mm;  $p = 0.289$ ).

### 3.2.2.4 Phenol Red Thread

Phenol red tear volume showed no treatment effect with time (end of first month:  $14.3 \pm 4.7$ mm; end of second month;  $14.2 \pm 4.2$ mm; end of third month:  $14.2 \pm 4.3$ mm; end of fourth month:  $13.4 \pm 4.2$ mm;  $p = 0.221$ ).

### 3.2.2.5 Lid Parallel Conjunctival Folds

Lid parallel conjunctival folds showed a treatment effect with time (end of first month:  $1.5 \pm 0.8$ ; end of second month;  $1.3 \pm 0.8$ ; end of third month:  $1.3 \pm 0.7$ ; end of fourth month:  $1.1 \pm 0.8$ ;  $p = 0.038$ ) with the significant different being from the first to the fourth month of treatment only ( $p = 0.014$ ).



**Figure 3.8:** LIPCOF over treatment time. N = 50. Error bars = 1 S.D.

### 3.2.2.6 Invasive Break-Up Time

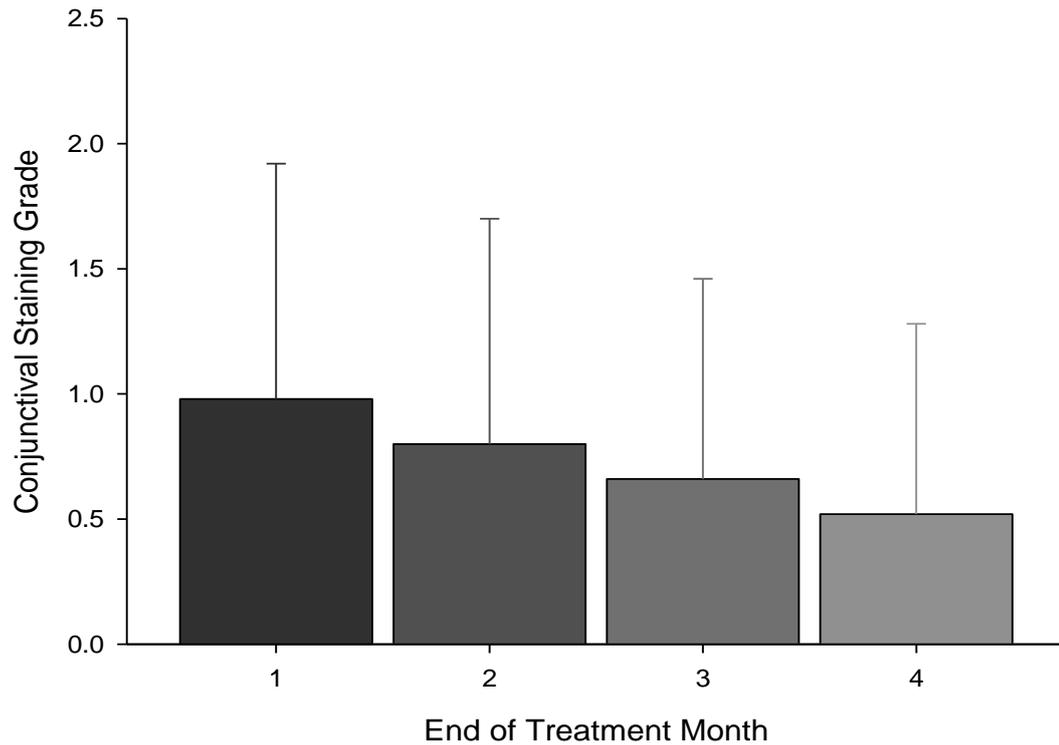
Invasive break-up time showed no treatment effect with time (end of first month:  $13.3 \pm 2.7$  seconds; end of second month;  $13.6 \pm 2.4$  seconds; end of third month:  $13.9 \pm 2.5$  seconds; end of fourth month:  $13.9 \pm 2.5$  seconds;  $p = 0.259$ ).

### 3.2.2.7 Corneal Staining

Corneal staining showed no treatment effect with time (end of first month:  $0.06 \pm 0.24$ ; end of second month;  $0.02 \pm 0.14$ ; end of third month:  $0.04 \pm 0.20$ ; end of fourth month:  $0.02 \pm 0.14$ mm;  $p = 0.629$ ).

### 3.2.2.8 Conjunctival Staining

Conjunctival staining showed a treatment effect with time (end of first month:  $0.98 \pm 0.94$ ; end of second month;  $0.80 \pm 0.90$ ; end of third month:  $0.66 \pm 0.80$ ; end of fourth month:  $0.52 \pm 0.76$ ;  $p = 0.012$ ) with the significant different being from the first to the fourth month of treatment only ( $p = 0.002$ ).



**Figure 3.9:** Conjunctival Staining over treatment time. N = 50. Error bars = 1 S.D.

### 3.2.2.9 Overall subjective Rating

#### 3.2.2.9.1 Overall Comfort

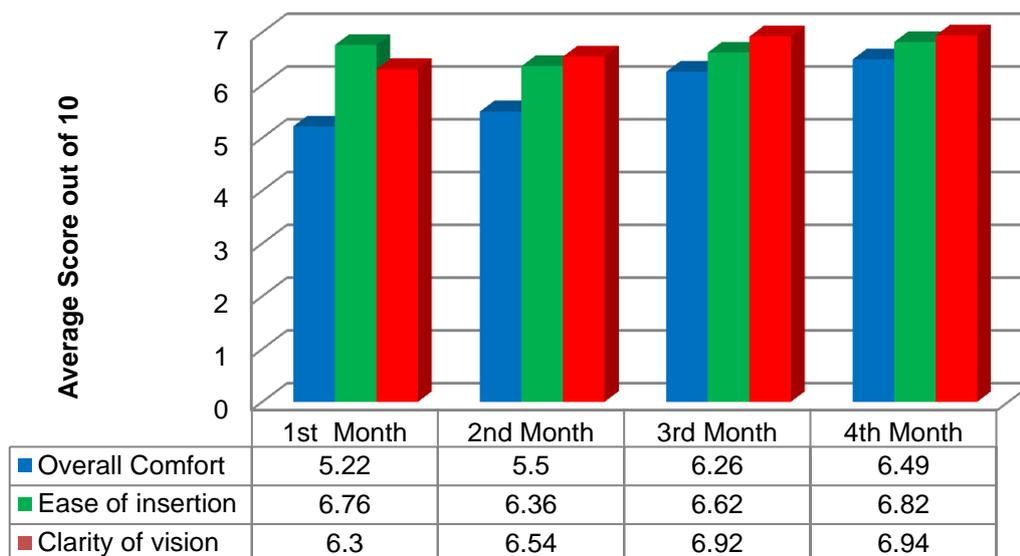
The overall comfort of the drops significantly improved with time (end of first month:  $5.2 \pm 2.9$ ; end of second month;  $5.5 \pm 2.8$ ; end of third month:  $6.26 \pm 2.6$ ; end of fourth  $6.5 \pm 2.2$ ;  $p = 0.003$ ; Figure 3.10).

#### 3.2.2.9.2 Overall Ease of Insertion

The overall ease of insertion of the drops was similar over the 4 month treatment period (end of first month:  $6.8 \pm 2.4$ ; end of second month;  $6.4 \pm 2.4$ ; end of third month:  $6.6 \pm 2.2$ ; end of fourth  $6.8 \pm 2.1$ ;  $p = 0.339$ ; Figure 3.10).

#### 3.2.2.9.3 Clarity of vision after use

The overall clarity of vision after instilling the drops improved with time (end of first month:  $6.3 \pm 2.6$ ; end of second month;  $6.5 \pm 2.3$ ; end of third month:  $6.9 \pm 2.2$ ; fourth  $6.9 \pm 1.9$ ;  $p = 0.036$ ; Figure 3.10).



**Figure 3.10:** Average score out of 10 for the overall comfort, ease of insertion and clarity of vision, when rated at the end of each month, by all patients. N=50.

### 3.3 Discussion

The aim of this chapter was to determine the relative effectiveness of the different categories of tear supplements as identified in the introduction (Chapter 1) as none or very little work has been done on determining the most effective treatment for an individual at diagnosis for dry eye disease. Dry eye disease was previously considered candidly as a nuisance to some patients, and was managed with various forms of soothing treatments (Volker-Dieben et al., 1987). However, dry eye is presently considered a condition worthy of substantial attention with regards to patient well-being and a considerable patient benefit can be achieved from active and timely intervention (Reddy et al., 2004).

On the whole, dry eye treatments are available as general sales list (GSL) products or pharmacy (P) medicines and therefore Optometrists registered in the UK can sell and supply these products to their patients (Doughty, 2007). Therefore with such great access to various artificial tear supplements and ocular lubricant products, it is important to know what the relative effectiveness of different product types as well as the evidence demonstrating that the treatment has actually improved the dry eye condition for the patient. Previous studies have generally only compared a single tear supplement to a placebo i.e. saline (Mengher et al., 1986; Condon et al., 1999; Craig et al., 2010). Some studies have only compared more than one artificial tear supplement in the same category (in terms of key ingredient), but not cross-category (Aragona et al., 2002; Aragona et al., 2002; Dieter et al., 2006; Pult et al., 2012). The number of

patients used in the trials have also been varied from as little as 10 patients (Mengher et al., 1986) to 80 (Pult et al., 2012). The period of application of these various treatments has also ranged widely from as little as 10 minutes (Pult et al., 2012) to 3 months (Aragona et al., 2002). Table 3.3 represents a comparison of these trials.

The greatest advantage of this study in comparison to the ones that have been represented in table 3.3 is that a total of 4 different artificial eye drops were used by the patients in a randomised order. A total of 3 different categories of key ingredients were examined (Sodium Hyaluronate, Liposomal Spray and Sodium Carboxymethylcellulose). The patients were asked to trial these drops for 1 month at a time and the total time of the study was 4 months. The number of tests performed at baseline and subsequent visits was greater than previous studies measuring symptomology as measured by OSDI, and evaluation of dry eye signs with NIBUT, NaFL TBUT, TMH, PRT wetting, LIPCOF, corneal and conjunctival staining. Patients were also advised to 'rate their favourite drops' in order to ascertain if subjective and objective preferences were the same for these subjects.

| Study                 | Drops Used                                                                     | Tests compared                                                                                                                                                 | Method                                                    | Number & type of patients   | Period of application | Conclusions                                                                                                             |
|-----------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-----------------------------|-----------------------|-------------------------------------------------------------------------------------------------------------------------|
| Mengher et al., 1986. | Sodium Hyaluronate (0.1%) Vs Sodium Chloride (0.9%)                            | Non Invasive tear film stability (NIBUT) & symptoms                                                                                                            | A cross over double masked clinical trial.                | 10 dry eyes                 |                       | Tear film stability significantly increased and symptoms decreased in eyes treated with sodium hyaluronate.             |
| Condon et al., 1999.  | Sodium Hyaluronate 0.1% Vs Saline 0.9%                                         | Schirmer, Rose Bengal Staining, Subjective assessment                                                                                                          | A randomised, double blind, crossover clinical trial      | 70 dry eye                  | 28 days               | Clear benefit of hyaluronan over saline, in both subjective and objective assessment. Hyaluronan well tolerated         |
| Aragona et al., 2002. | Hypotonic 0.4% Hyaluronate eye drops; & isotonic 0.4% Hyaluronate              | Subjective symptoms, break up time (BUT), corneal fluorescein staining, conjunctival rose bengal staining, Schirmer I test, & conjunctival impression cytology | Non- crossover but masked observer                        | 40 Sjögren's                | 90 days               | Pronounced hypo tonicity formulation showed better effects on corneo conjunctival epithelium than the isotonic solution |
| Aragona et al., 2002. | Sodium Hyaluronate Vs Saline                                                   | Bulbar impression cytology, slit lamp examinations, and subjective symptoms                                                                                    | Non- crossover randomised double blind study              | 86 medium to severe dry eye | 3 months              | Sodium hyaluronate improved ocular surface damage associated with dry eye syndrome                                      |
| Dieter et al., 2006.  | Liposomal eye spray Tears Again®, Vs eye gel containing triglycerides Liposic® | LIPCOF, BUT, Schirmer-I Test, tear meniscus, eyelid edge inspection, visual acuity, subjective feelings                                                        | The randomised, controlled, multi centre cross-over study | 74 dry eye                  | 6 weeks               | Phospholipid-liposomes outperformed viscous gels.                                                                       |

**Table 3.3:** Representing a comparison of studies trialling different artificial eye drops. The studies trialled different eye drops; comparing various dry eye tests utilising different methodology, with varying ages; varied levels of dry eye; with different treatment periods.

The DEWS report (2007) has suggested that the ideal artificial lubricant should be preservative-free, contain potassium, bicarbonate, and other electrolytes and have a polymeric system to increase its retention time (Gilbard et al., 1989; Holly et al., 1971; Grene et al., 1992; Ubels et al., 1995). The physical properties should include a neutral to slightly alkaline pH. Osmolarities of artificial tears have been measured to range from 181 to 354 mOsm/L (Perrigan et al., 2004). It is a requirement of the FDA that multi dose artificial tears contain preservatives to prevent microbial growth (Kaufman et al., 2003). However, preservatives such as Benzalkonium Chloride (BAK), which is the most frequently, used preservative in topical ophthalmic preparations and lubricant has epithelial toxic effects (Gasset et al., 1974; Wilson, 1979; Burstein 1980; 1984; Brubaker et al., 1985; Smith et al., 1991). BAK can damage the corneal and conjunctival epithelium, affecting cell-to-cell junctions and cell shape and microvilli, eventually leading to cell necrosis with sloughing of 1-2 layers of epithelial cells (Smith et al., 1991). Therefore preservative-free formulations are necessary for patients with severe dry eye (DEWS, 2007). Hence this study examined non-preserved drops with the key component categories identified in the introduction chapter (See section 1.7).

The literature suggests that each of the types of artificial tears used in this study should have a beneficial effect on dry eyes. Viscous agents such as hyaluronic acid contained in Clinitas Soothe and Hyabak protect the ocular surface epithelium. Agents such as hydroxymethylcellulose (HMC), which decrease rose bengal staining in dry eye subjects, (Versura et al., 1989) may either “coat and protect” the surface epithelium or help restore the protective effect of mucins. Artificial tear solutions containing electrolytes and or ions such as TheraTears have been shown to be beneficial in treating ocular surface damage due to dry eye (Gilbard et al., 1989; 1992; Bernal et al., 1993; Nelson et al., 1994; Ubels et al., 1995). Potassium and bicarbonate seem to be the most critical (DEWS, 2007). Potassium is important to maintain corneal thickness (Grene et al., 1992). In a dry eye rabbit model, a hypotonic tear-matched electrolyte solution (TheraTears® [Advanced Vision Research, Woburn, MA]) increased conjunctival goblet cell density and corneal glycogen content, and reduced tear osmolarity and rose bengal staining after 2 weeks of treatment (Gilbard et al., 1992). Bicarbonate containing solutions promote the recovery of epithelial barrier function in impaired corneal epithelium and aid in maintaining normal epithelial ultra-structure. They may also be important for maintaining the mucin layer of the tear film (Ubels et al., 1995).

Most clinical trials involving topical lubricant preparations will document some improvement (but not resolution) of subjective symptoms and improvement in some objective parameters (Nelson et al., 1992) as was found in this study. However, there are no studies suggesting whether tear drops which have different key ingredients, are similar in performance or not. However, Doughty and Glavin (2009) objectively reviewed the outcome of clinical studies where rose bengal (RB) stain was used as an outcome measure to assess the efficacy of artificial tears (AT) in patients with dry eye. Information was searched for on dry eye status, as reported using a grading scheme, after use of RB as a diagnostic test, before and after use of a specific regimen of artificial tears or ocular lubricants for approximately 30 days. The mean baseline scores and post-treatment scores were calculated, along with the net change and the percentage change in the RB scores (Doughty and Glavin, 2009). There is far less published information on how treatment with artificial tears or ocular lubricants might alter or improve any other staining of the conjunctiva or cornea with an alternative to RB stain (e.g. lissamine green) (Doughty and Glavin, 2009). While lissamine green might be being considered for routine use (Versura et al., 2006), there is a lack of similar analyses and work still to be done to establish normal values for lissamine green staining and its use as a measure for treatment outcomes (Doughty and Glavin, 2009). Rose Bengal is no longer widely available and was toxic to the eye, so previous studies of effectiveness will prove difficult to compare with future research. Doughty and Glavin, (2009) also reported that with RB grading schemes used by numerous different clinicians over the years, the treatment of dry eye with artificial tears or ocular lubricants can be expected to improve the condition of the exposed ocular surface. Assuming no improvement without treatment, the evidence from their review of the literature suggests 30 days treatment period can be projected to produce an overall improvement of around 25%, but with no unambiguous statistical differences between product types.

In Chapter 2, it has been shown that Lid Parallel Conjunctival Folds (LIPCOF) and conjunctival staining as measured by lissamine green are significantly correlated to one another, corneal staining, tear osmolarity and is significantly correlated to tear stability as measured by NIBUT, NaFL TBUT and tear volume measured by TMH and PRT test.

In this study, the patients were asked to continue using their artificial tears continuously, without a 'wash out' phase; in order to prevent the patients from discomfort without the use of artificial eye drops. The results identified that the LIPCOF showed a treatment effect with time, with a significant difference being from the first month to the fourth month of treatment, suggesting an improvement over time of the

conjunctival surface. The presence of conjunctival staining as measured by Lissamine green was found to be similar with each of the different artificial eye drops, however this dry eye metric showed a statistical improvement from baseline measurements, suggesting that the conjunctival ocular surface improves significantly with time with the use of artificial eye drops. These two measures (LIPCOF and conjunctival staining) appear to be the most sensitive measures of ocular surface dry eye related damage may be this remarkable as patients with low grades of conjunctival staining and LIPCOF were excluded. Certain percentage of patients with low degrees of LIPCOF and conjunctival staining who mentioned the improvement was much lower than of those with higher degrees of LIPCOF and conjunctival staining. Furthermore, not having observed the lipid layer with the tearscope, or the lids and meibomian glands with slit lamp, may be some weakness of this study, especially in terms of the use of Tears Again liposomal spray. The stability of the tear film may improve with better conjunctival tissue in terms of mucins as well as the tear lipid layer. The tear lipid layer can improve when meibomian gland secretion is treated, but not using a liposomal spray solely. The stability of the tears did not appear to show much improvement possibly due to the fact that the tear lipid layer contributes to the stability of the tear film. The tear film volume did not improve with time; the tear volume normally does not increase due to drops when observing the tear film the day after instillation.

It does not seem to matter much which drops are being used by the patients, as there appeared to be a significant difference (improvement) in appearance of the conjunctival tissue from the first month to the fourth and final month and an improvement from baseline measurements regardless of which drops were being used. These results show that long term use of artificial eye drops have an improvement on the ocular surface.

### **3.4 Conclusion**

Therefore from the results it can be deduced that artificial tear supplements do work for ocular comfort, and by observing the ocular surface an improvement in the conjunctival tissue as observed by the presence of LIPCOF and conjunctival folds. However, there does not seem to be an improvement in the tear film quality or volume despite the fact that the conjunctival tissue appears to show an improvement, which one would expect would provide better mucus layer which should in turn support the tear film. The stability of the tears also relies on a healthy tear lipid layer, which can improve with meibomian gland treatment and not just the Liposomal spray. The tear volume does not normally increase due to the use of artificial eye drops when observing the tears

the day after instillation. However, this study was only conducted over a four month period and if it was continued for a longer period the tear stability and volume would be expected to improve. It would also be beneficial to have a four day 'wash out' period before patients starting treatment of the next set of artificial tear supplements. Observation of the lids and meibomian gland dysfunction would also be greatly beneficial.

There does not seem to be any strong evidence of one class of artificial tear supplement treatment, being more effective than the others. The ocular comfort appeared to improve and so did the presence of conjunctival folds; however this was between all four treatments not between any specific treatments. The patients used these drops for one month and then carried on to use another tear supplement for the next month, with no wash-out period as it is difficult ethically to leave dry eye patients with no treatment. The data suggests that these improvements can be more due to the time rather than the specific drops.

The positive effect of the treatment appears to be significant within the first month, and the ocular signs of the conjunctival tissue, is significant over the four month trial period. This chapter looks at overall effect for a subject group, though the most important factor is that the practitioner can identify whether the patient that he / she is treating might benefit more from one treatment than another which will be investigated in chapter 4.

## **CHAPTER 4**

### **Ability to Predict Patient Preference for Artificial Tears**

#### **4.0 Introduction**

Dry eye disease is a common ocular disease resulting in visual disturbances, ocular discomfort and that result in affecting the quality of life of patients (Lin et al., 2014). Dry eye disease has several different factors involving tear film instability, increased tear film osmolarity and inflammation of the ocular surface causing potential damage to the ocular surface (DEWS, 2007). There are different classifications and diagnostic approaches for dry eye as discussed in detail in chapter 1.

There are currently a few therapies available for dry eye patients (DEWS, 2007). As the aims of dry eye treatment is to improve patient symptoms and signs there are a few treatment options available in order to achieve this. They are listed below:

- To improve tear volume by use of aqueous supplements (DEWS, 2007; Matheson, 2007; Farrell, 2010)
- To improve the quality of the tear mucous layer by TheraTears (Matheson, 2007)
- Improve the tear film lipid layer by diet, lid hygiene, hot compresses, tetracyclines, liposomal sprays (Dieter et al., 2006; DEWS, 2007; Matheson, 2007; DEWS, 2007; Geerling et al., 2011)
- Reduce tear drainage by punctal plugs (Dieter et al., 2006; DEWS, 2007; Matheson, 2007; Lin et al., 2014)
- Reduce tear evaporation by improvements to the tear lipid layer and paraffin ointment (DEWS, 2007, Matheson, 2007; Farrell, 2010)
- Reduce inflammation by the use of Omega 3, steroids, NSAIDs, anti-allergy products (DEWS, 2007; Matheson, 2007; Lin et al., 2014)

Other dry eye therapies include hormonal therapy which has reported an increase in tear production and tear lipid layer thickness and reduced symptoms by patients (Sator et al., 1998; Worda et al., 2001). Autologous serum has been indicated in the application of severe dry eye disease (Yoon et al., 2007) as it contains substances which support the proliferation and maturation of the normal ocular surface (Celebi et al., 2014). Acupuncture as a treatment for dry eye disease, has been based on reports which claim that acupuncture modulates both the autonomic nervous and immune systems (Kavoussi et al., 2007; Bäcker et al., 2008) which result in regulating the

function of the lacrimal gland. It is possible that salivary submandibular gland transplantation can replace deficient mucin and the aqueous tear film (DEWS, 2007). Patients have reported a subjective relief in their dry eye symptoms immediately after surgery (Soares et al., 2005).

It has been recommended that the primary factor for the therapeutic management of dry eye patients should be considered according to patients' symptoms and signs, not clinical tests and the best combination of medications to avoid symptoms (Behrens et al., 2006).

A cure for dry eye disease has still to be found (Farrell, 2010). Currently treatment objectives are directed towards either 'tear replacement' or 'tear retention', and are aimed principally at relieving the subjective symptoms associated with this condition (Farrell, 2010). Nevertheless, the underlying treatment goals will always be aimed at appropriate healing, epithelialisation, and the reestablishment of a normal ocular surface (Göbbels et al., 1992). In order to select the most appropriate treatment option the cause and severity of the dry eye should be established, and the management plan chosen to effectively target the nature of the condition.

An assessment of dry eye in patients wanting to wear contact lenses should be used as an indicator of when to strongly promote enhanced wetting lenses and to warn patients of potential issues, prompting a more frequent review schedule (Wolffsohn, 2014). Individual clinical dry eye tests such as non-invasive tear break-up time (NIBUT), tear meniscus height (TMH), phenol red test (PRT) and lid-parallel conjunctival folds (LIPCOF) are moderately related to self-rated ocular surface symptoms (as evaluated by the ocular surface disease index), but the strongest predictor of contact lens induced dry eye was a combination of NIBUT and nasal LIPCOF (Pult et al., 2011).

There are few peer review journal articles investigating the efficacy of numerous dry eye treatments with artificial tears or ocular lubricants (see table 3.3 in the previous chapter which reviews the pertinent studies). However, Doughty and Galvin (2009) objectively reviewed the outcome of clinical studies where rose bengal stain has been used as an outcome measure to assess the efficacy of artificial tears in patients with dry eye. They identified 33 suitable data sets when searching for journals from 1947 to 2008, and chose to use the rose bengal test for these analyses because of the long history of its use, hence providing the maximum chance of obtaining enough published data to see if any consistent differences could be seen between products. They

concluded that based on rose bengal grading schemes used by numerous different clinicians over the years, treatment of dry eye with artificial tears or ocular lubricants can be expected to improve the condition of the exposed ocular surface. Assuming no improvement without treatment, a 30 days treatment period can be projected to produce an overall improvement of around 25%, but with no un-ambiguous statistical differences between product types.

The U.S. Food and Drug Administration (FDA) have been interested in understanding the full extent of a patient's treatment experience as it applies to their day-to-day life and assessing their quality of life (Marquis et al., 2003). Clinicians, pharmaceutical companies and the scientific community are involving their patients when they evaluate their treatment and the value of the treatment that they are receiving (Mertzanis et al., 2005). It has been reported that dry eye patients can become frustrated with the development of their treatment with regular specialist visits and seeking treatment changes, and may well pursue alternative treatments (Thomas et al., 1998; Schiffman et al., 2000). Additionally, these dry eye patients have reported not attending for work, often losing approximately 5 working days per year with their dry eye symptoms (Schiffman 2000).

Optometrists in the UK have various prospects to develop their own interests and skills in the diagnosis and management of dry eye. The Clinical Management Guidelines (CMGs) of the College of Optometrists lists this condition as Tear Deficiency (Keratoconjunctivitis sicca) (accessed at [www.college-optometrists.org](http://www.college-optometrists.org)). Therefore, this management will allow for optometrists with suitable re-imburement, to undertake detailed assessments of dry eye and to be in an excellent position care for these patients (Doughty, 2010).

Currently there are three diplomas offered by the College of Optometrists which allow optometrists to prescribe additional medications (Needle et al., 2008). They are:

- Independent prescribing
- Supplementary prescribing
- Additional supply

Optometrists who have qualified to be an independent or supplementary prescriber can now have formalised prescribing rights (i.e. having a medicines prescription pad). Optometrists can, therefore encourage patient acceptance that their optometrists can

be their regular source of dry eye products. Optometrists can sell these dry eye products to their patients along with instructions on use of these products.

There are currently various co-management schemes in the community of patients with glaucoma, diabetes and cataracts by optometrists as well as the management of low vision (Margrain et al., 2005) and paediatric optometry (Karas et al, 1999). A survey conducted by Mason et al., (2002), reported that 26% of referrals by optometrist to the hospital eye service was due to anterior eye conditions (conjunctivitis, blepharitis and dry eyes), indicating a strong case to develop a co-management community dry eye scheme. Other reasons for referral in to the hospital eye service were suspected cataract (33%), glaucoma (13%) and retinopathy (10%) (Mason et al., 2002).

There is no evidence currently indicating whether patients would be willing to pay for a community based dry eye service. However, funding from the local clinical commissioning groups (CCG) could be sought in order to provide a better service for patients in the community. Evidence also suggests having once received care from optometrists, 55% of patients favoured to consult with their optometrist in future compared with 15% of patients who preferred to consult a GP (Chambers and Fisher, 1998). On the other hand, research conducted in the older population recognised that a worry about the costs would prevent them from attending for regular sight tests, although they are entitled to a free eye examination under the NHS (Smeeth, 1998). The lack of patient knowledge with regards to eye health, not understanding an optometrists' role as well as affordability of spectacles (Jessa et al, 2007), these could stop patients from seeking the care they require for their dry eye condition in a community based optometric practice. As a community based practice, it is always the aim to provide a great customer journey and experience. Boulding et al., (1993) reported that if customers are happy with their overall experience in the practice they would remain loyal customers.

There are foreseen complications in trying to investigate the cost of a consultation for a dry eye assessment, as the demographics age of the area in which the study was conducted was mainly over 60 years old. Patients entitled to free NHS sight tests include, over 60 years old, diabetics, glaucoma patients, low income patients, those with family history of glaucoma and complex prescriptions (College of Optometrists, 2010).

This chapter will investigate the preferred artificial tear drop chosen by the fifty subjects from the drops used in the study, namely; Clinitas Soothe, TheraTears, Tears Again

and Hyabak, and to see whether this could have been predicted from their presenting signs and symptoms or whether their choice is based on their signs and/or symptoms standing better with their preferred artificial eye drops compared to the three other artificial drops trialled. It will also investigate whether patients would be willing to pay for a dry eye community based service if it were available, and if so how much would they pay for their consultation.

#### **4.1 Methods**

As advocated by DEWS (2007), that when a battery of tests is performed, they should be performed in an arrangement that best preserves their reliability, and intervals should be left between the tests (Bron, 2001; Foulks and Bron, 2003). The tear film metrics were assessed in the following order due to the invasive nature of some tests. At baseline measurements were observed for the right eye followed by the left eye for every patient, after which on subsequent visits, only the right eye measurements were taken.

Prior to the 1 month usage of each of the artificial tears as described in chapter 3 (section 3.1.1); patients attended a baseline visit at which the same tests that were performed at the end of each month were conducted:

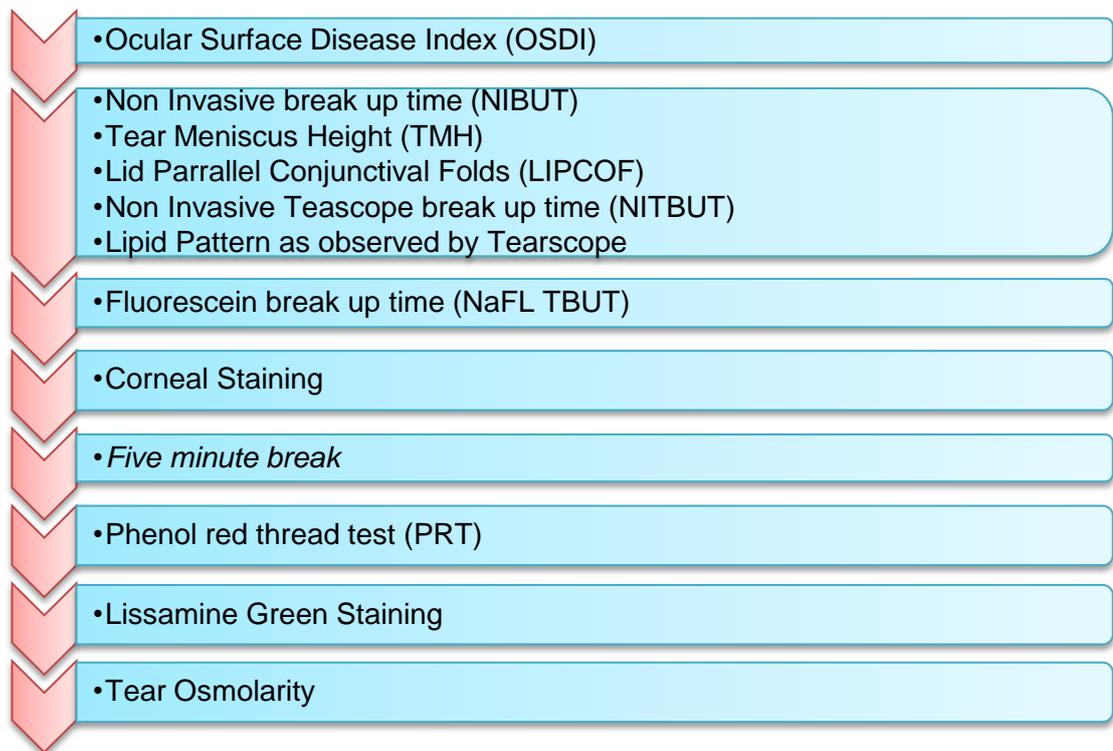
- Symptoms (OSDI)
- Non-invasive break-up time (NIBUT)
- Tear meniscus height (TMH)
- Lid Parallel Conjunctival Folds (LIPCOF)
- Fluorescein break up time (NaFL TBUT)
- Corneal staining
- Phenol red thread (PRT)
- Conjunctival staining

In addition, some more specialist tests of tear film composition and stability were performed at baseline:

- **Non-invasive Tearscope break up time (NITBUT)** - was measured using the Tearscope Plus (Keeler Ltd, Windsor, UK) in conjunction with a fine grid pattern insert mounted on a slit lamp bio-microscope (magnification 25 times) to produce an image of the fine grid pattern over the entire cornea via specular reflection. Subjects were instructed to blink normally and then keep their eyes

open for as long as possible. The NIBUT was defined as the time period between the last complete blink and the appearance of a break or distortion in the fine grid pattern (Guillon, 1998), measured using a digital stop-clock. This was repeated 3 times and the results were averaged to give a mean NITBUT value.

- **Lipid Layer Thickness** - was measured using the Tearscope Plus (Keeler Ltd, Windsor, UK) on a slit lamp bio-microscope. After blinking, the tear lipid layer is observed via specular reflection. Subjects were instructed to blink normally and then keep their eyes open for as long as possible. The observation patterns formed after a blink were compared with the pictures as provided by Keeler, as shown in figure 1.20.
- **Osmolarity** – osmolarity was measured by The TearLab (TearLab Ltd, San Diego, CA, USA). It requires only a very small volume of tears, therefore can be used in subjects with relatively dry ocular surfaces. Osmolarity is determined by measuring the impedance of an electric current passed through a very small sample of tears (< 50 nanolitres) (Sullivan, 2005). The TearLab Osmolarity System Pen was placed lightly onto the subjects lower tear meniscus from where it draws tears into the test card. An audible sound allows the practitioner to identify sufficient tears have been gathered. The "pen" was then transferred to the "TearLab Osmolarity System Reader" which analyses the collected tear sample, determining its osmolarity which it displays on its liquid crystal display (LCD; Tomlinson et al., 2006). The single use test card contains a microfluidic channel that is gently placed on the tear meniscus in the corner of the eye on the inner lower lid margin, and via passive capillary action, less than 50 nanoliters of tear sample is instantly and automatically collected when it comes in contact with tear fluid. The TearLab osmolarity test utilizes a temperature collected impedance measurement to provide an indirect assessment of osmolarity. After applying a lot specific calibration curve, osmolarity is calculated and displayed and a quantitative numerical value.



**Fig 4.1:** Summary of the tear film metrics, in the order represented due to the invasive nature of certain tests.

At the end of the study, participants were asked to state which drop of the four trialled was preferred. In addition patients were asked whether they would be willing to pay for an exclusive dry dye consultation, in their community practice, involving all the tests that were carried out in the study and then be advised appropriately on the most relevant eye drop that would grant them relief and successful treatment.

#### **4.1.2 Statistical Analysis**

The baseline characteristics of those patients that preferred each eye drops were compared with the values of those patients who preferred the other eye drops in order to determine whether their preference could have been predicted on presentation to the practice. Assessment of normal distribution conducted in chapter 2 using one-Sample Kolmogorov-Smirnov Tests showed that only NITBUT of the metrics used in that chapter was normally distributed. Of the additional measures used at baseline, osmolarity ( $Z=0.723$ ,  $p=0.672$ ) was normally distributed whereas lipid grade ( $Z=1.634$ ,  $p=0.010$ ) and Teascope derived NITBUT ( $Z =3.134$ ,  $p < 0.001$ ) was not.

For those patients that preferred each treatment type, their signs and symptoms with that treatment was compared with the treatments they did not prefer. Where data was

normally distributed, the analysis of variance between tear metrics was evaluated using parametric analysis, with related-samples Friedman's two-way analysis of variance by ranks where it was not. The data were analysed using SPSS 20 software (IBM Corporation, New York, USA).

## 4.2 Results

### 4.2.1 Drops preferred

The table below shows the total number of patients who preferred each artificial tear drops.

| Drop Preferred by Patient | Number of Patients | Number of patients in % |
|---------------------------|--------------------|-------------------------|
| Clinitas Soothe           | 17                 | 33                      |
| TheraTears                | 15                 | 31                      |
| Tears Again               | 11                 | 22                      |
| Hyaback                   | 7                  | 14                      |

**Table 4.1:** The table shows the number of patients who preferred each artificial eye drop.

### 4.2.2 Can the drop Preferred be predicted from Baseline Measures?

Table 4.2, compares the baseline characteristics of patients who preferred each drop compared to the patients who preferred other treatment. Clinitas Soothe ( $p = 0.03$ ) and Hyabak ( $p = 0.05$ ) were preferred by those with a higher Tearscope NITBUT. TheraTears ( $p = 0.01$ ) was preferred by those with a lower tear volume. Tears Again was preferred by those with a keratometer derived ( $p = 0.03$ ) or fluorescein higher TBUT ( $p = 0.01$ ), or a thinner (lower grade) lipid film layer ( $p = 0.04$ ).

|                                  | Age (yrs)   | OSDI        | NIBUT (sec) | TMH (mm)    | PRT (mm)    | LIPCOF (grade) | NaFL TBUT (sec) | Osmolarity (mOsm/L) | Tearscope NIBUT (sec) | Lipid Pattern (grade) |
|----------------------------------|-------------|-------------|-------------|-------------|-------------|----------------|-----------------|---------------------|-----------------------|-----------------------|
| <b>Clinitas Soothe</b>           |             |             |             |             |             |                |                 |                     |                       |                       |
| <b>Preferred Drop (n=17)</b>     | 58.4 ± 17.1 | 31.2 ± 19.8 | 13.5 ± 2.0  | 0.11 ± 0.02 | 16.4 ± 5.1  | 1.8 ± 0.6      | 13.3 ± 2.7      | 304.7 ± 11.2        | 8.0 ± 2.5             | 2.7 ± 0.8             |
| <b>Remaining Subjects (n=33)</b> | 62.0 ± 12.5 | 35.3 ± 20.3 | 13.1 ± 1.9  | 0.11 ± 0.02 | 13.0 ± 4.7  | 1.5 ± 0.8      | 13.1 ± 2.3      | 308.0 ± 14.30       | 7.1 ± 2.2             | 2.5 ± 1.2             |
| <b>TTest</b>                     | 0.28        | 0.12        | 0.54        | 0.95        | 0.09        | 0.06           | 0.55            | 0.49                | <b>0.03</b>           | 0.86                  |
| <b>TheraTears</b>                |             |             |             |             |             |                |                 |                     |                       |                       |
| <b>Preferred Drop (n=15)</b>     | 64.1 ± 9.5  | 35.2 ± 16.7 | 12.3 ± 2.0  | 0.11 ± 0.03 | 11.3 ± 4.8  | 1.7 ± 0.7      | 12.8 ± 2.5      | 305.6 ± 12.5        | 6.3 ± 2.2             | 2.7 ± 1.2             |
| <b>Remaining Subjects (n=35)</b> | 59.4 ± 15.7 | 33.3 ± 21.5 | 13.6 ± 1.8  | 0.11 ± 0.02 | 15.3 ± 4.8  | 1.5 ± 0.8      | 13.3 ± 2.4      | 307.4 ± 13.8        | 7.9 ± 2.2             | 2.5 ± 0.9             |
| <b>TTest</b>                     | 0.62        | 0.85        | 0.31        | 0.39        | <b>0.01</b> | 0.27           | 0.85            | 0.95                | 0.44                  | 1.00                  |
| <b>Tears Again</b>               |             |             |             |             |             |                |                 |                     |                       |                       |
| <b>Preferred Drop (n=11)</b>     | 60.6 ± 14.0 | 33.6 ± 24.5 | 13.4 ± 1.5  | 0.11 ± 0.02 | 14.1 ± 3.6  | 1.0 ± 0.9      | 13.0 ± 2.0      | 305.8 ± 10.6        | 7.9 ± 2.4             | 2.4 ± 1.2             |
| <b>Remaining Subjects (n=39)</b> | 60.8 ± 14.4 | 33.9 ± 18.8 | 13.1 ± 2.1  | 0.11 ± 0.02 | 14.2 ± 5.5  | 1.8 ± 0.7      | 13.3 ± 2.5      | 307.2 ± 14.2        | 7.3 ± 2.3             | 2.7 ± 1.0             |
| <b>TTest</b>                     | 0.94        | 0.46        | <b>0.01</b> | 0.57        | 0.77        | 0.05           | <b>0.03</b>     | 0.51                | 0.08                  | <b>0.04</b>           |
| <b>Hyabak</b>                    |             |             |             |             |             |                |                 |                     |                       |                       |
| <b>Preferred Drop (n=7)</b>      | 64.8 ± 11.0 | 40.5 ± 24.2 | 14.0 ± 2.0  | 0.12 ± 0.02 | 16.8 ± 6.2  | 1.8 ± 0.8      | 13.7 ± 2.7      | 311.3 ± 23.1        | 8.12 ± 1.87           | 2.2 ± 0.8             |
| <b>Remaining Subjects (n=43)</b> | 60.2 ± 14.6 | 32.9 ± 19.6 | 13.1 ± 1.9  | 0.11 ± 0.02 | 13.8 ± 4.9  | 1.6 ± 0.8      | 13.1 ± 2.4      | 306.2 ± 11.7        | 7.3 ± 2.4             | 2.7 ± 1.1             |
| <b>TTest</b>                     | 0.18        | 0.31        | 0.12        | 0.14        | 0.34        | 0.47           | 0.08            | 0.90                | <b>0.05</b>           | 0.53                  |

**Table 4.2:** Table showing the Age, Ocular Surface Disease Index (OSDI), Non-Invasive break up time (NIBUT sec), Tear Meniscus Height (TMH mm), Phenol Red Thread (PRT mm), Lid Parallel Conjunctival Folds (LIPCOF), Invasive break up time (NaFL TBUT sec), Tear Lab (mOsm/L), Tear scope break up time (sec) and lipid pattern for the 50 baseline subjects and then for the respective drops preferred by the subjects; Clinitas Soothe, TheraTears, Tears Again, Hyabak. (Average ± S.D.).

### 4.2.3 Does the preferred drop fit with the dry eye cluster subgroup?

Looking at the results from the cluster analysis performed for 5 clusters as described in chapter 2, it was found that the distribution of preference for each particular drop taken did not appear differ between the individual clusters (Table 4.3).

| Preferred Drops        | Cluster                             |   |   |   |    |    |
|------------------------|-------------------------------------|---|---|---|----|----|
|                        | Total                               | 1 | 2 | 3 | 4  | 5  |
|                        | Amounts of subjects in each cluster |   |   |   |    |    |
| <b>Clinitas Soothe</b> | 17                                  | 0 | 3 | 3 | 5  | 6  |
| <b>Tears Again</b>     | 11                                  | 0 | 2 | 1 | 6  | 2  |
| <b>TheraTears</b>      | 15                                  | 0 | 3 | 0 | 6  | 6  |
| <b>Hyabak</b>          | 7                                   | 1 | 1 | 1 | 1  | 3  |
| <b>TOTAL</b>           | 50                                  | 1 | 9 | 5 | 18 | 17 |

**Table 4.3:** The total number of patients for each preferred treatment in their relevant cluster.

Thirty five percent (6) of subjects who preferred Clinitas Soothe were grouped in cluster 5 followed by 29 % (5) in cluster 4. There were no subjects in who fell in cluster 1 and an equal percent of subjects in clusters 2 and 3 of 17.65% (3).

From the 11 subjects who preferred Tears Again 35% of these (6) were grouped in cluster 4. There were no subjects who fell in cluster 1 and only 18% (2) subjects who fell in clusters 2 and 5, and only 1 patient in cluster 3.

For the 15 subjects who preferred TheraTears there were an equal number of subjects falling in cluster 4 and 5 of 40% (6). However, there were no subjects who preferred this drop falling in clusters 4 and 3. There was 20% (3) of these subjects who fell in cluster 2.

For the 7 subjects who preferred Hyabak 43% (3) fell into cluster 5 and 14 (1) fell into clusters 1, 2, 3 and 4.

It should be noted that the majority of subjects enrolled in the randomised controlled trial of dry eye treatments were categorised from the larger group of 150 subjects studied in chapter 2, as falling in clusters 4 or 5, which were the patients with more symptoms.

|                                  | Cluster                              |                      |                      |                      |                      |                     |                      |
|----------------------------------|--------------------------------------|----------------------|----------------------|----------------------|----------------------|---------------------|----------------------|
|                                  | 1                                    | 2                    | 3                    | 4                    | 5                    | 6                   | 7                    |
|                                  | Number of patients in each cluster   |                      |                      |                      |                      |                     |                      |
|                                  | 3                                    | 4                    | 6                    | 12                   | 9                    | 4                   | 12                   |
|                                  | Symptomology as measured by OSDI (%) |                      |                      |                      |                      |                     |                      |
| <b>(Ave <math>\pm</math> SD)</b> | 24.97 $\pm$<br>4.96                  | 22.12 $\pm$<br>11.51 | 22.36 $\pm$<br>16.87 | 16.83 $\pm$<br>16.42 | 30.47 $\pm$<br>18.46 | 49.67 $\pm$<br>3.96 | 31.91 $\pm$<br>26.62 |

**Table 4.4:** The total number of patients who participated in the study for each cluster group and their symptomology as measured by the OSDI. (N = 50).

It can be seen from table 4.4, that from the fifty subjects who participated in the study, 12 patients were grouped in cluster 4 with an average OSDI score of  $16.83 \pm 16.87$ . There were 9 patients who were grouped together in cluster 5 with an average OSDI score of  $30.47 \pm 18.46$ .

From the 25 patients who recorded their symptoms, 4 patients were grouped in cluster 4 and 8 patients were grouped in cluster 5. The average OSDI of the patients who fell in cluster 4 was  $34.86 \pm 17.06$  and those who fell in cluster 5 was  $33.03 \pm 17.95$ .

It can be noted from this that the majority of these subjects who preferred the relevant drops fell in either clusters 4 and 5.

#### **4.2.4 Did the preferred artificial drop give patients better signs or symptoms compared to the other drops trialled?**

Table 4.5 compares the characteristics of patients who preferred each drop to those not preferred by the same patients.

There were 17 patients who preferred Clinitas soothe over the other drops trialled and for these patients there were no significant changes in the OSDI, NIBUT, TMH, LIPCOF and NaFL TBUT. However there was a significant difference in the patients overall comfort ( $p = 0.048$ ), ease of insertion ( $p = 0.014$ ) and clarity of vision ( $p = 0.041$ ).

There were 15 patients who preferred TheraTears over the other drops trialled and for these patients there were no significant changes in the OSDI, NIBUT, TMH, LIPCOF and NaFL TBUT. However there was a significant difference in the patients overall comfort ( $p = 0.002$ ), ease of insertion ( $p = 0.022$ ) and clarity of vision ( $p = 0.013$ ).

There were 12 patients who preferred Tears Again over the other drops trialled and for these patients there were no significant changes in the OSDI, NIBUT, TMH, LIPCOF and NaFL TBUT. However there was a significant difference in the ease of insertion ( $p = 0.036$ ) and clarity of vision ( $p = 0.036$ ). There did not appear to be any significant difference in patients overall comfort ( $p = 0.081$ ).

There were 6 patients who preferred Hyabak over the other drops trialled and for these patients there were no significant changes in the OSDI, NIBUT, TMH, LIPCOF and NaFL TBUT. There was a significant difference in the patients overall comfort ( $p = 0.042$ ) and no significance in clarity of vision ( $p = 0.068$ ), ease of insertion ( $p = 0.066$ ).

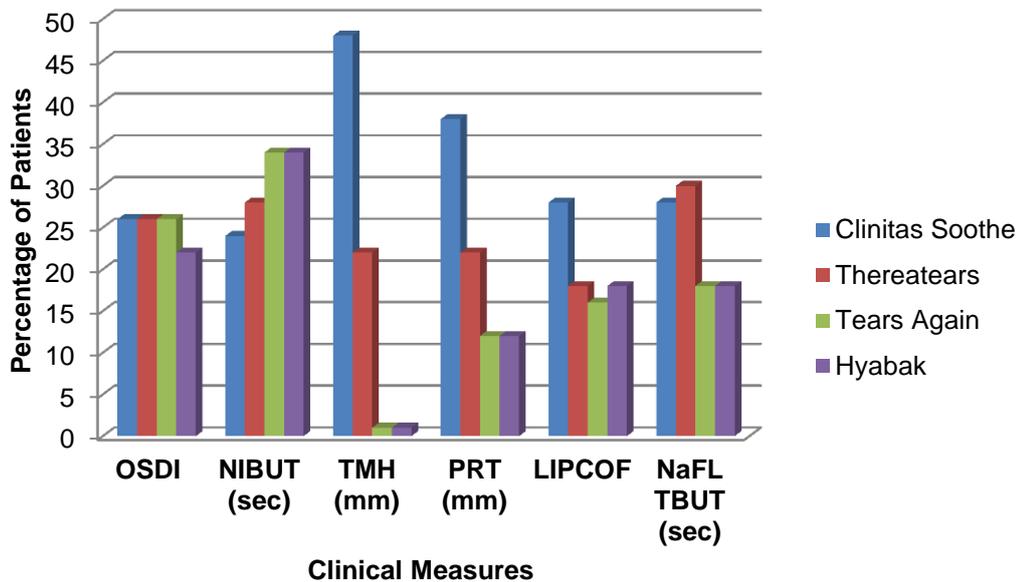
|                                         | Age (yrs)   | OSDI        | NIBUT (sec) | TMH (mm)   | PRT (mm)  | LIPCOF (grade) | NaFL TBUT (sec) | Overall Comfort | Ease of Insertion | Clarity of Vision |
|-----------------------------------------|-------------|-------------|-------------|------------|-----------|----------------|-----------------|-----------------|-------------------|-------------------|
| <b>Clinitas Soothe (N=17)</b>           |             |             |             |            |           |                |                 |                 |                   |                   |
| <b>Preferred Drop</b>                   | 58.4 ±17.1  | 25.1 ± 18.4 | 13.7 ±2.1   | 0.11±0.01  | 15.5 ±4.6 | 1.4 ±0.9       | 13.8 ±2.4       | 8.3 ±1.2        | 8.6 ±1.0          | 8.4 ±1.5          |
| <b>Average with Non-Preferred drops</b> | 58.4 ±17.1  | 25.2 ±18.5  | 14.1 ±2.1   | 0.11 ±0.01 | 15.6 ±4.4 | 1.2 ±0.8       | 14.2 ±2.3       | 6.1 ±2.8        | 7.1 ±2.4          | 7.2 ±2.0          |
| <b>ANOVA</b>                            |             | 0.756       | 0.408       | 0.053      | 0.924     | 0.689          | 0.932           | <b>0.048</b>    | <b>0.014</b>      | <b>0.041</b>      |
| <b>TheraTears (N=15)</b>                |             |             |             |            |           |                |                 |                 |                   |                   |
| <b>Preferred Drop</b>                   | 64.1 ±9.5   | 35.6 ±19.1  | 12.4±2.5    | 0.11 ±0.02 | 12.8 ±4.5 | 1.7 ±0.7       | 12.7 ±2.6       | 8.2 ±1.5        | 8.1 ±1.7          | 8.1 ±1.7          |
| <b>Average with Non-Preferred drops</b> | 64.1 ±9.5   | 28.1 ±19.2  | 12.5 ±2.7   | 0.11 ±0.02 | 12.4 ±3.8 | 1.5 ±0.8       | 12.8 ±2.9       | 5.5 ±2.5        | 6.4 ±2.1          | 6.4 ±2.0          |
| <b>ANOVA</b>                            |             | 0.256       | 0.703       | 0.749      | 0.932     | 0.887          | 0.589           | <b>0.002</b>    | <b>0.022</b>      | <b>0.013</b>      |
| <b>Tears Again (N= 11)</b>              |             |             |             |            |           |                |                 |                 |                   |                   |
| <b>Preferred Drop</b>                   | 60.6 ± 14.0 | 22.3 ± 18.2 | 13.3 ±2.3   | 0.11 ±0.01 | 13.6 ±4.1 | 1.3 ±0.6       | 13.7 ±2.3       | 8.3 ±1.0        | 8.5 ±1.1          | 8.4 ±1.1          |
| <b>Average with Non-Preferred drops</b> | 60.6 ± 14.0 | 27.7 ±21.0  | 13.3 ±2.4   | 0.11 ±0.01 | 13.3 ±4.3 | 1.1 ±0.7       | 13.8 ±2.8       | 5.8 ±2.7        | 6.2 ±2.2          | 5.9 ±2.6          |

|                                  |               |               |              |               |              |          |              |          |          |          |
|----------------------------------|---------------|---------------|--------------|---------------|--------------|----------|--------------|----------|----------|----------|
| ANOVA                            |               | 0.937         | 0.788        | 0.516         | 0.637        | 0.271    | 0.969        | 0.081    | 0.036    | 0.036    |
| <b>Hyabak<br/>(N=7)</b>          |               |               |              |               |              |          |              |          |          |          |
| Preferred Drop                   | 59.8<br>±17.1 | 24.8<br>±26.8 | 15.1<br>±2.0 | 0.11<br>±0.01 | 14.8<br>±3.5 | 1.0 ±0.9 | 14.9<br>±1.5 | 8.6 ±1.0 | 9.0 ±1.3 | 9.2 ±1.2 |
| Average with Non-Preferred drops | 59.8<br>±17.1 | 30.7<br>±24.2 | 13.9<br>±1.7 | 0.11<br>±0.01 | 14.7<br>±4.2 | 1.3 ±0.6 | 14.5<br>±1.6 | 6.2 ±3.0 | 7.5 ±2.1 | 7.6 ±2.1 |
| ANOVA                            |               | 0.042         | 0.278        | 0.102         | 0.785        | 0.234    | 0.674        | 0.042    | 0.066    | 0.068    |

**Table 4.5:** Table showing the Age, Ocular Surface Disease Index (OSDI), Non-Invasive break up time (NIBUT sec), Tear Meniscus Height (TMH mm), Phenol Red Thread (PRT mm), Lid Parallel Conjunctival Folds (LIPCOF), Invasive break up time (NaFL TBUT sec), Tear Lab (mOsms/L), Tear scope break up time (sec) and lipid pattern for the subjects who preferred their specific drops and then for the remaining drops not preferred by the same subjects; the respective drops preferred by the subjects; Clinitas Soothe, TheraTears, Tears Again, Hyabak.(Average ± S.D.).

#### 4.2.5 Did the preferred drop relate to the greatest improvement in clinical signs?

The percentage of cases where the preferred drop of a patient was also the one that gave patients the largest improvement in subjective ocular surface symptoms, tear film stability / volume and clinical signs can be seen in figure 4.2.



**Figure 4.2:** Patients whose artificial tear preference matched the drop that gave the largest improvement in subjective ocular surface symptoms, tear stability / volume and clinical signs.

The most improvement in OSDI score matched patient's preferred artificial tear for around one quarter of patients across all the drops trialled for OSDI, NIBUT, LIPCOF and NaFL TBUT. The greatest improvement is TMH and PRT matched patient's preference for Clinitas Soothe (48% and 38% respectively) whereas this was less likely to be the case for the other artificial tears trialled. Table 4.6 shows the average improvement in each of the metrics compared to baseline levels showing improvements, on average, of 45% for OSDI, 108% for NIBUT, 112% for PRT, 197.5% for LIPCOF and 111% for NaFL TBUT, but no improvement in TMH.

|                     | OSDI  | NIBUT<br>(sec) | TMH<br>(mm) | PRT<br>(mm) | LIPCOF | NaFL TBUT<br>(sec) |
|---------------------|-------|----------------|-------------|-------------|--------|--------------------|
| <b>Ave Baseline</b> | 33.86 | 13.20          | 0.11        | 14.02       | 1.58   | 13.17              |
| <b>SD Baseline</b>  | 20.04 | 1.92           | 0.02        | 5.14        | 0.51   | 2.41               |
| <b>Ave Improved</b> | 15.36 | 14.27          | 0.11        | 15.71       | 0.80   | 14.64              |
| <b>SD Improved</b>  | 14.70 | 2.31           | 0.01        | 4.69        | 0.81   | 2.30               |

**Table 4.6:** Showing the average and standard deviation of the various tear metrics for baseline measurements for 50 patients and the average and standard deviation of the improved results.

#### 4.2.6 Would they pay?

On completion of the study, the subjects were asked if they would be willing to pay for a dry eye service if it were available. Interestingly, only 2 subjects (4%) were not willing to pay for the service if available.

#### 4.2.7 How much would they pay?

The most that a patient was willing to pay for the service was £50. The average that the subjects were willing to pay was £17.00 with a standard deviation of £9.30. This data is represented in figure 4.3.



**Figure 4.3:** The amount each of the patients was willing to pay for a dry eye consultation in their area. N = 50.

### 4.3 Discussion

The eye drops used in this study were commercially available, unpreserved eye drops, currently used for the treatment of dry eye. Artificial eye drops have been designed with a focus on physical properties relating to wetting of the ocular surface and usually contain hydrophilic polymers, which lubricate the eye during blinking (Lemp, 1973). The ideal tear replacement should have a composition which is compatible with the maintenance of a normal ocular surface epithelium (Aragona et al., 2002). In the presence of ocular damage, the artificial tear solution should provide an environment in which the epithelium can recover the normal structure and function (Aragona et al., 2002).

Amongst the 50 patients participating in the study, the most frequently preferred artificial eye drop was Clinitas Soothe (17 patients), followed by TheraTears (15 patients), Tears Again (11 patients) and lastly Hyabak (7 patients). The patients rated these taking in to consideration the overall ease of insertion of the drops, overall comfort after using the drops and the clarity of their vision after having used the drops. It was important to investigate whether the patients' preferred drops could be predicted from the initial baseline measurements taken. Therefore, the baseline characteristics of patients who preferred each drop were compared to the patients who preferred the other treatments.

Clinitas Soothe and Hyabak were preferred by those with a higher Tearscope NITBUT which seems counterintuitive. The key lubricating ingredient in these two eye drops is sodium hyaluronate, which is a naturally occurring glycosaminoglycan of the extracellular matrix that plays an important role in development, wound healing and inflammation (Inoue et al., 1993). Sodium hyaluronate eye drops have shown efficacy in several trials for the treatment of dry eye (Sand et al., 1989; Shimmura et al., 1995; Hamano et al., 1996; Avisar et al., 1997; Yokoi et al., 1997; Papa et al., 2001; Aragona et al., 2002). Sodium hyaluronate has been used in the treatment of dry eyes because of its long ocular surface residence time (Graue et al., 1980; De Luise et al., 1984; Snibson et al., 1990; Shimmura et al., 1995; Aragona et al., 2002). Experimental data show that sodium hyaluronate eye drops do not alter the normal conjunctival epithelium, as may happen with other lacrimal substitutes. In fact, eye drops primarily containing this constituent do not interfere with secretory processes of goblet cells and do not damage the intercellular junctions as may happen with other tear substitutes (Aragona et al., 2002). Sodium hyaluronate eye drops increase pre-corneal tear film stability and corneal wettability; reduce the tear evaporation rate, and the healing time of corneal epithelium (Tsubota et al., 1992; Nakamura et al., 1993; Shimmura et al., 1995; Hamano et al., 1995).

Experiments in animals have shown that sodium hyaluronate promotes corneal epithelial wound healing by stimulating the migration, adhesion and proliferation of the corneal epithelium (Stuart et al., 1985; Nishida et al., 1991; Inoue et al., 1993). The mechanism of action of sodium hyaluronate on these cell functions remains controversial (Nishida et al., 1991; Nakamura et al., 1993; Fitzsimmons et al., 1992; Lindquist et al., 1993). Human studies have been confined to the in-vivo topical instillation of sodium hyaluronate drops in eyes with epithelial problems (Norn, 1981; Yokoi et al., 1995). The trans-membrane cell surface adhesion molecule (CD44) receptor which has been identified on healthy human corneal epithelial cells demonstrates an increase in inflammation proposing its significance in corneal epithelial cell physiology (Aruffo et al., 1990; Zhu et al., 1997). Its expression has also been found to correlate with corneal re-epithelialisation, suggesting its involvement in cell to cell and cell to substratum interactions that mediate cell migration during re-epithelialisation (Yu et al., 1998). Studies have also shown that CD44 expression is associated with proliferation of epithelial cells (Abbasi et al., 1993; Günthert et al., 1993; Lesley et al., 1993; Mackay et al., 1994); however, the reason for this association is not known. Sodium hyaluronate is said to form a compound with CD44 (Zhu et al., 1997). Conflicting results have been obtained regarding the efficacy of sodium hyaluronate on ocular surface damage. Wysesbeek et al., (1988), indicated that

hyaluronate is able to protect the corneal epithelium and Condon et al., (1999), have reported a reduction in cell degeneration as assessed by rose bengal. On the other hand, Nelson et al., (1988), have published a report stating that sodium hyaluronate did not change significantly the degree of squamous metaplasia of the bulbar conjunctival surface, as shown by impression cytology during a short term treatment period.

A topical application of sodium hyaluronate has been shown to confer both subjective and clinical improvement in patients with dry eye syndrome (Gill et al., 1973; Polack et al., 1982; De Luise et al., 1984; Stuart et al., 1985; Shimmura et al., 1995; Papa et al., 2001). A study conducted by Aragona et al., (2002), showed that for the tests considered (tear film break up time, fluorescein staining, rose bengal staining, and Schirmer test) there was no statistical significant difference between their treatment groups (i.e. the two groups were patients being treated with preservative free sodium hyaluronate or saline). However, they appeared to be an improvement over baseline for all. They concluded that sodium hyaluronate may effectively improve ocular surface damage associated with dry eye syndrome. Another study also conducted by Aragona et al., (2002), also confirmed that symptoms were statistically significantly improved as well as the BUT and fluorescein, and Rose Bengal scores from baseline. Gomes et al., (2004), investigated the effect of sodium hyaluronate on human corneal epithelial cell migration, proliferation, and CD44 receptor expression. They concluded that sodium hyaluronate promotes migration but not proliferation or CD44 expression on human corneal epithelial cells in vitro. The beneficial effect of sodium hyaluronate in corneal wound healing is likely to be related to rapid migration of cells leading to rapid wound closure. This may be facilitated by the adhesion between CD44 on the cells and hyaluronic acid.

TheraTears was preferred by those with a lower tear volume. A study by Matheson (2006) reported that 87.5 per cent of patients were free of dry eye symptoms at 1 week after treatment and 100 percent of the patients were free of dry eye symptoms after being treated with TheraTears. TheraTears is hypotonic and has been shown to produce sustained lowering of the elevated tear film osmolarity with continued treatment (Gilbard et al., 1992). TheraTears precisely matches the electrolyte balance of the human tear film (Gilbard, 1988; 1994; Gilbard et al., 1989). Therefore by lowering the elevated tear film osmolarity and providing this electrolyte balance TheraTears has been shown to lessen symptoms and restore conjunctival goblet cells in dry eye patients following LASIK (Lenton et al., 1998). Perrigin and colleagues (2004), examined 21 different lubricating agents; with one-third being preservative free and the remaining containing preservatives, concluding that from the 21 common ocular

lubricants tested, TheraTears has an osmolality value statistically significantly lower than all other products tested.

The patients who preferred Tears Again appeared to have lower tear lipid layer observation, and a significant improvement in keratometer derived TBUT, an increase NaFL TBUT, and a thinner (lower grade) lipid film layer. Dieter et al., (2006), found an improvement in LIPCOF, NIBUT, Schirmer, visual acuity and inflammation of the lid margin. The patients reported their subjective evaluation concerning efficacy and compatibility of the eye spray turned out to be more favourable with 74.6 % of the patients favouring the liposomal spray. Research conducted by Craig et al., (2010), concluded that subjective reports were consistent of improved comfort, statistically and clinically significant improvements in lipid layer thickness and tear film stability are observed in normal eyes for >1 hour after a single application of a phospholipid liposomal spray. Comfort improved relative to baseline in 46% of those treated at 30 min post-application and 68% preferred the liposomal spray.

The artificial tear which gave the most improvement in subjective ocular comfort, tear film stability or volume and clinical signs did not match patient's preferred artificial tear for the majority of patients except for TMH and PRT for Clinitas Soothe and even then, this was only the case in less than half of patients. Hence, preference for an artificial tears must be based on a more complex decision making process. Greater preference for an artificial tear could be expected to give better patient compliance, but unfortunately this may not relate to the formulation that is best for the patient's ocular physiology.

The tests identified in chapter 2 as contributing individually to the diagnosis and monitoring of dry eye would take no longer than 20 minutes including the advice given to the patient and any special instructions. The average cost of the materials including the staining dyes and the Tearscope chips and the lease of the equipment would cost no more than £25 (chips for Tearscope ~ £17.00 per pair, staining strips ~ £0.80, PRT ~ £2.00, equipment lease ~ £5.00) and this is not taking in to consideration the optometrists time which would estimate at £24 for a 20minute appointment. However, the average cost that patients from this trial were only willing to pay £17.00, the cost of a private sight test at the practice is £20. It has been reported that in order to know the 'true cost' of an optometrists' clinical time can range from approximately £50 for a 20 minute appointment in a busy practice, to £150 or more for a 30 minute appointment in a part time practice (Russ, 2008). The current NHS sight test fee (1st April 2014 to 31st March 2015) is £21.10 (FODO.com), whereas the average private sight test fee of

£21.30 (FODO, 2011), which do not cover an optometrists' clinical time and overheads of the practice. The survey conducted by Mason and Mason, (2002), concluded that 41% of optometrists were dissatisfied and 44% very dissatisfied with present methods for the GOS and other co-managements schemes. Customarily the profit from spectacles and contact lens sales at an optical practice has been utilised to finance the true cost of professional optometrist fees, such as eye examinations (Calver, 2010).

The reimbursement of the cost of the assessment of these dry eye patients could be discussed with the local health authorities who have consortium called the First Choice Eye care group, in order for the local health authority to either subsidise these payments or fund them for patients in the community. Currently the co management fees for optometrists' caring for post cataract patients; under the first choice eye care scheme is £40 per test. Also under this scheme, patients who present at the request of their GP or other health care professionals for conditions such as, ectropion, entropion, dry eye, red eye, photopsia, sudden loss of vision, sub conjunctival haemorrhage and any other eye condition; would get a fee of £50 on the initial visit and £25 on subsequent visits if the patient requires to be reviewed by the optometrist.

Doughty (2010) reported that at the time for 39 dry eye products currently marketed in 2010 the UK the recommended retail prices range from just £1.50 per bottle to as much as £36.20 for a multi-pack of a preservative-free product; the average cost per product (as packaged for retail sale) was approximately to £7.50. The average retail cost of multi-dose eye drop bottles were closer to £5.00 (range £1.50 to £13.80), while preservative-free eye drop products were much higher, averaging £13.00 (range £3.99 to £36.20). Patients using the preservative-free eye drops on an average of six times per day instead of QDS, due to moderate or severe dry eye, their estimated costs would range from £12.00 per month to as high as £56.85 per month, for an average of £32.18 per month (Doughty, 2010). Therefore patients would be paying for these drops if not eligible on the NHS. If a drug company wants to enlist its drug in order to have it prescribed on the NHS, it would have to apply to the DOH prescribing department who would analyse the evidence for the drug and the price the NHS would pay for it and is then agreed. Tears Again spray and TheraTears are currently unavailable on the NHS, and therefore cannot be prescribed to patients on the fp 10 (NHS prescription) from their GP. This is due to the drug company and DOH not agreeing on the price the NHS would pay for these artificial eye drops.

#### **4.4 Conclusion**

When trying to predict patient preference for artificial tears from baseline measurements, each individual category of artificial tears appeared to have a significant improvement in at least one tear metric test performed. However, the artificial tears were only used for one month and if patients had used them for a longer period there could be a significant difference from baseline in more than one test for each category of eye drop.

Undoubtedly from the study the patients preferred the artificial drops because their subjective responses were statistically significant than the signs. They rated the preferred drops much higher than the other drops.

The cost of specialist services is an arduous factor to explore in an optometric clinical setting, due to the patients being entitled to free NHS examinations due to low income or health reasons, as well as receiving help towards the cost of spectacles or contact lenses.

Even though patients are willing to pay for a dry eye service in their community, the average cost involved in charging them would be no less than £25, which would be a challenge as the average that they were willing to pay was £17. The cost of this type of specialist service may have an effect on patients expectations of the services received. However, we are entering in to talks with the local First Choice Eye care consortium financed by the CCG, to either get this cost financed completely or partially if referred by the GP.

## **CHAPTER 5**

### **Final Summary and Future Direction**

Dry eye is a significant problem where we are beginning to understand the mechanism. As outlined in chapter 1 there are various tests aimed at diagnosis and this should lead to effective treatment. There are numerous treatment options for dry eye disease e.g. blink exercises, lid hygiene and warm compresses, autologous serum tears, punctal plugs, anti-inflammatory therapy, essential fatty acids, environmental strategies and artificial eye drops.

Although there are many topical lubricants available, that may improve patient symptoms and ocular surface improvement, there is no evidence that any particular artificial tear treatment is superior to another (DEWS, 2007). Clinical trials involving topical artificial tears have reported some improvement of subjective symptoms and improvement in some clinical signs (Nelson et al., 1992). As there is currently no study investigating which treatment works best for different patients; the try and see approach of patients who have symptoms can't be much improved upon. However, patients are likely to give up on treatment and live with the long term reduction in quality of life caused by dry eye (Atkins, 2008; Doughty, 2009; Rogers, 2009), if their initial treatments are ineffective. Hence, from the various clinical treatments available for dry eye, it would help if practitioners not only knew which dry eye tests were the most effective to diagnose dry eye, but also indicated which treatment (artificial tears) should be attempted initially from evidence basis. Therefore, this thesis initially examined how clinical tests of dry eye were interrelated and whether distinct clusters of dry eye patients could be identified.

Dry eye disease is a common clinical condition whose aetiology and management challenges clinicians and researchers alike. Patients may attend the practice mentioning that they suffer from gritty, burning, irritated, eyes. Other symptoms include, foreign body sensation, blurred vision and photophobia, or uncomfortable feeling eyes particularly in the evening (Begley et al., 2003).

There are multiple clinical tests to evaluate the tear film, which either help evaluate the stability of the tear film, the volume of the tears or the tears' osmolarity. These tests include: non-invasive break up time (NIBUT), tear meniscus height (TMH) and regularity, phenol red thread test (PRT), sodium fluorescein tear break up time (NaFL TBUT) and tear lipid analysis. Other tests help to evaluate the effect of dry eye on the

ocular surface; these tests include: corneal staining, lissamine green conjunctival staining and lid parallel conjunctival folds (LIPCOF). Symptomology is also very important in order to diagnose correctly as well as to try and help with dealing with patient expectations of their treatments and as a measure of how the patients are feeling with their current dry eye treatment or dry eye condition.

A successful cure for dry eye disease has still to be found. At present treatment goals are directed towards either 'tear replacement' or 'tear retention', and are aimed primarily at relieving the subjective symptoms associated with this condition (Farrell, 2010). Artificial tears remain the essential agent used in the treatment and management of dry eye regardless of the cause or type (Farrell, 2010). There is currently a variety of products available on the market for the 'dry eye' patient to choose from. The various artificial tear supplements available are aqueous artificial tears, liposomes, ocular lubricants or viscoelastics. Each of these categories has an active ingredient and may or may not contain preservatives. Even though the primary principle of successful dry eye treatment is to improve the ocular surface and prevent damage to the cornea, it is also important to try to provide relief of symptoms and so offer the patient some degree of satisfaction (Asbell et al., 2010). The final point for relief or provision of satisfaction is, however, likely to vary between patients and the practitioners managing the patient. A patient with a dry eye is likely to suffer from some symptoms; hence, successful treatment may just be that the frequency of symptoms has subsided. Patient satisfaction with treatment may, also, be related to the cost, i.e. relief from the use of an inexpensive product may be considered adequate in comparison to gaining slightly more relief from use of a more expensive product.

The aim of chapter 2 was to find the correlation of dry eye tests in clinical practice. A large cohort typical of clinical optometric practice of 150 subjects was recruited. There was sampling bias as the patients were recruited from optometric practice and not from the general population and only one site in the UK was used. However, the population was relevant to patients likely to be managed by optometrists, at least in that location in the UK. A cluster analysis technique was conducted in order to appreciate if there was a presence of any groups of tear film metrics using cluster analysis. When investigating the correlation of the various tests conducted in practice in chapter 2, it was concluded that the tear stability tests are correlated. These results demonstrate that NIBUT and NaFL TBUT are both not necessary to perform in clinical practice. It is proposed it would be more appropriate to observe the tear stability by performing the NIBUT as the potential for fluorescein disrupting the tear film structure as has been suggested by other authors (Mengher et al., 1985; DEWS, 2007). The tear volume tests are also

related and so any of the two (tear meniscus height and phenol red test) can be used in clinical practice. In addition to a tear stability and tear volume test, it is worth performing: a validated questionnaire to assess patient symptomology such as the OSDI (self-completed so it need not consume consultation time and is a good symptomology metric to monitor and communicate to patients); LIPCOF, lissamine green conjunctival staining, corneal fluorescein staining and a measurement of the tear osmolarity. This combination test was found in chapter 2 to provide independent information towards the definition of dry eye and therefore its diagnosis and potentially optimal treatment (not just diagnosis as reviewed by DEWS (2007)).

Two factors influenced the DEWS (2007) recommendations of diagnostic tests for dry eye disease. Formerly, numerous tests derived from studies that were subject to various forms of bias i.e. spectrum bias where bias due to differences in the features of different populations e.g., sex ratios, age, severity of disease, which influences the sensitivity and/or specificity of a test and selection bias where bias built into an experiment by the method used to select the subjects who are to undergo treatment, meaning that the cut offs that they proposed may be unreliable. Secondly, several tests with excellent credentials are not available outside of specialist clinics. Therefore, offering a practical approach to the diagnosis of dry eye disease based on the quality of tests currently available and their practicality in a general clinic. It has also been suggested that practitioners appraise for themselves the credentials of each test by referring to the report (DEWS, 2007).

There are seven sets of validated questionnaires of differing length which practitioners can adopt for routine screening in their clinics, taking in to consideration the qualitative differences between the tests (DEWS, 2007). These tests have been summarised in table 5.1 below.



**Table 5.1:** A number of symptom questionnaires in current use (Taken from DEWS, 2007).

The dry eye component of the international classification criteria for Sjögren syndrome requires one ocular symptom (out of three) and one ocular sign (out of two) to be satisfied.

**For ocular symptoms:** a positive response to at least one of the following questions:

1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

**For ocular signs:** that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:

1. Schirmer I test, performed without anaesthesia ( $\leq 5$  mm in 5 minutes)
2. Rose bengal score or other ocular dye score ( $\geq 4$  according to Van Bijsterveld's scoring system) (Vitali et al., 2002).

## **Tear Evaluation**

**Tear osmolarity:** Tear hyperosmolarity may reasonably be regarded as the signature feature that characterizes the condition of "ocular surface dryness" (DEWS, 2007). In several studies, as illustrated in Table 1.8, development of a diagnostic osmolar cut-off value has utilized appropriate methodology, using an independent sample of dry eye patients. Hence, the recommended cut-off value of 316 mOsm/L can be said to be well validated (Tomlinson et al., 2006). As an objective measure of dry eye, hyperosmolarity is attractive as a signature feature, characterizing dryness (DEWS, 2007).

**Non-invasive break-up time:** If the studies shown in Table 1.8 that are potentially susceptible to selection or spectrum bias are ignored, the simple clinical alternative for dry eye diagnosis might be non-invasive TF BUT measurements that give moderately high sensitivity (83%) with good overall accuracy (85%) (DEWS, 2007).

DEWS (2007), has further recommended that an improved test performance can be achieved when tests are used in combination, either in series or in parallel. Taking this advice in consideration for the purpose of this study symptomology as measured by the OSDI, LIPCOF, TMH, NIBUT, TBUT, corneal staining, lissamine green staining and tear osmolarity (Details of all these tests have been described in detail in chapter 1).

It can also be concluded from our study that there is no consistent relationship found between signs and symptoms of DED. However, each measurement offers distinct information about the condition of the ocular surface. Symptoms alone are insufficient to diagnose DED, and more than one test should be carried out in order to achieve the desired results with treatment. All these tests are not common in standard optometric practice, although within the competencies of most optometrists. Hence the necessity for specialist dry eye clinics conducting these specific tests is merited, rather than practitioners 'diagnosing' and proposing inadequate treatments for DED on grounds of less relevant examinations carried out as a small subset of the full eye examination.

Chapter 3 reports on a randomised clinical trial which aimed to find the relative effectiveness of different categories of tear supplements. The choice of products were categories aimed to improve lipid, increase viscosity and the osmolarity of the tears, so should have generality to dry eye products currently on market. It was concluded that artificial tear supplements do work for ocular comfort, and by observing the ocular surface improvement in the conjunctival tissue as observed by the presence of LIPCOF and conjunctival staining. However there does not seem to be an improvement in the tear film quality or volume despite the fact that the conjunctival tissue appears to show an improvement, and one would think that in turn that would provide a better mucus layer which should in turn support the tear film. However, this study was only conducted over a four month period and if it was continued for a longer period improvement in the tear stability and volume might become evident.

There does not seem to be any strong evidence of one class of artificial tear supplement being more effective than the others when categorised as moisture retaining, lipid based or osmolarity based. The patients used these drops for one month and then carried on to use another tear supplement for the next month, with positive effects observed with visit regardless of treatment order. This suggests that improvements can be more due to the time rather than the specific drops. In practice this suggests the importance of explaining to patients that while there might be immediate relief to symptoms, further benefits to comfort and ocular surface damage can be gained by longer term use and aftercares should be scheduled accordingly. A

wash-out period between drops was considered in the study design, but as the patients were symptomatic of dry eye, a period without treatment was unlikely to be complied with and the ethics could be challenged. However, the masked, counter balanced sequence of drop use overcame bias between the examinations of the effectiveness of the different drops. The conjunctival signs of dry eye such as LIPCOF and lissamine green staining improved beyond the first month period. Hence, this suggests that these are particularly sensitive indicators of dry eye damage that can be restored in a relatively short time interval with treatment, even though an immediate association with comfort is not seen.

Few other studies have compared multiple treatments; however a lot of the authors have conducted studies with similar drops to saline or other drops in the category of the artificial tear supplements being trialled. Studies conducted by Mengher et al., 1986; Condon et al., 1999 and Aragona et al., 2002 all showed a benefit in the ocular surface and symptomology by using Sodium Hyaluronate. Dieter et al., (2006); Craig et al., (2010) and Pult et al., (2012), investigated the ocular effects with liposomal sprays and the results of these studies showed an improvement in ocular surface and ocular comfort. Therefore, for future work, a longer duration of treatments should be considered. It would also be beneficial to use the TearLab at each visit in order to observe the osmolarity results and calculate whether there is any correlation between the treatment and osmolarity (not undertaken in this study due to the cost).

The final part of this thesis (chapter 4) examined the ability to predict patient preference for artificial tears. If designed correctly a lipid based treatment should work best for those with higher lipid deficiency and so on. It was concluded that when trying to predict patient preference for artificial tears from baseline measurements, each individual category of artificial tears appeared to have a significant improvement in at least one tear metric test performed. It can be noted from this study that patients who preferred a particular artificial eye drop was mainly due to the fact that their eyes felt better, (i.e. it was subjective in that their eyes 'felt' comfortable, and objectively their eyes may not have appeared to look any better or have improved physiology). These patients obviously rated their preferred drops higher in overall performance to the rest of the drops used in the study (see section 3.2.2.9 and figure 3.10). Therefore there was some prediction of preference, but preference was not related to improvement in signs. Cluster grouping of dry eye signs and symptoms did not assist in predicted preference of treatment.

Patients were asked at the end of the study if they were willing to pay for a dry eye service in their community. This is because in the area in which the studies were conducted, many patients were going to their GPs for dry eye problems that could be effectively treated in the community. The average cost that the patients were willing to pay for this 'dry eye community service' was £17, but the minimum that would be feasible to charge for this service is £25. The LOCAL Optical Committee Support Unit (LOCSU) welcomed comments from the head of NHS England which promote community-based services as the future of UK healthcare (O'Hare, 2014). Sir David Nicholson, spoke of the need for increased investment to help the NHS move away from an 'unsustainable' hospital-based treatment system. He added that the extra money would be used to move to a new model of community-based services, without which the NHS will see a decline in the level of care and public support for the health service. He told the Guardian: 'A large proportion of hospital care should be delivered in community settings if the NHS is to cope with the pressures posed by the ageing population, the rise in the number of patients with one or more long-term conditions such as asthma or diabetes, and demand for new treatments' (O'Hare, 2014).

Managing director of LOCSU, Katrina Venerus, commented that there was a 'real urgency for fundamental change' in how eye health services are delivered in the UK. She said 'Innovation funding to support the development of community services would enable [Clinical Commissioning Groups (CCGs)] to succeed in reducing what Sir David referred to as its 'outmoded reliance on hospital-based care'. And also added 'We know that, despite the fact that research shows that nearly four out of five people attending eye casualty have conditions that can be deemed 'non-serious', just over 10% of CCGs have commissioned community-based minor eye condition services' (O'Hare, 2014). Therefore, in order for the public to seek expert advice about eyes from an optometrist, it would be greatly beneficial working with LOCSU and CCGs to develop the business case for dry eye clinics run by qualified optometrists.

In conclusion, this thesis has added to the academic literature on the most appropriate current clinical tests to conduct as part of a dry eye work-up to aid the choice of the optimum artificial tears treatment. Cluster analysis was performed for the first time on such a cohort, but was not found to aid the optimisation of treatment. All artificial treatments assessed offered similar benefits in signs and symptoms, despite being chosen to represent the range of formulations currently available. On the individual patient level, preference was predictable to some degree by the individual tear film tests prior to treatment which could inform practitioner treatment choices. Treatment effects continued for the full 4 month period that patients were using the different drops,

an improvement particularly in conjunctival tissue assessments, but tear stability improvements were not detected over this period. Therefore, in order to answer the question 'What is the optimum artificial treatment for dry eye?', there is no optimum artificial treatment to dry eye, as all the various drops used in the study presented similar benefits in signs and symptoms of the patients over the period of the study. Hence patients should be encouraged to have perseverance in the use of artificial tears and regular aftercares to encourage compliance. In addition, further research is warranted to determine the natural history of the benefits and whether this is predictable in individual patients. Finally this thesis has informed the need for and cost effectiveness of a local optometrist based dry eye service to manage this chronic condition.

## **REFERENCES**

- Abbasi AM, Chester KA, Talbot IC, Macpherson AS, Boxer G, Forbes A, Malcolm ADB, Begent RHJ. CD44 is associated with proliferation in normal and neoplastic human colorectal epithelial cells. *European Journal of Cancer*, **1993**; 29:1995–2002.
- Abelson MB, Ousler GW, Nally LA, Welch D, Krenzer K. Alternate reference values for tear film break-up time in normal and dry eye populations. In *Lacrimal Gland, Tear Film and Dry Eye Syndromes 3*, **2002**; 506:1121-1125. Springer US.
- Abelson MB, Smith I, Chapin M. Ocular allergic disease: Mechanisms, disease subtypes, treatment. *The ocular surface*, **2003**; 1:127-149.
- Acosta MC, Benítez-Del-Castillo JM, Wassfi MA, DíazValle D, Gegúndez JA, Fernandez C, García-Sánchez J. Relation between corneal innervation with confocal microscopy and corneal sensitivity with noncontact esthesiometry in patients with dry eye. *Investigative ophthalmology & visual science*, **2007**; 48:173-181.
- Adatia FA, Michaeli-Cohen A, Naor J, Caffery B, Bookman A, Slomovic A. Correlation between corneal sensitivity, subjective dry eye symptoms and corneal staining in Sjögren's syndrome. *Canadian journal of ophthalmology*, **2004**; 39:767-771.
- Akpek EK, Lindsley KB, Adyanthaya RS, Swamy R, Baer AN, McDonnell PJ. Treatment of Sjögren's syndrome-associated dry eye: An evidence-based review. *Ophthalmology*, **2011**; 118:1242-1252.
- Albietz JM, Bruce AS. The conjunctival epithelium in dry eye subtypes: effect of preserved and non-preserved topical treatments. *Current eye research*, **2001**; 22:8-18.
- Alex A, Edwards A, Hays JD, Kerkstra M, Shih A, De Paiva CS, Pflugfelder SC. Factors predicting the ocular surface response to desiccating environmental stress. *Investigative ophthalmology & visual science*, **2013**; 54:3325-3332.
- Allan A: Mucus – a protective secretion of complexity. *Trends in Biochemical Sciences*, **1983**; 8:169-173.
- Altinors DD, Akça S, Akova YA, Bilezikçi B, Goto E, Dogru M, Tsubota K. Smoking associated with damage to the lipid layer of the ocular surface. *American journal of ophthalmology*, **2006**; 141:1016-1021.
- Andersen JS, Davies IP, Kruse A, Lufstrom T, Ringmann LA. A Handbook of Contact Lens Management. *Jacksonville, FL, USA, Vistakon*, **1996**.
- Annunziato T, Davidson RG, Christensen M T, Deloach J, Pazandak B, Thurburn L, Gluck D, Lay M. Atlas of slit lamp findings and contact lens-related anomalies, southwest independent institutional review board, Fort Worth, TX, USA. (Circa **1992**).
- Anon. How GPs are paid. *BBC news* 18 December 2000 [Accessed from <http://news.bbc.co.uk/1/hi/health/1072662.stm> 8 July 2014]
- Aragona P, Di Stefano G, Ferreri F, Spinella R, Stilo A. Sodium hyaluronate eye drops of different osmolarity for the treatment of dry eye in Sjögren's syndrome patients. *British journal of ophthalmology*, **2002**; 86:879-884.
- Aragona P, Papa V, Micali A, Santocono M, Milazzo G. Long term treatment with sodium hyaluronate containing artificial tears reduces ocular surface damage in patients with dry eye. *British journal of ophthalmology*, **2002**; 86:181–184.

- Arffa RC. Toxic and allergic reactions to topical ophthalmic medications, in: *R.C. Arffa (Ed.), Grayson's Diseases of the Cornea, Mosby, St. Louis, 1997*; 669–683.
- Argüeso P, Balaram M, Spurr-Michaud S, Keutmann HT, Dana MR, Gibson LK. Decreased levels of the goblet cell mucin MUC5AC in tears of patients with Sjögren syndrome *Investigative ophthalmology & visual science*, **2002**; 43:1004-1011.
- Armstrong R, Dunne M, Prajapati B. Sample size estimation and statistical power analysis. *Optometry Today*, **2010**; 16.
- Armstrong RA, Slade SV, Eperjesi F. An introduction to analysis of variance (ANOVA) with special reference to data from clinical experiments in optometry. *Ophthalmic and Physiological Optics*, **2000**; 20:235-241.
- Aruffo A, Stanenkonic I, Melnick M, Underhill CB, Seed B. CD44 is a principal surface receptor for hyaluronate. *Cell*, **1990**; 61:1303–1313.
- Asbell PA, Spiegel S. Ophthalmologist perceptions regarding treatment of moderate-to-severe dry eye: Results of a physician survey. *Eye & Contact Lens*, **2010**; 36-38.
- Asbell PA. Increasing importance of dry eye syndrome and the ideal artificial tear: consensus views from a roundtable discussion\*. *Current Medical Research and Opinion*, **2006**; 22:2149-2157.
- Atkins N. Clinitas: A targeted approach to the management of dry eye disease. *Optician*, **2008**; 26-30.
- Avisar R, Creter D, Levinsky H, Savir H. Comparative study of tear substitutes and their immediate effect on the precorneal tear film. *Israel journal of medical sciences*, **1997**; 33:194–197.
- Bäcker M, Grossman P, Schneider J, Michalsen A, Knoblauch N, Tan L, Niggemeyer C, Linde K, Melchart D, Dobos GJ. Acupuncture in migraine: investigation of autonomic effects. *The Clinical journal of pain*, **2008**; 24:106–115.
- Balaram M, Schaumberg DA, Dana MR. Efficacy and tolerability outcomes after punctal occlusion with silicone plugs in dry eye syndrome. *American journal of ophthalmology*, **2001**; 131:30-36.
- Ball GV. Symptoms in Eye Examination. Butterworth-Heinemann, London, **1982**; 114-116.
- Bandeem-Roche K, Muñoz B, Tielsch JM, West SK, Schein OD. Self -reported assessment of dry eye in a population-based setting. *Investigative ophthalmology & visual science*, **1997**; 38:2469-2475.
- Barabino S, Rolando M, Camicione P, Ravera G, Zanardi S, Giuffrida S, Calabria G. Systemic linoleic and  $\gamma$ -linolenic acid therapy in dry eye syndrome with an inflammatory component. *Cornea*, **2003**; 22:97-101.
- Basinger K, Johnson Y. The Specialist's Guide to Successful Contact Lens Patient Care: No-nonsense Solutions to the Tear Dilemma. *Contact Lens Spectrum*, **1994**; 9:20–24.
- Baudouin C. The vicious circle in dry eye syndrome: a mechanistic approach. *Journal Francais D'Ophthalmologie*, **2007**; 30:239-246.

- Baxter SA, Laibson PR. Punctal plugs in the management of dry eyes. *The ocular surface*, **2004**; 2:255-265.
- Begley CG, Caffery B, Nichols KK, Chalmers R. Responses of contact lens wearers to a dry eye survey. *Optometry & Vision Science*, **2000**; 77:40-46.
- Begley CG, Caffrey B, Chalmers RL, Mitchell GL. Use of the dry eye questionnaire to measure symptoms of ocular irritation in patients with aqueous tear deficient dry eye. *Cornea*, **2002**; 21:664-670.
- Begley CG, Chalmers RL, Abetz L, Venkataraman K, Mertzanis P, Caffery BA, Snyder C, Edrington T, Nelson D, Simpson T. The relationship between habitual patient-reported symptoms and clinical signs among patients with dry eye of varying severity. *Investigative ophthalmology & visual science*, **2003**; 44:4753-4761.
- Behrens A, Doyle JJ, Stern L, Chuck RS, McDonnell PJ, Azar DT, Dua HS. Dysfunctional tear syndrome: A Delphi approach to treatment recommendations. *Cornea*, **2006**; 25:900–907.
- Benelli U, Nardi M, Posarelli C, Albert TG. Tear osmolarity measurement using the TearLab™ Osmolarity System in the assessment of dry eye treatment effectiveness. *Contact Lens and Anterior Eye*, **2010**; 33:61-67.
- Benjamin WJ, Hill RM. Human Tears: Osmotic characteristics. *Investigative Ophthalmology & Visual Science* **1983**; 24:1624-1626.
- Berdy GJ, Abelson MB, Smith LM, George MA. Preservative-free artificial tear preparations: assessment of corneal epithelial toxic effects. *Archives of ophthalmology*, **1992**; 110:528-532.
- Bernal DL, Ubels JL. Artificial tear composition and promotion of recovery of the damaged corneal epithelium. *Cornea*, **1993**; 12:115-120.
- Bernal DL, Ubels JL. Quantitative evaluation of the corneal epithelial barrier: Effect of artificial tears and preservatives. *Current Eye Research*, **1991**; 10:645-656.
- Berry M, Pult H, Purslow C, Murphy PJ. Mucins and ocular signs in symptomatic and asymptomatic contact lens wear. *Optometry & Vision Science*, **2008**; 85: E930–E938.
- Best N, Drury L, Wolffsohn JS. Clinical evaluation of the Oculus Keratograph. *Contact lens and anterior eye*, **2012**; 35:171-174.
- Bischoff G, Khaireddin R. Lipid substitution bei kontaktlinsenassoziiertem Trockenem Auge. *Aktuelle Kontaktologie*, **2011**; 7:24–28.
- Bjerrum K. Dry eye symptoms in patients and normals. *Acta Ophthalmologica Scandinavica*, **2000**; 14-15.
- Bjerrum K. Study design and study populations. *Acta Ophthalmologica Scandinavica*, **2000**; 10-13.
- Bjerrum KB. Test and symptoms in keratoconjunctivitis sicca and their correlation. *Acta Ophthalmologica Scandinavica*, **1996**; 74:436-441.
- Blades KJ, Patel S. The dynamics of tear flow within a phenol red impregnated thread. *Ophthalmic and Physiological Optics*, **1996**; 16:409–415.

Boulding W, Kalra A, Staelin R, Zeithaml V. A Dynamic Process Model of Service Quality: From Expectations to Behavioural Intentions. *Journal of marketing research*, **1993**; 1:7-27.

Bowman SJ, Booth DA, Platts RG, Fields A, Rostron J. UK Sjögren's Interest Group. Validation of the Sicca Symptoms Inventory for clinical studies of Sjögren's syndrome. *The Journal of rheumatology*, **2003**; 30:1259-1266.

Brewitt H, Joost P. Klinische Studie zur Wirksamkeit eines nicht konservierten Tränenersatzmittels. *Klinische Monatsblätter für Augenheilkunde*, **1991**; 199:160–164.

Brignole F, Pisella PJ, Dupas B, Baeyens V, Baudouin C. Efficacy and safety of 0.18% Sodium Hyaluronate in patients with moderate dry eye syndrome and superficial keratitis. *Graefe's Archive for Clinical and Experimental Ophthalmology*, **2005**; 243:531-538.

Brignole F, Pisella PJ, Goldschild M, De Saint Jean M, Goguel A, Baudouin C. Flow cytometric analysis of inflammatory markers in conjunctival epithelial cells of patients with dry eyes. *Investigative ophthalmology & visual science*, **2000**; 41:1356-1363.

Brodwall J, Alme G, Gedde-Dahl S, Smith J, Lilliedahl NP, Kunz PA, Sunderraj P). A comparative study of polyacrylic acid (Viscotears®) liquid gel versus polyvinylalcohol in the treatment of dry eyes. *Acta Ophthalmologica Scandinavica*, **1997**; 75:457-461.

Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea*, **2003**; 22:640–650.

Bron AJ, Tiffany JM, Gouveia SM, Yokoi N, Voon LW. Functional aspects of the tear film lipid layer. *Experimental eye research*, **2004**; 78:347–360.

Bron AJ, Tiffany JM, Yokoi N, Gouveia SM. Using osmolarity to diagnose dry eye: a compartmental hypothesis and review of our assumptions. *Advances in Experimental Medical Biology*, **2002**; 506:1087-1095.

Bron AJ, Tiffany JM. Pseudoplastic materials as tear substitutes. An exercise in design. *The Lacrimal System (Van Bijsterveld, OP, Lemp, MA and Spinelli, D., eds.)*. Kugler and Ghedini, Amsterdam, **1991**; 27-33.

Bron AJ, Tiffany JM. The contribution of Meibomian disease to dry eye. *Cornea*, **2004**; 2:149-164.

Bron AJ. Diagnosis of dry eye. *Survey of ophthalmology*, **2001**; 45:S221-S226.

Brubaker R, McLaren J. Uses of the fluorophotometer in glaucoma research. *Ophthalmology*, **1985**; 92:884-890.

Buchholz P, Steeds CS, Stern LS, Doyle JJ, Wiederkehr DP, Katz LM, Figueirido FC. Utility assessment to measure the impact of dry eye disease. *The ocular surface*, **2006**; 4:155-161.

Burstein N. Corneal cytotoxicity of topically applied drugs, vehicles and preservatives. *Survey of ophthalmology*, **1980**; 25:15-30.

Burstein N. The effects of topical drugs and preservatives on the tears and corneal epithelium in dry eye. *Transactions of the ophthalmological societies of the United Kingdom*, **1984**; 104:402-409.

Byun YJ, Kwon SM, Seo KY, Kim SW, Kim EK, Park WC. (2012). Efficacy of combined 0.05% cyclosporine and 1% methylprednisolone treatment for chronic dry eye. *Cornea*, **2012**; 31:509-513.

Calonge M. The treatment of dry eye. *Survey of ophthalmology*, **2001**; 45:S227-S239.

Calver R. The Health and Social Security Act 1984 and the price of spectacles among corporate practices in the United Kingdom (1980–2007): a review. *Ophthalmic and Physiological Optics*, **2010**; 30:113-123.

CCLRU. CCLRU grading scales (Appendix D). In: Contact Lenses (eds Phillips AJ, Speedwell L.). *Butterworth-Heinemann, Oxford, UK*. **1997**; 863- 867.

Celebi ARC, Ulusoy C, Mirza GE. The efficacy of autologous serum eye drops for severe dry eye syndrome: a randomized double-blind crossover study. *Graefe's Archive for Clinical and Experimental Ophthalmology*, **2014**; 252:619-626.

Chambers C, Fisher A. Management of Acute Eye Conditions in the Community. Evaluation Project. Stoke on Trent: North Staffordshire Medical Audit Advisory Group, **1998**.

Chang YH, Lin HJ, Li WC. (2005). Clinical evaluation of the traditional Chinese prescription Chi-Ju-Di-Huang-Wan for Dry Eye. *Phytotherapy Research*, **2005**; 19:349-354.

Chen HT, Chen KH, Hsu WM. Toxic keratopathy associated with abuse of low-dose anaesthetic: a case report. *Cornea*, **2004**; 23:527-529.

Chia EM, Mitchell P, Rochtchina E, Lee AJ, Maroun R, Wang JJ. Prevalence and associations of dry eye syndrome in an older population: the Blue Mountains Eye Study. *Clinical & experimental ophthalmology*, **2003**; 31:229-232.

Cho P, Kwong YM. A pilot study of the comparative performance of two cotton thread tests for tear volume. *Journal of the British Contact Lens Association*, **1996**; 19:77–82.

Cho P. Reliability of a portable non-invasive tear break-up time test on Hong Kong-Chinese. *Optometry & Vision Science*, **1993**; 70:1049-1054.

Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II—a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. *Annals of epidemiology*, **2000**; 10:125-134.

Christen WG, Manson JE, Glynn RJ, Ajani UA, Schaumberg DA, Sperduto RD, Buring JE, Hennekens CH. Low-dose aspirin and risk of cataract and subtypes in a randomized trial of US physicians. *Neuro-Ophthalmology*, **1998**; 5:133-142.

Chung JH, Fagerholm P, Lindstrom B. Hyaluronate in healing of corneal alkali wound in the rabbit. *Experimental eye research*, **1989**; 48:569–576.

Chung YW, Oh TH, Chung SK. The effect of topical cyclosporine 0.05% on dry eye after cataract surgery. *Korean Journal of Ophthalmology*, **2013**; 27:167-171.

College of Optometrists. Annual General Meeting minutes, **2010**. <http://www.college-optometrists.org/en/utilities/document-summary.cfm/docid/5973A726-1059-4B53-B47D2F750CDA922E>.

Çömez AT, Tufan HA, Kocabiyik Ö, Gencer B. Effects of lubricating agents with different osmolalities on tear osmolarity and other tear function tests in patients with dry eye. *Current eye research*, **2013**; 38:1095-1103.

Condon PI, McEwen CG, Mackintosh G, Prescott RJ, McDonald C. Double blind, randomised, placebo controlled, crossover, multicentre study to determine the efficacy of a 0.1%(w/v) sodium hyaluronate solution (Fermavisc) in the treatment of dry eye syndrome. *British journal of ophthalmology*, **1999**; 83:1121–1124.

Craig JP, Blades K, Patel S. Tear lipid layer structure and stability following expression of the meibomian glands. *Ophthalmic and Physiological Optics*, **1995**; 15:569-574.

Craig JP, Müller A, Mooi J. “The impact of fluorescein quantity on tear film break-up”. *Contact Lens and Anterior Eye*, **2002**; 25: 202.

Craig JP, Purslow C, Murphy PJ, Wolffsohn. Effect of a liposomal spray on the pre-ocular tear film. *Contact Lens and Anterior Eye*, **2010**; 33:83–87.

Craig JP, Tomlinson A. Age and gender effects on the normal tear film. *In Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2* **1998**; 411-415. Springer US.

Craig JP, Tomlinson A. Importance of the lipid layer in human tear film stability and evaporation. *Optometry and Vision Science*, **1997**; 74:8–13.

Cuevas M, González-García MJ, Castellanos E, Quispaya R, De La Parra P, Fernández I, Calaonge M. Correlations among symptoms, signs, and clinical tests in evaporative-type dry eye disease caused by meibomian gland dysfunction (MGD). *Current eye research*, **2012**; 37:855-863.

Dausch D, Lee S, Dausch S, Kim JC, Schwert G, Michelson W. Comparative study of treatment of the dry eye syndrome due to disturbances of the tear film lipid 1 layer with lipid-containing tear substitutes. *Klinische Monatsblätter für Augenheilkunde*, **2006**; 223:974–983.

De AF Gomes B, Santhiago MR, de Azevedo MN, Moraes HV Jr. Evaluation of dry eye signs and symptoms in patients with systemic sclerosis. *Graefe's Archive for Clinical and Experimental Ophthalmology*, **2012**; 250:1051-1056.

De Luise VP, Peterson SW. The use of topical Healon tears in the management of refractory dry-eye syndrome. *Annals of ophthalmology*, **1984**; 16:823–824.

De Paiva CS, Corrales RM, Villarreal AL, Farley WJ, Li DQ, Stern ME, Pflugfelder SC. Corticosteroid and doxycycline suppress MMP-9 and inflammatory cytokine expression, MAPK activation in the corneal epithelium in experimental dry eye. *Experimental eye research*, **2006**; 83:526-535.

Deakin M. *Occupation profile optometrist*. **2008**. [Accessed from [http://www.prospects.ac.uk/downloads/occprofiles/profile\\_pdfs/C3\\_Optometrist.pdf](http://www.prospects.ac.uk/downloads/occprofiles/profile_pdfs/C3_Optometrist.pdf) 8 July 2014]

DEWS report - The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop. *Ocular Surf*, **2007**; 5:75-92.

Di Pascuale M A, Goto E, Tseng SC. Sequential changes of lipid tear film after the instillation of a single drop of a new emulsion eye drop in dry eye patients. *Ophthalmology*, **2004**; 111:783-791.

Di Pascuale MA, Espana EM, Kawakita T, Tseng SC. Clinical characteristics of conjunctivochalasis with or without aqueous tear deficiency. *British journal of ophthalmology*, **2004**; 88:388-392.

Dieter D, Suwan L, Sabine D, Chan KJ, Gregor S, Wanda M. Comparative study of treatment of the dry eye syndrome due to disturbances of the tear film lipid layer with lipid-containing tear substitutes Efficacy of lipid-containing tear substitutes. *Klin Monatsbl Augenheilkd*, **2006**; 223:974-983.

Dogru M, Özmen A, Ertürk H, Sanli Ö, Karatas A. Changes in tear function and the ocular surface after topical olopatadine treatment for allergic conjunctivitis: an open-label study. *Clinical therapeutics*, **2002**; 24:1309-1321.

Doughman DJ. Clinical tests. *International ophthalmology clinics*, **1973**; 13:199-220.

Doughty MJ, Blades KA, Ibrahim N. Assessment of the number of eye symptoms and the impact of some confounding variables for office staff in non-air-conditioned buildings. *Ophthalmic and Physiological Optics*, **2002**; 22:143-155.

Doughty MJ, Glavin S. Efficacy of different dry eye treatments with artificial tears or ocular lubricants: a systematic review. *Ophthalmic and Physiological Optics*, **2009**; 29:573-583.

Doughty MJ, Jalota V, Bennett E Naase T, Oblak E. Use of a high molecular weight fluorescein (fluorexon) ophthalmic strip in assessments of tear film break-up time in contact lens wearers and non-contact lens wearers. *Ophthalmic and Physiological Optics*, **2005**; 25:119-127.

Doughty MJ, Laiquzzaman M, Oblak E, Button NF. The tear (lacrimal) meniscus height in human eyes: a useful clinical measure or an unusable variable sign? *Contact Lens and Anterior Eye*, **2002**; 25:57-65.

Doughty MJ, Lee CA, Ritchie S, Naase T. An assessment of the discomfort associated with the use of rose bengal 1% eye drops on the normal human eye: a comparison with saline 0.9% and a topical ocular anaesthetic. *Ophthalmic and Physiological Optics*, **2007**; 27:159–167.

Doughty MJ, Whyte J, Li W The phenol red thread test for lacrimal volume—does it matter if the eyes are open or closed? *Ophthalmic and Physiological Optics*, **2007**; 27:482-489.

Doughty MJ. Borderline to Moderate Dry Eye. *Optometry Today*, **2010**; 50:16.

Doughty MJ. The scope and options on use of entry level ophthalmic drugs by UK-based Optometrists. *Optometry Today* **2007**; 47:56–60.

Dundas M, Walker A and Woods RL. Clinical grading of corneal staining of non-contact lens wearers. *Ophthalmic and Physiological Optics*, **2001**; 21:30-35.

Durrie D, Stahl J. A randomized clinical evaluation of the safety of Systane® Lubricant Eye Drops for the relief of dry eye symptoms following LASIK refractive surgery. *Clinical ophthalmology (Auckland, NZ)*, **2008**; 2:973.

Ebrahim S, Peyman GA, Lee PJ. Applications of liposomes in ophthalmology. *Survey of ophthalmology*, **2005**; 50:167–182.

- Edwards C, Stillman P. Minor Illness or Major Disease? Eye Disorders. *Pharmaceutical Journal*, **1993**; 250:839-843.
- Efron N, Morgan PB. Hydrogel contact lens dehydration and oxygen transmissibility. *Eye & Contact Lens*, **1999**; 25:148–151.
- Efron N. Efron Grading Scales for Contact Lens Complications (Millennium Edition), **2000**; Butterworth-Heinemann.
- Ehlers N. The pre corneal tear film. *Acta Ophthalmologica*, **1965**; 81:5-136.
- Ellwein L. The Eye Care Technology Forum: impacting eye care cost and effectiveness. *Ophthalmology*, **1994**; 101:199-201.
- Epidemiology of dry eye. Report of the epidemiology Subcommittee of the Dry eye WorkShop (DEWS). *Ocular Surface*, **2007**; 5:93-107.
- Evangelista, M, Koverech A, Messano M, Pescosolido N. Comparison of three lubricant eye drop solutions in dry eye patients. *Optometry & Vision Science*, **2011**; 88:1439-1444.
- Farrell J, Patel S, Grierson DG, Sturrock RD. A clinical procedure to predict the value of temporary occlusion therapy in keratoconjunctivitis sicca. *Ophthalmic and Physiological Optics*, **2003**; 23:1– 8.
- Farrell J. Dry Eye – Tear Retention. *Optician*, **2010**; 29-32.
- Farrell J. Dry Eye Part 3: Treatment. *Optician*, **2010**; 20-24.
- Farrell J. Dry Eye. *Optician*, **2010**.
- Farris RL, Gilbard JP, Stuchell N, Mandell UD. Diagnostic tests in keratoconjunctivitis sicca. *Eye & Contact Lens*, **1983**; 9:23-28.
- Farris RL, Stuchell RN, Mandel ID. Basal and reflex human tear analysis. I. Physical measurements: osmolarity, basal volumes, and reflex flow rate. *Ophthalmology*, **1981**; 88:852-857.
- Farris RL, Stuchell RN, Mandel ID. Tear osmolarity variation in the dry eye. *Transactions of the American Ophthalmological Society*, **1986**; 84:250-268.
- Farris RL. Staged therapy for the dry eye. *Eye & Contact Lens*, **1991**; 17: 207-215.
- Farris RL. Tear osmolarity—a new gold standard? In *Lacrimal Gland, Tear Film and Dry Eye Syndromes*, **1994**; 350:495-503. Springer US.
- Federation of Ophthalmic and Dispensing Opticians (FODO). Optics at a glance 2010. **2011**; [http://www.fodo.com/downloads/resources/Optics-at-a-glance\\_2011\\_web\[1\].pdf](http://www.fodo.com/downloads/resources/Optics-at-a-glance_2011_web[1].pdf) *Federation of Ophthalmic and Dispensing Opticians* **2007**. [Accessed from <http://www.fodo.com/> 8 July 2014]
- Feenstra R, Tseng S. What is actually stained by rose bengal? *Archives of ophthalmology*, **1992**; 110,984-993.
- Finis D, Hayajneh J, König C, Borrelli M, Schrader S, Geerling G. (2014). Evaluation of an Automated Thermodynamic Treatment (LipiFlow®) System for Meibomian Gland

- Dysfunction: A Prospective, Randomized, Observer-Masked Trial. *The ocular surface*, **2014**; 12:146-154.
- Finis D, Pischel N, Schrader S, Geerling G. (2013). Evaluation of lipid layer thickness measurement of the tear film as a diagnostic tool for Meibomian gland dysfunction. *Cornea*, **2013**; 32:1549-1553.
- Fischer FH, Wiederholt M. Human precorneal tear film pH measured by microelectrodes. *Graefe's Archive for Clinical and Experimental Ophthalmology*, **1982**; 218:168-170.
- Fitzsimmons TD, Fagerholm P, Harfstrand A, Schenholm M. Hyaluronic acid in the rabbit cornea after excimer laser superficial keratectomy. *Investigative ophthalmology & visual science*, **1992**; 33:3011–3016.
- Flanagan JL, Willcox MDP. Role of lactoferrin in the tear film. *Biochimie*, **2009**; 91:35-43.
- Fonn D, Situ P, Simpson T. Hydrogel lens dehydration and subjective comfort and dryness ratings in symptomatic and asymptomatic contact lens wearers. *Optometry & Vision Science*, **1999**; 76:700–704.
- Foulks GN, Bron AJ. Meibomian gland dysfunction: a clinical scheme for description, diagnosis, classification, and grading. *The ocular surface*, **2003**; 1:107-126.
- Franklin RM, Kenyon KR, Tomasi TB. Immuno histologic studies of human lacrimal gland: localization of immunoglobulins, secretory component and lactoferrin. *The Journal of Immunology*, **1973**; 110:984-992.
- Frost-Larsen K, Isager H, Manthorpe R. Sjögren's syndrome treated with bromhexine: a randomised clinical study. *British medical journal*, **1978**; 1:1579.
- Fuentes-Páez G, Herreras JM, Cordero Y, Almaraz A, González MJ, Calonge M. Lack of concordance between dry eye syndrome questionnaires and diagnostic tests. *Archivos de la Sociedad Española de Oftalmología (English Edition)*, **2011**; 86:3-7.
- Fujishima H, Toda I, Shimazaki J, Tsubota K. Allergic conjunctivitis and dry eye. *British Journal of Ophthalmology*, **1996**; 80:994-997.
- Furrer P, Mayer JM, Gurny R. Ocular tolerance of preservatives and alternatives. *European journal of pharmaceuticals and biopharmaceutics*, **2002**; 53:263–280.
- Gambaro S, Bellussi M, Formenti F, Lore V, Spinelli D. The use of a carbopolmannitol gel combination in the treatment of dry eye. In *The lacrimal system. Symposium on the lacrimal system*, **1990**; 103-107.
- Gasset AR, Ishii Y, Kaufman H, Miller T. Cytotoxicity of ophthalmic preservatives. *American journal of ophthalmology*, **1974**; 78:98-105.
- Gasson A, Morris J. The Contact Lens Manual. A Practical Fitting Guide (2nd Edition) Butterworth-Heinemann, Oxford. **1998**; 59-60.
- Geerling G, MacLennan S, Hartwig D. Autologous serum eye drops for ocular surface disorders. *British Journal of Ophthalmology*, **2004**; 88:1467-1474.

Geerling G, Tauber J, Baudouin C, Goto E, Matsumoto Y, O'Brien T, Rolando M, Tsubota K, Nichols KK. The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. *Investigative ophthalmology & visual science*, **2011**; 52:2050-2064.

Gilbard J, Pardo D. Lubricant eye drops – the electrolyte factor, *Optometry Today*, **2005**.

Gilbard J. Tear film osmolarity and keratoconjunctivitis sicca. Lubbock TX, Dry eye institute, **1986**.

Gilbard JP, Farris RL, Santamaria J 2nd. Osmolarity of tear micro volumes in keratoconjunctivitis sicca. *Archives of ophthalmology*, **1978**; 96:677-681.

Gilbard JP, Farris RL. Ocular surface drying and tear film osmolarity in thyroid eye disease. *Acta ophthalmologica*, **1983**; 61:108-116.

Gilbard JP, Farris RL. Tear osmolarity and ocular surface disease in keratoconjunctivitis sicca. *Archives of ophthalmology*, **1979**; 97:1642-1646.

Gilbard JP, Rossi SR, Azar DT, Heyda KGI. Effect of punctal occlusion by Freeman silicone plug insertion on tear osmolarity in dry eye disorders. *Eye & Contact Lens*, **1989**; 15:216-218.

Gilbard JP, Rossi SR, Gray KL, Hanninen LA, Kenyon KR. Tear film osmolarity and ocular surface disease in two rabbit models for keratoconjunctivitis sicca. *Investigative ophthalmology & visual science*, **1988**; 29:374–378.

Gilbard JP, Rossi SR, Gray, Heyda K. Ophthalmic solutions, the ocular surface, and a unique therapeutic artificial tear formulation. *American Journal of Ophthalmology*, **1989**; 107:348-355.

Gilbard JP, Rossi SR, Heyda KG: Tear film and ocular surface changes after closure of the meibomian gland orifices in the rabbit. *Ophthalmology*, **1989**; 96:1180–1186.

Gilbard JP, Rossi SR. An electrolyte-based solution that increases corneal glycogen and conjunctival goblet-cell density in a rabbit model for keratoconjunctivitis sicca. *Ophthalmology*, **1992**; 99:600-604.

Gilbard JP. Human tear film electrolyte concentrations in health and dry-eye disease. *International ophthalmology clinics*, **1994**; 34:27-36.

Gilbard JP. Non-toxic ophthalmic preparations. *US patent 4775531*. Washington, DC: U.S. Patent and Trademark Office, **1988**.

Gilbard JP. Tear film osmolarity and keratoconjunctivitis sicca. *Eye & Contact Lens*, **1985**; 11:243-250.

Gilbard JP. The diagnosis and management of dry eyes. *Otolaryngologic clinics of North America*, **2005**; 38:871-885.

Gilbard, J. Dry eye, blepharitis and chronic eye irritation: divide and conquer. *Journal of Ophthalmic Nursing and Technology*, **1999**; 18:109-116.

Gill GW, Frost JK, Miller KA. A new formula for a half-oxidized hematoxylin solution that neither over stains nor requires differentiation. *Acta cytologica*, **1973**; 18:300–311.

- Glasson MJ, Keay L, Stapleton F, Sweeney D, Wilcox MD. Differences in clinical parameters and tear film of tolerant and intolerant contact lens wearers. *Investigative ophthalmology & visual science*, **2003**; 44:5116-5124.
- Göbbels M, Spitznas M. Corneal Epithelial Permeability of Dry Eyes before and after treatment with artificial tears. *Ophthalmology*, **1992**; 9:873-878.
- Golding TR, Bruce AS, Mainstone JC. Relationship between tear meniscus parameters and tear film breakup. *Cornea*, **1997**; 16:649–661.
- Gomes JAP, Amankwah R, Powell-Richards A, Dua HS. Sodium hyaluronate (hyaluronic acid) promotes migration of human corneal epithelial cells in vitro. *British Journal of ophthalmology*, **2004**; 88:821–825.
- Goren MB, Goren SB. Diagnostic tests in patients with symptoms of keratoconjunctivitis sicca. *American Journal of Ophthalmology*, **1988**; 106:570-574.
- Goto E, Shimazaki J, Monden Y, Takano Y, Yagi Y, Shimmura S. Low concentration homogenized castor oil eye drops for non-inflamed obstructive meibomian gland dysfunction. *Ophthalmology*, **2002**; 109:2030–2035.
- Goto E, Tseng SC. Differentiation of lipid tear deficiency dry eye by kinetic analysis of tear interference images. *Archives of ophthalmology*, **2003**; 121:173-180.
- Goto E, Tseng SCG. Kinetic analysis of tear interference images in aqueous tear deficiency dry eye before and after punctal occlusion. *Investigative ophthalmology & visual science*, **2003**; 44:1897–1905.
- Goto E, Yagi Y, Matsumoto Y, Tsubota K. Impaired functional visual acuity of dry eye patients. *American journal of ophthalmology*, **2002**; 133:181-186.
- Goto T, Zheng X, Klyce SD, Kataoka H, Uno T, Yamaguchi M, Hirano S, Okamoto S, Ohashi Y. Evaluation of the tear film stability after laser in situ keratomileusis using the tear film stability analysis system. *American journal of ophthalmology*, **2004**; 137:116-120.
- Goto T, Zheng X, Okamoto S, Ohashi Y. Tear film stability analysis system: introducing a new application for videokeratography. *Cornea*, **2004**; 23:S65-S70.
- Gower I. Ophthalmic goods and services. *Hampton: Key Note Ltd. 15th ed. 2006*.
- Graue EL, Polack FM, Balazs EA. The protective effect of Na-hyaluronate to corneal endothelium. *Experimental Eye Research*, **1980**; 31:119–127.
- Greiner JV, Glonek T, Korb DR, Booth R, Leahy CD. Phospholipids in meibomian gland secretion. *Ophthalmic research*, **1996**; 28:44-49.
- Greene K, MacKeen DL, Slagle T, Cheeks L. Tear potassium contributes to maintenance of corneal thickness. *Ophthalmic research*, **1992**; 24:99-102.
- Greene RB, Lankston P, Mordaunt J, Harrold M, Gwon A, Jones R. Unpreserved carboxymethylcellulose artificial tears evaluated in patients with keratoconjunctivitis sicca. *Cornea*, **1992**; 11:294– 301.
- Guillon JP, Guillon M. Tear film examination of the contact lens patient. *Contax*, **1988**; 14-18.

Guillon JP, Guillon M. The role of tears in contact lens performance and its measurement in Ruben M, Guillon M. eds. *Contact Lens Practice*. London: Chapman and Hall **2004**; 466 – 468.

Guillon JP, Guillon M. The role of tears in contact lens performance and its measurement. In: Ruben M, Guillon M, eds. *Contact Lens Practice*. London: Chapman and Hall **1994**; 453-484.

Guillon JP. Non-invasive Tearscope Plus routine for contact lens fitting. *Contact Lens and Anterior Eye*, **1998a**; 21:S31-S40.

Guillon JP. The Keeler Tearscope Plus- an improved device for assessing the tear film. *Optician*, **1997**; 213:66-72.

Guillon M, Styles E, Guillon JP, Maissa C. Preocular tear film characteristics of non-wearers and soft contact lens wearers. *Optometry & Vision Science*, **1997**; 74: 273-279.

Guillon, JP. Use of the Tearscope Plus and attachments in the routine examination of the marginal dry eye contact lens patient. In *Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2*, **1998b**; 859-867. Springer US.

Günthert U. CD44: a multitude of isoforms with diverse functions. In *Adhesion in Leukocyte Homing and Differentiation* **1993**; 47–63. Springer Berlin Heidelberg.

Guo MH, Cui EC, Li XY, Zong L. Diverse needling methods for dry eye syndrome: a randomized controlled study. *J Acupunct Tuina Sci*, **2013**; 11: 84-88.

Gupta A, Sadeghi PB, Akpek EK. Occult thyroid eye disease in patients presenting with dry eye symptoms. *American Journal of Ophthalmology*, **2009**; 147:919-923.

Hamano H, Hori M, Mitsunaga S, Kojima S, Maeshima J. Tear test (preliminary report). *Journal Japanese Contact lens Society*, **1982**; 24:103-107. (In Japanese)

Hamano H, Kaufman HE. The physiology of the cornea and contact lens applications. *Churchill Livingstone, New York*, **1987**.

Hamano T, Horimoto K, Lee M, Komemushi S. Sodium hyaluronate eye drops enhance tear film stability. *Japanese journal of ophthalmology*, **1995**; 40:62–65.

Hardberger R, Hanna C, Boya CM. Effects of drug vehicles on ocular contact time. *Archives of ophthalmology*, **1975**; 93:42-45.

Hays RD, Mangione CM, Ellwein L, Limbald AS, Spritzer KL, McDonnell PJ. Psychometric properties of the NEI -Refractive Error Quality of Life instrument. *Ophthalmology*, **2003**; 110:2292-301.

Heath G. Therapeutic management of dry eye: Current and developing therapies. *Optometry Today*, **2004**; 24-29.

Heiligenhaus A, Koch JM, Kemper D, Kruse FE, Waubke T N. Therapie von Benetzungstörungen. *Klinische Monatsblätter für Augenheilkunde*, **1994**; 204:162-168.

Herreras JM, Pastor C, Calonge M, Asensio VM. Ocular surface alteration after long-term treatment with an ant glaucomatous drug. *Ophthalmology*, **1992**; 99:1082 -1088.

Hirji N, Patel S, Callander M. Human tear film pre-rupture phase time (TP-RPT) -A non-invasive technique for evaluating the pre-corneal tear film using a novel keratometer mire. *Ophthalmic and Physiological Optics*, **1989**; 9:139-142.

Hirji N, Patel S. Tear - An overview and step-by-step guide to their clinical evaluation. *Optician*, **2010**.

Hirotsu Y, Yokoi N, Komuro A, Kinoshita S. Age-related changes in the mucocutaneous junction and the conjunctivochalasis in the lower lid margins. *Nippon Ganka Gakkai Zasshi, Acta Societatis Ophthalmologicae Japonicae*, **2003**; 107:363–368.

Höh H, Schirra F, Kienecher C, Ruprecht KW. [Lid-parallel conjunctival folds are a sure diagnostic sign of dry eye]. *Der Ophthalmologe: Zeitschrift der Deutschen Ophthalmologischen Gesellschaft*, **1995**; 92:802-808.

Holly F, Lemp M. Surface chemistry of the tear film: Implications for dry eye syndromes, contact lenses, and ophthalmic polymers. *Contact Lens Society American Journal*, **1971**; 5:12-19.

Holly F, Lemp MA. Formation and rupture of the tear film. *Experimental Eye Research*, **1973**; 15:515-525.

Holly FJ, Lemp MA. Tear physiology and dry eyes. *Survey of ophthalmology*, **1977**; 22: 69-87.

Holly FJ. Surface Chemical Evaluation of Artificial Tears and their Ingredients. II. Interaction with a Superficial Lipid Layer. *Contact Lens Forum* **1978**; 4:52-65.

Holly FJ. Tear film physiology. *American journal of optometry and physiological optics*, **1980**; 57:252-257.

Holly FJ. What is New in Artificial Tears. *Contact Lens Forum*, **1991**; 16:19-20.

Hong J, Liu Z, Hua J, Wei A, Xue F, Yang Y, Sun X, Xu J. Evaluation of Age-Related Changes in Non-invasive Tear Breakup Time. *Optometry & Vision Science*, **2014**; 91:150-155.

Hong J, Sun X, Wei A, Cui X, Li Y, Qian T, Wang W, Xu J. Assessment of tear film stability in dry eye with a newly developed Keratograph. *Cornea*, **2013**; 32:716-721.

<http://www.dryeyezone.com/encyclopedia/aqueouslayer.html>

<http://www.fodo.com/resource-categories/nhs-sight-test-fees>

[http://www.reviewofcontactlenses.com/content/d/irregular\\_cornea/c/27820/](http://www.reviewofcontactlenses.com/content/d/irregular_cornea/c/27820/)

<http://www.tearlab.com/products/doctors/productinfo.htm>

<http://www.tearlab.com/products/doctors/productinfo.htm>

<https://www.dssresearch.com/knowledgecenter/toolkitcalculators/samplecalculator.aspx>

Inoue M, Katakami C. The effect of hyaluronic acid on corneal epithelial cell proliferation. *Investigative ophthalmology & visual science*, **1993**; 34:2313–2315.

International Dry Eye Workshop. The definition and classification of dry eye disease. In: 2007 Report of the International Dry Eye Workshop (DEWS). *Ocular Surface*, **2007**; 5:75–92.

Jaanus S. Number 1: managing the dry eye. *Clinical Eye and Vision Care*, **1990**; 2:38-44.

James MJ, Cleland LG, James MJ. Dietary n-3 fatty acids and therapy for rheumatoid arthritis. In *Seminars in arthritis and rheumatism* **1997**; 27:85-97. WB Saunders.

Jensen JL, Bergem HO, Gilboe IM, Husby G, Axéll T. Oral and ocular sicca symptoms and findings are prevalent in systemic lupus erythematosus. *Journal of oral pathology & medicine*, **1999**; 28:317-322.

Jessa Z, Evans B, Thomson D, Rowlands D. Vision screening of older people. *Ophthalmic and Physiological Optics*, **2007**; 27:527-546.

Johnson ME, Murphy PJ, Boulton M. Effectiveness of sodium hyaluronate eye drops in the treatment of dry eye. *Graefe's Archive for Clinical and Experimental Ophthalmology*, **2006**; 244:109-112.

Johnson ME, Murphy PJ. The Effect of instilled fluorescein solution volume on the values and repeatability of TBUT measurements. *Cornea*, **2005**; 24:811–817.

Johnson ME. The association between symptoms of discomfort and signs in dry eye. *The ocular surface*, **2009**; 7:199-211.

Jones DT, Monroy D, Ji Z, Artherton SS, Pflugfelder SC. Sjögren's syndrome: cytokine and Epstein-Barr viral gene expression within the conjunctival epithelium. *Investigative ophthalmology & visual science*, **1994**; 35:3493-3504.

Jones LT. The lacrimal secretory system and its treatment. *American Journal of Ophthalmology*, **1966**; 62:47-60.

Kaercher T, Thelen U, Brief G, Morgan-Warren RJ, Leaback R. A prospective, multicentre, non-interventional study of Optive Plus® in the treatment of patients with dry eye: the pro lipid study. *Clinical ophthalmology (Auckland, NZ)*, **2014**; 8:1147.

Kamiya K, Nakanishi M, Ishii R, Kobashi H, Igarashi A, Sato N, Shimizu K. Clinical evaluation of the additive effect of diquafosol tetrasodium on sodium hyaluronate monotherapy in patients with dry eye syndrome: a prospective, randomized, multicentre study. *Eye*, **2012**; 26:1363-1368.

Kanno Y, Loewenstein WR. Intercellular diffusion. *Science*, **1964**; 143:959-960.

Kanski JJ. Clinical Ophthalmology- a Systemic Approach, 2nd ed, Oxford, *Butterworth-Heinemann*, **1989**; 46-58.

Kanski JJ. Clinical Ophthalmology- a Systemic Approach, 2nd ed, Oxford, *Butterworth-Heinemann*, **1989**; 8-11.

Karas MP, Donaldson L, Charles A, Silver J, Hodes D, Adams GG. Paediatric community vision screening—a new model. *Ophthalmic and Physiological Optics*, **1999**; 19:295-299.

Kaufman B, Novack GD. Compliance issues in manufacturing of drugs. *The ocular surface*, **2003**; 1:80-85.

- Kavoussi B, Ross BE. The neuroimmune basis of anti-inflammatory acupuncture. *Integrative Cancer Therapies*, **2007**; 6:251–257.
- Kawai M, Yamada M, Kawashima M, Inoue M, Goto E, Mashima Y, Tsubota K. Quantitative evaluation of tear meniscus height from fluorescein photographs. *Cornea*, **2007**; 26:403–406.
- Khairuddin R, Schmidt KG. Vergleichende Untersuchung zur Therapie des evaporativen trockenen Auges. *Klinische Monatsblätter für Augenheilkunde*, **2010**; 227:128–134.
- Khanal S, Tomlinson A, Pearce EI, Simmons PA. Effect of an oil in water emulsion on the tear physiology of patients with mild to moderate dry eye. *Cornea*, **2007**; 26:175–181.
- Khanal S. Diagnosis and management of dry eye. PhD thesis, *Glasgow-Caledonian University*, **2006**.
- Kilp H, Brewitt H. Cytotoxicity of preservatives: a scanning electron microscopic and biochemical investigation, *Chibret International Journal of Ophthalmology*, **1984**; 1:4–20.
- Kim EC, Choi JS, Joo CK. A comparison of vitamin a and cyclosporine a 0.05% eye drops for treatment of dry eye syndrome. *American journal of ophthalmology*, **2009**; 147:206-213.
- Kinney KA. Detecting dry eye in contact lens wearers. *Contact Lens Spectrum*, **1998**; 13:21-28.
- Kinoshita S, Awamura S, Nakamichi N, Suzuki H, Oshiden K, Yokoi, N. A multicentre, open-label, 52-week study of 2% rebamipide (OPC-12759) ophthalmic suspension in patients with dry eye. *American journal of ophthalmology*, **2014**; 157:576-583.
- Kinoshita S, Awamura S, Oshiden K, Nakamichi N, Suzuki H, Yokoi N. Rebamipide (OPC-12759) in the treatment of dry eye: a randomized, double-masked, multicentre, placebo-controlled phase II study. *Ophthalmology*, **2012**; 119:2471-2478.
- Klaassen-Broekema N, Mackor AJ, Van Bijsterveld OP. The diagnostic power of the tests for tear gland related keratoconjunctivitis sicca. *The Netherlands journal of medicine*, **1992**; 40: 113-116.
- Knop E, Knop N, Millar T, Obata H, Sullivan DA. The international workshop on meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. *Investigative ophthalmology & visual science*, **2011**; 52:1938-1978.
- Koh S, Ikeda C, Takai Y, Watanabe H, Maeda N, Nishida K. Long-term results of treatment with diquafosol ophthalmic solution for aqueous-deficient dry eye. *Japanese journal of ophthalmology*, **2013**; 57:440-446.
- Korb D. Survey of preferred tests for diagnosis of the tear film and dry eye. *Cornea*, **2000**; 19:483-486.
- Korb DR, (Ed.). The tear film: its role today and in the future. In: Korb DR, Craig J, Doughty M, Guillion J-P, Tomlinson A, Smith G eds. *The Tear Film: Structure, Function and Clinical Examination*. Boston: *Butterworth-Heinemann*, **2002**; 9–13.

Korb DR, Baron DF, Herman JP, Finnemore VM, Exford JM, Hermosa JL, Leahy CD, Glonek T, Greiner JV. Tear film lipid layer thickness as a function of blinking. *Cornea*, **1994**; 13:354-359.

Korb DR, Greiner JV, Glonek T, Whalen A, Hearn S L, Esway JE, Leahy CD. Human and rabbit lipid layer and interference pattern observations. In *Lacrimal Gland, Tear Film and Dry Eye Syndromes 2*, **1998**; 305-308. Springer US.

Korb DR, Greiner JV, Herman J. Comparison of fluorescein break-up time measurement reproducibility using standard fluorescein strips versus the Dry Eye Test (DET) method. *Cornea*, **2001**; 20:811-815.

Korb DR, Greiner JV. Increase in tear film lipid layer thickness following treatment of meibomian gland dysfunction. In *Lacrimal Gland, Tear Film and Dry Eye Syndromes 1994*; 350:293-298. Springer US.

Korb DR, Herman JP, Greiner JV, Scaffidi RC, Finnemore VM, Exford JM, Blackie CA, Douglass T. Lid wiper epitheliopathy and dry eye symptoms. *Eye & contact lens*, **2005**; 31:2-8.

Korb DR, Herman JP. Corneal staining subsequent to sequential fluorescein instillations. *Journal of the American Optometric Association*, **1979**; 50:361-367.

Kremer JM. n-3 Fatty acid supplements in rheumatoid arthritis. *The American journal of clinical nutrition*, **2000**; 71: 349S-351S.

Kulkarni SP, Bhanumathi B, Thoppil SO, Bhogte CP, Vartak BD, Amin PD Dry eye syndrome. *Drug development and industrial pharmacy*, **1997**; 23:465-471.

Kunert KS, Keane-Myers AM, Spurr-Michaud S, Tisdale AS, Gipson IK. Alteration in goblet cell numbers and mucin gene expression in a mouse model of allergic conjunctivitis. *Investigative ophthalmology & visual science*, **2001**; 42:2483-2489.

Kunert KS, Tisdale AS, Gipson IK. Goblet cell numbers and epithelial proliferation in the conjunctiva of patients with dry eye syndrome treated with cyclosporine. *Archives of ophthalmology*, **2002**; 120:330-337.

Künzel P. The treatment of the contact lens related dry eye: a prospective, randomised, controlled study. *Die Kontaktlinse*, **2008**; 41:4-10.

Kurihashi K, Yanagihara N, Nishihama H, Suehiro S, Kondo T. A new tear test—fine thread method. *Pract Otol Kyoto*, **1975**; 68:533-554.

Lal H, Khurana AK. Tear immunoglobulins and lysozyme levels in corneal ulcers. In *Lacrimal Gland, Tear Film and Dry Eye Syndromes*, **1994**; 355-358. Springer US.

Lawrence MS, Redmond DE Jr, Elsworth JD, Taylor JR, Roth RH. The D1 receptor antagonist, SCH 23390, induces signs of parkinsonism in African green monkeys. *Life sciences*, **1991**; 49:229-234.

Lebowitz HM, Chang RK, Mandell AI. Gel tears. A new medication for the treatment of dry eyes. *Ophthalmology*, **1984**; 91:1199-1204.

Lee AJ, Lee J, Saw SM, Gazzard G, Koh D, Widjaja D, Tan DTH. Prevalence and risk factors associated with dry eye symptoms: a population based study in Indonesia. *British Journal of Ophthalmology*, **2002**; 86:1347-1351.

Lee JE, Kim NM, Yang JW, Kim SJ, Lee JS, Lee JE. A randomised controlled trial comparing a thermal massager with artificial teardrops for the treatment of dry eye. *British Journal of Ophthalmology*, **2013**; 2013.

Lee S, Dausch S, Maierhofer G, Dausch D. A new therapy concept with a liposome eye spray for the treatment of the dry eye. *Klinische Monatsblätter für Augenheilkunde*, **2004**; 221:825–836.

Lemp MA, Bron AJ, Baudouin C, Benítez del Castillo JM, Geffen D, Tauber J, Foulks GN, Pepose JS, Sullivan BD. Tear osmolarity in the diagnosis and management of dry eye disease. *American journal of ophthalmology*, **2011**; 151:792-798.

Lemp MA, Hamill JR. Factors affecting tear film breakup in normal eyes. *Archives of ophthalmology*, **1973**; 89:103-105.

Lemp MA, Holly FJ. Ophthalmic polymers as ocular wetting agents. *Annals of ophthalmology*, **1972**; 4:15-20.

Lemp MA, Zimmerman LE. Toxic endothelial degeneration in ocular surface disease treated with topical medications containing benzalkonium chloride. *American journal of ophthalmology*, **1988**; 105:670–673.

Lemp MA. Advances in understanding and managing dry eye disease. *American journal of ophthalmology*, **2008**; 146:350-356.

Lemp MA. Artificial tear solutions. *International ophthalmology clinics*, **1973**; 13:221–229.

Lemp MA. Report of the National Eye Institute/Industry workshop on clinical trials in dry eyes. *Eye & Contact Lens*, **1995**; 21:221-232.

Lemp MA. The mucin-deficient dry eye. *International ophthalmology clinics*, **1973**; 13:185-190.

Lemp, MA. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop. *Ocular Surface*, **2007**; 75-92.

Lenton LM, Albietsz JM. Effect of carmellose-based artificial tears on the ocular surface in eyes after laser in situ keratomileusis. *Journal of refractive surgery (Thorofare, NJ: 1995)*, **1998**; 15:S227-S231.

Lesley J, Hyman R, Kincade PW. CD44 and its interaction with extracellular matrix. *Advances in immunology*, **1993**; 54:271–335.

Li DQ, Chen Z, Song XJ, Luo L, Pflugfelder SC. Stimulation of matrix metalloproteinases by hyperosmolarity via a JNK pathway in human corneal epithelial cells. *Investigative ophthalmology & visual science*, **2004**; 45:4302–4311.

Liao SL, Kao SCS, Tseng JHS, Chen MS, Hou PK. Results of intraoperative mitomycin C application in dacryocystorhinostomy. *British journal of ophthalmology*, **2000**; 84:903–906.

Lim KJ, Lee JH. Measurement of the Tear Meniscus Height Using. *Korean Journal of Ophthalmology*, **1991**; 5:34-36.

- Limberg MB, McCaa C, Kissling GE, Kaufman HE. Topical application of hyaluronic acid and chondroitin sulphate in the treatment of dry eyes. *American journal of ophthalmology*, **1987**; 103:194-197.
- Lin H, Yiu SC. Dry eye disease: A review of diagnostic approaches and treatments. *Saudi Journal of Ophthalmology*, **2014**; 28: 173-181.
- Lin PY, Tsai SY, Cheng CY, Liu JH, Chou P, Hsu WM. Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Ophthalmology*, **2003**; 110:1096-1101.
- Lindgren T, Andersson K, Dammstrom BG, Norback D. Ocular, nasal, dermal and general symptoms among commercial airline crews. *International archives of occupational and environmental health*, **2002**; 75:475-483.
- Lindquist TD, Edenfield M. Cytotoxicity of viscoelastics on cultured corneal epithelial cells measured by plasminogen activator release. *Journal of refractive and corneal surgery*, **1993**; 10:95–102.
- Lithgow FW. Eloisin. Tratamiento de eleccion de la hiposecrecion lagrimal. *An Inst Barraquer (Barc)* **1996**; 25:713–719.
- Little SA, Bruce AS. Repeatability of the phenol-red thread and tear thinning time tests for tear film function. *Clinical and Experimental Optometry*, **1994a**; 77:64-68.
- Liu X, Wang S, Kao AA, Long Q. The effect of topical pranopfen 0.1% on the clinical evaluation and conjunctival HLA-DR expression in dry eyes. *Cornea*, **2012**; 31:1235-1239.
- Liu Z, Pflugfelder SC. Corneal surface regularity and the effect of artificial tears in aqueous tear deficiency. *Ophthalmology*, **1999**; 106:939-943.
- Loran DFC, French CN, Lam SY, Papas E. Reliability of the wetting value of tears. *Ophthalmic and Physiological Optics*, **1987**; 7:53-56.
- Lozato PA, Pisella PJ, Baudouin C. The lipid layer of the lacrimal tear film: physiology and pathology. *Journal français d'ophtalmologie*, **2001**; 24:643–658.
- Lucca JA, Nunez JN, Farris RL. A comparison of diagnostic tests for keratoconjunctivitis sicca: lactoplate, Schirmer, and tear osmolarity. *Eye & Contact Lens*, **1990**; 16:109-112.
- Luo L, Li D, Corrales RM, Pflugfelder S. Hyperosmolar saline is a pro inflammatory stress on the mouse ocular surface. *Eye & contact lens*, **2005**; 31:186-193.
- Luo L, Li DQ, Doshi A, Farley W, Corrales RM, Pflugfelder SC. Experimental dry eye stimulates production of inflammatory cytokines and MMP-9 and activates MAPK signaling pathways on the ocular surface. *Investigative ophthalmology & visual science*, **2004**; 45:4293-4301.
- Machado LM, Castro CS, Fontes BM. Staining patterns in dry eye syndrome: rose bengal versus lissamine green. *Cornea*, **2009**; 28:732-734.
- Mackay CR, Terpe HJ, Stauder R, Marston WL, Stark H, Günthert U. Expression and modulation of CD44 variant isoforms in humans. *The Journal of cell biology*, **1994**; 124:71–82.

- Mackie IA, Seal DV. The questionably dry eye. *British Journal of Ophthalmology*, **1981**; 65:2-9.
- Macri A, Pflugfelder SC. Correlation of the Schirmer 1 and fluorescein clearance tests with the severity of corneal epithelial and eyelid disease. *Archives of ophthalmology*, **2000**; 118:1632-1638.
- Mader TH, Stulting RD. Keratoconjunctivitis sicca caused by diphenoxylate hydrochloride with atropine sulfate (Lomotil). *American journal of ophthalmology*, **1991**; 111:377-378.
- Mainstone JC, Bruce AS, Golding TR. Tear meniscus measurement in the diagnosis of dry eye. *Current eye research*, **1996**; 15:653-661.
- Management and therapy of dry eye disease: Report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop. *Ocular Surface*, **2007**; 5:163-178.
- Mangione CM, Lee PP, Pitts J, Gutierrez P, Berry S, Hays RD. Psychometric properties of the National Eye Institute visual function questionnaire (NEI-VFQ). *Archives of Ophthalmology*, **1998**; 116:1496-1504.
- Margrain TH, Ryan B, Wild JM. A revolution in Welsh low vision service provision. *British Journal of ophthalmology*, **2005**; 89:933-934.
- Marquardt R. Diagnostische tests zur beurteilung des tränenfilms. *Klinische Monatsbl Augenheilk*, **1986**; 189:87-91.
- Marquardt R. The Treatment of Dry Eye with a New Liquid Gel. *Klinische Monatsbl Augenheilk*, **1986**; 189:51-54.
- Marquis P, Piau E, Abetz L, Arnould B. Improving reports of pro data to support an effectiveness claim. *Value Health*, **2003**; 6:293.
- Mason A, Mason J. Optometrist prescribing of therapeutic agents: findings of the AESOP survey. *Health Policy*, **2002**; 60:185-197.
- Mathers WD, Lane JA, Zimmerman MB. Tear film changes associated with normal aging. *Cornea*, **1996**; 15:229-234.
- Matheson A. Dry eye Management the TheraTears Way. *Optician*, **2006**; 6067.
- Matheson, A. Dry Eye, Assessment and Management. **2007**; 1-17.
- Matsumoto Y, Ohashi Y, Watanabe H, Tsubota K. Efficacy and safety of diquafosol ophthalmic solution in patients with dry eye syndrome: a Japanese phase 2 clinical trial. *Ophthalmology*, **2012**; 119:1954-1960.
- McCarty CA, Bansal AK, Livingston PM, Stanislavsky YL, Taylor HR. The epidemiology of dry eye in Melbourne, Australia. *Ophthalmology*, **1998**; 105:1114-1119.
- McCulley JP, Aronowicz JD, Uchiyama E, Shine WE, Butovich IA. Correlations in a change in aqueous tear evaporation with a change in relative humidity and the impact. *American journal of ophthalmology*, **2006**; 141:758-760.
- McCulley JP, Dougherty JM, Deneau DG. Classification of chronic blepharitis. *Ophthalmology*, **1982**; 89:1173-1180.

- McCulley JP, Shine W. A compositional based model for the tear film lipid layer. *Transactions of the American Ophthalmological Society*, **1997**; 95:79-93.
- McCulley JP, Shine WE. Eyelid disorders: the meibomian gland, blepharitis, and contact lenses. *Eye and Contact Lens*, **2003**; 29:S93–95, discussion S115–8, S192–194.
- McDonald MB. The Changing Landscape of Dry Eye Diagnosis. <http://www.refractiveeyecare.com/2012/10/the-changing-landscape-of-dry-eye-diagnosis/> **2012**.
- McDonald M. Latest trends in dry eye treatments (advertorial). *Cornea Society News*, **2007**; 3:7-8.
- McGinnigle S, Eperjesi F, Naroos S. Optometric management of dry eye. *Optometry Today*, **2011**; 45-48.
- McMonnies CW, Ho A. Marginal dry eye diagnosis: history versus biomicroscopy. *The Preocular Tear Film in Health, Disease, and Contact Lens Wear*. Lubbock, TX: Dry Eye Institute, **1986**; 32-40.
- McMonnies CW, Ho A. Patient history in screening for dry eye conditions. *Journal of the American Optometric Association*, **1987**; 58:296-301.
- McMonnies CW. Key questions in a dry eye history. *Journal of the American Optometric Association*, **1986**; 57: 512 – 517.
- McMonnies CW. Responses to a dry eye questionnaire from a normal population. *Journal of the American Optometric Association*, **1987**; 58:588-591.
- McNamara NA, Polse KA, Fukunaga SA, Maebori JS, Suzuki RM. Soft lens extended wear affects epithelial barrier function. *Ophthalmology*, **1998**; 105:2330-2335.
- Meller D, Tseng SC. Conjunctivochalasis: literature review and possible pathophysiology. *Survey of ophthalmology*, **1998**; 43:225-232.
- Mengher LS, Bron AJ, Tonge SR, Gilbert DJ. A non-invasive instrument for clinical assessment of the pre-corneal tear film stability. *Current eye research*, **1985**; 4:1-7.
- Mengher LS, Bron AJ, Tonge SR, Gilbert DJ. Effect of fluorescein instillation on the pre-corneal tear film stability. *Current eye research*, **1985**; 4:9-12.
- Mengher LS, Pandher KS, Bron AJ, Davey CC. Effect of sodium hyaluronate (0.1%) on break-up time (NIBUT) in patients with dry eyes. *British journal of ophthalmology*, **1986**; 70:442-447.
- Mertzanis P, Abetz L, Rajagopalan K, Espindle D, Chalmers R, Snyder C, Caffery B, Begley C. The relative burden of dry eye in patients' lives: comparisons to a US normative sample. *Investigative ophthalmology & visual science*, **2005**; 46:46-50.
- Miljanovic B, Dana MR, Sullivan DA, Schaumberg DA. Prevalence and risk factors for dry eye syndrome among older men in the United States. *Investigative Ophthalmology & Visual Science*, **2007**; 48:4293.
- Miller K, Walt J, Mink D, Satram-Hoang S, Wilson SE, Perry HD, Asbell PA, Pflugfelder SC. Minimal clinically important difference for the ocular surface disease index. *Archives of ophthalmology*, **2010**; 128:94–101.

Miller WL, Doughty MJ, Narayanan S, Leach NE, Tran ABA, Gaume AL, Bergmanson JP. A comparison of tear volume (by tear meniscus height and phenol red thread test) and tear fluid osmolality measures in non-lens wearers and in contact lens wearers. *Eye & contact lens*, **2004**; 30:132-137.

Mishima S, Gasset A, Klyce Jr SD, Baum JL. Determination of tear volume and tear flow. *Investigative Ophthalmology & Visual Science*, **1966**; 5:264-276.

Mishima S, Maurice DM. The oily layer of the tear film and evaporation from the corneal surface. *Experimental eye research*, **1961**; 1:39-45.

Miyawaki S, Nishiyama S. Classification criteria for Sjogren's syndrome--sensitivity and specificity of criteria of the Japanese Ministry of Health and Welfare (1977) and criteria of European community (1993). *Nihon rinsho. Japanese journal of clinical medicine*, **1995**; 53:2371-2375.

Montés-Micó R. Role of the tear film in the optical quality of the human eye. *Journal of Cataract & Refractive Surgery*, **2007**; 33:1631-1635.

Moon JW, Lee HJ, Shin KC, Wee WR, Lee JH, Kim MK. Short term effects of topical cyclosporine and viscoelastic on the ocular surfaces in patients with dry eye. *Korean Journal of Ophthalmology*, **2007**; 21:189-194.

Morgan P, Maldonado-Codina C. Corneal staining: do we really understand what we are seeing? *Contact Lens and Anterior Eye*, **2009**; 32:48-54.

Morgan PB, Efron N, Brennan NA, Hill EA, Raynoe MK, Tullio AB. Risk factors for the development of corneal infiltrative events associated with contact lens wear. *Investigative ophthalmology & visual science*, **2005**; 46:3136-3143.

Morgan PB, Efron N, Morgan S, Little SA. Hydrogel contact lens dehydration in controlled environmental conditions. *Eye & contact lens*, **2004**; 30:99-102.

Moscovici BK, Holzchuh R, Chiacchio BB, Santo RM, Shimazaki J, Hida RY. Clinical treatment of dry eye using 0.03% tacrolimus eye drops. *Cornea*, **2012**; 31:945-949.

Moss SE, Klein R, Klein BE. Incidence of dry eye in an older population. *Archives of ophthalmology*, **2004**; 122:369-373.

Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. *Archives of ophthalmology*, **2000**; 118:1264-1268.

Muñoz B, West SK, Rubin GS, Schein OD, Quigley HA, Bressler SB, Bandeen-Roche K. Causes of blindness and visual impairment in a population of older Americans: The Salisbury Eye Evaluation Study. *Archives of Ophthalmology*, **2000**; 118:819-825.

Murube J. Tear osmolarity. *The ocular surface*, **2006**; 4:62-73.

Nagayova B, Tiffany JM. Components responsible for the surface tension of human tears. *Current eye research*, **1999**; 19:4-11.

Nakamori K, Odawara M, Nakajima T, Mitzutani T, Tsubota K. Blinking is controlled primarily by ocular surface conditions. *American journal of ophthalmology*, **1997**; 124:24-30.

Nakamura M, Hikida M, Nakano T, Ito S, Hamano T, Kinoshita S. Characterization of water retentive properties of hyaluronan. *Cornea*, **1993**; 12:433-436.

Nakamura S, Okada S, Umeda Y, Saito F. Development of a rabbit model of tear film instability and evaluation of viscosity of artificial tear preparations. *Cornea*, **2004**; 23:390-397.

Needle JJ, Petchey R, Lawrenson JG. A survey of the scope of therapeutic practice by UK optometrists and their attitudes to an extended prescribing role. *Ophthalmic and Physiological Optics*, **2008**; 28:193-203.

Nelson J, Drake M, Brewer J, Tuley M. Evaluation of a physiological tear substitute in patients with keratoconjunctivitis sicca. In *Lacrimal Gland, Tear Film and Dry Eye Syndromes* **1994**; 453-457. Springer US.

Nelson JD, Farris RL. Sodium hyaluronate and polyvinyl alcohol artificial tear preparations: a comparison in patients with keratoconjunctivitis sicca. *Archives of ophthalmology*, **1988**; 106:484-487.

Nelson JD, Gordon JF. Topical fibronectin in the treatment of keratoconjunctivitis sicca. Chiron Keratoconjunctivitis Sicca Study Group. *American journal of ophthalmology*, **1992**; 114:441-447.

Nelson JD, Wright JC. Tear film osmolality determination: an evaluation of potential errors in measurement. *Current eye research*, **1986**; 5:677-682.

Nelson JD. Impression cytology. *Cornea*, **1988**; 7:71-81.

Nepp J, Schauersberger J, Schild G, Jandrasits K, Haslinger-Akramian J, Derbolav A, Wedrich A. The clinical use of viscoelastic artificial tears and sodium chloride in dry-eye syndrome. *Biomaterials*, **2001**; 22:3305-3310.

Nichols BA, Chiappino ML, Dawson CR. Demonstration of the mucous layer of the tear film by electron microscopy. *Investigative ophthalmology & visual science*, **1985**; 26:464-473.

Nichols JJ, Sinnott IT. Tear film, contact lens, and patient-related factors associated with contact lens-related dry eye. *Investigative ophthalmology & visual science*, **2006**; 47:1319-1328.

Nichols JJ, Ziegler C, Mitchell GL, Nichols KK. Self-reported dry eye disease across refractive modalities. *Investigative ophthalmology & visual science*, **2005**; 46:1911-1914.

Nichols KK, Begeley CG, Caffery B, Jones LA. Symptoms of ocular irritation in patients diagnosed with dry eye. *Optometry & Vision Science*, **1999**; 76:838-844.

Nichols KK, Mitchell GL, Zadnik K. The repeatability of clinical measurements of dry eye. *Cornea*, **2004**; 23:272-285.

Nichols KK, Nichols JJ, Mitchell GL. The lack of association between signs and symptoms in patients with dry eye disease. *Cornea*, **2004**; 23:762-770.

Niederhorn JY, Stern ME, Pflugfelder SC, De Paiva CS, Corrales RM, Gao J, Siemasko K. Desiccating stress induces T cell-mediated Sjögren's syndrome-like lacrimal keratoconjunctivitis. *The Journal of Immunology*, **2006**; 176:3950-3957.

Nishida T, Nakamura M, Mishima H, Otori T. Hyaluronan stimulates corneal epithelial migration. *Experimental eye research*, **1991**; 53:753-758.

- Norn MS. Desiccation of the precorneal film. *Acta ophthalmologica*, **1969**; 47:865-880.
- Norn MS. *External eye: Methods of examination*. Copenhagen: Scriptor. **1974**; 76-78.
- Norn MS. Preoperative protection of cornea and conjunctiva. *Acta ophthalmologica*, **1981**; 59:587-594.
- Norn MS. Semi quantitative interference study of fatty layer of pre corneal film. *Acta ophthalmologica*, **1979**; 57:766-774.
- Norn MS. Tear film break-up time: a review. *The Preocular Tear Film: In Health, Disease and Contact Lens Wear*, **1986**; 3:52-56.
- Norn MS: Lissamine green. Vital staining of the cornea and conjunctiva. *Acta Ophthalmologica*, **1973**; 51:483-91.
- O'Hare R. LOCSU welcomes NHS chief's recommendations. *Optometry Today*, **2014**; 54:6.
- O'Toole L. Therapeutics in practice: Disorders of the tears and lacrimal system. *Optometry Today*, **2005**; 47-51.
- Oden NL, Liliensfeld DE, Lemp MA, Nelson JD, Ederer F. Sensitivity and specificity of a screening questionnaire for dry eye. In *Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2*, **1998**; 807-820. Springer US.
- Ogasawara K, Mitsubayashi K, Tsuru T, Karube L. Electrical conductivity of tear fluid in healthy persons and keratoconjunctivitis sicca patients measured by a flexible conductimetric sensor. *Graefe's archive for clinical and experimental ophthalmology*, **1996**; 234: 542-546.
- Olson MC, Korb DR, Grainer JV. Increase in tear film lipid layer thickness following treatment with warm compresses in patients with meibomian gland dysfunction. *Eye & contact lens*, **2003**; 29:96-99.
- Opitz DL, Tyler KF. Efficacy of azithromycin 1% ophthalmic solution for treatment of ocular surface disease from posterior blepharitis. *Clinical and Experimental Optometry*, **2011**; 94:200-206.
- Owens H, Phillips JR. Tear spreading rates: post-blink. In *Lacrimal Gland, Tear Film, and Dry Eye Syndromes 3*, **2002**; 1201-1204. Springer U.
- Papa V, Aragona P, Russo S, Di Bella A, Russo P, Milazzo G Comparison of hypotonic and isotonic solutions containing sodium hyaluronate on the symptomatic treatment of dry eye patients. *Ophthalmologica*, **2001**; 215:124-127.
- Patel S, Farrell J, Blades KJ, Grierson DJ. The value of a phenol red impregnated thread for differentiating between the aqueous and non-aqueous deficient dry eye. *Ophthalmic and Physiological Optics*, **1998**; 18:471-476.
- Patel S, Farrell JC. Age-related changes in precorneal tear film stability. *Optometry & Vision Science*, **1989**; 66:175-178.
- Patel S, Murray D, McKenzie A, Shearer DS, McGrath BD. Effects of fluorescein on tear breakup time and on tear thinning time. *American journal of optometry and physiological optics*, **1985**; 62:188-190.

- Patel S, Wallace I. Tear meniscus height, lower punctum lacrimale, and the tear lipid layer in normal aging. *Optometry & Vision Science*, **2006**; 83:731-739.
- Paulsen E, Otkjaer A, Andersen KE. The coumarin herniarin as a sensitizer in German chamomile [*Chamomilla recutita* (L.) Rauschert, Compositae]. *Contact Dermatitis*, **2010**; 62:338–342.
- Perrigan DM, Morgan A, Quintero S, Perrigin J, Brown S, Bergmanson J. Comparison of osmolality values of selected ocular lubricants. *Investigative Ophthalmology and Visual Science*, **2004**; 45:3901.
- Peterson RC, Wolffsohn JS, Fowler CW. Optimization of anterior eye fluorescein viewing. *American journal of ophthalmology*, **2006**; 142:572-575.
- Pflugfelder SC, Jones D, Ji Z, Afonso A, Monroy D. Altered cytokine balance in the tear fluid and conjunctiva of patients with Sjögren's syndrome keratoconjunctivitis sicca. *Current eye research*, **1999**; 19:201-211.
- Pflugfelder SC, Lui Z, Uouroy D, Li D-Q, Carvajal ME, Price-Schiavi SA, Idris N, Solomon A, Perez A, Carraway KL. Detection of sialomucin complex (MUC4) in human ocular surface epithelium and tear fluid. *Investigative ophthalmology & visual science*, **2000**; 41:1316-1326.
- Pflugfelder SC, Solomon A, Stern ME The diagnosis and management of dry eye: A twenty-five-year review. *Cornea*, **2000**; 19:644–649.
- Pflugfelder SC, Tseng SC, Sanabria O, Kell H, Garcia CG, Felix C, Feuer W, Reis BL. Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. *Cornea*, **1998**; 17:38-56.
- Pflugfelder SC, Tseng SC, Yoshino K, Monroy D, Felix C, Reis BL. Correlation of goblet cell density and mucosal epithelial membrane mucin expression with rose bengal staining in patients with ocular irritation. *Ophthalmology*, **1997**; 104:223-225.
- Pflugfelder SC. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop. *The Ocular Surface*, **2007**; 5:163-178.
- Pharmakakis NM, Katsimpris JM, Melachrinou M, Koliopoulos JX. Corneal complications following abuse of topical anaesthetics. *European journal of ophthalmology*, **2001**; 12:373-378.
- Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. *British Journal of Ophthalmology*, **2002**; 86:418-423.
- Polack FM, McNiece MT. The Treatment of Dry Eyes with Na Hyaluronate (Healon (R)). *Cornea*, **1982**; 1:133–136.
- Port MJ, Asaria TS. The assessment of human tear volume. *Journal of the British Contact Lens Association*, **1990**; 13:76-82.
- Prabhasawat P, Tesavibul N, Kasetsuwan N. Performance profile of sodium hyaluronate in patients with lipid tear deficiency: randomised, double-blind, controlled, exploratory study. *British journal of ophthalmology*, **2007**; 91:47-50.

- Pult H, Purslow C, Murphy PJ. The relationship between clinical signs and dry eye symptoms. *Eye*, **2011**; 25:502–510.
- Pult H, Gill F, Riede-Pult BH. Effect of three different liposomal eye sprays on ocular comfort and tear film. *Contact Lens and Anterior Eye*, **2012**; 35:203–207.
- Pult H, Murphy PJ, Purslow C. A novel method to predict the dry eye symptoms in new contact lens wearers. *Optometry & Vision Science*, **2009**; 86:1042-1050.
- Pult H, Purslow C, Berry M, Murphy PJ. Clinical tests for successful contact lens wear: relationship and predictive potential. *Optometry & Vision Science*, **2008**; 85:E924-E929.
- Pult H, Riede-Pult BH. A new modified fluorescein strip: Its repeatability and usefulness in tear film break-up time analysis. *Contact Lens and Anterior Eye*, **2012**; 35:35-38.
- Pult H, Sickenberger W, Sickenberger B. LIPCOF and contact lens wearers: a new tool to forecast subjective dryness and degree of comfort of contact lens wearers. *Contactologia*, **2000**; 22:74-79.
- Pult H. The Predictive Ability of Clinical Tests for Dry Eye in Contact Lens Wear (PhD Thesis). *Cardiff University: Cardiff*, **2008**.
- Rahman MQ, Chuah KS, Macdonald ECA, Trusler JPM, Ramaesh K. The effect of pH, dilution, and temperature on the viscosity of ocular lubricants—shift in rheological parameters and potential clinical significance. *Eye*, **2012**; 26:1579-1584.
- Rajagopalan K, Abetz I, Mertzanis P, Espindle MA, Begley C, Chalmers R, Caffery B, Snyder C, Nelson JD, Simpson T, Edrington T. Comparing the Discriminative Validity of Two Generic and One Disease-Specific Health-Related Quality of Life Measures in a Sample of Patients with Dry Eye. *Value in health*, **2005**; 8:168-174.
- Ralph RA. Conjunctival goblet cell density in normal subjects and in dry eye syndromes. *Investigative Ophthalmology & Visual Science*, **1975**; 14:299-302.
- Reddy P, Grad O, Rajagopalan K. The economic burden of dry eye: a conceptual framework and preliminary assessment. *Cornea*, **2004**; 23:751–761.
- Reich W, Ladwig KJ, Lange W. Dryness of the eyes after cataract surgery. *Z prakt Augenheilkd*, **2008**; 29:1–8.
- Rieger G. Lipid-containing eye drops: a step closer to natural tears. *Ophthalmologica*, **1990**; 201:206-212.
- Rieger G. The importance of the precorneal tear film for the quality of optical imaging. *British journal of ophthalmology*, **1992**; 76:157-158.
- Rodríguez-Torres LA, Porrás-Machado DJ, Villegas-Guzmán AE, Molina-Zambrano JA. Analysis of incidence of ocular surface disease index with objective tests and treatment for dry eye. *Archivos de la Sociedad Española de Oftalmología (English Edition)*, **2010**; 85:70-75.
- Rogers J. Environmental dry eyes in soft contact lens wear. *Optician*, **2009**; 26-31.
- Rolando M, Brezzo G, Giordano P, Campagna P, Burlando S, Calabria G. The effect of different benzalkonium chloride concentrations on human normal ocular surface. *The lacrimal system. New York: Kugler and Ghedini*, **1991**; 87-91.

- Rolando M, Refojo MF, Kenyon KR. Tear water evaporation and eye surface diseases. *Ophthalmologica*, **1985**; 190:147-149.
- Rolando M, Refojo MF. Tear evaporimeter for measuring water evaporation rate from the tear film under controlled conditions in humans. *Experimental eye research*, **1983**; 36:25-33.
- Ruskell GL, Bergmanson JPG. Anatomy and physiology of the cornea and related structures. *Contact Lenses 5th Edition* **2007**; 48-50.
- Russ M. Professional fees: Part 2 - Fee and product pricing. *Optician*, **2008**; 235:14-16.
- Saeed N, Qazi ZA, Butt NH, Siddiqi A, Maheshwary N, Khan M A. Effectiveness of sodium hyaluronate eye gel in patients with dry eye disease: A multi-centre, open label, uncontrolled study. *Pakistan journal of medical sciences*, **2013**; 29:1055.
- Saettone MF, Chetoni P, Tilde Torracca M, Burgalassi S, Giannaccini B. Evaluation of muco-adhesive properties and in vivo activity of ophthalmic vehicles based on hyaluronic acid. *International journal of pharmaceuticals*, **1989**; 51:202-212.
- Sahlin S, Chen E. Evaluation of the lacrimal drainage function by the drop test. *American journal of ophthalmology*, **1996**; 122:701-708.
- Sakamoto R, Bennett ES, Henry VA, Paragina S, Narumi T, Izumi Y, Kamei Y, Nagatomi E, Miyanaga Y, Hamano H, Mitsunaga S. The phenol red thread tear test: a cross-cultural study. *Investigative ophthalmology & visual science*, **1993**; 34:3510-3514.
- Sanchez MA, Arriola-Villalobos P, Torralbo-Jimenez P, Girón N, De la Heras B, Vanrell RH, Álvarez-Barrientos A, Benítez-del-Castillo JM. The effect of preservative-free HP-Guar on dry eye after phacoemulsification: a flow cytometric study. *Eye*, **2010**; 24:1331-1337.
- Sand BB, Marner K, Norn MS. Sodium hyaluronate in the treatment of keratoconjunctivitis sicca. *Acta ophthalmologica*, **1989**; 67:181-183.
- Santodomingo-Rubido J, Wolffsohn JS, Gilmartin B. Comparison between graticule and image capture assessment of lower tear film meniscus height. *Contact Lens and Anterior Eye*, **2006**; 29:169-173.
- Sato M, Fukayo S, Yano E. Adverse environmental health effects of ultra-low relative humidity indoor air. *Journal of occupational health*, **2003**; 45:133-136.
- Sator MO, Joura EA, Golaszewski T, Gruber D, Frigo P, Metka M, Hommer A, Huber JC. Treatment of menopausal keratoconjunctivitis sicca with topical oestradiol. *BJOG: An International Journal of Obstetrics & Gynaecology*, **1998**; 105:100-102.
- Saude T. In: Ocular anatomy and physiology. *Blackwell Scientific, Boston MA*, **1993**; 96-104.
- Scaffidi RC, Korb DR. Comparison of the efficacy of two lipid emulsion eye drops in increasing tear film lipid layer thickness. *Eye & contact lens*, **2007**; 33:38-44.
- Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. *American journal of ophthalmology*, **2003**; 136:318-326.

Schein O, Tielsch J, Muñoz B, Bandeen-Roche K, West S. Relation between signs and symptoms of dry eye in the elderly: a population-based perspective. *Ophthalmology*, **1997**; 104:1395-1400.

Schein OD, Hochberg MC, Muñoz B, Tielsch JM, Bandeen-Roche K, West S. Dry eye and dry mouth in the elderly: a population-based assessment. *Archives of internal medicine*, **1999**; 159:1359-1363.

Schein OD, Muñoz B, Tielsch JM, Bandeen-Roche K, West S. Prevalence of dry eye among the elderly. *American journal of ophthalmology*, **1997**; 124:723-728.

Schein OD, Tielsch JM, Muñoz B, Bandeen-Roche K, West S. Relation between signs and symptoms of dry eye in the elderly: a population-based perspective. *Ophthalmology*, **1997**; 104:1395-1401.

Schendowich, B. Readers' Forum Four-Point Plan to Achieve Comfortable Contact Lens Wear. *Contact Lens Spectrum*, **2003**; 18:50-51.

Scherz W, Dohlman CH. Is the lacrimal gland dispensable? Keratoconjunctivitis sicca after lacrimal gland removal. *Archives of ophthalmology*, **1975**; 93:281-283.

Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface disease index. *Archives of Ophthalmology*, **2000**; 118:615-621.

Schiffman RM, Walt JG, Jacobsen G, Doyle JJ, Lebovics G, Sumner W. Utility assessment among patients with dry eye disease. *Ophthalmology*, **2003**; 110:1412-1419.

Schirmer O. Studies on the physiology and pathology of the secretion and drainage of tears. *Albrecht von Graefes Arch Klin Ophthalmol*, **1903**; 56:197-291.

Schirra F, Höh H, Kienecker C, Ruprecht KW. Using LIPCOF (lid-parallel conjunctival folds) for assessing the degree of dry eye, it is essential to observe the exact position of that specific fold. In *Lacrimal Gland, Tear Film, and Dry Eye Syndromes*, **1998**; 2:853-858. Springer US.

Schofield J. Specialist conference report – Lively and Interactive. *Optician*, **2004**; 5976: 228.

Seedor JA, Lamberts D, Bergmann RB, Perry HD. Filamentary keratitis associated with diphenhydramine hydrochloride (Benadryl). *American journal of ophthalmology*, **1986**; 101:376-377.

Serin D, Karsloglu S, Kyan A, Alagoz G. A simple approach to the repeatability of the Schirmer test without anaesthesia: eyes open or closed? *Cornea*, **2007**; 26:903–906.

Shafaa MW. Efficacy of topically applied liposome-bound tetracycline in the treatment of dry eye model. *Veterinary ophthalmology*, **2011**; 14:18-25.

Shimazaki J, Goto E, Ono M, Shimmura S, Tsubota K. Meibomian gland dysfunction in patients with Sjögren syndrome. *Ophthalmology*, **1998**; 105:1485-1488.

- Shimmura S, Ono M, Shinozaki K, Toda I, Takamura E, Mashima Y, Tsubota K. Sodium hyaluronate eye drops in the treatment of dry eyes. *British journal of ophthalmology*, **1995**; 79:1007–1011.
- Shimmura S, Shimazaki J, Tsubota K. Results of a population-based questionnaire on the symptoms and lifestyles associated with dry eye. *Cornea*, **1999**; 18:408-411.
- Shimmura S, Ueno R, Matsumoto Y, Goto E, Higuchi A, Shimazaki J, Tsubota K. Albumin as a tear supplement in the treatment of severe dry eye. *British journal of ophthalmology*, **2003**; 87:1279-1283.
- Shine WE, McCulley JP. Keratoconjunctivitis sicca associated with meibomian secretion polar lipid abnormality. *Archives of ophthalmology*, **1998**; 116:849-852.
- Silberberg A, Meyer FA. Structure and function of mucus. In *Mucus in Health and Disease –II*. **1982**; 53-74. Springer US.
- Singh O, Khanam Z, Misra N, Srivastava MK. Chamomile (*Matricaria chamomilla* L.): an overview. *Pharmacognosy Reviews*, **2011**; 5:82–95.
- Skyberg K, Skulberg KR, Eduard W, Skåret E, Levy F, Kjuus H. Symptoms prevalence among office employees and associations to building characteristics. *Indoor Air*, **2003**; 13:246-252.
- Smeeth L. Assessing the likely effectiveness of screening older people for impaired vision in primary care. *Family practice*, **1998**; 15:S24–S29.
- Smith G. Pathology of the Tear Film. In: The Tear Film, Structure Function and Clinical Examination (Eds Korb et al), *Butterworth-Heinemann, Oxford*, **2002**; 114.
- Smith J, Nichols KK, Baldwin EK. Current patterns in the use of diagnostic tests in dry eye evaluation. *Cornea*, **2008**; 27:656-662.
- Smith LM, George MA, Berdy GJ, Abelson MB. Comparative effects of preservative free tear substitutes on the rabbit cornea: a scanning electron microscopic evaluation (ARVO abstract). *Investigative ophthalmology & visual science*, **1991**; 32:733.
- Snell RS, Lemp MA. Clinical anatomy of the eye. (*2<sup>nd</sup> Ed*). Malden, MA, USA: Blackwell Science. **1998**; 90-124.
- Soares EJ, França VP Transplantation of labial salivary glands for severe dry eye treatment. *Arquivos brasileiros de oftalmologia*, **2005**; 68:481–489.
- Solomon R, Perry HD, Donnenfeld ED, Greenman HE. Slit lamp biomicroscopy of the tear film of patients using topical Restasis and Refresh Endura. *Journal of Cataract & Refractive Surgery*, **2005**; 31:661–663.
- Sommer AL, Green WR. Goblet cell response to vitamin A treatment for corneal xerophthalmia. *American Journal of Ophthalmology*, **1982**; 94:213-215.
- Sommer AL. Nutritional blindness. Xerophthalmia and keratomalacia. *Oxford University Press*, **1982**.
- Sorbara L, Talsky C. Contact lens wear in the dry eye patient: predicting success and achieving it. *Canadian Journal of Optometry*, **1988**; 50:234-241.

- Stanković-Babić G, Cekić S. Autologous serum in treatment of dry eye. *Medicinski prehled*, **2012**; 65:511-515.
- Stern ME, Beuerman RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC. A unified theory of the role of the ocular surface in dry eye. In *Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2*, **1998**; 643-651. Springer US.
- Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclosporin a ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. *Ophthalmology*, **2000**; 107:967-974.
- Stuart JC, Linn JG. Dilute sodium hyaluronate (Healon) in the treatment of ocular surface disorders. *Annals of ophthalmology*, **1985**; 17:190–192.
- Sulley A. Contact Lens management of the marginal dry eye. *In print*, **2004**.
- Sullivan B. 4th International Conference on the Lacrimal Gland, Tear Film DEWS diagnostic Methodology. *The Ocular Surface & Ocular Surface and Dry Eye Syndromes*, **2007**; 5:123.
- Sullivan B. Clinical results of a first generation lab-on-chip nanolitre tear film osmometer (abstract). *Ocular Surface*, **2005**; 3:S3.
- Sullivan BD, Evans JE, Dana MR, Sullivan DA. Influence of aging on the polar and neutral lipid profiles in human meibomian gland secretions. *Archives of ophthalmology*, **2006**; 124:1286-1292.
- Sullivan BD, Whitmer D, Nichols KK, Tomlinson A, Foulks GN, Geerling G, Pepose JS, Kosheleff V, Porreco A, Lemp MA. An objective approach to dry eye disease severity. *Investigative ophthalmology & visual science*, **2010**; 51:6125-6130.
- Sullivan DA. Androgen deficiency & dry eye syndromes. *Archivos de la sociedad Espanola de oftalmologia*, **2004**; 79:49-50.
- Sullivan DA. Tearful relationships? Sex, hormones, the lacrimal gland, and aqueous-deficient dry eye. *The ocular surface*, **2004**; 2:92-123.
- Suzuki M, Massingale ML, Ye F, Godbold J, Elfassy T, Vallabhajosyula M, Asbell PA. Tear osmolarity as a biomarker for dry eye disease severity. *Investigative ophthalmology & visual science*, **2010**; 51:4557–4561.
- Taban ME, Chen B, Perry JD. Update on punctal plugs. *Compr Ophthalmol Update*, **2006**; 7:205-212.
- Tei M, Spurr-Michaud SJ, Tisdale AS, Gipson IK. Vitamin A deficiency alters the expression of mucin genes by the rat ocular surface epithelium. *Investigative ophthalmology & visual science*, **2000**; 41:82-88.
- Terry JE. Eye disease of the elderly. *Journal of the American Optometric Association*, **1984**; 55:23–29.
- Thomas E, Hay EM, Hajeer A, Silman AJ Sjögren's syndrome: a community-based study of prevalence and impact. *Rheumatology*, **1998**; 37:1069 –1076.

Toda I, Ide T, Fukumoto T, Ichihashi Y, Tsubota K. Combination therapy with Diquafosol Tetrasodium and Sodium Hyaluronate in patients with dry eye after laser in situ Keratomileusis. *American journal of ophthalmology*, **2014**; 157:616-622.

Tomić M, Kaštelan S, Metež Soldo K, Salopek-Rabatić J. Influence of BAK-Preserved Prostaglandin Analog Treatment on the Ocular Surface Health in Patients with Newly Diagnosed Primary Open-Angle Glaucoma. *Bio Medical Research International*, **2013**; 2013.

Tomlinson A, Blades, KJ, Pearce EI. What does the phenol red thread test actually measure? *Optometry & Vision Science*, **2001**; 78:142-146.

Tomlinson A, Bron AJ, Korb DR, Amano S, Paugh JR, Pearce EI, Yee R, Yokoi N, Arita R, Dogru M. The international workshop on meibomian gland dysfunction: report of the diagnosis subcommittee. *Investigative ophthalmology & visual science*, **2011**; 52:2006–2049.

Tomlinson A, Geisbrecht J. The ageing tear film. *Journal of the British Contact Lens Association*, **1993**; 16:67-69.

Tomlinson A, Khanal S, Ramaesh K, Diaper C, McFayden A. Tear Film Osmolarity: Determination of a Referent for Dry Eye Diagnosis. *Investigative ophthalmology & visual science*, **2006**; 47:4309-4315.

Tomlinson A, Khanal S. Assessment of tear film dynamics: quantification approach. *The ocular surface*, **2005**; 3:81-95.

Tsubota K, Fujihara T, Saito K, Takeuchi T. Conjunctival epithelium expression of HLA-DR in dry eye patients. *Ophthalmologica*, **1998**; 213:16-19.

Tsubota K, Monden Y, Yagi Y, Goto E, Shimmura S. New treatment of dry eye: the effect of calcium ointment through eyelid skin delivery. *British journal of ophthalmology*, **1999**; 83:767-770.

Tsubota K, Nakamori K. Dry eyes and video display terminals. *New England Journal of Medicine*, **1993**; 328:584-584.

Tsubota K, Nakamori K. Effects of ocular surface area and blink rate on tear dynamics. *Archives of Ophthalmology*, **1995**; 113:155-158.

Tsubota K, Yamada M. Tear evaporation from the ocular surface. *Investigative ophthalmology & visual science*, **1992**; 33:2942-2950.

Tuberville AW, Frederick WR, Wood TO. Punctal occlusion in tear deficiency syndromes. *Ophthalmology*, **1982**; 89:1170-1172.

Ubels JL, McCartney MD, Lantz WK, Beaird J, Dayalan A, Edelhauser HF. Effects of preservative-free artificial tear solutions on corneal epithelial structure and function. *Archives of ophthalmology*, **1995**; 113:371-378.

Uchiyama E, Aaronwicz JD, Butowich IA, McCulley JP. Pattern of Vital Staining and its correlation with Aqueous Tear Deficiency and Meibomian gland dropout. *Eye & contact lens*, **2007**; 33:177-179.

Ueta M, Sotozono C, Koga A, Yokoi N, Kinoshita S. Usefulness of a New Therapy Using Rebamipide Eye drops in Patients with VKC/AKC Refractory to Conventional Anti-Allergic Treatments. *Allergology International*, **2014**; 63:75-81.

Van Bijsterveld OP. Diagnostic tests in the sicca syndrome. *Archives of ophthalmology*, **1969**; 82:10-14.

Vehige J, Simmons PA, Anger C, Graham R, Tran L, Brady N. Cytoprotective properties of CMC when used prior to wearing contact lenses treated with cationic disinfecting agent. *Eye and Contact Lens*, **2003**; 29:177-180.

Veres A, Tapasztó B, Kosina-Hagyó K, Somfai GM, Németh J. Imaging lid-parallel conjunctival folds with OCT and comparing its grading with the slit lamp classification in dry eye patients and normal subjects. *Investigative ophthalmology & visual science*, **2011**; 52:2945-2951.

Versura P, Frigato M, Mulé R, Malavolta N, Campos EC. A proposal of new ocular items in Sjögren's syndrome classification criteria. *Clin Exp Rheumatol*, **2006**; 24:567-572.

Versura P, Maltarello M, Stecher F, Caramazza R, Laschi R. Dry eye before and after therapy with hydroxypropylmethylcellulose. *Ophthalmologica*, **1989**; 198:152-162.

Viso E, Rodriguez-Ares MT, Gude F. Prevalence of and associated factors for dry eye in a Spanish adult population (the Salnes Eye Study). *Ophthalmic epidemiology*, **2006**; 16:15-21.

Vitale S, Goodman LA, Reed GF, Smith JA. Comparison of the NEI -VFQ and OSDI questionnaires in patients with Sjogren's syndrome-related dry eye. *Health and quality of life outcomes*, **2004**; 2:44.

Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Weisman MH. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European consensus Group. *Annals of the rheumatic diseases*, **2002**; 61:554-558.

Vitali C, Moutsopoulos HM, Bombardieri S. The European Community Study Group on diagnostic criteria for Sjögren's syndrome. Sensitivity and specificity of tests for ocular and oral involvement in Sjögren's syndrome. *Annals of the rheumatic diseases*, **1994**; 53:637-647.

Volker D, Fitzgerald PATRICK, Major GABOR, Garg MANOHAR. Efficacy of fish oil concentrate in the treatment of rheumatoid arthritis. *The Journal of rheumatology*, **2000**; 27: 2343-2346.

Volker-Dieben HJ, Kok-Van Alphen CC, Hollander J., Kruit PJ, Batenburg K. The palliative treatment of dry eye. *Documenta ophthalmologica*, **1987**; 67:221-227.

Walcott B, Cameron RH, Brink PR. The anatomy and innervation of lacrimal glands. In *Lacrimal Gland, Tear Film and Dry Eye Syndromes*, **1994**; 350:11-18. Springer US.

Wang L, Gaigalas AK, Abbasi F, Marti GE, Vogt R and Schwarz A. Quantitating fluorescence intensity from fluorophores: practical use of MESF values. *Journal of research-national institute of standards and technology*, **2002**; 107:339-354.

Watanabe A, Yokoi N, Kinoshita S, Hino Y, Tsuchihashi Y. Clinicopathologic study of conjunctivochalasis. *Cornea*, **2004**; 23:294–298.

Willis RM, Folberg R, Krachmer JH, Holland EJ. The treatment of aqueous deficient dry eye with removable punctal plugs. *Ophthalmology*, **1987**; 94:514-518.

Wilson II, Fred M. Adverse external ocular effects of topical ophthalmic medications. *Survey of ophthalmology*, **1979**; 24:57–88.

Wolffsohn JS. BCLA Pioneers Lecture – Evidence basis for patient selection: How to predict contact lens success. *Contact lens & anterior eye: the journal of the British Contact Lens Association*, **2014**; 37:63-64.

Wolkoff P, Nøjgaard JK, Troiano P, Piccoli B. Eye complaints in the office environment: precorneal tear film integrity influenced by eye blinking efficiency. *Occupational and environmental medicine*, **2005**; 62:4-12.

Worda C, Nepp J, Huber JC, Sator MO. Treatment of keratoconjunctivitis sicca with topical androgen. *Maturitas*, **2001**; 37:209–212.

Wright JC, Meger GE. A review of the Schirmer test for tear production. *Archives of ophthalmology*, **1962**; 67:564-565.

[www.bon.de/download/TearscopeE.pdf](http://www.bon.de/download/TearscopeE.pdf)

[www.college-optometrists.org](http://www.college-optometrists.org)

Wysenbeek YS, Loya N, Sira BI, Ophir I, Shual YB. The effect of sodium hyaluronate on the corneal epithelium. An ultrastructural study. *Investigative ophthalmology & visual science*, **1988**; 29:194–199.

Xu KP, Yagi Y, Toda I, Tsubota K. Tear Function Index A New Measure of Dry Eye. *Archives of ophthalmology*, **1995a**; 113:84-88.

Yeh S, Song XJ, Farley W, Li DQ, Stern ME, Pflugfelder SC. Apoptosis of ocular surface cells in experimentally induced dry eye. *Investigative ophthalmology & visual science*, **2003**; 44:124-129.

Yokoi N, Kinoshita S, Bron AJ, Tiffany JM, Sugita J, Inatomi T. Tear meniscus changes during cotton thread and Schirmer testing. *Investigative ophthalmology & visual science*, **2000**; 41:3748–3753.

Yokoi N, Kinoshita S. Clinical evaluation of corneal epithelial barrier function with the slit-lamp Fluorophotometer. *Cornea*, **1995**; 14:485-489.

Yokoi N, Komuro A, Nishida K, Kinoshita S. Effectiveness of hyaluronan on corneal epithelial barrier function in dry eye. *British journal of ophthalmology*, **1997**; 81:533–536.

Yokoi N, Komuro A. Non-invasive methods of assessing the tear film. *Experimental eye research*, **2004**; 78:399-407.

Yokoi N, Mossa F, Tiffany JM, Bron AJ. Assessment of meibomian gland function in dry eye using meibometry. *Archives of ophthalmology*, **1999**; 117:723-729.

Yokoi N, Takehisa Y, Kinoshita S. Correlation of tear lipid layer interference patterns with the diagnosis and severity of dry eye. *American journal of ophthalmology*, **1996**; 122:818-824.

Yoon KC, Heo H, Im SK, You IC, Kim YH, Park YG. Comparison of autologous serum and umbilical cord serum eye drops for dry eye syndrome. *American journal of ophthalmology*, **2007**; 144:86–92.

Young G, Efron N. Characteristics of the pre-lens tear film during hydrogel contact lens wear. *Ophthalmic and Physiological Optics*, **1991**; 11:53-58.

Yu FX, Guo J, Zhang Q. Expression and distribution of adhesion molecule CD44 in healing corneal epithelia. *Investigative ophthalmology & visual science*, **1998**; 39:710–717.

Zhang W, Wang Y, Lee BTK, Liu C, Wei G, Lu W. A novel nanoscale dispersed eye ointment for the treatment of dry eye disease. *Nanotechnology*, **2014**; 25:125101.

Zhang XR, Cai RX, Wang BH, Li QS, Liu YX, Xu Y. The analysis of histopathology of conjunctivochalasis. [*Zhonghua yan ke za zhi*] *Chinese journal of ophthalmology*, **2004**; 40:37–39.

Zhao H, Jumblatt JE, Wood TO, Jumblatt MM. Quantification of MUC-5AC protein in human tears. *Cornea*, **2001**; 20:873-877.

Zhivov A, Kraak R, Bergter H, Kundt G, Beck R, Guthoff RF. Influence of benzalkonium chloride on Langerhans cells in corneal epithelium and development of dry eye in healthy volunteers. *Current eye research*, **2010**; 35:762-769.

Zhu SN, Nölle B, Duncker G. Expression of adhesion molecule CD44 on human corneas. *British journal of ophthalmology*, **1997**; 81:80–84.

## APPENDIX A: ETHICS FORM



### ETHICS FORM

All parts of the *Ethics Application* must be written concisely using terminology that would be understandable to an educated lay person on an ethics committee.

Title: **Optimising the Treatment of Dry Eyes**

Principal Investigator: Prof James Wolffsohn

Contact Details: [j.s.w.wolffsohn@aston.ac.uk](mailto:j.s.w.wolffsohn@aston.ac.uk) x4160

Other Staff / Students involved: Laika Essay (OD student)

#### A. PROJECT OBJECTIVES / BACKGROUND

A1. What are the primary research questions / objective?

To determine the optimum pharmaceutical treatment for dry eye from pre-treatment clinical tear film assessment

A2. Where will the study take place?

Clinical Optometric Practice Specsavers Opticians, 83 Victoria Road west, Thornton – Cleve leys, FY5 1AJ, Lancashire. Tel: 01253 864 130

A3. Describe the statistical methods and/or other relevant methodological approaches to be used in the analysis of the results (*e.g. methods of masking / randomization*)

Randomized order, investigator masked, repeated measure treatment. **The subjects will not be masked as this would not affect the sterility of the solutions.**

A4. List the clinical techniques to be conducted on patients as part of the study and indicate whether they fall within the scope of normal professional practice of the individual to perform them

Tear film will be assessed using the tearscope (lipid thickness and break-up time, tear meniscus height, lid wiper epitheliopathy, lissamine green and fluorescein staining, phenol red test, a dry eye questionnaire and comfort/use diary.

**ENCLOSE AN OUTLINE OF THE STUDY RATIONALE AND METHODOLOGY** Attached

#### B. RESEARCH PARTICIPANTS

B1. How many participants will be recruited? Please provide justification (power analysis software available from <http://www.psych.uni-duesseldorf.de/abteilungen/aap/gpower3/>)

50 patients will be recruited allowing at least 15 degrees of freedom if the clinical measures are grouped into 3 categories.

B2. What restrictions will there be on participation (age, gender, language comprehension etc.)?

**Self-reported dry eye for at least a year with no seasonal element and a desire for treatment**

No reaction to previous solutions applied to the ocular surface.

On stable medication or not taking any medication known to affect the tear film

Non-contact lens wearers

Not had eye surgery within the previous 3 months

No active ocular surface pathology

At least 18 years of age

Willing to take part in the study

B3. How will potential research participants in the study be (i) identified, (ii) approached and (iii) recruited? *If research participants will be recruited via advertisement then attach a copy of the advertisement in the appendix of the ethics report.*

Patients meeting the inclusion criteria assessed as part of their normal clinical eye examination will be given the information sheet and may agree to take part in the study at any time after this by contacting the practice.

B4. Will the participants be from any of the following groups? *Tick as appropriate and justify any affirmative answers.*

- Children under 16:
- Adults with learning disabilities:
- Adults who are unconscious or very severely ill:
- Adults who have a terminal illness:
- Adults in emergency situations:
- Adults with mental illness (particularly if detained under Mental Health Legislation):
- Adults suffering from dementia:
- Prisoners:
- Young Offenders:
- Healthy volunteers:
- Those who could be considered to have a particularly dependent relationship with the investigator, e.g. those in care homes, students:
- Other vulnerable groups:
- other than dry eyes
- patients

Participants will need to be healthy patients (other than dry eyes) to enable recruitment. It will be made clear to them that choosing not to take part will not affect their clinical treatment.

B5. What is the expected total duration of participation in the study for each participant?

4 months

B6. Will the activity of the volunteer be restricted in any way either before or after the procedure (e.g. diet or ability to drive)? *If so then give details.*

No, although patients will be asked to report possible large changes in lifestyle over the duration of the study

B7. What is the potential for pain, discomfort, distress, inconvenience or changes to life-style for research participants during and after the study?

Lissamine green instillation, fluorescein instillation and phenol red testing can be slightly uncomfortable for a short period. The tear film supplements should assist rather than hinder comfort. The patients will be required to attend additional visits to assess the health of their eyes, but these will be free and the free comfort drops should compensate for this inconvenience.

B8. What levels of risk are involved with participation and how will they be minimized?

A reaction to the preservative in a tear supplement, in which case the drop can be stopped immediately and the optometrist consulted if desired. [The Phenol Red thread and tear lab are highly unlikely to significantly damage the cornea or conjunctiva, there are no known cases of clinically significant damage or lasting symptoms.](#)

B9. What is the potential for benefit for research participants?

Free dry eye treatment for 4 months and the identification of the optimum treatment for them.

B10. If your research involves individual or group interviews/questionnaires, what topics or issues might be sensitive, embarrassing or upsetting? Is it possible that criminal or other disclosures requiring action could take place during the study?

No upsetting or disclosure questions

### C. CONSENT

C1. Will a signed record of informed consent be obtained from the research participants? *If consent is not to be obtained, please explain why not.*

Yes

ENCLOSE A PARTICIPANTS INFORMATION SHEET (including a clear statement of what will happen to a volunteer) & CONSENT FORM Attached

C2. *Who will take consent and how it will be done?*

The optometrist – Laika Essa BSc (Hons)

C3. How long will the participant have to decide whether to take part in the research? *Justify your answer.*

As long as they need – the subjects can be considered as non – participants after a month has elapsed

C4. What arrangements are in place to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

The practice holds contact details on all patients

C5. Will individual research participants receive any *payments/reimbursements* or any other *incentives* or *benefits* for taking part in this research? *If so, then indicate how much and on what basis this has been decided?*

Free tear supplements. Subjects will not be reimbursed for any additional travel required for multiple visits.

C6. How will the results of research be made available to research participants and communities from which they are drawn?

By publication on completion of the study. The participant will be offered a summary sheet of their individual findings at the end of the study.

### D. DATA PROTECTION

D1. Will the research involve any of the following activities? *Delete as appropriate and justify any affirmative answers.*

Examination of medical records by those outside the NHS, or within the NHS by those who would not normally have access:

Electronic transfer of data by e-mail:

Sharing of data with other organizations:

Use of personal addresses, postcodes, faxes, emails or telephone numbers:

Publication of direct quotations from respondents:

Publication of data that might allow identification of individuals:

Use of audio/visual recording devices:

The data spreadsheet will be password protected with Microsoft encryption

D2. Will data be stored in any of the following ways? *Delete as appropriate and justify any affirmative answers.*

Manual files:

Home or other computers:

University computers:

The data spreadsheet will be password protected with Microsoft encryption

D3. What measures have been put in place to ensure confidentiality of personal data? *Give details of whether any encryption or other anonymisation procedures will be used, and at what stage.*

The data spreadsheet will be password protected with Microsoft encryption. Patient contact details will not be recorded as can be linked to patient files

D4. If the data is not anonymised, where will the analysis of the data from the study take place and by whom will it be undertaken?

At the university/practice and by the investigators.

D5. Other than the study staff, who will have access to the data generated by the study?

No one

D6. Who will have control of, and act as the custodian for, the data generated by the study?

Prof J Wolffsohn

D7. For how long will data from the study be stored [minimum 5 years]? *Give details of where and how the data will be stored.*

5 years in a locked data storage room and on computer storage in encrypted pass worded form

## E. GENERAL ETHICAL CONSIDERATIONS

E1. What do you consider to be the main ethical issues or problems that may arise with the proposed study, and what steps will be taken to address these?

Patients' time to take part in the study, but this is voluntary and they benefit from free consultation and free tear film supplements.

**APPENDIX B: ETHICS APPROVAL**



**Response from AOREC**

25<sup>th</sup> March 2010

**Project title:** *Optimising the Treatment of Dry Eyes*

**Reference Number:** Essa OD

**Researchers:** Laika Essa and Prof James Wolffsohn

I am pleased to inform you that the Audiology / Optometry Research Ethics Committee has approved the above named project.

The details of the investigation will be placed on file. You should notify The Committee of any difficulties experienced by the volunteer subjects, and any significant changes which may be planned for this project in the future.

Yours sincerely

A handwritten signature in purple ink, appearing to read "J. Wolffsohn". The signature is written in a cursive style with a large, sweeping flourish at the end.

Chair AOREC

**APPENDIX C: OSDI QUESTIONNAIRE**

**Ocular Surface Disease Index<sup>®</sup> (OSDI<sup>®</sup>)<sup>2</sup>**

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

| <b>Have you experienced any of the following during the last week?</b> | All of the time | Most of the time | Half of the time | Some of the time | None of the time |
|------------------------------------------------------------------------|-----------------|------------------|------------------|------------------|------------------|
| 1. Eyes that are sensitive to light? . . . . .                         | 4               | 3                | 2                | 1                | 0                |
| 2. Eyes that feel gritty? . . . . .                                    | 4               | 3                | 2                | 1                | 0                |
| 3. Painful or sore eyes? . . . . .                                     | 4               | 3                | 2                | 1                | 0                |
| 4. Blurred vision? . . . . .                                           | 4               | 3                | 2                | 1                | 0                |
| 5. Poor vision? . . . . .                                              | 4               | 3                | 2                | 1                | 0                |

Subtotal score for answers 1 to 5

| <b>Have problems with your eyes limited you in performing any of the following during the last week?</b> | All of the time | Most of the time | Half of the time | Some of the time | None of the time | N/A |
|----------------------------------------------------------------------------------------------------------|-----------------|------------------|------------------|------------------|------------------|-----|
| 6. Reading? . . . . .                                                                                    | 4               | 3                | 2                | 1                | 0                | N/A |
| 7. Driving at night? . . . . .                                                                           | 4               | 3                | 2                | 1                | 0                | N/A |
| 8. Working with a computer or bank machine (ATM)? . . . . .                                              | 4               | 3                | 2                | 1                | 0                | N/A |
| 9. Watching TV? . . . . .                                                                                | 4               | 3                | 2                | 1                | 0                | N/A |

Subtotal score for answers 6 to 9

| <b>Have your eyes felt uncomfortable in any of the following situations during the last week?</b> | All of the time | Most of the time | Half of the time | Some of the time | None of the time | N/A |
|---------------------------------------------------------------------------------------------------|-----------------|------------------|------------------|------------------|------------------|-----|
| 10. Windy conditions? . . . . .                                                                   | 4               | 3                | 2                | 1                | 0                | N/A |
| 11. Places or areas with low humidity (very dry)? . . . . .                                       | 4               | 3                | 2                | 1                | 0                | N/A |
| 12. Areas that are air conditioned? . . . . .                                                     | 4               | 3                | 2                | 1                | 0                | N/A |

Subtotal score for answers 10 to 12

Add subtotals A, B, and C to obtain D (D = sum of scores for all questions answered)

Total number of questions answered (do not include questions answered N/A)

Please turn over the questionnaire to calculate the patient's final OSDI<sup>®</sup> score.

**Appendix D: PATIENT CONSENT FORM**



Personal Identification Number for this study: \_\_\_\_\_

**CONSENT FORM**

**Title of Project:** Optimising the Treatment of Dry Eyes

**Research Venue:** Clinical Optometric Practice

**Name of Investigator(s):** Laika Essa and James Wolffsohn

**Please initial box**

1. I confirm that I have read and understand the information sheet dated .....  
 (version .....) for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time,  
 without giving any reason, without my legal rights being affected.
3. I agree to take part in the above study.

\_\_\_\_\_  
Name of Research Participant      \_\_\_\_\_  
Date      Signature

\_\_\_\_\_  
Name of Person taking Consent      \_\_\_\_\_  
Date      Signature

**1 copy for research participant; 1 copy for practice.**