The effects of glaucoma medication on the ocular surface

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Doctor of Philosophy

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Thesis Abstract

The aim of this research was to establish the effects of glaucoma medication on the ocular surface. It is well known that ocular surface disease (OSD) is a prevalent issue in medically treated glaucoma and ocular hypertension (OHT) patients. The cause of this has often been attributed to the preservatives which are added to the ocular hypotensive drops used in the management of glaucoma and OHT. Though preservative-free (PF) alternatives would provide the best benefit-to-risk ratio, it is not cost effective to prescribe these to every patient attending glaucoma clinics. There is a need, therefore, to decipher which individuals are most at risk to developing OSD in their lifetime, when treated for glaucoma or OHT.

This thesis sought to address the issue surrounding OSD in glaucoma clinics through the compilation of a series of investigations looking at; the efficacy, safety and tolerability of preserved versus PF medication, current clinical approaches to OSD in UK glaucoma clinics, adherence rates in glaucoma treatment, the prevalence of OSD and Dry Eye Disease (DED) in glaucoma prior to the initiation of treatment, and the predisposing factors associated with developing OSD and DED when medically managed for glaucoma or OHT.

In turn, this thesis has found

- Preservative-free ocular hypotensive drops to be just as effective as preserved drops in lowering the intraocular pressure (IOP), with better tolerability.
- OSD is highly prevalent in glaucoma clinics, and using the Tear Film & Ocular Surface Society Dry Eye WorkShop II (TFOS DEWS II) Diagnostic test battery for OSD, levels are >96% amongst new, follow up and treated patients
- Cost is the biggest barrier for clinicians in prescribing PF treatment.
- There is room for improvement in patient education regarding drop instillation technique, information at diagnosis and written aids to support such advice.
- Glaucoma clinics need to establish routine ocular surface checks for optimal co-management of glaucoma/OHT and OSD.
- More robust research is required to determine predisposing factors to DED in medically managed glaucoma/OHT patients, but polypharmacy, alcohol consumption, blepharitis, thicker CCT, higher baseline IOP and tear break-up-time <2 seconds are potentially suggestive markers.

Keywords: dry eye disease, glaucoma, ocular hypertension, ocular surface disease, preservatives, preservative-free, ocular hypotensive drops, eye drops

Dedication

To my wonderful parents,

Thank you for all the sacrifices you have made in life so that your children can fulfil their dreams.
We will forever be indebted to you.

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List of abbreviations

Abbreviation	
51Cr	Chromium 51
ADDE	Aqueous deficient Dry Eye
AGPs	Advanced Nurse Practitioners specialising in glaucoma
AMaT	Audit Management and Tracking
AUC	Area under curve
BAK	Benzalkonium chloride
BLQ	Below the level of quantification
BOSS	Beaver Dam Offspring Study
CAG	Closed angle glaucoma
CAGS	Closed angle glaucoma suspect
Cmax	Maximum concentration
CMO	Cystoid macular oedema
CNTGS	Collaborative Normal Tension Glaucoma Study
COAG	Chronic open angle glaucoma
DA	Dosing aid
DED	Dry eye disease
DEWS	Dry Eye Workshop
ECLO	Eye Clinic Liaison Officer
EDE	Evaporative Dry Eye
EDTA	Edetate Disodium
EGC	Enhanced Glaucoma Clinic
EMGT	Early Manifest Glaucoma Trial
FB	Foreign body
FBUT	Fluorescein break up time
FMD	Frequency of Missed Dose
FRs	Free radicals
GAT	Goldmann applanation tonometry
GCD	Goblet cell density
HRT	Hormone replacement therapy
H&S	History and Symptoms
IC	Impression cytology
IOP	Intraocular pressure
KCS	Keratoconjunctivitis Sicca
LSCM	Laser Scanning Confocal Microscopy
MAO	Monoamine oxidase
MG	Meibomian gland
MGD	Meibomian gland dysfunction
MMA	Mean Microcyst Area
MMAS	Morisky Measure of Adherence Scale

MMD	Mean Microcyst Density
MPR	Medication Possession Ratio
NaFl	Sodium Fluorescein
NEI	National Eye Institute
NIBUT	Non-invasive break-up time
NICE	The National Institute for Health and Care Excellence
NK	Natural killer
OCT	Optical Coherence Tomography
OHTS	Ocular Hypertension Treatment Study
ONH	Optic nerve head
OSD	Ocular surface disease
OSDI	Ocular Surface Disease Index
OT	Ophthalmic technician
PAC	Primary Angle Closure
PACG	Primary Angle Closure Glaucoma
PACS	Primary Angle Closure Suspect
PBS	Physiological buffered saline
PDS	Pigment dispersion syndrome
PGA	Prostaglandin analogue
POAG	Primary open angle glaucoma
PQ	Polyquad
Px	Patient
PXF	Pseudoexfoliation
QoL	Quality of life
RA	Rheumatoid arthritis
RAPD	Relative Afferent Pupillary Defect
RGC	Retinal ganglion cells
RHH	Russells Hall Hospital
ROC	Receiver operating characteristic
RTC	Randomised controlled trial
SEM	Scanning electron microscopy
SLT	Selective laser trabeculoplasty
SOC	Stabilised Oxochloro complex
SPK	Superficial Punctate Keratitis
TBUT	Tear break-up time
TFOS	Tear Film and Ocular Surface Society
TM	Trabecular meshwork
TMA	Tear meniscus cross sectional area
Tmax	Time to maximum concentration
TMC	Tear meniscus radius of curvature
TMH	Tear meniscus height
TMW	Tear meniscus width
Tx	Treatment
UD	Unit dose
UKEGS	UK and Eire Glaucoma Society
VFs	Visual fields

VGC	Virtual Glaucoma Clinic
WDF	Wavelength dependent fringes

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Chapter 1

Introduction and literature review

1.1 Introduction

Glaucoma is one of the leading causes of irreversible sight loss in the world, with an estimated 76 million people being affected by the disease globally in 2020, and a further 111.8 million people expected to do so by 2040 (Tham et al., 2014). The objective of all treatment available today is to tackle a known risk factor: raised intraocular pressure (IOP). By lowering IOP, disease progression should reduce (Heijl et al., 2002).

One of the primary methods of lowering IOP in the UK involves the use of topical medication, in the form of eye drops (National Institute for Health and Care Excellence, 2017). However, prolonged use of topically preserved medication has been shown to lead to ocular surface disease (OSD) (Baudouin et al., 1999, Rossi et al., 2013b). In turn, this can lead to discomfort and intolerance, and could thereby affect patient adherence and persistence with treatments (Chawla et al., 2007). Poor persistence can result in poor IOP control and subsequently increase the risk of vision loss (Konstas et al., 2000). It is therefore vital to improve the understanding of the prevalence, risk factors and the impact of OSD in glaucoma clinics for better management, by both the consultants and patients alike.

1.2 What is glaucoma?

Glaucoma is a disease of the optic nerve head (ONH) which leads to characteristic changes in the visual field. There are pathological alterations in the neuroretinal rim accompanied by progressive death of retinal ganglion cells (RGCs) (McMonnies, 2017, Shon et al., 2014). The RGCs pass through the ONH, and so their degeneration over time leads to the classic ‘cupping’ appearance of the optic disc (Nickells et al., 2012). Though the main accepted cause of these changes is raised IOP, it is not always the case (Klein et al., 1992, National Institute for Health and Care Excellence, 2022). Glaucoma can therefore be subdivided into several categories depending on the underlying factors influencing the disease.

In order to fully appreciate the different types of glaucoma and their aetiologies, it is important to understand the fundamentals of the structure of the eye. Aqueous humour is produced by the ciliary body and is responsible for nourishing the lens and cornea, both of which are absent of blood vessels (Kwon et al., 2009). The aqueous humour travels through the pupil into the anterior chamber where it drains through the Trabecular Meshwork (TM) into Schlemm’s canal and also via the uveoscleral route (Weinreb et al., 2014).

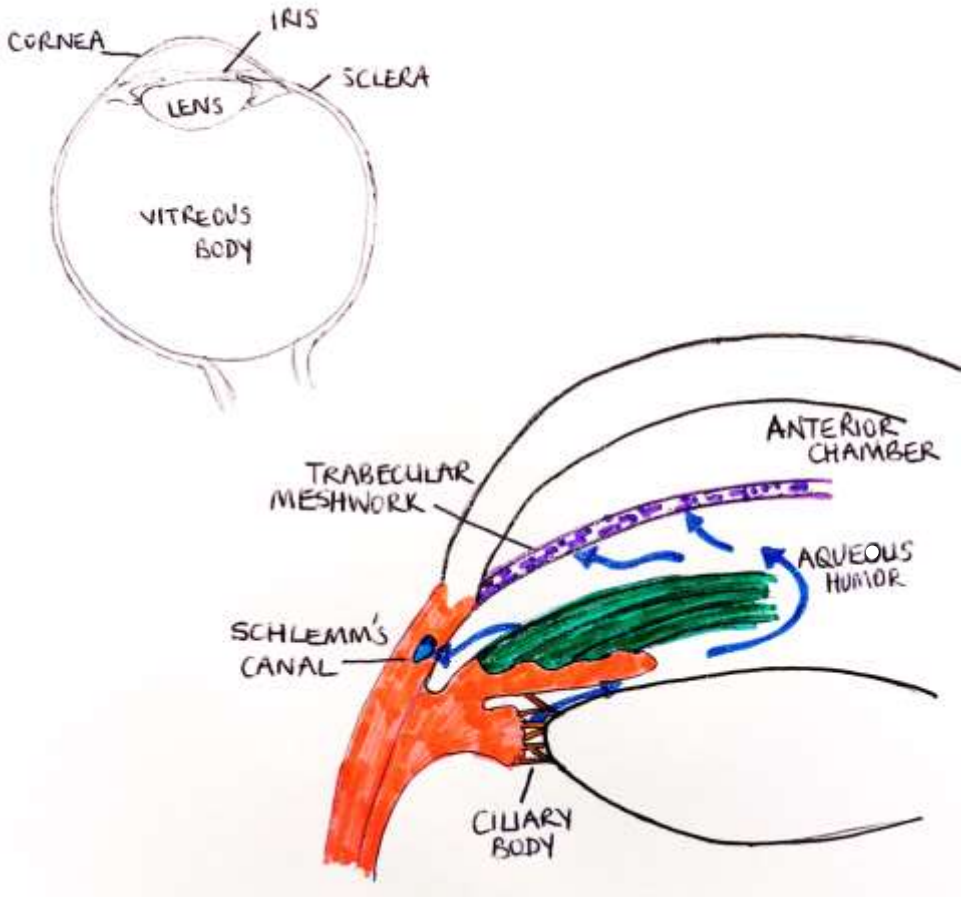


Figure 1.1: The anatomy of the anterior eye, showing the key anatomical structures linked to aqueous humour flow. Adapted from (Kwon et al., 2009)

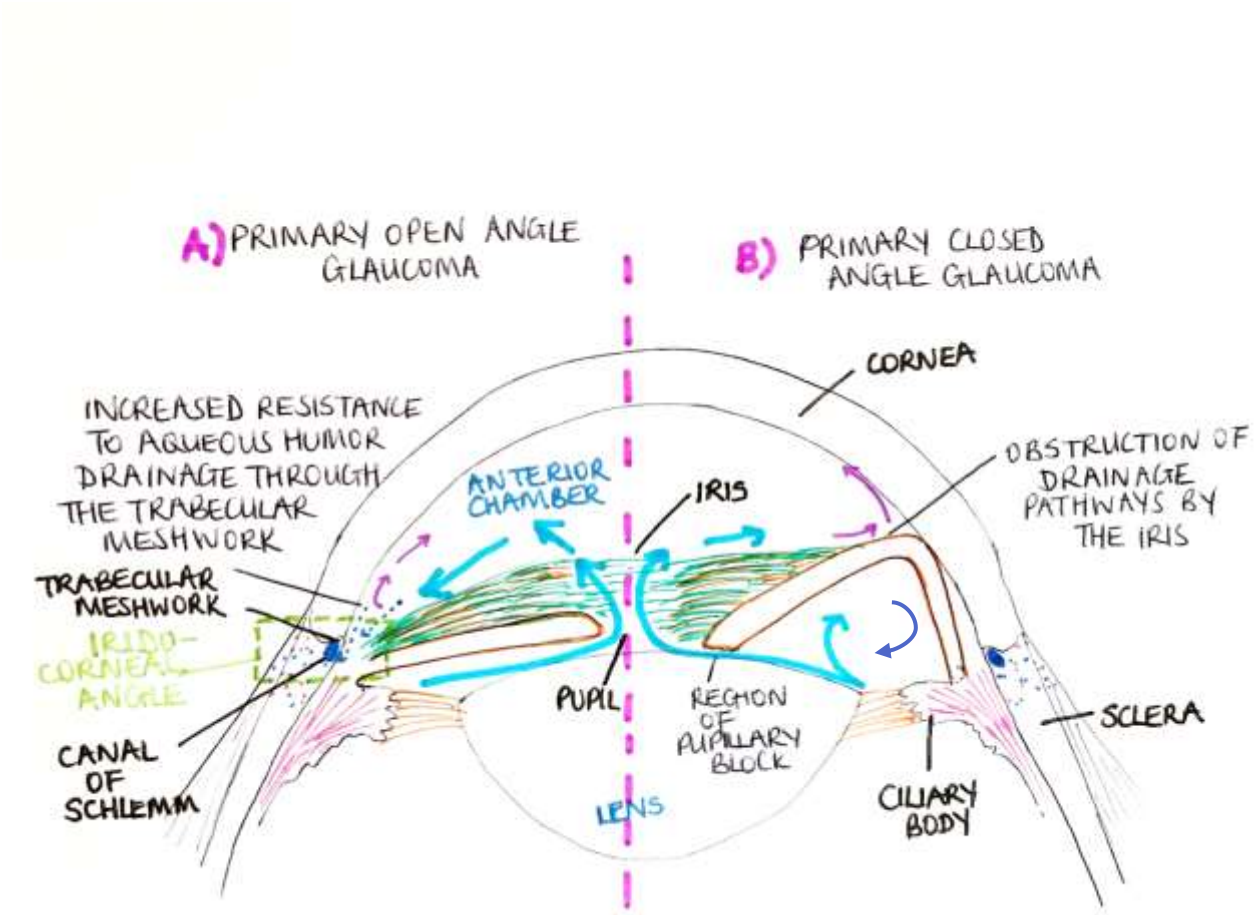


Figure 1.2 Aqueous drainage pathways in a) Primary open angle glaucoma and b) Primary closed angle glaucoma. Adapted from (Weinreb et al., 2014)

It is the iridocorneal angle (the angle between the iris and the cornea) which forms the basis of glaucoma classifications (Kwon et al., 2009). The most common type of glaucoma is primary open angle glaucoma (POAG). This is when the iridocorneal angle is wide open but the outflow of the aqueous humour is in some way restricted (Figure 1.2) (National Institute for Health and Care Excellence, 2022, Weinreb et al., 2014). This may result in elevated IOPs, but not in all cases. Where the IOP is at an acceptable level yet there are glaucomatous signs such as cupping and corresponding visual field loss, the name 'Normal Tension Glaucoma' (NTG) is usually given (Kwon et al., 2009).

1.2.1 Closed angle glaucoma

Closed angle glaucoma (CAG), otherwise known as Primary Angle Closure Glaucoma (PACG), occurs when the iridocorneal angle closes leading to pupillary block and a sharp

increase in the IOP (National Institute for Health and Care Excellence, 2022, Weinreb et al., 2014). The drainage pathway is obstructed by the iris, and so fluid builds up dramatically behind it (Weinreb et al., 2014). The majority of closed angle glaucoma cases are amongst the Asian population, with over 80% of people with angle closure glaucoma being in Asia (See et al., 2011, Quigley and Broman, 2006).

Angle closure can be subdivided into 3 main categories: Primary Angle Closure Suspect (PACS) (where the iridocorneal angle is narrow and could possibly close, with no other signs such as peripheral anterior synachiae, elevated IOPs or visual field defects), Primary Angle Closure (PAC) (where the angle has closed causing elevated IOPs with or without synachiae, but no disc or visual field changes), and finally, Primary Angle Closure Glaucoma (PACG), where the angle has shut, the IOPs are elevated and there are glaucomatous signs present (See et al., 2011, Foster et al., 2002). The management depends upon the presentation and type of angle closure. Some therapies will be prophylactic such as in cases of PACS, to minimise the risk of complete angle closure, while others are invasive to lower IOP as much as possible to prevent irreversible damage and vision loss (Emanuel et al., 2014).

Due to the sudden nature of the disease, acute angle closure can have severe consequences over a relatively short period, making it a medical emergency (National Institute for Health and Care Excellence, 2022, Weinreb et al., 2014). This is unlike POAG, where symptoms are typically not reported until the condition is advanced (Kroese and Burton, 2003). Common symptoms of CAG include pain, headaches, misty vision, nausea and red eye (Weinreb et al., 2014). It is crucial to intervene quickly, to save any sight (National Institute for Health and Care Excellence, 2022).

1.2.2 Primary open angle glaucoma

Primary open angle glaucoma (POAG) is the most common type of glaucoma, with 74% of glaucoma cases falling into this category in 2020 (Quigley and Broman, 2006). The highest prevalence of POAG is amongst the African population (Tham et al., 2014), which rises which age. Although the rate of increase of POAG prevalence is higher amongst the Caucasians and Hispanics, Afro-Caribbean’s show the highest prevalence levels within each age bracket up until 80 years old (Kapetanakis et al., 2016).

In POAG, whilst it is accepted that there is a reduction in the outflow of the intraocular fluid, the mechanisms are poorly understood (King et al., 2013). Commonly, it is caused by increased IOP, which is thought to cause mechanical compression of the nerves passing through the optic nerve head. This combined with ischaemia and vascular complications, leads to ganglion cell death (King et al., 2013). The main treatment therefore, aims to lower IOPs, whether through surgery, laser or topical medication (National Institute for Health and Care Excellence, 2022).

POAG is a chronic disease and the immediate effects are not experienced by individuals. It is with time that the visual field starts to get affected, and only when these changes are severe, that individuals may report symptoms of the disease (Hollands et al., 2013). Due to the nature of the disease and patients being asymptomatic in early stages, adherence is poorer in less advanced cases (Tsai et al., 2003).

1.2.3 Sub-classification of glaucoma

It should be noted that glaucoma can develop secondary to other conditions, such as trauma or inflammatory disorders. Figure 1.3 below offers a brief outline of the primary and secondary types of glaucoma and their main treatment options.

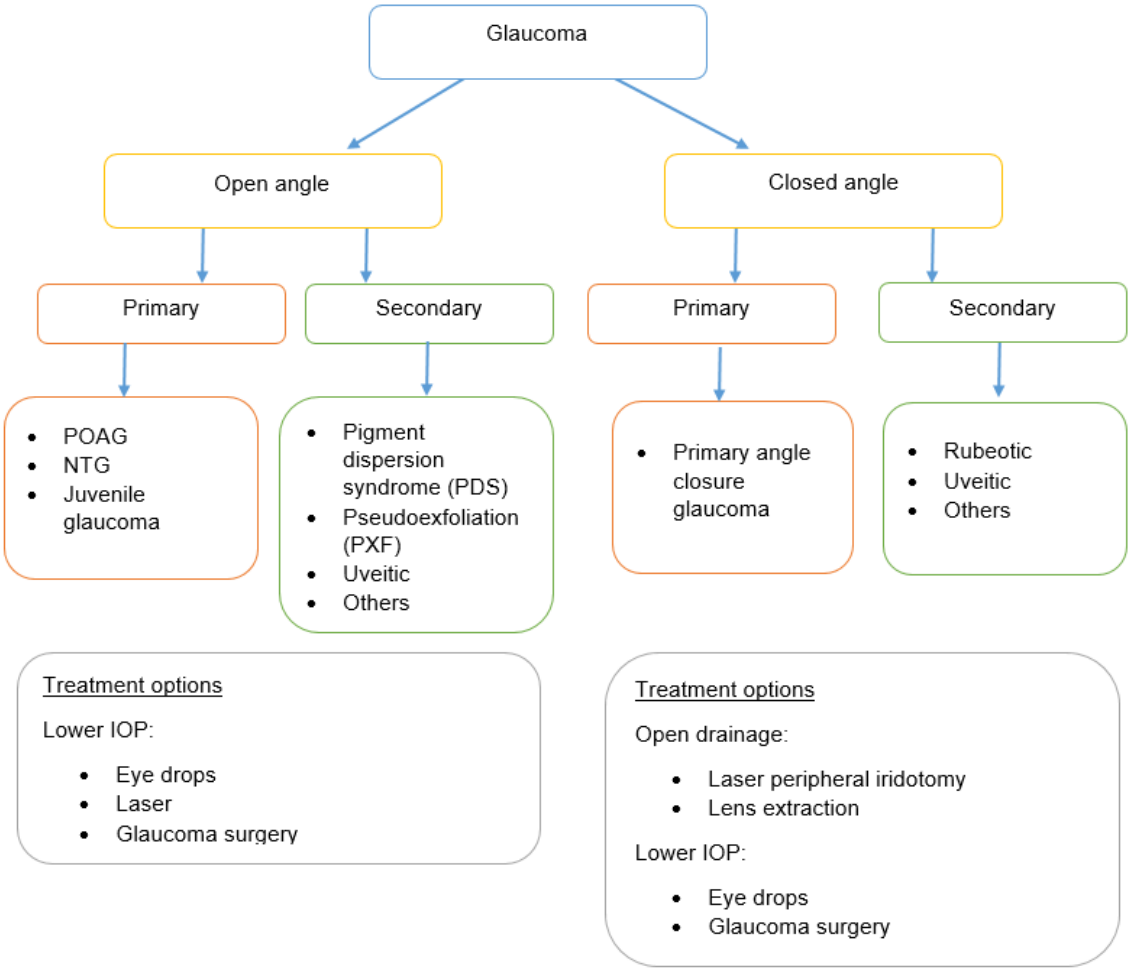


Figure 1.3: The sub classification of glaucoma adapted from the review by King and colleagues (2013) (King et al., 2013)

1.2.4 Ocular hypertension

Ocular hypertension (OHT) refers to the condition of having elevated IOPs in the absence of glaucomatous signs (Gordon and Kass, 2018). The Ocular Hypertension Treatment Study (OHTS) set out to explore the effects of medically managing patients with raised IOPs. It was found that by managing OHT early in the pathway, the 5 year incidence of glaucoma is reduced by 60% (Gordon and Kass, 2018). By 60 months, the probability of developing POAG was significantly lower in the group treated with ocular hypotensive drops, than those who were simply observed during the course of the study (4.4% vs 9.5%, respectively) (Kass et al., 2002). The National Institute for Health and Care Excellence (NICE) advise intervention in patients where the IOP is 24mmHg or higher, who have a lifetime risk of vision loss (National Institute for Health and Care Excellence, 2017). It is estimated that

about 3-5% of people over 40 years have OHT in the UK (National Institute for Health and Care Excellence, 2022)

1.3 The use of topical drugs in glaucoma

In most cases of glaucoma, topical medication in the form of eye drops plays an important role in lowering IOP. In early 2022, NICE amended their guidelines to include recommendations for 360° selective laser trabeculoplasty (SLT) for newly diagnosed glaucoma and OHT patients who require treatment to lower their IOP. Prior to this, generic prostaglandin analogues (PGAs) were regarded as first line therapy in cases of OHT and chronic open angle glaucoma (COAG) (otherwise referred to as POAG). Where SLT is not suitable, declined by the patient, ineffective or in the interim period whilst awaiting SLT or glaucoma surgery, clinicians are advised to offer generic PGA eye drops to manage IOPs. Pharmacological intervention in the form of hypotensive eye drops still forms the mainstay of ongoing glaucoma and OHT treatment (National Institute for Health and Care Excellence, 2017).

Research suggests that PGAs provide the most IOP reduction, followed by non-selective beta blockers, alpha adrenergic agonists, selective beta blockers and carbonic anhydrase inhibitors, in that order (European Glaucoma Society, 2017, van der Valk et al., 2005a). Monotherapy is generally considered first with the hope that one drug alone will help to reduce IOPs to a satisfactory level. If this is not effective or well tolerated, the drug may be changed to one from the other groups of anti-glaucoma medication, or perhaps preservative-free (PF) drops may need to be considered. Where target IOP is not reached even with such changes, then combination therapy may be needed, or alternatively, surgical or laser interventions may be required (2017, National Institute for Health and Care Excellence, 2017).

1.3.1 Commonly used drugs in glaucoma management

Class of glaucoma medication	Name of drug	Mechanism of action	~IOP reduction	Local Side effects	Systemic Side effects	Contra-indications
Prostaglandin analogue	• Latanoprost • Tafluprost • Travoprost	Increase in uveo-scleral outflow	25-35%	Ocular irritation such as stinging and burning, conjunctival hyperaemia, changes to iris colour, lengthening and darkening of eyelashes, darkening of the skin around the eyes, uveitis, macular oedema	Breathing difficulties or worsening of asthma, potential headaches, angina and muscle pain	Contact lenses-however, if removed prior to drop instillation and reinsert-ed at least 15 minutes after, then this is okay
Prostamide	• Bimatoprost	Increase in uveo-scleral outflow	25-35%			

β-Adrenergic blockers **a) Non Selective**	• Timolol • Levobunolol • Carteolol • Metipranolol	Decrease aqueous humour production	20-25%	Ocular irritation with symptoms of burning, stinging and signs of hyperaemia, dry eyes and potential superficial punctate keratitis (SPK)	Respira-tory difficulties, heart problems, depression and erectile dysfunction	Respiratory issues such as asthma and COPD. Also, heart problems such as heart block, brady-cardia and cardiac failure
b) β-1-Selective	• Betaxolol	Decrease aqueous humour production	≈20%			
α-Adrenergic agonists	• Apraclonidine	Decrease aqueous humour production	25-35%	Ocular irritation, allergic blepharo-conjunctivitis, conjunctival blanching, hypersensi-tivity, dry eyes	Central nervous system problems, dry mouth and nose, fatigue, respiratory problems in young children	Young children, those with postural hypoten-sion, oral mono-amine oxidase (MAO) inhibitor users, very low body weight, patients with cerebral or coronary insuffici-ency, patients with renal or
	• Brimonidine	Decrease in aqueous humour production followed by increased uveo-scleral outflow	18-25%			

						hepatic failure
Carbonic Anhydrase Inhibitors a) Topical	• Brinzolamide • Dorzolamide	Decrease in aqueous humour production	20%	Burning, stinging, ocular irritation, dry eyes, SPK, blurred vision	Headache, dizziness, pares-thesia, transient myopia	Low endothelial cell count as it increases risk of corneal oedema
b) Oral	• Acetazolamide		30-40%		Pares-thesia , loss of appetite, nausea, vomiting, diarrhoea, renal problems	Low sodium or potassium levels, or in patients with kidney or liver disease/ dysfunction
Parasympa-thomimetics/ cholinergic drugs	• Pilocarpine • Carbachol	Increase in aqueous outflow	20-25%	Miosis and accommoda-tive myopia leading to blurred vision, conjunctival hyperaemia, potential angle closure	Headaches , broncho-spasm and intestinal cramps	Hypo-tension, gastric issues, patients at risk of retinal detach-ments, bradycardia

Table 1.1: Common drugs used in the management of glaucoma. Table adapted from Weinreb and colleagues (2014) and the European Glaucoma Society (Weinreb et al., 2014, 2017, European Glaucoma Society, 2021). This table is not exhaustive of all potential side effects and some patients may experience more problems than others. This table aims to give a brief overview of possible

issues which may arise from oral or topical glaucoma medication. It should be noted that every medication has some impact on the ocular surface of the eye. Ocular irritation seems to be the most common local side effect across all types of glaucoma drops. More recently, osmotics and RHO inhibitors have been added to the list by the European Glaucoma Society, though the latter is yet to establish a place in the UK (European Glaucoma Society, 2021, Joint Formulary Committee, 2022, Saha et al., 2022).

It may be necessary to give combination therapy where one drug alone is not producing the desired effects or failing to reach the target IOP. It is ideal to give combined drug medication where possible, as opposed to separate dispensing bottles. This helps with adherence through simpler regimes and reduces the amount of preservatives present on the ocular surface, at a given time (European Glaucoma Society, 2017, Holló et al., 2014, Patel and Spaeth, 1995).

1.3.2 Combination eye drops available in glaucoma clinics

Group of drugs combinations	Trade Name	Combination of drugs	Typical frequency	Preservative
Prostaglandin Analogues/Prostamides & β-blockers	Xalacom	Latanoprost 0.005% &Timolol 0.5%	One instillation per day, usually on a morning	BAK 0.02%
	Duotrav	Travoprost 0.004% & Timolol 0.5%		Polyquad 0.01%
	Ganfort	Bimatoprost 0.03% & Timolol 0.5%		BAK 0.05%
	Taptiqom	Tafluprost 0.0015% & Timolol		-
Carbonic Anhydrase Inhibitors & β-blockers	Cosopt	Dorzolamide 2% & Timolol 0.5%	Two instillations per day, 12 hours apart	BAK 0.0075%
	Azarga	Brinzolamide 1% & Timolol 0.5%		BAK 0.1%
α-Agonists & β-blockers	Combigan	Brimonidine 2% & Timolol 0.5%	Two instillations	BAK 0.05%

			per day, 12 hours apart	
Carbonic Anhydrase Inhibitors & α-Agonists	Simbrinza	Brinzolamide 1% & Brimonidine 0.2%	Two instillations per day, 12 hours apart	BAK 0.03%

Table 1.2: Common combination therapies available in glaucoma clinics. Table adapted from Katsanos and colleagues (2016) (Katsanos et al., 2016, Steven et al., 2018, Joint Formulary Committee, 2022, Electronic Medicines Compendium, 2022).

The compounds listed in the tables outlined above mostly come in their preserved forms, though some are available in unit doses (Joint Formulary Committee, 2022). This allows for a longer shelf life and ultimately aims to prevent microbial contamination (Freeman and Kahook, 2009, Steven et al., 2018). It has been widely discussed that it is the preservatives in glaucoma drops which lead to problems of the ocular surface (Pisella et al., 2002, Baudouin et al., 2010, Gomes et al., 2017).

Since the management of glaucoma and OHT relies massively on topical treatment via eye drops, there can be direct implications on the homeostasis of the ocular surface. Disruption to the ocular surface can lead to consequential problems of ocular surface disease (OSD).

1.4 What is ocular surface disease?

Gipson (2007) defined the ocular surface system as a combination of “the surface and glandular epithelia of the cornea, conjunctiva, lacrimal gland, accessory lacrimal glands, and meibomian gland, and their apical (tears) and basal (connective tissue) matrices, the eyelashes with their associated glands of Moll and Zeis, those components of the eyelids responsible for the blink, and the nasolacrimal duct.” (Gipson, 2007). In essence, the ocular surface is the “interface between the eye and the outer world” (Rolando and Zierhut, 2001).

The ocular surface is a complex system, with its constituents being responsible for maintaining a smooth, refractive surface, as well as acting as a protective barrier for the eyes (Gipson, 2007). The eyes are constantly challenged by both internal and external factors, and so it is vital for the ocular surface to be able to adapt to such conditions quickly. In fact, slight stimulation of the lid margin can induce a tear turnover rate of 300% (Jordan and Baum, 1980).

The components of the ocular surface work together to maintain homeostatic conditions to ensure good health of the eyes. If this balance is disrupted, a series of responses will be elicited to combat the events, such as inflammation and excess tearing (Pflugfelder, 2003). If the balance is not restored promptly, it can lead to the appearance of OSD (Rolando and Zierhut, 2001). Such is the case in dry eye disease (DED), when OSD becomes symptomatic. When OSD translates to DED, symptoms such as burning, stinging, ocular discomfort, visual disturbance and tearing can appear (Messmer, 2015, Report of the International Dry Eye Workshop, 2007).

DED is a subset of OSD. OSD is a broad term encompassing a variety of ocular surface conditions, some of which imitate DED. As a result, differential diagnosis is required to correctly manage the presenting OSD. The Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) Diagnostic Methodology report includes tests and questions that can be employed to aid in this differential diagnosis, to separate DED from other OSDs (Wolffsohn et al., 2017). In this thesis, OSD is broadly used and refers to signs of ocular surface damage irrespective of symptoms, and DED is applied when such signs convert to symptoms.

DED has been a topical issue for the past few decades, with an increase in its awareness over the years (Craig et al., 2017). There have been numerous attempts at producing a universal definition to allow for a consensual approach to DED, in terms of diagnosis and management.

In 2007, after years of advances in the understanding of DED, TFOS DEWS proposed their first official definition of DED as follows:

> “Dry eye is 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.”(Report of the International Dry Eye Workshop, 2007)

However, the definition failed to include key aetiological factors or describe potential measurable outcomes of the disease, and 77% of the TFOS DEWS II members wanted it to be revised (Craig et al., 2017). With this in mind, and more research and understanding of the neurosensory role in DED, an updated definition was published in July 2017 incorporating previously omitted points:

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

With a clear definition of DED, it was important to establish a classification system for clinicians to use, to aid in both the diagnosis and management of the disease. Previous classification systems failed to identify the link between evaporative and aqueous deficient components of the disease, though they did appreciate that influencing factors can both be external and internal. Such is the case in the National Eye Industry (NEI) Workshop Report of 1995 and the TFOS DEWS I model in 2007 (A. Lemp, 1995, Foulks et al., 2007). A revised classification system was proposed in the TFOS DEWS II report (Figure 1.4) highlighting a clinical decision algorithm, allowing for a triaging process in the identification and management of DED (Craig et al., 2017).

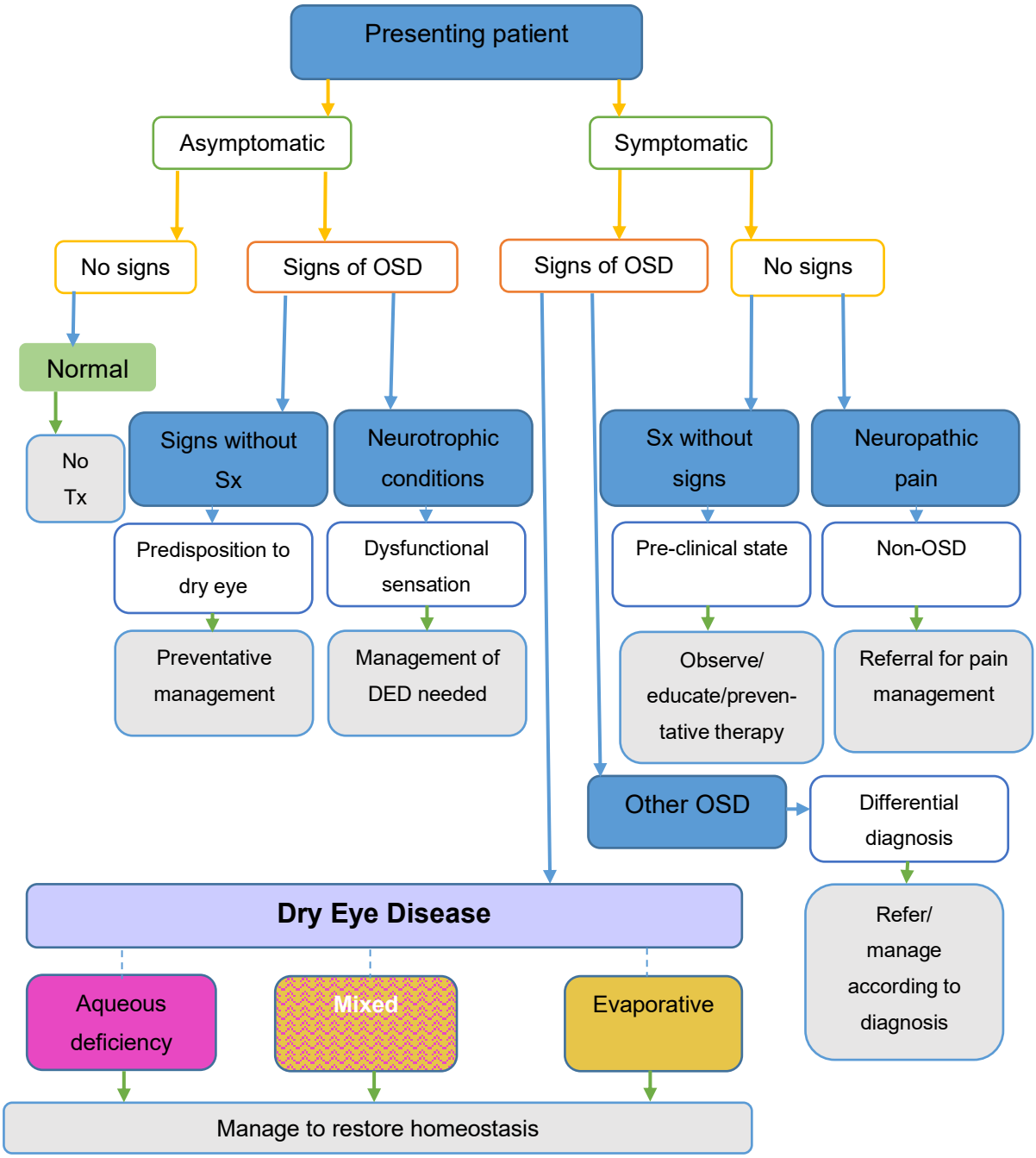


Figure 1.4: The revised classification system adapted from TFOS DEWS II (Craig et al., 2017). Sx=Symptoms, Tx=Treatment

It is clear to see that patients can present with or without signs and symptoms and depending upon the presenting factors, it can determine not only whether they have DED but also dictate the management pathway. For example, if a patient presents with signs of OSD,

but no symptoms, or vice versa, then preventative measure may have to be taken as it may either suggest a pre-clinical form of DED, or a predisposition to it (Figure 1.4)(Craig et al., 2017).

1.5 Causes of DED

It is the disruption to the homeostasis of the ocular surface which leads to OSD and DED. This can be down to intrinsic, extrinsic and iatrogenic factors. These factors can in turn cause aqueous deficient and evaporative issues, affecting the otherwise versatile ocular surface. The tear film helps to nourish the cornea and provide a smooth refractive surface, so its interruption can trigger ocular surface problems such as in DED. The ocular surface maintains a healthy balance by counteracting the evaporation of the tears with tear production and distribution, through homeostatic responses. If this cycle is not maintained, it can lead to hyperosmolarity and tear film instability, both of which contribute to inflammation. There may also be mechanical stress on the ocular surface through friction (Bron et al., 2017).

DED is therefore subdivided into Evaporative Dry Eye (EDE), where the rate of tear evaporation is higher than the rate of production, and Aqueous deficient Dry Eye (ADDE) where the lacrimal secretion is less than the rate of evaporation (Bron et al., 2017). The concept of DED is a complicated one, in the sense that EDE and ADDE are linked and mostly overlap. For example, though the initiating cause of DED may be a deficiency in tear production, after tear break up, there is some element of evaporation present. It has also been said by Bron and colleagues (2017), that all forms of DED are evaporative in nature, as without it, hyperosmolarity cannot occur. The term ‘hyper-evaporative’ DED is thus regarded more fitting (Bron et al., 2017).

The tear film forms an essential element of the ocular surface. It is about 3μm in thickness, 3μl in volume and is comprised of 3 components. The outermost layer is the lipid layer, which is responsible for reducing the amount of tear evaporation from the surface. Most of the lipids in this layer are secreted by the meibomian glands, located at the upper and lower lid margins. When the meibomian glands are damaged or blocked, as in meibomian gland dysfunction (MGD), it can lead to DED by disrupting this element of the tear film. The middle layer, known as the aqueous layer, forms the bulk of the tear film. It is responsible for delivery of nutrients and washing away debris and toxins (Dartt and Willcox, 2013). It is mainly produced by the lacrimal and accessory glands (Matossian et al., 2019). The

innermost layer is responsible for interacting with the epithelial cells and is known as the mucin layer (Matossian et al., 2019). The majority of the mucins within this layer are produced by the goblet cells of the conjunctival epithelium (Dartt and Willcox, 2013). The three-layer tear film model was originally proposed by Wollf (Wolff, 1946, Holly and Lemp, 1977) and has been widely accepted due to its simplicity, enabling visualisation of the layers and their interaction with each other (Willcox et al., 2017). However, this very simplicity has also received criticism (Doane, 1994). The mucin layer decreases in concentration from the epithelium to the aqueous layer (Dilly, 1994), and such a gradient has allowed the two to be coined as the mucoaqueous layer as a whole, owing to their integration (Willcox et al., 2017, Cher, 2008). A disturbance to any of these layers of the tear film can cause ocular surface problems, which may be evaporative, deficient, or a combination of the two, in nature.

There are numerous contributors of DED, some of which are briefly listed below. This list is merely an overview, and as mentioned, some of these causes may overlap.

Extrinsic Factors:

- Humidity (Uchiyama et al., 2007)
- Heat (Khurana et al., 1991)
- Pollution (Gupta et al., 2002)

Intrinsic Factors:

- Sex (Schaumberg et al., 2009, Schaumberg et al., 2003)
- Genetics (Vehof et al., 2014b)
- Sjögren Syndrome (Sullivan et al., 2003)
- Comorbidities (Dana et al., 2019)
- Aging (Schaumberg et al., 2003, Schaumberg et al., 2009)
- Hormones (Connor et al., 1999)

Iatrogenic Factors:

- Ocular surgery (Denoyer et al., 2015)
- Systemic Medication (Paulsen et al., 2014)
- Preservatives in topical medication (Ishibashi et al., 2003)

1.5.1 The Vicious Cycle

The initial cause of homeostatic imbalance can channel into the 'Vicious Cycle'; a series of events leading to inflammation and hyperosmolarity. These events trigger each other, and so lead to a continuation of the disease cycle. Tear hyperosmolarity is the centre of this figure, which in turn leads to inflammatory responses. Such responses cause goblet cell, epithelial cell and glycocalyx damage. This results in an unstable tear film, which consequently exacerbates hyperosmolarity (Bron et al., 2017). Figure 1.5 demonstrates the processes in the vicious cycle as imaged in the TFOS DEWS II Pathophysiology report.

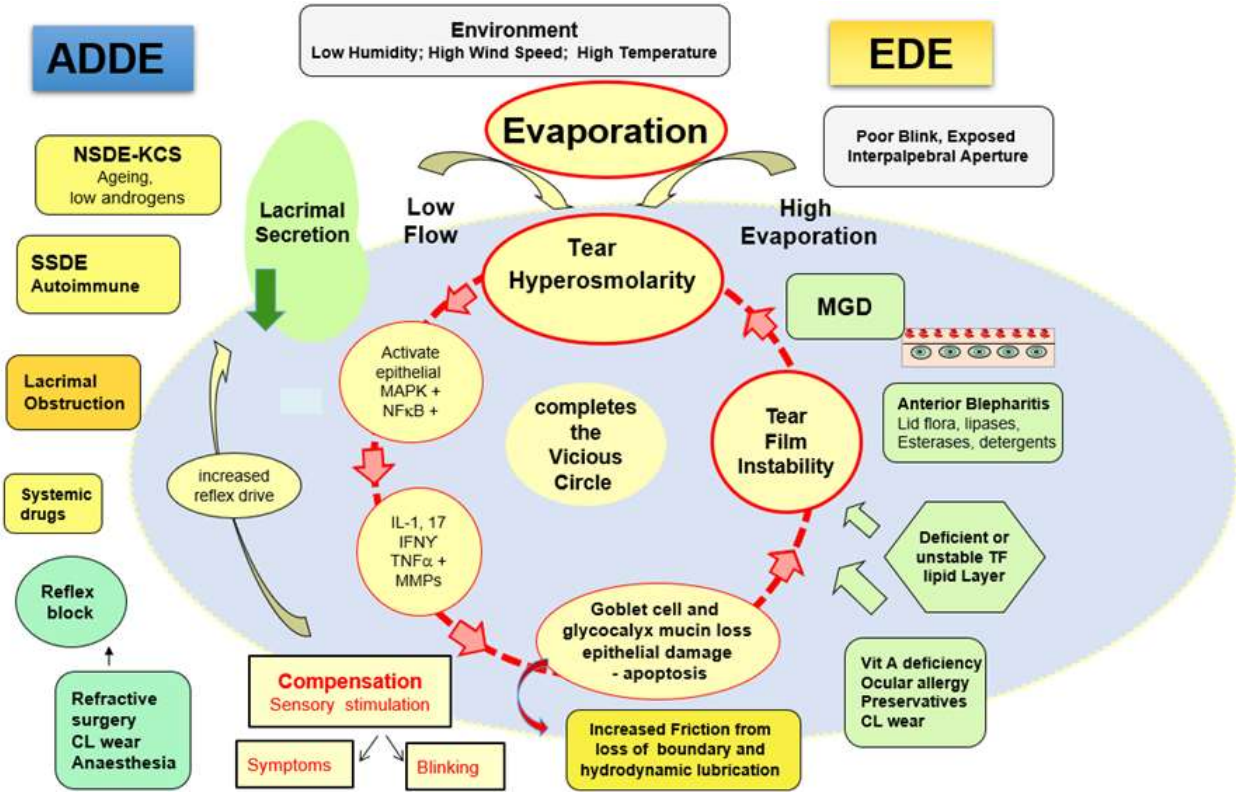


Figure 1.5: The Vicious Cycle of DED adapted from the TFOS DEWS II Pathophysiology report (Bron et al., 2017)

1.5.2 The prevalence of OSD in glaucoma

The advancements in knowledge of DED have increased vastly over the recent years, and there is much more awareness of the disease amongst both clinicians and patients (Haddad et al., 2017). TFOS DEWS II carried out a literature search, looking at global human-based studies across 10 years (2005-2015), and concluded that the prevalence of DED varies between 5%-50%. There seems to be variability of the rates of DED depending on whether

studies based their diagnosis on signs or symptoms, with higher prevalence rates amongst those studies where the diagnosis was primarily based on signs (Stapleton et al., 2017).

Furthermore, prevalence rates are higher amongst women than men, across all ages (Stapleton et al., 2017). The prevalence of DED in women rises from 14% at 50 years of age to 22% at 80 years of age. In men, however, the prevalence shows both a smaller and later increase, from 7% at 60 to 69 years of age, to 13% in those aged 80 years and over (Matossian et al., 2019). This is backed by a fellow study by United States National Health and Wellness survey (2017) which showed that though women consistently showed higher prevalence levels than men, the difference was much more significant amongst older participants (Farrand et al., 2017).

Prevalence rates also seem to be influenced by race. In the epidemiology literature review conducted by TFOS DEWS II, Asians were found to have a higher prevalence of DED than Caucasians, as demonstrated by higher tear instability and ocular surface staining results (Stapleton et al., 2017).

Disparity between studies in terms of prevalence of DED may further be influenced by factors such as climate and geographical location. Some studies have investigated the impact of extrinsic factors such as location, sunlight exposure and humidity on the ocular surface (Tandon et al., 2020). An example of such was the 'Sun Exposure, Environment and Dry Eye Disease' (SEED) study carried out by Tandon and colleagues (2020) which looked at the prevalence and risk factors of DED across various regions of India. Comparisons were made between plain, hilly and coastal locations using an array of DED tests such as TBUT and corneal staining as well as the use of the OSDI and a lifestyle questionnaire. Recruitment was made of 12,021 participants over 40 years of age, making it the largest population-based study utilising the TFOS DEWS II diagnostic criteria for evaluation of DED (Tandon et al., 2020) .

Results of this study found a distinct difference in prevalence rates amongst the different geographical locations. The prevalence of DED was highest in the Northern plains, standing at 41.3%. Prevalence rates were lower for hilly and coastal locations (24% and 9.9%, respectively). Suggestion has been made that such variations may be directly related to sun-exposure, humidity levels and air pollution levels in these locations. Air pollution was highest in the Northern plains and lowest in the coastal regions. In this particular study, a positive association was found between cumulative sun exposure and DED. Furthermore, low

humidity appeared to be a direct risk factor for DED. Prevalence of DED was highest in Northern plains, where humidity was the lowest, whilst coastal areas had the lowest DED prevalence rates and the highest humidity levels (Tandon et al., 2020).

Prevalence rates of DED appear to be influenced not only by intrinsic factors such as age, sex and race, but also external factors such as geographical location and humidity levels. It may not be surprising then, that the prevalence of DED globally shows much variation. The prevalence of symptomatic DED was found to be 6.8% in the USA (Farrand et al., 2017), 11% in Spain (Viso et al., 2009), 32% in India (Titiyal et al., 2018), 32.1% in Saudia Arabia (Alshamrani et al., 2017), 42% in Africa (Akowuah and Kobia-Acquah, 2020) and 50.1% in China (Guo et al., 2010). Of course, such individual prevalence studies are further influenced by the diagnostic criteria used in the study, the demographic of patients included as well as the specific location for each region.

Treated glaucoma patients have also been shown to have high prevalence rates of OSD. Leung and colleagues (2008) reported that 59% of glaucoma and OHT patients concurrently suffered from dry eyes. Moreover, severe dry eyes were reported by 27% of glaucoma and OHT patients. Symptoms in this study were reported using the Ocular Surface Disease Index (OSDI), a questionnaire designed to grade the severity of dry eyes through 12 questions about symptoms and visual function (Schiffman et al., 2000). The results were corroborated by objective measurements such as Tear Break Up Time (TBUT), which revealed abnormal tear quality in 79% of patients, and reduced tear production using the Schirmer's test in 61% of patients (Leung et al., 2008).

In addition, it has been widely suggested that the use of glaucoma drops increases the risk of OSD (Rossi et al., 2012, Wong et al., 2018). Rossi and colleagues (2002) set out to explore the risk factors for developing OSD in treated glaucoma and OHT patients, as well as looking at the prevalence of OSD. This cross-sectional, observational study found that the number of drops used, as well as the period of time over which the drops have been used, both influence the probability of developing OSD. They also emphasised that it is the duration of exposure to the preservative benzalkonium chloride (BAK) which contributes to these increased risks (Rossi et al., 2012).

Matthews and colleagues (2013) took a different approach to exploring the link between OSD and glaucoma. The study grouped the participants into two categories: glaucoma suspects and glaucoma subjects. This categorisation was based purely on visual fields

results, rather than which glaucoma drops were used, as in other glaucoma versus OSD studies. The OSDI questionnaire was also split into two sections to establish vision related scores and discomfort related scores, rather than an overall score which is the normal practice (Mathews et al., 2013).

Their results highlighted that poorer OSDI scores are likely to be down to VF loss rather than OSD related ocular discomfort. By separating the two units of the OSDI questionnaire, it was easier to see that visual disability such as difficulty with reading and driving may actually be influenced by poorer contrast sensitivity and visual field losses in cases of glaucoma subjects and those with more advanced glaucoma (Mathews et al., 2013).

Notwithstanding the idea that VF loss drives OSDI scores to some extent, several studies have highlighted the link between poor vision and discomfort. For instance, Moldonado-Codina and colleagues (2021) found that in contact lens wear, ocular discomfort may be amplified when the perceived vision is regarded as being poor (Maldonado-Codina et al., 2021). Similarly, Basuthkar Sundar Rao and Simpson (2015) simulated ocular discomfort using a pneumatic stimuli and presented trial lenses offering clarity and defocus to the participant. Discomfort was influenced by the presence of defocus (Basuthkar Sundar Rao and Simpson, 2015). This association between vision and comfort plays an important factor in ocular discomfort investigations, since multiple sources may act simultaneously, resulting in both ‘visual’ discomfort as well as ‘physical’ discomfort, both of which will be reflected in the OSDI score.

In the study by Mathews and colleagues (2013), significantly more corneal staining was observed in the glaucoma subjects group than the glaucoma suspects group. The total OSDI scores were also significantly higher amongst the glaucoma subjects group than the glaucoma suspects, driven by the vision-related sub-scores, but the overall discomfort-related sub-scores were similar for both subgroups. Mathews and colleagues (2013) suggested this might be down to similar reasons as in diabetic ocular surfaces, where the corneal sensitivity is reduced (Mathews et al., 2013). In diabetics, this is due to poor diabetic control (Dogru et al., 2001, Mathews et al., 2013). This suggestion is backed by Van Went and colleagues (2011), who found decreased corneal sensitivity amongst patients on preserved glaucoma medication, compared to untreated patients or those on PF medication (Van Went et al., 2011). This may well explain the poor correlation between signs and symptoms of OSD in glaucoma clinics (Ghosh et al., 2012).

Though the study by Matthews and colleagues (2013) highlighted the confounding overlap between visual symptoms caused by glaucoma and OSD, the study is limited with the conclusions that can be drawn from it as both groups had patients on topical glaucoma medication, and this was not well distributed between the groups. Of the glaucoma subjects, 75% were receiving topical glaucoma drops, as opposed to 41% of the glaucoma suspects. This could potentially have impacted the discomfort side of the OSDI scores and skewed some of the results. Further to this, the study failed to look at the duration over which the glaucoma was treated. It may have been possible that those who previously were intolerant to one type of medication, were changed to other forms of therapy, which again could impact the discomfort scores obtained, particularly if the latter therapy is better tolerated (Mathews et al., 2013).

Perhaps it would have been better to investigate untreated and treated glaucoma patients, while still dividing the OSDI questionnaire into two parts, in order to establish better links between OSD signs, symptoms and glaucoma treatment.

Nonetheless, it is clear to see that there is a connection between glaucoma treatment and OSD, whether that is through symptoms or observed signs, and so it is an area that must be explored in order to provide best overall care in glaucoma clinics.

1.6 The role of preservatives in glaucoma

Preservatives are chemical compounds added to medicines to prevent microbial contamination, inhibit microbial growth and to maintain sterility (Freeman and Kahook, 2009). Their use in ophthalmic preparations is critical, especially in multi-dose formulations, where contamination could not only pose a sight-threating infection risk, but could also change the original preparation (Baudouin et al., 2010). Multi-dose containers are preferred over single dose units when it comes to eye drops for cost effectiveness. This does however, increase the risk of contamination whether that be by handling, contact with the eye and adnexa or through air borne microbes. The risks are emphasised if multi-dose bottles are kept open for long periods past their initial opening. This led to regulations limiting the duration of use once eye drops had been opened (Baudouin et al., 2010, Chibret, 1997, Mark Santillo et al., 2019) .

There are a number of different preservatives used in topical medication, the most common one being benzalkonium chloride, otherwise known as BAK. It is a quaternary ammonium

compound, initially being used as a germicide back in the early nineteen hundreds, before taking off in the 1940s as a preservative (Freeman and Kahook, 2009, Domagk, 1935, Steven et al., 2018, Merchel Piovesan Pereira and Tagkopoulos, 2019, PRICE, 1950). It has been favoured as a preservative due to its efficacy and minimal short term allergic responses in clinical trials, especially when compared to its predecessors composed of mercury derivatives (Baudouin et al., 2010, Charnock, 2006, van der Valk et al., 2005b).

However, clinical trials do not necessarily reflect real life scenarios, where individuals may be on numerous topical drops, have a previous history of OSD and where effects may not manifest for a few years. Randomised controlled trials (RCTs) tend to be utilised to test the efficiency of drugs post development. These trials tend to be short and specific; they usually only cover a period of less than 12 months and test only one reference drug (Baudouin et al., 2010, Day et al., 2013, Aptel et al., 2016). In reality, as in glaucoma, patients tend to be on multi-therapy, most likely over their lifetime. This masks the real-life issues that could be encountered by glaucoma patients using topical medication.

BAK is still one of the most common preservatives found in topical medication. BAK is a detergent type of preservative, and so it causes cell death by interfering with the lipids of the cell membranes. This interruption leads to cell lysis through instability (Freeman and Kahook, 2009). BAK is also a great fungicide and spermicide, and if combined with Edetate Disodium (EDTA) 0.1%, its bacterial spectrum is increased further (Baudouin et al., 2010, Charnock, 2006).

Though it is good at destroying membranes of bacteria, it is undeniable that it may in fact impact the cell membranes of normal cells too. De Saint Jean and colleagues (1999) found that concentrations of BAK even as low as 0.1% and 0.05% caused immediate cell lysis. Those conjunctival cells treated with 0.01% of BAK showed a delayed response through apoptosis. Cells treated with 0.005% to 0.0001% of BAK apoptosed within 24-72 hours of initial treatment (De Saint Jean et al., 1999). It is clear to see that even low concentrations of BAK can have detrimental effects on ocular surface cells, and that the manner and speed of such damage is related to the dose. In the glaucomatous eye, there is continuous administration of drops into the eyes, at least once a day if not more, which may lead to an accumulation of BAK. Typical concentrations of BAK in glaucoma drops tend to vary between 0.004% (Levobunolol) to 0.1% (Brinzolamide and Timolol combination drops) (Steven et al., 2018).

One proposed hypothesis backing the use of BAK in glaucoma medication was the notion that it enhances penetration into the aqueous chamber, through the corneal epithelium. The idea was that this would allow for better delivery of the active drug compound, and thus provide better efficacy. Pellinen and Lokkila (2009) set out to test this theory in rabbit eyes. The pharmacokinetic study administered Tafluprost of 0.015% in a 30micrl single dose, both with 0.01% of BAK preservative and without it. The penetration of drug into the aqueous humour was then checked, which ultimately, showed no difference between the preserved and PF compound (Pellinen and Lokkila, 2009).

However, Majumder and colleagues (2008) found that the addition of 0.005% BAK did increase the permeation of Acyclovir by almost threefold. The addition of EDTA 0.01% to the BAK compound increased permeability through the cornea by 2.5-fold (Majumdar et al., 2008). Indeed, in order for such pharmacokinetic characteristics to be beneficial, it would be expected that they would aid in reducing intraocular pressures (IOPs). It appears that the use of BAK associated with increasing corneal penetration is limited to non-glaucoma drugs such as acyclovir (Majumdar et al., 2008).

Various studies have looked into the efficacy of preserved versus PF glaucoma drops when it comes to IOP control. In 2006, Easty and colleagues (2006) looked at the effectiveness of 0.1% timolol gel in its preserved and unpreserved form. The comparison showed insignificant differences, with both types of the gel producing an average reduction of 24% from baseline measures (Easty et al., 2006). Similarly, Aptel and colleagues (2016) investigated the efficacy and pharmacokinetics of latanoprost in both its preserved and PF form. They measured the IOP at various time points, during a 12-week, crossover-type study. Results showed that there was no difference in overall diurnal IOP control, and both the PF and preserved showed similar efficacy at each IOP time point (Aptel et al., 2016).

Regardless of the evidence in the body of literature, BAK still seems to be the leading force of preservatives used glaucoma drops. PF options are viable when eye drops are issued as unit dose (UD) vials or in specially manufactured multi-dose containers (PETIT BEN SAIDANE, 2017).

1.6.1 Preservatives in glaucoma medication

Medication	Brand Name	Preservative	Preservative concentration
Prostaglandin Analogues			
Latanoprost	Xalatan	BAK	0.02%
Bimatoprost	Lumigan	BAK	0.02%
Travoprost	Travatan	Polyquad	0.01%
Beta Blockers			
Timolol	Timolol	BAK	0.01%
Levobunolol	Betagan	BAK	0.004%
Betaxolol	Betoptic	BAK	0.01%
Alpha Agonists			
Brimonidine	Alphagan	BAK	0.005%
Apraclonidine	Iopidine	BAK/Propylene Glycol	0.01%
Carbonic Anhydrase Inhibitors			
Brinzolamide	Azopt	BAK/EDTA	0.01%
Dorzolamide	Trusopt	BAK	0.0075%
Combination Therapy			
Latanoprost+Timolol	Xalacom	BAK	0.02%
Lumigan+Timolol	Ganfort	BAK	0.05%
Travatan+Timolol	DuoTrav	Polyquad	0.01%
Brinzolamide+Timolol	Azarga	BAK	0.1%
Dorzolamide+Timolol	Cosopt	BAK	0.0075%
Brimonidine+Timolol	Combigan	BAK	0.05%
Brimonidine+Brinzolamide	Simbrinza	BAK	0.03%

Table 1.3: Glaucoma medications and their preservatives. Adapted from the review by Steven and colleagues (2018) citing the British National Formulary 2017 (Steven et al., 2018, Joint Formulary Committee, 2022)

1.6.2 Preservative-Free alternatives in glaucoma medication

Medication	Brand Name	Drug Concentration
Prostaglandin Analogues		
Latanoprost	Monopost	0.005%
Bimatoprost	Lumigan UD	0.03%
Tafluprost	Saflutan	0.015%
Beta Blockers		
Timolol	Tiopex/Timoptol UD	0.1%, 0.25%, 0.5%
Carbonic Anydrase Inhibitors		
Dorzolamide	Trusopt PF	2%
Combination Therapy		
Bimatoprost+Timolol	Ganfort UD	0.03%, 0.5%
Tafluprost+Timolol	Taptiqom	0.015%, 0.5%
Dorzolamide+Timolol	Cosopt PF	2%, 0.5%

Table 1.4: Preservative-Free glaucoma medication. Adapted from the review by Steven and colleagues (2018) citing the British National Formulary 2017 (Steven et al., 2018, Joint Formulary Committee, 2022)

1.6.3 Alternative preservatives to BAK

The toxicity of BAK has led to the development of alternative preservatives, with the hope that they will maintain sterility whilst minimising ocular side effects. Types of such preservatives include oxidative ones, such as SofZia®, an ionic buffered preservative, and Purite®, a stabilized oxychloro complex (Freeman and Kahook, 2009). Oxidative preservatives work by altering the DNA make up of bacterial cells, being small enough to penetrate cell walls so allowing interference with the protein and lipid components of the cells, and thereafter breaking down into less harmful compounds (Freeman and Kahook, 2009).

SofZia® is one of the newer preservatives used in glaucoma medication. When tested for its toxicity compared with BAK based drugs, there was a lower incidence of keratoconjunctival epitheliopathy, particularly in the cornea, with no significant difference in IOP lowering amongst the drugs regardless of what preservative was present (Aihara et al., 2013).

However, when tested against BAK for safety, SofZia provided less antimicrobial protection than BAK (Ryan et al., 2011).

1.6.3.1 Common preservatives & their mode of action

Preservative Name	Type of preservative	Mode of action	Drug examples
SofZia	Oxidative	Composed of boric acid, zinc, sorbitol and propylene glycol. Once exposed to the tear film, the substance becomes inactive, breaking down into components which are comfortable to the ocular surface(Kahook, 2007).	Travatan Z
Sodium perborate/GenAqua	Oxidative	Composed of sodium perborate, which catalyses into hydrogen peroxide, water and oxygen. It works by interfering with membrane bound enzymes, and in turn altering protein synthesis within bacterial cells	Genteal
Stabilised Oxochloro complex/SOC/Purite	Oxidative	Made up of chlorine dioxide, chlorite and chlorate. It breaks down to water, oxygen, sodium and chlorine free radicals (FRs). It is these FRs which prevent	Alphagan P

		protein synthesis within the microbial cells through glutathione oxidation, in turn causing cell death.	
Polyquaternium-1/Polyquad	Detergent	Derivative of BAK. It works by attracting bacterial cells, and acting on their cell walls.	Tears Naturale II
Chlorobutanol	Detergent	Previously used in hypnotic and sedative agents. It causes cell lysis by interfering with cell membrane lipid conformation (Tomlinson and Trees, 1991). Limited use due to its instability at room temperature.	TobraDex ointment
Cetrimonium chloride	Detergent	Antiseptic and surfactant properties, but risk of keratinization and inflammatory responses as demonstrated in rat studies(Becquet et al., 1998)	Civigel
Benzalkonium chloride/BAK	Detergent	Disturbs cellular membranes and interferes with cellular junctions, allowing penetration into the anterior chamber. Also known to cause necrosis and apoptosis.	Azopt, Lumigan, Xalatan

Edetate disodium/EDTA	Chelating agent	Works due to its ability to chelate, as well as inactivating trace amounts of heavy metals. It acts as a preservative enhancer when combined with other compounds. For example, N-hydroxymethylglycinate with EDTA has been shown to have good antimicrobial properties whilst having low toxicity on corneal cells (Cristaldi et al., 2018).	Betagan

Table 1.5: Common preservatives and their mode of action. Table adapted from (Freeman and Kahook, 2009)

1.6.4 The effect of preservatives on ocular structures

The negative effects of preservatives have been well documented over the years. Particularly, their effect on the ocular surface leading to OSD and DED.

1.6.4.1 Preservatives vs the ocular surface

In 1999, a large-scale epidemiology survey was conducted by 249 ophthalmologists on 4107 glaucoma patients, studying the signs and symptoms of OSD in preserved versus PF drops. Patients using preserved drops showed higher incidence rates across all categories of OSD symptoms compared with those on PF drops. Such symptoms included discomfort upon instillation (43% of patients in the preserved group compared to 17% in the PF group), stinging or burning sensation (40% in preserved group vs 22% in PF group) and foreign body sensation (31% in preserved group vs 14% in PF group) (Pisella et al., 2002).

These symptoms were backed by clinical signs, which were also significantly more pronounced in the preserved group than the PF group. Conjunctival redness was present in

41% of patients on preserved drops compared to 20% in the PF group. Also, mild, superficial, punctate keratitis was present in 17% of the preserved group compared with 8.9% of the PF group (Pisella et al., 2002).

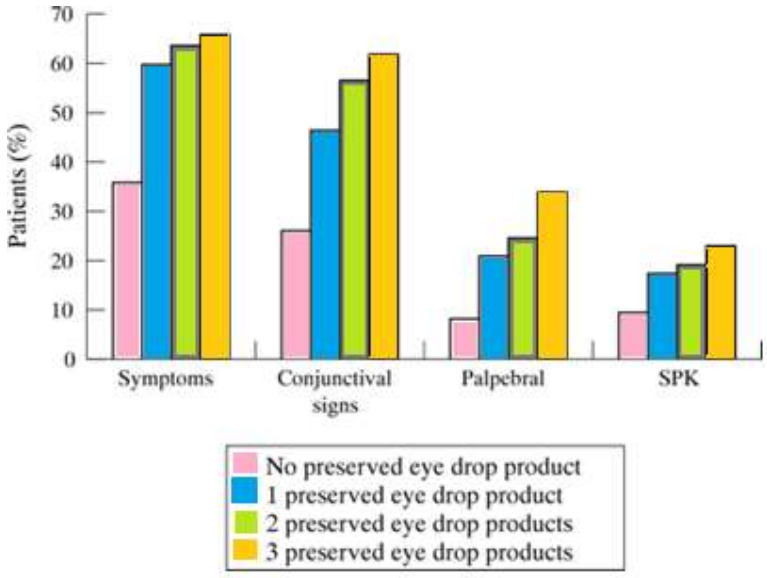


Figure 1.6: The relationship between signs and symptoms of OSD, to the number of preserved eye drops adapted from (Pisella et al., 2002)

It is clear to see that not only is the frequency of signs and symptoms of OSD related to whether the drop is preserved or not, it also positively correlates with the number of preserved drop instillations. The occurrence of DED in medically treated glaucoma is therefore dose dependent (Pisella et al., 2002). Rossi and colleagues (2009) confirmed this with their observational survey, which found higher prevalence rates in those patients with a higher number of glaucoma drops; 5% where no drops are used, 11% where one eye drop is used, 39% where two eye drops are used and 43% where three eye drops are used. This study also highlighted the negative impact of dry eye symptoms on the quality of life of patients (Rossi et al., 2009).

A similar multicentre, cross-sectional survey was performed in four European countries between 1997 and 2003 by Jaenen and colleagues (2007) looking at the side effects of preserved versus PF drops in glaucoma patients. Nine thousand, six hundred and fifty-eight patients were included in this large-scale study, and both the symptoms and ocular signs were significantly more prevalent in the preserved group compared to the PF group. There was also a significant decrease in such signs and symptoms once the preserved drops had

been stopped or changed to a PF option (Jaenen et al., 2007). The overall incidence of ocular symptoms ranged from 30% to 50% (Baudouin et al., 2010, Jaenen et al., 2007).

Likewise, another large-scale, observational study on dry eye prevalence in glaucoma was carried out in Germany by Erb and colleagues in 2008. A total of 20,506 patients were recruited from across 900 centres in Germany, with a clear aim of investigating the association between glaucoma, age, concomitant diseases, dry eyes and medication. The findings showed that dry eye was most prevalent amongst women than men (56.9% vs 45.7%), with this difference becoming more apparent after the age of 50. Hypertension and diabetes appeared to be strongly related to dry eyes in glaucoma, the prevalence being 48.1% and 22.5% respectively. There was also some discrepancy amongst the subgroups of glaucoma; prevalence levels were highest in those with PXF glaucoma, then POAG, and lastly PDS glaucoma. One proposed hypothesis was that PXF usually requires multiple drops for treatment, whereas POAG is usually treated by one (Erb et al., 2008).

1.6.4.2 Preservatives vs the crystalline lens

The effect of preservatives on the crystalline lens is a topic that is widely discussed. There appears to be an association between topical glaucoma medication and the formation of cataracts (Baudouin et al., 2010, Herman et al., 2006, Bontzos et al., 2017). In 2002, the Early Manifest Glaucoma Trial (EMGT) looked at the relationship between lowering IOPs and the progression of glaucoma. The results mimicked those of other glaucoma studies with regards to an increased incidence of cataract formations or extractions, including the Ocular Hypertension Treatment Study (OHTS) and the Collaborative Normal Tension Glaucoma Study (CNTGS) (Anderson, 2003, Herman et al., 2006, Heijl et al., 2002). The EMGT found an increase in the nuclear lens opacity development in those treated for their glaucoma compared to the control group. Posterior subcortical and cortical cataract formation appeared to be on par between the treated group and the control group. There were also higher rates of patients requiring cataract extraction surgery in the treated group than the controls (Heijl et al., 2002).

Similarly, the OHTS found that those who were treated for their glaucoma had an increased rate of cataract extraction/filtration surgery; 7.6% in those treated compared with 5.6% in the non-treated group. The grading of posterior subcapsular cataracts was on average slightly higher in the treated group than the controls; all other types of cataracts were graded similarly (Herman et al., 2006). Likewise, the CNTGS found those treated for the glaucoma

had a higher incidence of cataract formation, though predominantly in those who underwent glaucoma surgery (Anderson, 2003).

Consideration should be taken as to what contributes to the lens opacification, the presence of preservatives or the active drug compounds within the glaucoma drops. Goto and colleagues (2003) examined this on biological cultures of human epithelial lens cells. It was found that BAK was the most damaging to epithelial lens cells, and stimulates mediators involved in inflammatory and apoptotic processes, which could ultimately promote lens opacification (Baudouin et al., 2010, Goto et al., 2003).

1.6.4.3 Preservatives vs the retina

The term 'Pseudophakic Preservative Maculopathy' was coined by Miyake and colleagues (2002) due to the role preservatives appear to play in the development of cystoid macular oedema (CMO) in pseudophakic and aphakic eyes. Preserved timolol was compared with PF timolol, with regards to the occurrence of CMO and the presence of aqueous flare. The incidence of CMO and aqueous flare was significantly higher in the preserved group. The overall conclusion was that it is the preservatives rather than the principal agents in glaucoma medication, which contribute to the mechanism of post-operative CMO (Miyake et al., 2003).

1.6.4.4 Preservatives vs the trabecular meshwork

The trabecular meshwork (TM) is responsible for draining the aqueous humour from the eye. When the TM is healthy and fully functioning, it contributes to homeostasis of the eyes by adjusting outflow to maintain normal IOPs (Abu-Hassan et al., 2014, Acott et al., 2014). In glaucoma, the function of the TM is impaired, with trabecular cell loss and faster senescence (Baudouin et al., 2010). It has been suggested that preservatives, namely BAK, contribute to the oxidative stress and cell death (Debbasch et al., 2001, Baudouin et al., 2012a).

Hamard and colleagues (2003) looked at the effect of preservatives on TM cells by measuring apoptotic marker expressions on cultured TM cells. They compared preserved glaucoma drugs to unpreserved drugs. Findings showed that in a 1/100 dilution, unpreserved beta-blockers showed no apoptotic effects, whereas preserved latanoprost, beta blockers and BAK significantly increased apoptotic expression markers. The most toxic effects seemed to be produced at concentrations higher than would be found in the aqueous

humour, however, there may be a cumulative effect present in reality, which should be considered (Hamard et al., 2003). It has been shown that BAK has the ability to penetrate deeper ocular structures and linger around in the TM in chronically treated glaucoma patients (Desbenoit et al., 2013).

Likewise, Chang and colleagues (2014) found that BAK negatively affected cell viability in a human TM cell line, when compared to tafluprost free acid (the active form of tafluprost). Cell death increased with exposure to BAK, which was both time and dose dependent. When BAK was combined with tafluprost, there was a slight increase in cell viability when comparing to treatment with BAK alone, which suggests that tafluprost may provide some cytoprotection against BAK (Chang et al., 2015).

1.6.5 The effect of preservatives on surgical procedures

Glaucoma filtration surgeries are common procedures performed to lower IOP. A type of such filtration surgery is trabeculectomy, which was introduced back in the 1960s and even to this day provides good IOP lowering, with an average of 12.7±5.8mmHg after 1 year (Gedde et al., 2007). Preservatives can affect the success of such surgeries.

Broadway and colleagues (1994) looked at the relationship between topical glaucoma drops and the outcomes of trabeculectomy surgeries. One hundred and six patients were assessed post trabeculectomy surgery for their success rates. The findings showed that long- term combination therapy increased the risk of surgery failure. Those who were just on beta-blockers had a success rate of 93%, but those on beta-blockers, sympathomimetics and miotics had a success rate which was significantly lower at 43%. These results were backed by the comparison of preoperative conjunctival cell counts of the two groups; failure was linked to the presence of macrophages, lymphocytes and fibroblasts. Therefore, inflammation induced by preoperative topical treatment has been linked to lower success rates of trabeculectomy (Broadway et al., 1994).

Furthermore, it was found that by changing the preoperative regimen, there was a reduction in inflammatory cells and the success of trabeculectomy surgery improved (Broadway et al., 1996).

A more recent study by Biomer and Bert (2013) also found that the use of drops containing BAK increases the risk of surgery failure, though, this was irrespective of the number of

drops used (Boimer and Birt, 2013). These findings were not resonated in all studies, however. Öztürker and colleagues (2014) found no significant link between the use of preserved glaucoma drops and the success rate of trabeculectomy surgey (Öztürker et al., 2014).

1.6.6 Preservative vs Preservative-Free

There has been much movement towards the inclusion of PF options in glaucoma medication, particularly since the toxicity of BAK has been so widely discussed. Many *in vitro* and *in vivo* studies have looked into the differences between preserved and unpreserved drops in glaucoma use. Some of these are discussed below.

1.6.6.1 Switching Studies

Pisella and colleagues (2002) looked at the relationship between preserved and PF drops and OSD. They found that after the first visit, 349 of 4107 patients needed changing from preserved to PF medication due to heightened ocular irritation and signs of OSD. At the second visit, it was found that this resulted in significant reductions in all signs and symptoms of OSD. Symptoms decreased by 2.7-5.2 fold, with conjunctival hyperaemia reducing by 45% (Pisella et al., 2002).

At a cellular level, Campagna and colleagues (1997) found that by switching to PF timolol from the preserved version, not only did the subjective symptoms diminish, there was an increase in mucus cells and improvement of the impaired conjunctival epithelial cells too (Baudouin et al., 2010, Campagna et al., 1997).

1.6.6.2 Preserved to reduced preservatives

Pisella and colleagues (2002) also reduced the amount of preservatives being exposed to the ocular surface by decreasing the number of preservative-containing drops in 57 patients initially on preserved drops at the first visit. After this amendment and by the second visit, the signs and symptoms of OSD were markedly lower across the spectrum (Pisella et al., 2002).

The large-scale study carried out by Jaenen and colleagues (2007) produced similar findings. In the group of patients who had the number of preserved drops reduced between visits, most ocular symptoms declined by two-four times. Stinging on first instillation of the

drops had reduced by 48% when the number of preserved drops were decreased (Jaenen et al., 2007).

1.6.6.3 Comparison studies

Pellinin and colleagues (2012) looked at the cytotoxic effects of preserved and PF glaucoma drugs, both *in vivo* and *in vitro*. Preserved latanoprost, bimatprost and travoprost were compared with PF tafluprost. Results showed that the cytotoxicity of the preserved formulations depended on the concentration of BAK, and PF Tafluprost was the least toxic compound in the study.

More recently, El Ameen and colleagues (2018) looked at the tolerability of glaucoma medication by comparing the signs and symptoms observed in patients who were medically treated with PGAs for at least six months. Those who were on PF latanoprost reported significantly less problems both on instillation of their drops as well as between instillations. In addition, such findings were corroborated in the PF group with clinical findings of significantly lower conjunctival hyperaemia scores than those on preserved latanoprost, travoprost and bimatoprost (El Ameen et al., 2018).

1.6.7 Adherence, glaucoma and preservatives

Adherence and compliance are often terms used interchangeably in medical articles to describe the degree to which patients follow the physician's recommendation (Osterberg and Blaschke, 2005). The term compliance is generally less preferred by clinicians as it suggest passive behaviour from patients rather than a commitment to a therapeutic plan (Osterberg and Blaschke, 2005). Both terms are used in this literature. Regardless of which name is used, it is undeniable that patients will only truly benefit from their treatment, if the correct regimen is employed.

Tsai and colleagues (2003) produced a classification system for the barriers most commonly experienced by patients in glaucoma clinics. The main aim of the taxonomy of such barriers was to optimise the regimens set out by clinicians and to better educate patients on their treatment. Though the sample size was small (48 patients), 71 barriers were identified, which were then grouped into 4 categories: situational/environmental factors, medication regimens, patient factors and prescriber factors (Tsai et al., 2003).

Categories	Sample statement
1. Region factors	
Refill	I only forget to take my drops when I run out.
Cost of medication	When my insurance stopped paying for my medication I didn't take my drops.
Complexity	It was harder when I was taking 4 medications, now that I am taking 3 it is better.
Change	When I first started taking the drops I had a harder time remembering.
Side effects	I decided to quit taking my drops because I had a bad reaction from them.
2. Patient factors	
Knowledge/skill	Sometimes I miss my eye when taking my drops.
Memory	Sometimes I just forget to take my drops.
Motivation/health beliefs	I quit taking my drops because I didn't see benefit to them and didn't think they were working.
Co-morbidity	It is harder to keep track of my drops because I am taking so many other medications.
3. Provider factors	
Dissatisfaction	I quit taking my drops because I was dissatisfied with my doctor's care.
Communication	I stopped taking my drops because I didn't understand initially that I need to take them forever.
4. Situational/environmental factors	
Accountability/lack of support	Living alone I had problems taking my drops; now I live with my daughter and have no problems.
Major life events	Two years ago when my wife died I had a hard time taking my drops.
Travel/away from home	When I am on vacation it is more difficult to take my drops.
Competing activities	I miss my drops on Sunday mornings when I go to church.
Change in routine	Lifestyle changes that occur on the weekends, such as not getting up at a normal hour, cause me to forget to take my drops.

Table 1.6: Table from the study by Tsai and colleagues (2003), demonstrating the categories affecting adherence, and a sample statement for each (Tsai et al., 2003).

Of the barriers highlighted in this study, 49% were environmental in nature, 32% were related to medicine regimen, 16% were patient related and 3% physician related. Eighty-six percent of patients had complicated routines, taking more than one glaucoma drug, which could explain why a high percentage of reported problems were related directly to medicine regimen (Tsai et al., 2003).

There have not been many reports of side effects playing a major factor for non-adherence in glaucoma patients, though it is widely speculated that PF options would allow for better tolerability which in turn would ultimately lead to better compliance (Baudouin, 2008). A recent study conducted by McClelland and colleagues (2019) found that 24.2% of patients reported side effects (such as red eyes in 14.1%), but there was no correlation found between 'drops stinging on insertion' and adherence. The study did find overall lower adherence rates than previously documented in a questionnaire based study, at 41.1% (McClelland et al., 2019). When such a study was conducted in a clinical environment, the

adherence rates appeared to be higher (Rees et al., 2014), suggesting that full disclosure may only be revealed outside of the clinical setting (McClelland et al., 2019). Adherence can be hard to measure, and many self-reporting questionnaire-based studies rely on patients' honesty and admissions to form a picture of compliance to glaucoma medication.

Lemij and colleagues (2015) looked at the overall patient satisfaction with glaucoma therapy. Eighty-nine percent of patients reported that they were satisfied with their treatment, despite 25% having discomfort on instillation, and approximately half having problems between instillations. Forty-seven percent of patients had hyperaemia, and more than a third of patients were using ocular lubricants. Surprisingly though, only a small percentage of patients were dissatisfied with their therapy. Univariate analysis revealed that dissatisfaction was strongly linked to hyperaemia and OSD (Lemij et al., 2015).

Furthermore, the same study found that more than 80% of patients had switched their medication at some point, and whilst ineffectiveness was the main reason for this change, almost one quarter changed their medication due to intolerance to the drops. A proposed reason for the poor correlation between signs and symptoms has been put down to reduced corneal sensitivity in those chronically using preserved glaucoma drops (Van Went et al., 2011). Perhaps this is why OSD appears to be somewhat masked in adherence studies.

On the other hand, Chawla and colleagues (2007) found that adverse effects was the third most common reason for poor adherence, though the sample size was small at 83 patients. The cross-sectional study used a questionnaire-based approach to assess compliance. The results showed 'forgetfulness' to be the leading cause of poor compliance (42%), followed by difficulty with the drops, either from not knowing how to use them or due to practical problems (21%). The inconvenience of them, particularly their frequency, and the lack of perceived benefits, were also linked to poor adherence (Chawla et al., 2007).

Furthermore, patients on 'once a day' drops had better compliance than those on multiple drops a day (Chawla et al., 2007). There also appears to be an association between good patient understanding of the disease and better compliance; those who do not understand the consequences of the disease are less likely to adhere to the recommended regime (McClelland et al., 2019, Chawla et al., 2007). McClelland and colleagues (2006) found that those whose adherence improved over a 6-month period, stated that better drop instillation techniques, better knowledge of the disease and an easier regimen were factors that helped.

On the contrary, difficulty instilling drops and more drops to be instilled resulted in poorer adherence, yet 85.2% were unwilling to ask for help (McClelland et al., 2019).

The implication of non-adherence is the detrimental consequence it could have in terms of vision loss. Surprisingly, Olthoff and colleagues (2005) found no significant link between non-adherence and progression of visual field loss (Olthoff et al., 2005). However, this may be related to the fact that progression of glaucomatous field loss can be slow, and better methods to measure adherence may be needed to draw more feasible conclusions (Robin and Grover, 2011).

In addition, studies have shown that hypotensive drugs slow down the progression of visual field loss in glaucomatous patients (Heijl et al., 2002). Thus, one can derive from such prior studies that poor adherence would invariably affect the progression of glaucoma to some extent, and so it should be classed as a risk factor. In fact, Stewart and colleagues (1993) did find a positive correlation between adherence and preservation of sight (Stewart et al., 1993), whilst Konstas and colleagues (2000) found a strong association between poor compliance, higher IOPs and worse visual fields (Konstas et al., 2000).

Moreover, poor adherence can have huge cost implications. In the US alone, 33-69% of hospital admissions are down to poor adherence, often resulting in adverse drug reactions (Osterberg and Blaschke, 2005, McDonnell and Jacobs, 2002, Senst et al., 2001). The consequence of this has been estimated to cost around $100billion a year (Osterberg and Blaschke, 2005, Senst et al., 2001).

It has been shown that ultimately, patient-clinician communication is vital in encouraging adherence. Particularly, in stressing the consequence of vision loss from glaucoma if it is not well managed (Friedman et al., 2008). It has been proposed that perhaps a patient-centred approach may be best; by actively involving patients in decision making it would allow for more transparency between practitioners and patients (Hahn, 2009).

1.7 Summary

OSD and glaucoma are two complex diseases which are highly intertwined. The need for hypotensive drops to manage IOPs in glaucomatous and ocular hypertensive patients exposes the ocular surface to toxic preservatives, which can have cumulative, detrimental effects. With emerging side effects caused by such preservatives, various other issues can

arise such an intolerance, non-adherence, ineffectiveness of treatment and cost implications. The literature review has highlighted the perceived benefits of switching from preserved to PF glaucoma medication to address such issues. Certain limitations exist in the current literature review, since included studies have not been carried out as randomised controlled trials (RCTs), so may have been prone to confounding factors. In order to establish a more conclusive cause-effect relationship, by minimising confounding variables and by reducing bias, comparisons must be made using RCTs. A systematic review with meta-analysis of studies investigating the efficacy, safety and tolerability of preserved versus PF glaucoma medication would allow for a more robust comparison and allow for better understanding of the effects of glaucoma medication on the ocular surface.

As well as the need for a systematic review, there is lack of reporting of the current clinical habits of clinicians in the UK, with regards to the prescribing of PF ocular hypotensive drops and the management of, and attitudes towards, OSD in a glaucoma focussed clinic. The real benefit of PF medication as discussed in this literature review would only be of benefit if such findings are translated into real life practice. To date, there appears to be no cross-sectional survey which aims to look at the issue of OSD in glaucoma clinics from a clinician's perspective, and truly investigate the barriers which pose themselves to clinicians from prescribing PF treatment.

In addition, it is important to link how the current clinical practice affects patients in glaucoma clinics. By delving into patient education and adherence, and by identifying the issues which patients face when treated with ocular hypotensive drops, a better management plan can be formed. The literature review has touched upon the fact that most clinical trials run over a short term, and so the problems of OSD may not present within such a small timeframe. Assessing patients who have been on long-term medical management, and specifically focussing on the incidence of side effects, education on drop instillation, reasons for missed doses and the issue of OSD, and exploring the resultant adherence issues linked to these factors, is an area that warrants further exploration in UK glaucoma clinics.

Though the literature describes the prevalence and risk factors of OSD in treated glaucoma and OHT patients, there is a void in the information available, since there are currently no prevalence rates for patients in glaucoma clinics prior to treatment. This is a fundamental element to consider. If patients are screened at diagnosis of glaucoma or OHT for the presence of OSD, those with a positive result of the latter could benefit from PF treatment from the beginning. Moreover, since such information is lacking in the literature, there is a

suggestion that the true number of patients with simultaneous glaucoma and OSD may well be undercounted.

Furthermore, there is lack of data available in the current literature investigating such treatment-naïve patients and following their treatment journeys to understand which individuals have predisposing factors to developing OSD in the course of their treatment. Not all patients who are treated with preserved medication will develop ocular surface problems, and it is pivotal to identify the risk factors which make some patients more susceptible to this. Based on the literature review, there appears to be no study which has looked at preserved treatment of glaucoma and OHT, and retrospectively analysed the clinical and non-clinical features of the patients who develop OSD as a result of this therapy. To illuminate on this matter would help to shape new algorithms for decision making on which patient would truly benefit from PF ocular hypotensive drops.

Evidently, there are many gaps in knowledge surrounding the double dilemma of OSD and glaucoma. This thesis will aim to address these unanswered questions to help bridge these shortcomings, by examining the effects of glaucoma medication on the ocular surface.

1.8 Aims and hypotheses of the thesis

The primary aim of this thesis is to investigate the effects of topical glaucoma medication on the ocular surface. This is an overarching question which can be broken down into further components, as illustrated by Figure 1.7 below.

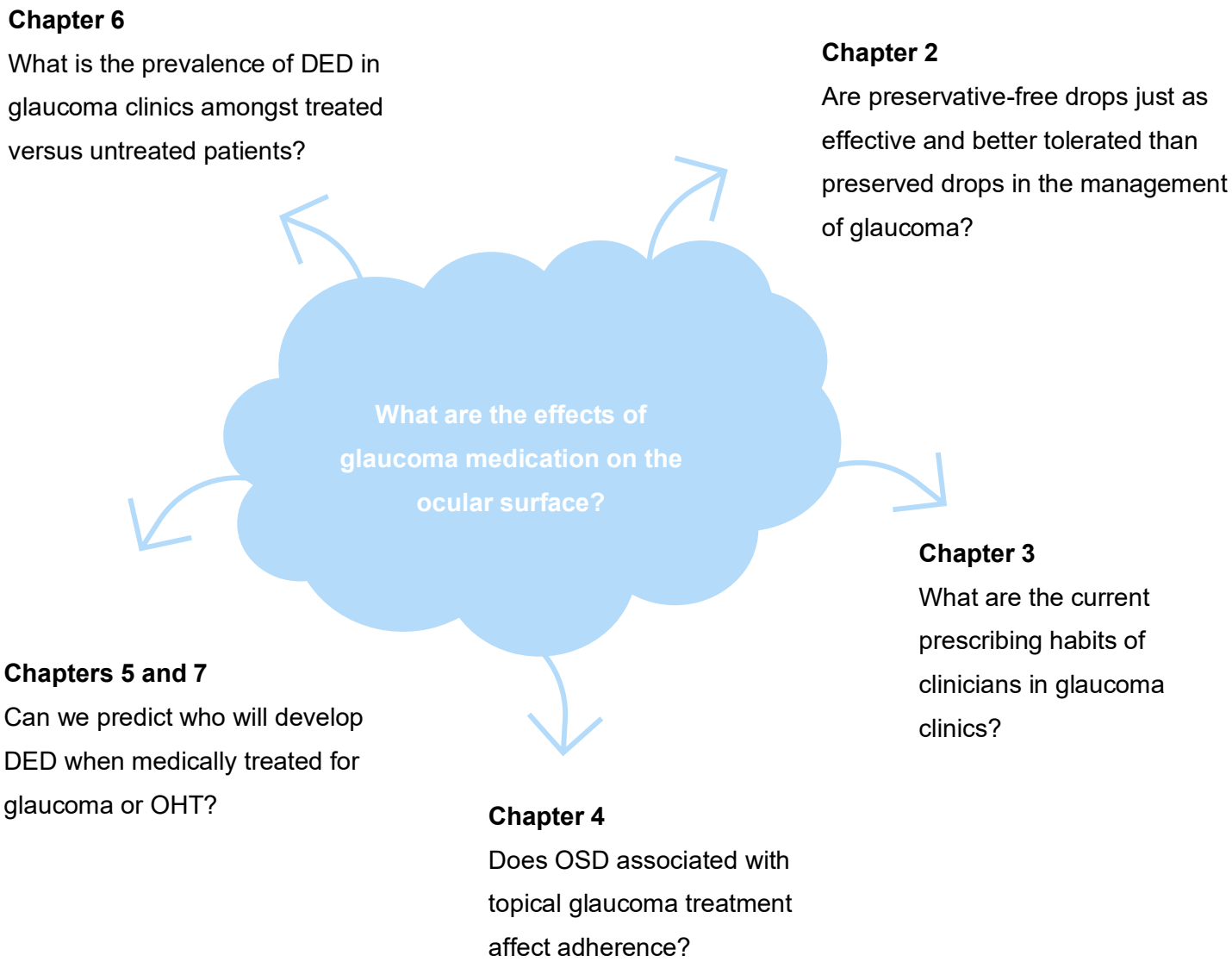


Figure 1.7: Diagram illustrating the questions to be addressed in this thesis

The literature review has provided some background information on the use of topical drugs in the treatment of glaucoma and OHT, the consequences of preservatives in such drugs on the ocular surface and the potential problems that OSD can have on those individuals being medically managed by hypotensive drops. This thesis will aim to shed light on the questions outlined above in the subsequent chapters, which have the following individual aims:

Chapter 2

- To compare the incidence of ocular surface signs and symptoms with preserved and PF eye drops in the management of glaucoma and OHT.
- To assess the effectiveness of preserved versus PF eye drops in the management of glaucoma and OHT in relation to IOP control.
- To compare differences in pharmacokinetic profiles between preserved and PF eye drops in the management of glaucoma and OHT.
- To compare differences at a cellular level between preserved and PF eye drops in the management of glaucoma and OHT.

Chapter 3

To establish current clinical practice in the medical management of glaucoma amongst a group of specialist clinicians in the UK.

Chapter 4

- To investigate the factors that influence adherence.
- To measure adherence in a UK hospital glaucoma clinic.
- To look at current procedures in glaucoma clinics for patient education.
- To investigate the link between patient education and adherence.
- To investigate the link between side effects to glaucoma medication and adherence.
- To estimate the incidence of side effects from glaucoma medication.
- To compare adherence at a UK hospital glaucoma clinic with a national cohort of glaucoma and OHT patients.

Chapter 5

- To investigate the demographics of the glaucoma patients presenting at Russells Hall Eye Clinic, (Dudley NHS Trust, UK), in the West Midlands.
- To identify risk factors associated with developing OSD during medical glaucoma treatment.

Chapter 6

To investigate the prevalence of OSD and DED in a new glaucoma patient clinic at Russells Hall Hospital (Dudley NHS Trust, UK) in the West Midlands, comparing prevalence rates amongst untreated, suspect glaucoma/OHT patients with newly treated glaucoma/OHT patients.

Chapter 7

- To investigate the time point at which patients treated with preserved treatment will go on to develop DED
- To investigate the factors predisposing individuals to developing DED when treated with preserved treatment
- To investigate the baseline characteristics of patients commenced on PF treatment at diagnosis

Based on the findings of the literature review, the following hypotheses will be tested:
1. Preservative-free drops are just as effective as preserved drops in lowering IOP whilst offering better tolerability (Chapter 2)

2. There will be risk factors which are associated with developing DED when medically treated for glaucoma or OHT (Chapter 5 & 7)

3. Symptomatic OSD caused by topical medication for glaucoma or OHT will negatively affect adherence (Chapter 4)

4. Poor patient education or a lack of it will negatively affect adherence (Chapter 4)

5. DED is a prominent issue in glaucoma clinics (Chapter 3 & 6)

6. Being treated for glaucoma or OHT using topical treatment will increase the chances of developing DED (Chapter 7)

Chapter 2

The effectiveness of preserved versus preservative-free eye drops in the treatment of glaucoma: a systematic review

2.1 Introduction

2.1.1 Rationale

The National Institute for Health and Care Excellence (NICE), defines glaucoma as ‘a group of eye diseases that cause progressive optic neuropathy’ (National Institute for Health and Care Excellence, 2022). Glaucoma presents with pallor and/or pathological ‘cupping’ of the optic nerve, caused by the degeneration of the ganglion cells, which is accompanied by corresponding visual field loss (Weinreb and Khaw, 2004, Gupta and Weinreb, 1997, Quigley and Green, 1979, National Institute for Health and Care Excellence, 2022). Usually, the cause of the optic nerve damage is associated with an increase in intraocular pressure (IOP), but this is not always the case, and the underlying cause is mostly unknown (Weinreb and Khaw, 2004, Collaborative Normal-Tension Glaucoma Study Group, 1998). It has been speculated that there are underlying mechanical and vascular factors which ultimately lead to optic nerve damage (Fechtner and Weinreb, 1994, Satilmis et al., 2003).

Ocular hypertension (OHT) describes the condition of elevated IOP, with no optic nerve cupping or field loss present (Gordon and Kass, 2018). There is a risk that OHT can progress to glaucoma (Kass et al., 2002) and so both conditions need to be managed in a timely manner to reduce progression and to prevent loss of vision (Heijl et al., 2002)..

The main method of controlling glaucoma and OHT is by reducing IOP. To date, it is the only viable and adjustable risk factor. It has been shown that reducing the IOP helps to slow down the progression of glaucoma (Leske et al., 2003). There is also evidence that treating elevated IOP in OHT patients slows or prevents progression to POAG (Kass et al., 2002).

Hypotensive eye drops dominate the treatment of glaucoma and OHT. Depending on their mechanism of action, hypotensive eye drops either reduce aqueous humour production, or increase uveoscleral outflow, and thus, reduce the IOP. Currently, the recommended first line medical therapy for the management of glaucoma is a drug from the prostaglandin analogue (PGA) family (European Glaucoma Society, 2017). PGAs have been favoured due to their successful IOP lowering effect, combined with a good safety profile. A previous meta-analysis of randomised controlled trials (RCTs), demonstrated that PGAs offer the most reduction in IOP, followed by non-selective beta-blockers, alpha-adrenergic agonists, selective beta-blockers and carbonic anhydrase inhibitors (van der Valk et al., 2005b).

Many of the available eye drops prescribed in the treatment of glaucoma and OHT contain preservatives, despite the increasing availability of non-preserved drugs. These preservatives provide sterility and add a longer shelf life; their antimicrobial action ensures avoidance, or at least a reduction in the risk, of eye infections (Baudouin et al., 2010, Rahman et al., 2006, Semwal et al., 2014). Preserved hypotensive drops have an added advantage of lower costs than their preservative-free (PF) alternatives (Steven et al., 2018, Joint Formulary Committee, 2022).There are a number of different preservatives available on the market, but the most commonly used agent in hypotensive eye drops is Benzalkonium Chloride (BAK). This quaternary ammonium compound has detergent properties, destroying cell membranes and so providing protection against pathogens (Baudouin et al., 2010, Freeman and Kahook, 2009).

However, these cytotoxic effects can also impact human cells, and it has been widely discussed that this results in detrimental effects on the ocular surface and on ocular structures such as trabecular meshwork and lens epithelial cells (Goto et al., 2003, Pisella et al., 2004, Baudouin et al., 2012b). At a subjective level, preservatives in eye drops can induce unwanted side effects and cause adverse reactions (see Section 1.5.4). There is a threat of OSD when medically treated for glaucoma or OHT.

The prevalence of OSD in glaucoma and OHT patients appears to be high. Leung and colleagues (2008) found that 59% of patients reported dry eye type symptoms in at least one eye and 27% reported such symptoms to be severe (Leung et al., 2008). They found that signs did not always correlate with symptoms, echoing findings from similar studies which investigated signs and symptoms of dry eyes (Kyei et al., 2018, Schein et al., 1997).

OSD may often be overlooked in glaucoma patients, as the primary measure of treatment efficacy is the reduction of IOPs to a reasonable level. However, OSD can have a significant impact on one’s quality of life, especially with increasing severity of glaucoma (Skalicky et al., 2012). It is plausible to assume that symptoms of OSD may deter drop instillation and lead to poor compliance (Chawla et al., 2007, Zimmerman et al., 2007a). In turn, this can lead to poor IOP control, worsening of the glaucoma and subsequently result in irreversible vision loss. Described often as the ‘thief in the night’, the consequences of poorly managed IOPs in glaucoma are not always evident immediately to the individual and so stringent management of the condition is so very important to preserve sight (Havener et al., 1955). Poor compliance can also make treatment seem ineffective, when it may offer the highest benefit to risk ratio to the patient.

Furthermore, Batra and colleagues (2014) found that diligent management of OSD not only improved the condition itself over a 24-month period, it also concurrently led to a reduction in IOP (Batra et al., 2014). They coined the term: 'OSD exacerbated glaucoma' and recommend a combination approach in the management of OSD and glaucoma. Though the sample size was small, it is not the first study exploring the benefits of a better ocular surface when it comes to glaucoma. A poor ocular surface, most notably caused by a reaction to the aforementioned preservatives, can limit the success of filtration surgeries (Broadway et al., 1994).

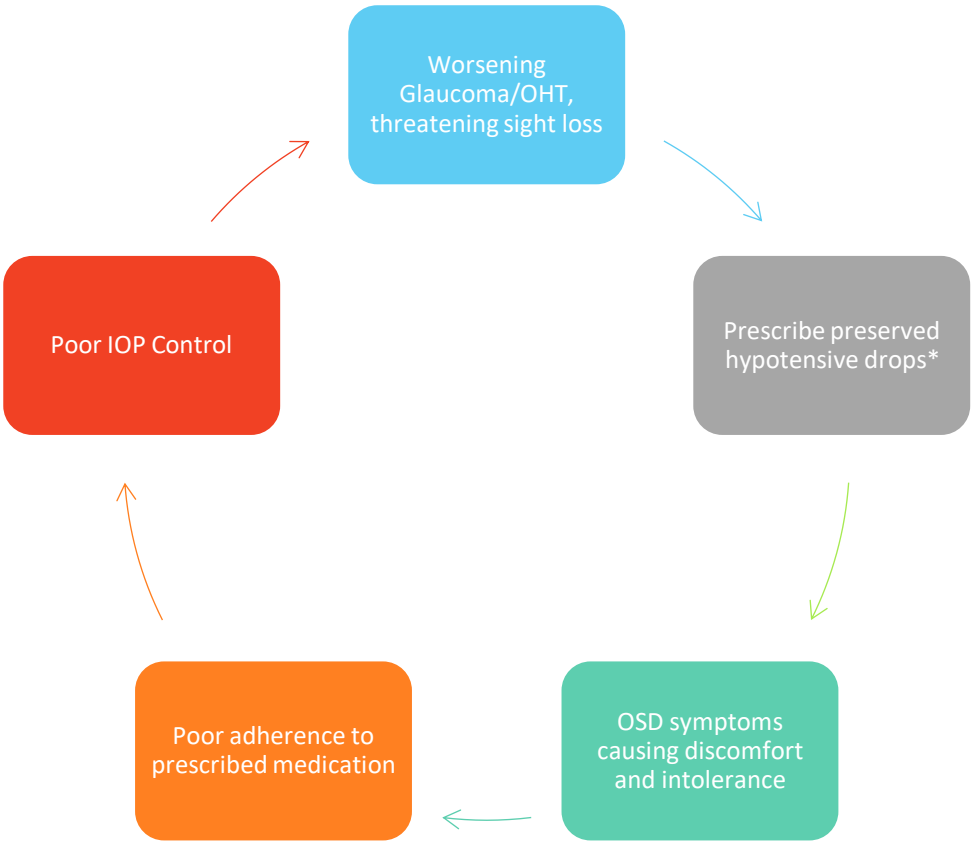


Figure 2.1: The cycle of intolerance to preserved glaucoma drops. It is the grey box* which can be altered and could ultimately positively influence this cycle. Whether that is through changing to PF alternatives, adding artificial tears to the regimen or exploring other forms of therapy. It should be noted that glaucoma can be managed by laser therapy and surgery too, and this cycle is not exhaustive of such procedures, and merely aims to show the cyclic effects of OSD on glaucoma and OHT with pharmacological management.

It has been estimated that by 2040, 111.8 million people will have glaucoma globally (Tham et al., 2014). Based on previous numbers, 59% of these people could suffer from dry eyes (Leung et al., 2008). Some studies have shown that adverse events to treatment can greatly impact adherence (Chawla et al., 2007). However, adherence is difficult to measure and

patients may report satisfaction with drops even though they encounter ocular irritation and undesirable side effects (Lemij et al., 2015) . There is, therefore, a need to investigate the impacts of preserved and unpreserved medication in a randomised controlled manner, to eliminate confounding variables and to objectively compare the two formulations. If PF eye drops are non-inferior to preserved eye drops, and provide a better pharmacological, tolerability and safety profile, then they might provide a suitable solution to patients suffering from both OSD and glaucoma.

A recent review by Hedengran and colleagues (2020) compared the efficacy of BAK preserved eye drops to alternatively preserved or PF eye drops in the treatment of glaucoma (Hedengran et al., 2020). However, as it was inclusive of alternatively preserved drops (other than with BAK), it does not allow proper comparison of preserved and PF ocular hypotensive treatment.

Another more recent systematic review and meta-analysis also compared the efficacy and safety of preserved and PF medication in glaucoma, but it focussed on beta-blockers only (Skov et al., 2022).

There is currently no systematic review in place which compares the safety and efficacy of preserved versus PF glaucoma drops, with particular emphasis on symptomology and ocular signs. This systematic review sets out to fill this gap in knowledge by examining preserved and unpreserved formulations in parallel, with focus not only on the efficacy of treatment in terms of IOP control, but also to look at adverse events and differences at a pharmacokinetic, cellular and *in vivo* level.

2.1.2 Objectives

Primary objectives:

- To compare the incidence of ocular surface signs and symptoms with preserved and PF eye drops in the management of glaucoma and OHT.
- To assess the effectiveness of preserved versus PF eye drops in the management of glaucoma and OHT in relation to IOP control.

Secondary objectives:

- To compare differences in pharmacokinetic profiles between preserved and PF eye drops in the management of glaucoma and OHT.
- To compare differences at a cellular level between preserved and PF eye drops in the management of glaucoma and OHT.

2.2 Methods

2.2.1 Search Strategy

2.2.1.1 Literature search

A literature search was performed on Web of Science and PubMed from inception to March/April 2020. The focus was on RCTs which investigated the efficacy of preserved versus PF eye drops in the treatment of glaucoma and/or OHT. The search terms used were as follows: *preserv* AND *glaucoma* AND medication. There was no constraint set on language. An updated search was ran on 01/03/2021 on PubMed and on 02/03/2021 on the Web of Science, and studies which met the inclusion criteria from this search were subsequently incorporated into the review.

2.2.1.2 Inclusion/Exclusion Criteria

Studies were included if they compared the efficacy of preserved versus PF glaucoma drops, and were conducted as RCTs. Exclusions included studies involving animals and *in vitro,* cell culture laboratory studies. Editorials, letters and conference proceedings were also excluded from this review. A final exclusion was set for studies which compared the efficacy of drops versus gels. Studies were only included in the analysis if the treatment medium was consistent between the preserved and unpreserved formulations.

2.2.1.3 Data Extraction

The data was independently assessed by two reviewers (JW and SVM). Titles, abstracts and main texts were checked and considered against the eligibility criteria set out as above. The inclusive data was collated into a standardised table and duplicates were removed. The data underwent a multi-staged screening process; initially all preserved versus PF glaucoma/OHT studies were included, and then all non-RCTs were removed. The final stage of screening

included reading full texts and removing those that did not meet the inclusion criteria. In the event of a reviewer screening disagreement, a meeting was held for discussion to reach a consensus. At the final stages of full text screening, a third author was used (GBB) to reach a consensus on any discrepancies in opinion on inclusions. An independent author was used to help translate the French articles included in this review. The review followed the reporting protocol set out by the 'Preferred Reporting Items for Systematic review and Meta-Analysis' (PRISMA) (Moher et al., 2009).

2.2.1.4 Data synthesis

Most of the studies included in this review presented baseline and endpoint IOPs for the preserved and PF options. In those studies where IOPs were taken over a 24-hour period, the mean 24-hour IOP was taken for analysis. Where the raw data was not available for review, IOPs were taken as an estimate from the graphs. Lastly, in those studies which recorded IOPs as a change over the course of the treatment and across time-points, the mean IOP value at baseline and endpoint was used in data interpretation. Where such data manipulation was required for analysis, it has been clearly marked in the results tables. Diurnal variation was accounted for in most studies as IOP readings were taken at regular time intervals (Tajunisah et al., 2007, Liu et al., 2003). A methodology table has been included to show the procedures employed by the included studies to take measurements, as well as highlighting the consistency of measurements (Appendix 1).

2.2.1.5 Assessment of heterogeneity

The efficacy of preserved versus PF drops is assessed across four categories in this review: IOP control, signs of OSD, symptoms of OSD and pharmacological changes. Some studies will have assessed all of these categories, whilst others only investigated one or two of these. This produces some difficulty in comparing studies directly due to clinical diversity. Furthermore, those studies which investigated the same variables, have done so using differing procedures and methods. In turn, this results in some methodological diversity. Ultimately, such variability means that the data needed to assess heterogeneity is missing in places, and so it cannot be quantified. The methodology table in Appendix 1 highlights the differences in methods and data collection between the included studies. Studies which looked at IOP seemed consistent enough to compare, as did those which looked at conjunctival hyperaemia and even symptoms to some extent. In these cases, a meta-analytic approach was used for the analysis of the results.

2.3 PRISMA flowchart outlining the search strategy

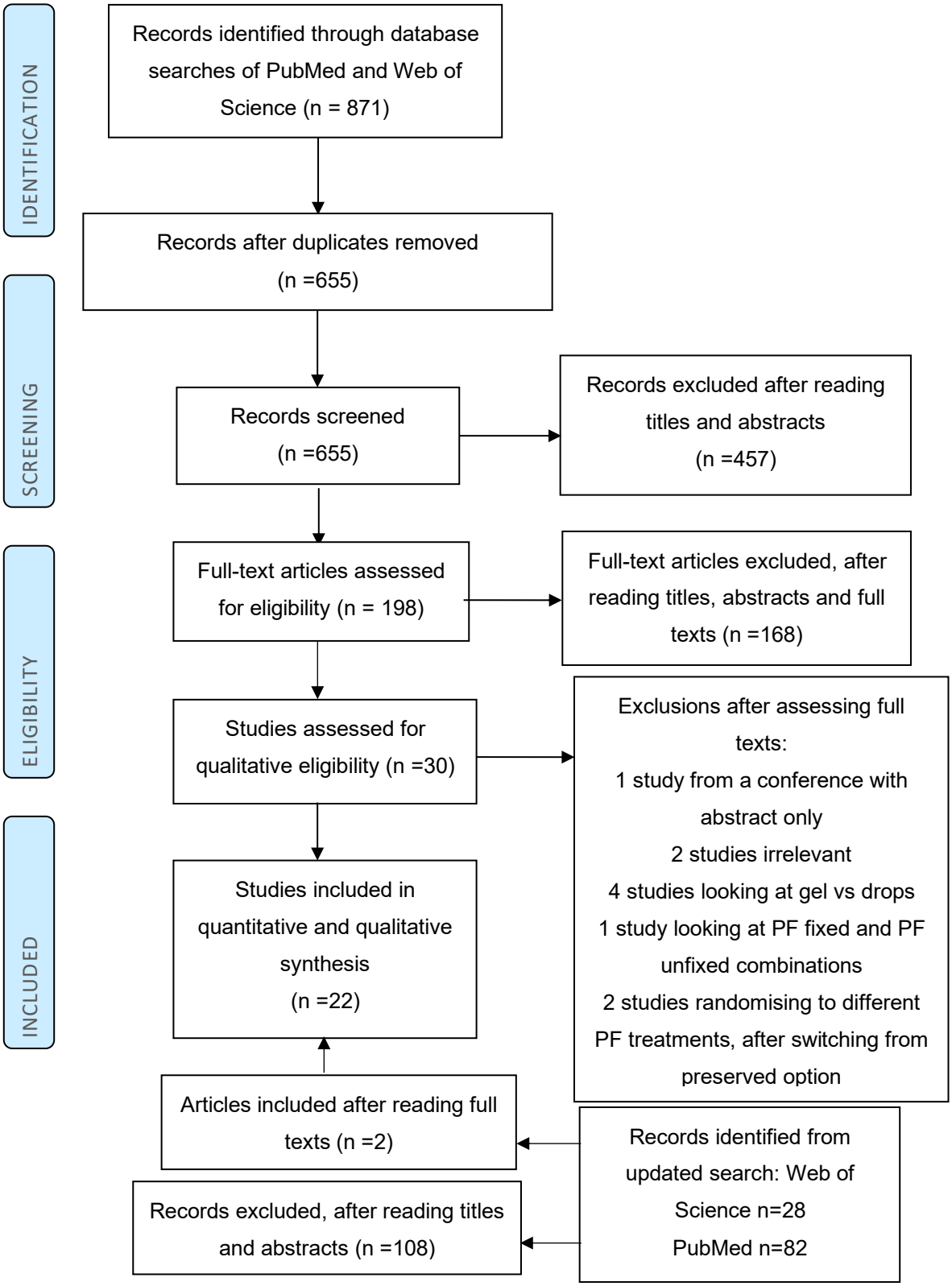


Figure 2.2: Flowchart outlining the screening process in the selection of articles for the systematic review.

2.4 Results

The literature search identified a total of 871 articles for potential review. Of these, 408 were identified on Web of Science in March 2020, and 463 were from PubMed, with the literature search being conducted on 07/04/2020 for the latter. After removing duplicates, 655 articles remained, of which 457 were excluded due to irrelevance and/or not meeting the inclusion criteria. Full text analysis of the remainder revealed 20 articles which were suitable for the systematic review and meta-analysis. The updated search carried out on 01/03/2021 and 02/03/2021 produced a further two studies which met the inclusion criteria, and so a total of 22 studies have been used in the analysis. Figure 2.2 presents the PRISMA flowchart, outlining the selection process for the inclusive studies.

2.4.1 Characteristics of the studies

A table of characteristics summarising the study sample size, location, demographics, methods, interventions and main outcomes has been attached in Appendix 2. The number of participants in the included studies ranged from 16 to 597. The methodology table in Appendix 1 highlights which studies employed power calculations; since not all have this in place, some of the studies are not powered. The studies were conducted independently across Europe, USA and Asia. The IOP was assessed in most of the studies (21/22), be that as a primary or secondary outcome measure. Of the selected studies in this review, 17 examined ocular signs and 16 assessed ocular symptoms, with regards to the tolerability of preserved and PF glaucoma treatment.

2.4.2 IOP

IOPs were assessed in 21 of the included studies, comprising a total of 2571 subjects. When looking at the efficacy of preserved and PF glaucoma eye drops, IOP appears to be the primary measure outcome for most studies. Table 2.2 provides an outline of the change in IOP across the treatment period for each study, while Figure 2.3 displays the percentage change in IOP from baseline to endpoint for each treatment. Table 2.1 summarises these percentage drops to illustrate the differences between preserved and unpreserved treatments in each study, as well as highlighting the weighted percentage drops.

Mastropasqua and colleagues (2014) compared preserved latanoprost and timolol to their unpreserved versions, hence the results of both have been included (Mastropasqua et al., 2014b). Similarly, for Mohammed and colleagues (2020), PF drops were compared to Polyquad (PQ) preserved drops and BAK preserved drops, and so both have been accounted for in the results (Mohammed et al., 2020). Shedden and colleagues (2010), compared the IOPs at both trough and peak levels, and again this has been taken into account during analysis (Shedden et al., 2010). Figure 2.3 and table 2.1 show these individual results within these studies, however, for the overall weighted percentage drops, an average was taken for preserved and PF options in these studies to avoid over-counting of subjects. As with the meta-analysis carried out by Hedengran and colleagues (2020), a difference of ≥2mmHg was considered as significant in this review (Hedengran et al., 2020).

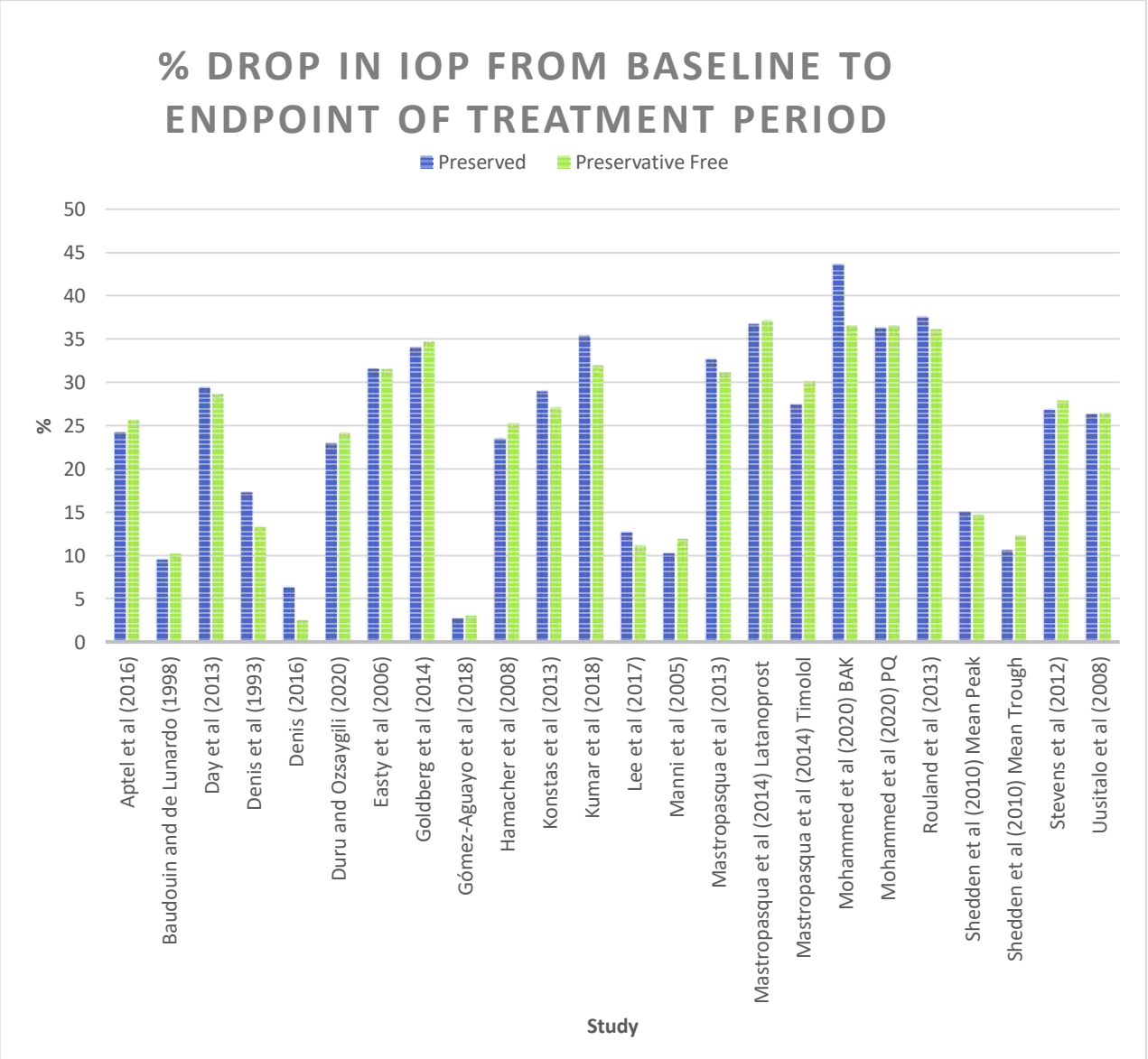


Figure 2.3: The percentage drop in IOPs from baseline to endpoints for each study.

Author	% Drop		Difference	No. of subjects	Preserved Weighted %drop	PF Weighted %drop
	Preserved	PF				
Aptel et al., (2016)	24.2	25.6	-1.4	26	0.2	0.3
Baudouin and de Lunardo (1998)	9.5	10.1	-0.7	30	0.1	0.1
Day et al., (2013)	29.3	28.6	0.7	586	6.7	6.5
Denis et al., (1993)	17.2	13.2	4.0	27	0.2	0.1
Denis (2016)	6.3	2.5	3.8	183	0.4	0.2
Duru and Ozsaygili, (2020)	22.9	24.2	-1.2	21	0.2	0.2
Easty et al., (2006)	31.6	31.5	0.1	146	1.8	1.8
Goldberg et al., (2014)	34.0	34.7	-0.7	540	7.1	7.3
Gómez-Aguayo et al., (2018)	2.7	3.0	-0.3	51	0.1	0.1
Hamacher et al., (2008)	23.5	25.2	-1.8	41	0.4	0.4
Konstas et al.,(2013)	28.9	27.0	1.9	38	0.4	0.4
Kumar et al., (2018)	35.4	31.9	3.4	44	0.6	0.5
Lee et al., (2017)	12.6	11.1	1.6	20	0.1	0.1
Manni et al., (2005)	10.2	11.9	-1.7	20	0.1	0.1
Mastropasqua et al., (2013)	32.6	31.1	1.5	30	0.4	0.4
Mastropasqua et al., (2014) Latanoprost	36.7	37.1	-0.4			
Mastropasqua et al., (2014) Timolol	27.4	30.1	-2.7	80	1.0	1.0
Mohammed et al., (2020) BAK	43.5	36.5	7.0			
Mohammed et al., (2020) PQ	36.2	36.5	-0.3	35	0.5	0.5
Rouland et al., (2013)	37.5	36.1	1.4	353	5.1	5.0
Shedden et al., (2010) Mean Peak	15.0	14.6	0.3			
Shedden et al., (2010) Mean Trough	10.5	12.2	-1.7	258	1.3	1.3
Stevens et al., (2012)	26.8	27.9	-1.1	26	0.3	0.3
Uusitalo et al., (2008)	26.3	26.4	-0.1	16	0.2	0.2
			Total	**2571**	**27.2**	**26.7**

Table 2.1: Summary of the included studies with their individual percentage changes in IOPs over the course of the treatment. The table highlights the difference in percentage change between the preserved and PF options, as well as demonstrating the weighted percentage drop for each study and the overall weighted percentage drop for preserved and PF treatment. Mastropasqua et al., (2014), Mohammed et al., (2020) and Shedden et al., (2010) all had two arms within their studies. In these instances, the average percentage drop for preserved and PF options was taken for each study, and this was subsequently used to calculate the weighted percentage drops, ensuring each study is only counted once to determine the overall weighted percentage drop.

Overall, the relative change in IOPs from baseline to endpoint seems similar for most preserved and PF hypotensive drops. Four studies show a percentage drop difference of greater than 3% between the preserved and PF treatments. Denis and colleagues (1993), Denis (2016), Kumar and colleagues (2018) and Mohammed and colleagues (2020) (BAK) all seem to favour preserved drops in terms of IOP reduction from start of treatment to endpoint (>3% difference between treatments). Though the PF formulations in these studies also show an IOP drop over the course of the treatment, it does not seem to be as much what the preserved option offers. However, individually, these percentage differences equate to small values of IOP, the largest difference being for Mohammad and colleagues (2020) for the BAK treatment arm, at 2.6mmHg. The other three studies show a difference of well below 2mmHg. According to the reference point of 2mmHg using the Hedengran and colleagues (2020) review, the study by Mohammad and colleagues (2020) may be considered statistically significant in supporting preserved treatment (Hedengran et al., 2020).

However, though statistically this difference in IOP may be of significance, clinically, such result is insignificant. The European Glaucoma Society states that there is no target IOP algorithm as such, however, depending on baseline IOP and stage of the disease, a percentage reduction of 20% to 40% may be sufficient to control disease progression (European Glaucoma Society, 2021). Similarly, in a review by Jonas and colleagues (2017), it is suggested that progression is halted with IOP reductions of 30-50% from baseline (Jonas et al., 2017). Using these recommended percentage reductions and applying them to the study by Mohammed and colleagues (2020) (BAK), the smallest proposed reduction of 20% for the preserved option equates to a change of 5.4mmHg from baseline, and for the PF option, 5.0mmHg, to deem it a clinically significant change. Since the difference of 2.6mmHg between the treatments is below these calculated values, clinically the difference between preserved and PF IOP reduction is insignificant.

Furthermore, a mean, weighted percentage drop across all studies reveals a reduction in IOP of 27.2% for preserved treatments, and 26.7% for the unpreserved treatments, and with a difference of 0.48%, this is not significant (t-test, p=0.253).

Author	Number of Participants	Study duration	Preserved Option	Preservative	Preservative-free Option	Mean Baseline IOP (mmHg) For Preserved	Mean Endpoint IOP (mmHg) For Preserved	Mean Baseline IOP (mmHg) For PF	Mean Endpoint IOP (mmHg) For PF
(Denis, 2016)	183	84 days	Latanoprost 0.005% eyedrops (Xalatan®)	BAK	Latanoprost 0.005 % preservative-free eye drops (Monoprost)	15.9±2.2	14.9±2.3	16.0±2.5	15.6±2.8
(Hamacher et al., 2008)	43 ITT, 41 PP	4 weeks O	Tafluprost 0.0015%	BAK	Tafluprost 0.0015% PF	22.6~	17.3~	23.0~	17.2~
(Lee et al., 2017)	20	12 months O	0.0015% Tafluprost (Taflotan®)	0.001% BAK	0.0015% Tafluprost (Taflotan-S® unit dose)	17.00 ± 2.59	14.85 ± 3.05•	16.70 ± 3.02	14.85 ± 3.05•
(Mastropasqua et al., 2013)	30 (+30 controls)	6 months	Latanoprost 0.005% (Xalatan)	0.02% BAK	PF Tafluprost 0.0015% (Taflotan)	24.75 ± 1.94	16.68 ± 1.4	24.68 ± 2.02	17.0 ± 0.89
(Mastropasqua et al., 2014b)	80 (+30 controls)	3 months	a) Latanoprost 0.005% (Xalatan) b) Timolol 0.5 %, (Timoptol)	a) 0.02% BAK b) BAK	a) PF-Latanoprost 0.005 % (Optigen) b) PF-timolol 0.5 % (Timolol Novartis)	a) 25.98±1.39 b) 25.95±1.52	a) 16.45± 1.7 b) 18.84± 1.23	a) 25.96±2.16 b) 25.52±1.65	a) 16.34±2.03 b) 17.85± 1.34

(Goldberg et al., 2014)	561 (540 completed the study)	12 weeks	Bimatoprost/Timolol preserved	BAK	Bimatoprost/Timolol PF	24.6[#]	16.23[α]	24.7[#]	16.13[α]
(Shedden et al., 2010)	261 (254 completed the study)	12 weeks	Preserved Dorzolamide 2%/Timolol 0.5% combination (COSOPT™)	BAK	PF Dorzolamide 2%/Timolol 0.5% combination (COSOPT™)	Mean Trough: 23.7 Mean Peak: 21.4	Mean Trough: 21.2 Mean Peak: 18.2	Mean Trough: 23.7 Mean Peak: 21.2	Mean Trough: 20.8 Mean Peak: 18.1
(Denis et al., 1993)	27	14 days with a 7-10 day washout period between treatments	Betaxolol 0.25%	BAK	Betaxolol 0.25% unit dose	26.1	21.6 [(a)]	25.7	22.3[(a)]
(Aptel et al., 2016)	30 ITT (PP 26, PK 29)	12 weeks [O]	Preserved Latanoprost 0.005% (Xalatan)	0.02% BAK	PF Latanoprost 0.005% (Monoprost)	21.9 ± 4.4*	16.6 ± 3.2*	21.9 ± 4.4*	16.3 ± 3.3*
(Day et al., 2013)	597	12 weeks	Preserved Bimatoprost 0.03%	0.005% BAK	PF Bimatoprost 0.03%	23.81[#]	16.83[#]	23.83[#]	17.01[#]
(Easty et al., 2006)	175 (146 in PP)	12 weeks	T-Gel 0.1% MD (Preserved Timolol)	BAK	T-Gel 0.1% SDU (PF Timolol)	23.51±1.75	16.09±2.74^	23.76± 1.98	16.28± 2.63^

(Konstas et al., 2013)	40 (38 completed study)	6 months [O]	Preserved Latanoprost 0.005% solution (Xalatan)	0.02% BAK	PF Tafluprost 0.0015% solution (Saflutan)	24.9[β]	17.7 [β]	24.4 [β]	17.8 [β]
(Manni et al., 2005)	20	120 days in total [O]	Preserved timolol 0.5% eyedrops (Timoptol)	BAK	PF timolol 0.5% (Timolabak)	18.6±1.3[§]	16.7±0.9[§]	19.3±1.1[§]	17.0± 1.3[§]
(Rouland et al., 2013)	402 received treatment, 392 completed the study. mITT=353	3 months	Preserved 0.005% Latanoprost (BPL)	0.02% BAK	PF Latanoprost (T2345)	24.0±1.7[∞]	15.0±2.0[∞]	24.1± 1.8[∞]	15.4±2.3[∞]
(Uusitalo et al., 2008)	16 healthy volunteers	16 days with 4-week washout between treatments	Tafluprost 0.015%	BAK	Preservative-free Tafluprost 0.015%	13.3~	9.8~	14~	10.3~
(Baudouin and de Lunardo, 1998)	30	6 days [O]	2% Carteolol	BAK 0.005%	PF 2% Carteolol	13.7	12.4	13.8	12.4
(Gómez-Aguayo et al., 2018)	51	12 months [O] (treatment duration 60 days)	KOF-preserved version of 0.5% timolol+0.2% brimonidine+ 2.0% dorzolamide fixed combination	BAK	PRO-122-a preservative-free 0.5% timolol+0.2% brimonidine+2.0% dorzolamide fixed combination	12.13 ± 1.8[λ]	11.80 ± 2.1 [λ]	13.60 ± 2.9 [λ]	13.19 ± 3.2[λ]

(Kumar et al., 2018b)	44 completed the study	12 weeks of treatment	Latoprost 0.005%	BAK 0.02%	LACOMA-0.005% latanoprost	26.25 ±2.69	16.97 ±1.88	25.36 ±1.93	17.26 ±1.83
(Stevens et al., 2012)	28 recruited, but 26 used in analysis	1 month	Preserved Timolol Maleate (0.5%)	BAK	PF Timolol Maleate (0.5%)	23.00±2.57	16.83±2.87	22.88±2.57	16.50±2.99
(Duru and Ozsaygili, 2020)	21 patients, 42 eyes	4 weeks	Preserved Brimonidine 0.15% (Alphagan-P)	sodium chlorite (Purite®)	PF Brimonidine 0.15% (Brimogut)	23.09±1.86	17.8±2.06	23.85±1.74	18.09±1.97
(Mohammed et al., 2020)	36, 1 dropout after baseline measures	24 months	**PQ** -Travoprost 0.004% monotherapy -Travoprost 0.004%/Timolol 0.5% combination therapy **BAK** -Bimatoprost 0.01% -Travoprost 0.04%	Polyquad BAK	**PF** -Latanoprost 0.005% -Timolol 0.5% -Dorzolamide 2%	PQ:28.7 BAK:27.1	PQ:18.3 BAK:15.3	25.2	16.0

Table 2.2: Overview of IOP changes from baseline to endpoint of each study, for both preserved and preservative-free options of glaucoma hypotensive eye-drops.

* 8pm measurement at baseline and 6weeks of treatment, ^Endpoint measurement at Week 12, Hour 2, # Mean worse eye IOP averaged across all time-points in the PP, PP= Per Protocol Population, PK=Pharmacokinetics, ITT=Intent-to-treat population, α calculated by averaging the IOP change across all time points in the 12 weeks, β mean 24 hour IOP, ◯ crossover study, ~ approximate values taken from graph (baseline measure at 8am, endpoint measure at 8pm), λ Base IOP after 1st treatment period before crossover, ᵐmITT=modified intent-to-treat population, ● Mean IOP of both therapies combined, at 12 months, § IOPs after 60 days of 1st treatment before crossover, (a) mean IOP on Day 7

	Symptoms																
Author	**Study dura-tion**	**No. of Partici-pants**	**Irritation/ Burning**		**Stinging on instillation**		**Itching/Pruritus**		**Tearing**		**FB Sensation**		**Eye dryness**		**Blurred Vision**	
			P	**PF**	**P**	**PF**	**P**	**PF**	**P**	**PF**	**P**	**PF**	**P**	**PF**	**P**	**PF**
(Hamacher et al., 2008)	4 weeks	P=42 PF=43	×	×	×	×	1	1	0	1	1	1	×	×	1	0
(Lee et al., 2017)	12 months	20	Modified OSDI score calculated using summed score of stinging sensation, itching, dryness, foreign body sensation, and conjunctival injection with “0” =no discomfort, “1”=mild discomfort and “2”=severe discomfort. Preserved=1.14 ± 0.69◊ PF=0.80 ± 1.39◊														
(Uusitalo et al., 2008)	16 days (but 4-week wash-out in bet-ween)	16	1	1	×	×	2	2	0	1	1	1	×	×	×	×
(Mastropasqua et al., 2013)	6 months	30 and 30 controls	OSDI scores at 6 months: Preserved=12.75 ± 4.8 PF=5.85 ± 4.18														
(Sheddon et al., 2010)	12 weeks	261 (254 comple	28	21	×	×	×	×	×	×	×	×	×	×	×	×

		-ted full study)														
(Aptel et al., 2016)	12 weeks	30 ITT	2	3	5	3	13	12	3	2	3	5	0	1	1	2
(Day et al., 2013)	12 weeks	597 but P=295 PF= 301	×	×	×	×	12	12	×	×	2	7	9	5	×	×
(Easty et al., 2006)	12 weeks	175 (PP=146)	10	5	×	×	×	×	×	×	2	4	4	5	11	9
(Mohammed et al., 2020)	24 months	35	OSDI scores->**BAK:** Mean score >20 at 12 months for 5/9 patients and >30 for 3/9 patients at 24 months. **PQ:** Mean score >12 for 4/8 patients from 6 months on. 1 patient scored more >20 at 24 months. **PF:** Mean score <12 for 6/7 patients, at all time points													
(Denis, 2016)	84 days	183	Symptom scores-> On Instillation-> Preserved: 1.6 ± 2.3 PF: 0.9 ± 1.3 Between instillations->Preserved: 1.3 ± 2.2 PF: 0.9 ± 1.5													
(Goldberg et al., 2014)	12 weeks	560 include-ed in AE analy-sis	5	6	×	×	5	12	×	×	6	6	3	9	×	×
(Konstas et al., 2013)	6 months	38	2	0	4	4	2	0	2	1	2	2	×	×	4	1

(Rouland et al., 2013)	3 months	402 received treatment, 392 completed the study	19.9%=38	7.3%=16	Symptoms (pruritus, burning/stinging, blurred vision, sticky eye sensation, eye dryness sensation, foreign body sensation) graded on scale: (0)=none, (1)=present but not disturbing, (2)=disturbing, (3)=very disturbing. Total score=sum of symptom scores/number of symptoms Mean score for PF= 0.18±0.66 Mean score for Preserved: 0.46±1.05											
(Baudouin and de Lunardo, 1998)	6 days in total with 5 day wash-out period between cross-over	30	Visual analogue scale [from 0mm (not irritating) to 100mm (extremely irritating)] 3.66 (6.33) mm for preserved versus 2.83 (5.83) mm for PF (p=0.27, non-significant)													
(Gómez-Aguayo et al., 2018)	60 days of treatment	51	18	12	×	×	1.51 Ω	1.37 Ω	9	8	16	14	2.00 Ω	1.73 Ω	×	×
(Duru and	4 weeks	21 patients	0.52±0.92 ab	1.19±1.20 ab	0.66±1.19 b	0.61±1.20 b	0.33±0.57 b	0.23±0.53 b	0.47±0.92 b	0.61±0.97 b	×	×	×	×	0.61±1.16 b	0.42±1.20 b

Ozsaygili , 2020)		, 42 eyes														

Table 2.3: Overview of ocular symptoms present in the inclusive studies. Reported numbers relate to the number of patients experiencing such symptoms, unless otherwise stated.

* Only compared single PF therapy not triple PF therapy,× not measured in the study, Ω ocular discomfort questionnaire score with 0= no inconvenience, 10= unbearable inconvenience, ◊ at 6 months of initial treatment, before crossover to alternative therapy, 'OSDI' Ocular Surface Disease Index, [a] Symptom on instillation, [b] mean symptom score, ITT=Intent-to-treat population, P= Preserved treatment, PF=PF treatment

NB: Signs and symptoms are recorded at the end of the treatment

	Signs										
Author	**Study duration**	**Conjunctival Hyperaemia**		**TBUT (secs)**		**Corneal Staining**		**Punctate Keratitis**		**Schirmer Test (mm)**	
		P	**PF**	**P**	**PF**	**P**	**PF**	**P**	**PF**	**P**	**PF**
(Hamacher et al., 2008)	4 weeks	2	6	×	×	×	×	0	1	×	×
(Lee et al., 2017)	12 months	×	×	4.42 ± 1.71◊	5.00 ± 1.88◊	0.14 ± 0.37◊	0.40 ± 0.51◊	×	×	5.14 ± 3.67◊	4.60 ± 3.97◊
(Uusitalo et al., 2008)	16 days (but 4-week washout in between)	16 (6 mild, 9 moderate, 1 severe)	15 (9 mild, 6 moderate, 0 severe)	×	×	×	×	×	×	×	×
(Mastropasqua et al., 2013)	6 months	×	×	10.18 ± 1.47	12.12 ± 2.41	×	×	×	×	14 ± 2.19	15.87 ± 1.66
(Shedden et al., 2010)	12 weeks (but signs just recorded as 'conjunctiva, cornea etc.'	3	4	×	×	22	32	31	22	×	×
(Aptel et al., 2016)	12 weeks	7	5	×	×	3	2	×	×	×	×
(Day et al., 2013)	12 weeks	77	72	×	×	×	×	9	9	×	×

(Goldberg et al., 2014)	12 weeks	55	59	×	×	×	×	7	8	×	×
(Kumar et al., 2018b)	12 weeks of treatment	Score/ Grade 0.47	Score/ Grade 0.43	8.02	11.63	×	×	×	×	×	×
(Gómez-Aguayo et al., 2018)	60 days of treatment	14	18	6.41 ± 1.4	6.65 ± 2.9	×	×	×	×	×	×
(Denis, 2016)	84 days	1.1 ± 0.8	0.9 ± 0.7	×	×	×	×	×	×	×	×
(Easty et al., 2006)	12 weeks	'Neither of the study medications had any notable effect on the ocular signs assessed in the slit lamp examination and fluorescein staining.'									
(Konstas et al., 2013)	6 months	6	5	×	×	×	×	×	×	×	×
(Manni et al., 2005)	120 days in total (+3 week washout in between and before treatment)	×	×	7.6±1.6	9.0±1.1	×	×	×	×	×	×
(Rouland et al., 2013)	3 months	54	44	×	×	Assessed but values not presented, just stated as 'no difference between treatment groups'		×	×	×	×

(Baudouin and de Lunardo, 1998)	6 days with 5 day washout period in between treatments	×	×	7.7±5.5 (after 3 days of treatment)	8.4±5.7 (after 3 days of treatment)	Grade 0.1±0.4	Grade 0.1±0.3	×	×	17.03±13.91 (@5mins)	13.3±10.4 (@5mins)
(Duru and Ozsaygili, 2020)	4 weeks	×	×	5.76±1.78	6.38±1.77	×	×	×	×	10.71±8.40	11.33±8.91

Table 2.4: Overview of ocular signs present in the inclusive studies. Reported numbers relate to the number of patients experiencing such signs, unless otherwise stated.

* Only compared single PF therapy, not triple PF therapy, × not measured in the study, Ω ocular discomfort questionnaire score with 0= no inconvenience, 10= unbearable inconvenience, ◊ at 6 months of initial treatment, before crossover to alternative TBUT= Tear break up time
P=Preserved treatment PF=Preservative-free treatment NB: Signs and symptoms are recorded at the end of the treatment

2.4.3 Symptoms

The symptoms observed in the included studies were summarised into the following categories: 'Irritation/Burning', 'Stinging on instillation', 'Itching/Pruritus', 'Tearing', 'Foreign Body (FB) Sensation', 'Eye dryness' and 'Blurred Vision'. This list is by no means exhaustive of the symptoms one may experience during the treatment of glaucoma, however, it aims to highlight the main ocular issues reported across the RCTs. By collating the 'most common' symptoms, it allowed for analysis of symptom related differences between preserved and unpreserved glaucoma treatment.

Sixteen studies investigated the relationship between preserved and PF treatment and the incidence of ocular symptoms. Of these, eight presented the data as the number of patients reporting symptoms. The remaining studies used some sort of a scoring system to account for symptomatic occurrences. Gómez-Aguayo et at (2018) and Rouland et al (2013) used a combination of both numbers and a scoring system. Table 2.3 provides an overview of all symptom assessed studies, with corresponding results for each category. A meta-analysis was performed on the 10 studies which recorded the incidence of symptoms as a number or percentage. Where a series of symptoms was reported in a study, the number of participants reporting them were summed together. Where participants reported more than one symptom, and so the total number of symptoms reported exceeded the total number of subjects for a study, only the 'burning/stinging' symptom was used in the analysis.

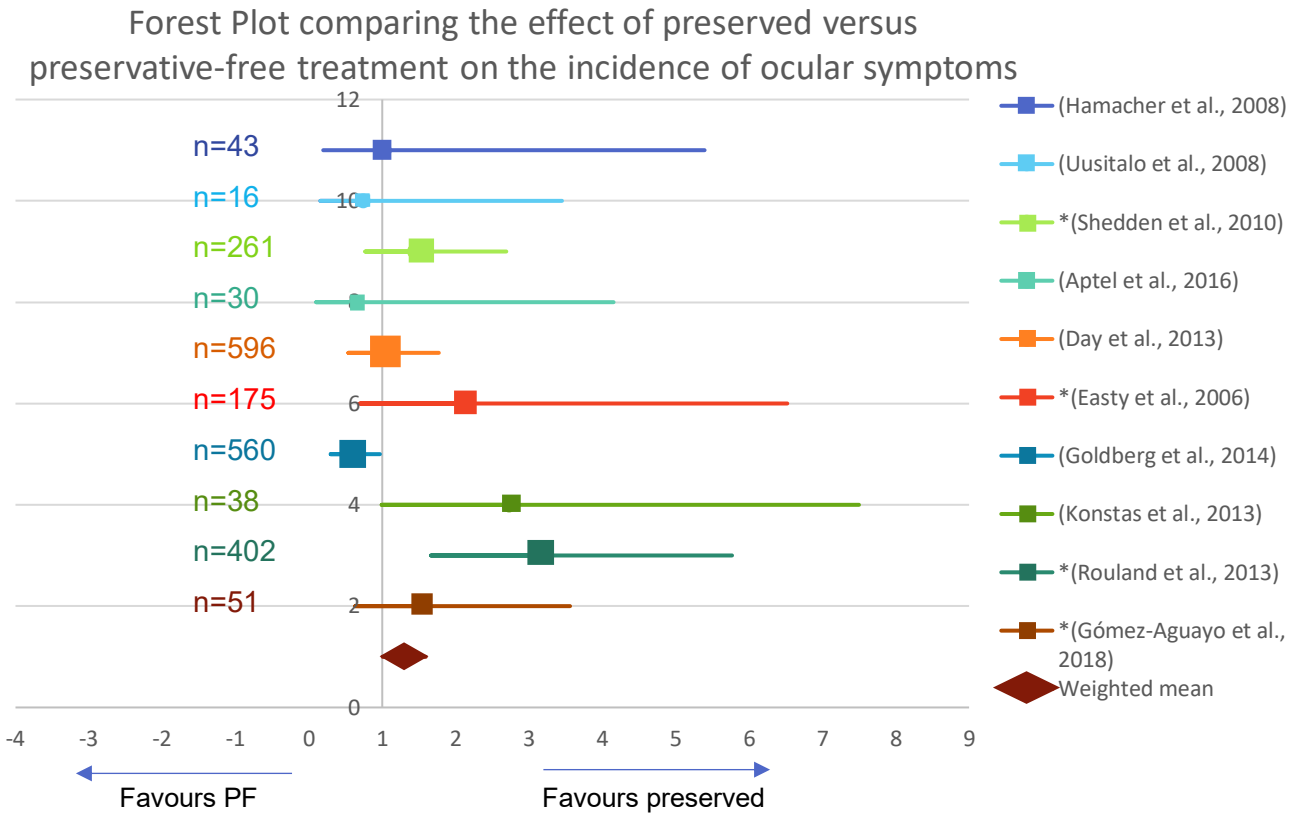


Figure 2.4 Forest plot demonstrating the odds of developing ocular symptoms with preserved and PF glaucoma eye drops. All studies used a sum of the symptoms for calculation of the odds ratios. Those marked with a * used 'stinging/burning' symptoms only for the evaluation. The weight of each study is depicted as the number of participants treated (n) and symbolised by proportioned squares.

Study	***OR***	***95% CI***	
(Hamacher et al., 2008)	1.026	0.195	5.394
(Uusitalo et al., 2008)	0.733	0.156	3.450
**(Shedden et al., 2010)*	1.438	0.768	2.691
(Aptel et al., 2016)	0.643	0.100	4.153
(Day et al., 2013)	0.976	0.538	1.771
**(Easty et al., 2006)*	2.132	0.697	6.521
(Goldberg et al., 2014)	0.536	0.297	0.968
(Konstas et al., 2013)	2.727	0.992	7.499
**(Rouland et al., 2013)*	3.099	1.664	5.768
**(Gómez-Aguayo et al., 2018)*	1.500	0.632	3.560
Weighted Mean	**1.265**	**1.005**	**1.593**

	Preserved & Symptoms	*Preserved & No symptoms*	*PF & Symptoms*	*PF & No symptoms*
TOTAL	186	976	155	1029

Table 2.5 Odds ratios and upper and lower confidence intervals for each study investigating symptoms. Below this, a summary of the weighted means is given for all of the studies.

The forest plot in figure 2.4 demonstrates the association between the type of medication (preserved or PF) and the odds of developing ocular symptoms. All studies but two cross the vertical midline at 1, suggesting that there is a lack of evidence to suggest increased odds of either medication type in these studies. The study by Goldberg and colleagues (2014) appears to favour PF treatment in increasing odds of developing ocular symptoms [Odds ratio (OR) 0.536, 95% confidence intervals (CI) 0.297-0.968] (Goldberg et al., 2014), whilst the study by Rouland and colleagues (2013) appears to favour preserved treatment for increased odds of ocular symptoms (OR 3.099, 95% CI 1.664-5.768) (Rouland et al., 2013). Results using the overall weighted means indicate that exposure to preservatives is associated with increased odds of developing ocular symptoms (OR 1.265, 95% CI 1.005-1.593).

2.4.3.1 Descriptive analysis of symptoms

Baudouin and de Lunardo, (1998), who used a visual analogue scale to compare symptoms of ocular irritation between the two treatment groups, found that PF carteolol was scored at just 2.83%, whereas the preserved counterpart was scored at 3.7%. Although this shows that PF carteolol is better tolerated amongst patients, both values are close to the zero end of the 100-point scale, and the difference between the two groups is minimal. It should also be noted that this study only used young, healthy individuals, over a treatment period of 6 days, which is unrealistic when trying to relate such findings to the typical glaucoma population who are mostly older, typically on multiple drops and on lifelong treatment (Baudouin and de Lunardo, 1998).

Similarly, Rouland and colleagues (2013) used a scoring system to grade all the specified symptoms, apart from ‘Irritation/Burning’, which were classified by the percentage of subjects experiencing them in each treatment group. The mean symptom scores were 0.18±0.66 for the PF formulation and 0.46±1.05 for the preserved option. The maximum score on this scale was 3, and both treatments produced a score of <1 with a marginal difference between them, but of statistical significance (p=0.001) (Rouland et al., 2013).

Lee and colleagues (2017) and Mastropasqua and colleagues (2013) used modified OSDI and OSDI scores, respectively, to compare the incidence of symptoms. Mastropasqua and colleagues (2013) found significant differences in OSDI scores at 6 months for the preserved and PF group with values of 12.8 ± 4.8 and 5.9 ± 4.18, respectively ($p<0.05$). The increase in OSDI scores from baseline to months 1 and 6 was also significant for the preserved group ($p<0.05$) (Mastropasqua et al., 2014b). Likewise, Lee and colleagues (2017) found that symptoms were significantly improved when switching from preserved to PF treatment after 6 months ($p=0.03$). Equally, symptoms significantly worsened when switching from PF to preserved treatment after 1 month ($p=0.02$), though they did recover by month 6. The modified OSDI scores at 6 months of each treatment were 1.14 ± 0.69 for preserved and 0.80 ± 1.39 for PF (Lee et al., 2017).

Three of the newer studies added to the review in March/April 2021 also used scoring systems to grade ocular irritation. This has meant that the results could not be incorporated into the forest plot and so a quantitative comparison could not be made directly against the other studies.

One of these studies was by Mohammed and colleagues (2020) who, like Lee et al (2017) and Mastropasqua et al (2013), used OSDI scores to compare the dry eye symptoms experienced by patients in the preserved and unpreserved groups. It was found that BAK preserved drops resulted in higher scores; the mean score was more than 20 at 12 months for 5/9 patients and more than 30 for 3/9 patients at 24 months, which was significant when compared to the PF group ($p<0.0001$). Polyquad preserved drops also resulted in mean scores of more than 12 for 4/8 patients from 6 months on and 1 patient scored more than 20 at 24 months. PF drops showed the lowest scores, with a mean score of less than 12 for 6/7 patients, at all time points. The remarkable finding from these OSDI scores was the significant correlation of them to the markers inflammatory markers IL 1β, IC IL10 (by Impression Cytology) and IL 1β (by tear analysis) (Mohammed et al., 2020).

Duru and Ozsaygili (2020) used a scoring system for symptoms ‘upon instillation’ and ‘between instillations’. Both preserved and unpreserved options showed good overall tolerance amongst patients. The only statistically significant difference was on ‘burning’ upon instillation, where PF Brimonidine produced a higher score (1.19±1.20) than preserved Brimonidine (0.52±0.92) ($p=0.01$) (Duru and Ozsaygili, 2020).

Denis (2016) recorded symptom scores at baseline and at the end of the 84-day trial. Again, symptom scores were divided into those that occurred 'on instillation' and those that occurred 'between instillations'. It was found that the PF treatment resulted in a significantly greater decrease in symptom scores from baseline to endpoint both on instillation (PF from 2.9±2.9 to 0.9±1.3 ($p = 0.0035$), preserved from 2.5±3.0 to 1.6±2.3) and between instillations (PF from 2.7±3.1 to 0.9±1.5 ($p = 0.0003$), preserved from 1.6±2.3 to 1.3±2.2). The characteristics table in Appendix 2 highlights the percentage drops for all the individual categories of symptoms in this study (Denis, 2016).

2.4.4 Signs

The assessment of the ocular surface can be conducted using a vast number of tests. This review encompasses the most common techniques used for the evaluation of the anterior eye, in the analysis of the preserved and PF effects of glaucoma medication. Assessment of the conjunctival hyperaemia, tear break-up time (TBUT), corneal staining, punctate keratitis and Schirmer test appeared to be the most frequent procedures employed in these studies. Seventeen out of the 22 studies investigated signs commonly associated with glaucoma medication. Though there is some variance amongst studies in the measure of these, with some using a battery of these aforementioned tests, whilst others rely on a single measure, all of the included studies measured the presence of signs of ocular surface problems to some extent. Due to the heterogenous nature of the data, and the great variance in reporting outcomes amongst studies in measuring these variables, a meta-analysis was not possible as a whole. A qualitative analysis has been carried out for all signs except conjunctival hyperaemia, where data was sufficient for some quantitative analysis.

2.4.4.1 Conjunctival hyperaemia

Conjunctival hyperaemia appears to be the most common side effect noted from the use of hypotensive drops. Eleven out of the 22 studies assessed conjunctival hyperaemia. The methods employed to assess hyperaemia varied between studies, with some studies using a photographic scale for grading (Rouland et al., 2013, Kumar et al., 2018b, Goldberg et al., 2014, Day et al., 2013). Dennis (2016) used the Efron grading scale (Denis, 2016). Others simply scored it as being present or absent (Gómez-Aguayo et al., 2018). Aptel and colleagues (2016) used a descriptive scale, while the remaining did not mention methods used to grade conjunctival hyperaemia (Aptel et al., 2016, Hamacher et al., 2008, Uusitalo et al., 2008, Shedden et al., 2010, Konstas et al., 2013).

Odds ratios were calculated for all the studies which used a percentage or number to represent subjects displaying signs of conjunctival hyperaemia. This was applicable to all studies except those of Kumar and colleagues (2018) and Dennis (2016), who used a scoring system to work out means for the preserved and unpreserved groups of patients (Kumar et al., 2018b, Denis, 2016). For Uusitalo and colleagues (2008), signs of hyperaemia were divided entirely into mild, moderate and severe. For the purposes of this analysis, moderate and severe values were taken as showing the presence of conjunctival hyperaemia, whilst mild signs of this were grouped with no presence of conjunctival hyperaemia (Uusitalo et al., 2008).

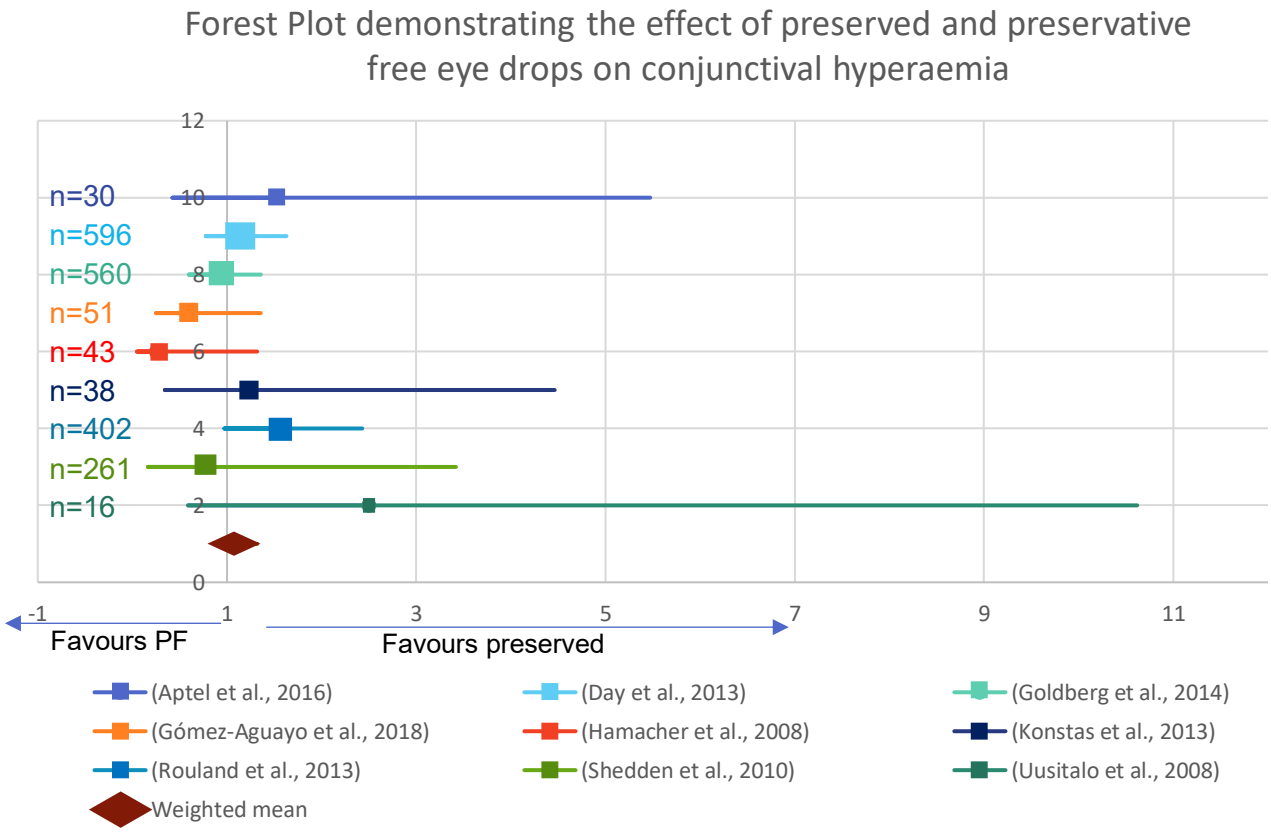


Figure 2.5 Forest plot demonstrating the effect of preserved and PF glaucoma eye drops on the incidence of conjunctival hyperaemia. The weight of each study is depicted as the number of participants treated (n), and symbolised by proportioned squares.

	Study	OR	95% CI	
(Hamacher et al., 2008)		0.257	0.050	1.319
(Uusitalo et al., 2008)		2.500	0.589	10.618
(Shedden et al., 2010)		0.750	0.165	3.419
(Aptel et al., 2016)		1.522	0.423	5.472
(Day et al., 2013)		1.123	0.775	1.628
(Goldberg et al., 2014)		0.899	0.596	1.357
(Konstas et al., 2013)		1.238	0.343	4.462
(Rouland et al., 2013)		1.536	0.972	2.429
(Gómez-Aguayo et al., 2018)		0.583	0.251	1.356
Weighted Mean		**1.072**	**0.871**	**1.319**

	Preserved & Hyperaemia	*Preserved & No Hyperaemia*	*PF & Hyperaemia*	*PF & No Hyperaemia*
TOTAL	228	848	220	877

Table 2.6 Odds ratios and upper and lower confidence intervals for each study investigating conjunctival hyperaemia. Below this, a summary of the weighted means is given for all of the studies.

Five of the nine studies show an OR>1 and four show and OR<1 suggesting there is no clear direction of effect. The confidence intervals of all studies cross the vertical midline at 1 indicating the lack of evidence to support the increased odds of developing conjunctival hyperaemia with either therapy (Figure 2.5). Furthermore, the pooled analysis corroborates this further and with an OR of 1.072, and 95% CI 0.871-1.319, there is insufficient evidence of a statistically significant difference between preserved and PF therapies. The study by Uusitalo and colleagues (2008), presents quite large confidence intervals, particularly at the upper limit, which require further investigation (Uusitalo et al., 2008).

2.4.4.2 Descriptive analysis of signs

Kumar et al (2018) evaluated mean hyperaemia scores within each group, rather than counting the number of subjects with or without hyperaemia. The results of such have to be qualitatively assessed against the above findings of the other studies. The difference in hyperaemia scores was statistically significant at week 2, with the preserved score being 0.68, and for

preservative- free being 0.45 (p=0.025). This difference was not sustained at week 12, as both groups showed similar scores with insignificant and minimal differences (Kumar et al., 2018b).

Similarly, Denis (2016) also used a scoring system to grade conjunctival hyperaemia. This was taken at baseline and endpoint. The PF group changed from a score of 1.4±0.8 at baseline to 0.9 ± 0.7 on day 84, whereas the preserved group changed from 1.2 ± 0.9 at baseline to 1.1 ± 0.8 on day 84. The difference in the two groups was significant (p = 0.0004), and this result was confirmed for the contralateral eye too. Further to this, when looking at hyperaemia scores specifically of grades 2 or 3, there was a greater reduction of these from baseline to endpoint in the unpreserved group than in the preserved group (-33% vs -6% respectively) (Denis, 2016).

2.4.4.3 Tear break up time

TBUT was reported in seven out of the 22 studies. Unfortunately, a quantitative approach could not be taken to compare and contrast these studies due to the type of data obtained and the variability in the methods used in recording TBUT. Thus, a qualitative approach has been taken instead, and the studies investigating TBUT and the methods used to assess this are outlined below.

Lee and colleagues (2017) conducted a switchover study and found that those who were randomised to the 'non-preserved to preserved' treatment arm, had a reduction in TBUT (p=0.06) at 12 months. However, they also found that those who began non-preserved treatment, showed a significant drop in TBUT in the first month (p=0.03). This did rectify by month 6, with TBUT returning to near baseline values. Furthermore, those who switched to non-preserved treatment after 6 months of preserved treatment did not show a vast increase in TBUT, but the TBUT was maintained to near baseline measures (Lee et al., 2017).

Mastropasqua and colleagues (2013) found the mean TBUT to be 10.18 ± 1.47 seconds for the preserved group and 12.12 ± 2.41 seconds for the PF group, at 6months. For the preserved group, this was a significant reduction (p<0.001) compared with baseline and month one measures. In this particular study, comparisons were made between the preserved and PF groups to a group of controls, who administered buffered saline solution, and a group who were just given the vehicle of latanoprost, including 0.02% BAK. It is this latter group, of the vehicle containing BAK 0.02%, that showed a significantly lower TBUT at 6 months compared to all the other groups (p<0.001), including the group treated with latanoprost alone (Mastropasqua et al., 2013).

Baudouin and de Lunardo (1998) looked at TBUT at intervals following instillation, up to 3 hours post drop administration. TBUT was decreased for both drug formulations at 3 hours, but this reduction from baseline values was significant for the preserved formulation (p=0.001), whereas it was an insignificant reduction for the PF formulation. Such findings were echoed in this study after 3 days of treatment, where the reduction in TBUT was significantly reduced for the preserved carteolol group, from 10.4 to 7.7 seconds (p=0.04) (Baudouin and de Lunardo, 1998).

Unlike the other studies, Manni and colleagues (2005) found a statistically significant reduction in TBUT for both the preserved and unpreserved group, at days 30 and 60 of treatment. At day 60, in the first sequence of treatment before crossover, preserved TBUT averaged at 7.6±1.6 seconds, whereas PF averaged at 9.0±1.1 seconds (Manni et al., 2005).

These findings did not resonate with Gómez-Aguayo and colleagues (2018). As with Manni and colleagues (2005), this research was also conducted as a crossover study. The TBUT was maintained throughout the study for each treatment sequence, which does not support the findings by the abovementioned studies. The TBUT was also similar within treatments with preserved being at 6.41 ± 1.4 seconds and preservative-free at 6.65 ± 2.9 seconds after 1 month of treatment (Manni et al., 2005, Gómez-Aguayo et al., 2018).

On the other hand, Kumar et al (2018) found that TBUT decreased across weeks 4 and 12 for both groups, but significantly for the preserved cohort ($p<0.0001$) and insignificantly the PF cohort. Furthermore, there was a significant difference in mean TBUT between the groups at week 4 (10.43 seconds vs 11.68 seconds for preserved and PF groups, respectively, $p<0.043$) and week 12 (8.02 seconds vs 11.63 seconds, for preserved and PF groups respectively, $p<0.0001$) (Kumar et al., 2018b).

Duru and Ozsaygili (2020) also found a decrease in TBUT for both groups from baseline to week 4. At baseline, the TBUT for the preserved group was 9.38±2.83 seconds and 9.95±2.06 seconds for the PF group (p=0.16). By week 4, this reduced to 5.76±1.78 seconds for the preserved group and 6.38±1.77 seconds for the PF group (p=0.08). Though significance levels are stated in this study, it is not clear whether they are based between the preserved and PF options, or whether they refer to changes from baseline (Duru and Ozsaygili, 2020).

2.4.4.4 Corneal observations

Although corneal staining (Section 2.4.7.1) and punctate keratitis (Section 2.4.7.2) may be nested within one another, some studies such as that by Shedden and colleagues (2010), mention these two conditions as separate entities within their research. Therefore, they are both described below as separate occurrences and exactly as what they are referred to in the respective studies.

2.4.4.4.1 Corneal staining

Corneal staining was assessed in five of the included studies.

Lee and colleagues (2017) graded corneal erosion (staining) using a scale from 0 to 3, classifying according to the area of erosion (0=little or no erosion, 1=1/3 of corneal area staining, 2=2/3 of corneal area staining, 3=the involvement of the entire cornea). Switching from unpreserved to preserved increased the corneal erosion scores from 0.40±0.51 to 0.60±0.54 (months 6 to 12). Likewise, corneal erosion scores worsened from months 6 to 12 when switching from preserved to preservative-free, with scores of 0.14±0.37 to 0.25±0.46. Both treatment changes led to an increase in corneal erosion, but neither increase was significant (Lee et al., 2017).

Shedden and colleagues (2010) did not specify corneal staining as such. However, the ocular adverse events were classed depending on which structure was affected. The cornea was affected in 16.8% of subjects in the PF group and in 24.6% of the preserved group. This percentage does include both worsening and emergent ocular signs, but baseline measures were not specified and so it is difficult to deduce whether one treatment had a bigger impact on the cornea compared to the other during the course of the treatment (Shedden et al., 2010).

Aptel and colleagues (2016) graded punctate corneal staining according to the following scale: absent, some punctates of <10%, punctates affecting an area of less than 50%, punctates affecting >50% of the corneal area. The incidence of such staining was low for both groups, in the worse eye analysis, with three in the preserved group and two in the non-preserved group (Aptel et al., 2016).

Similarly, Baudouin and de Lunardo (1998) found no differences between treatment groups in relation to corneal stain scoring. The grading was done on a scale of 0 to 4, depending on the

extent of staining. On the final day of treatment, day 3, both treatments were graded at 0.1. This was equally unremarkable at 30 minutes, 1 hour and 3 hours post instillation for both groups (Baudouin and de Lunardo, 1998).

Rouland and colleagues (2013) did not disclose any values for corneal staining, though it was assessed on a four-point scale (none, mild, moderate, severe) with other objective signs. Results of this study were simply classed as showing no difference between treatments for such signs (Rouland et al., 2013).

2.4.4.4.2 Punctate Keratitis

Four studies evaluated punctate keratitis.

Day and colleagues (2013) found that although the incidence of punctate keratitis for the safety population in both groups was 9, an increased severity of punctate keratitis of Grade 1 or more was more frequent in the bimatoprost group (6.8%) compared to the PF bimatoprost group (3.7%) ($p=0.086$).

Goldberg and colleagues (2014) found no real difference between the groups in terms of punctate keratitis. Two-point-five percent of patients in the preserved group showed signs of punctate keratitis, compared with 2.9% in the preservative-free group (Goldberg et al., 2014).

Equally, Hamacher and colleagues (2008) found a minute incidence of punctate keratitis. There was only one person in the PF group who showed such signs (Hamacher et al., 2008).

Shedden and colleagues (2010) found a difference between treatments and the incidence of punctate keratitis. In the PF group, 16.8% of patients presented with punctate keratitis, compared with 23.8% in the preserved group ($p>0.05$). As mentioned before, these percentages include both emergent as well as pre-existing cases which have worsened. Baseline values for each group are needed to depict a true picture of these observations (Shedden et al., 2010).

2.4.4.5 Schirmer Test

Schirmer test was used in four studies.

Mastropasqua and colleagues (2013) investigated Schirmer test 1 to compare the impact of preserved and PF treatment on the ocular surface. It was found that those on the PF treatment had insignificant changes from baseline to month 1 and month 6. However, in the preserved group, the results at 6 months were significantly worse than they were at baseline and month 1 ($p<0.001$) (Mastropasqua et al., 2013).

Schirmer's test was also investigated by Baudouin and de Lunardo (1998). After 3 days of treatment, no difference was found between the treatments, although compared to baseline measures, Schirmer test values were reduced for both preserved and preservative-free options (Baudouin and de Lunardo, 1998).

Similarly, Lee and colleagues (2017) found slight fluctuations in Schirmer test results over the course of each treatment sequence, but these changes were insignificant (Lee et al., 2017).

Likewise, Duru and Ozsaygili (2020) also found some changes from baseline to endpoint in Schirmer test results in both the preserved and unpreserved groups, but again, these changes were not of much significance. At baseline, the preserved group had a Schirmer result of 11.80±9.08mm and the PF group had a result of 12.23±9.54mm ($p=0.51$). By week 4, this had decreased to 10.71±8.40mm for the preserved group and 11.33±8.91mm for the PF group ($p=0.39$) (Duru and Ozsaygili, 2020).

2.5 Discussion

The aim of this review was to compare the differences in preserved and PF glaucoma treatments, not only by means of IOP control, but also to investigate the impact of these drug formulations on the occurrence of signs and symptoms of OSD, both at a clinical and subclinical level. A review by Baudouin and colleagues (2010), reported the effects of preservatives extensively, emphasising the negative impact on the ocular structures (Baudouin et al., 2010). The adverse effects of preserved drops may lead to intolerance and ultimately, non-adherence. In diseases such as glaucoma, where the condition is mostly asymptomatic in the early stages, this can lead to detrimental and irreversible changes. To ensure good adherence, patients must feel confident that the treatment is benefitting them as well as producing minimal side effects. A review looking at RCTs was therefore important, to investigate the effects of preserved and PF medication in controlled environments, where bias and confounding factors are minimised, ensuring accurate comparisons can be made.

The body of literature used in this review shows that both preserved and PF treatment are equally as effective at lowering IOP. The mean, weighted IOP changes of 27.2% for preserved treatments, and 26.7% for the unpreserved treatments, align well with the proposed IOP changes expected according to European Glaucoma Society guidelines. Depending on the severity of the glaucoma and initial IOP, a reduction of 20% could be adequate for early glaucoma, whereas a 30% reduction may be needed for moderate glaucoma (European Glaucoma Society, 2017). The reductions seen in this review therefore fit these requirements and serve to control the glaucoma and OHT. This is beneficial, as it indicates that those patients who do not tolerate preservatives in eye drops, or those with predisposing conditions making them susceptible to OSD, can be treated equally well with PF hypotensive drops as with their preserved counterparts.

There were some methodological differences in obtaining IOP measurements in the included studies. Whilst some studies looked at changes in IOP from baseline to endpoint of treatment, others looked at diurnal variations. This made like for like comparisons difficult, since averages had to be taken across time-points where baseline and endpoint IOPs were not explicitly stated. This may explain some of the variations seen in IOPs across the studies. Such fluctuations had minimal implications on the overall data however, and the results are in line with other recent similar systematic reviews indicating either insignificant differences in IOP changes between preserved and unpreserved hypotensive drops (Hedengran et al., 2020), or clinically irrelevant differences (Skov et al., 2022). Furthermore, diurnal variations were addressed in most of the included studies, since measurements were taken at consistent time points (Appendix 1) (Tajunisah et al., 2007).

The occurrence of signs and symptoms in these studies was a primary objective measure for this review. There was, however, much variability with the assessment and grading of these, which made analysis difficult. This might explain the lack of statistical significance found between the treatments.

For sixteen studies, symptomology was investigated and comparisons were made between preserved and PF treatment. For ten of these, a count of the number of patients within each category of symptoms was made. In our analysis, the symptoms were summed to retrieve an overall incidence of ocular adverse events. Though in theory this idea would work well, the lack of consistency in recording between studies meant that for some, only ‘stinging/burning’ symptoms were used, as reporting of more than one symptom produced a symptom count which exceeded the number of participants in the study.

Results of this meta-analysis using the overall weighted means suggest that exposure to preservatives is associated with increased odds of developing ocular symptoms (OR 1.265, 95% CI 1.005-1.593). This finding would perhaps hold more value, had the data been more consistent between studies in terms of both data collection and presentation, whereby collation of results from the studies would be more complete. The methodological differences have possibly led to some miscounting of the true number of patients experiencing symptoms. In some studies, patients only reported singular symptoms, whereas in others, patients would be counted in more than one category. The latter makes analysis difficult as it is unclear exactly what the total number of symptomatic patients was. Perhaps in future studies, looking at a sum of such symptoms would serve as a better overall indicator, as the current technique may have led to some undercounting.

Regardless, the qualitative analysis supports the quantitative findings and on the whole, PF treatment is favoured for tolerance. Symptoms were significantly worse for the preserved treatment than PF in three studies (Rouland et al., 2013, Mastropasqua et al., 2013, Mohammed et al., 2020). In the study by Baudouin and de Lunardo (1998), symptoms scores were also worse for the preserved group than the unpreserved group, although these differences were small (Baudouin and de Lunardo, 1998). In the crossover study by Lee and colleagues (2017), symptoms significantly worsened when switching from PF to preserved treatment, and significantly improved when switching from preserved to PF treatment (Lee et al., 2017). Similarly, for Denis (2016), there was a significant reduction in symptoms from baseline to endpoint for the PF treatment arm (Denis, 2016). The only study finding negative effects from PF treatment was by Duru and Ozsaygili (2020); though most symptomology measures were insignificant between the two treatments, ‘burning on instillation’ was significantly worse for the PF treatment (Duru and Ozsaygili, 2020).

Ocular surface signs were also considered in the meta-analysis, though this was limited to conjunctival hyperaemia as this was the only consistent sign reported in the studies, where reporting was made by classifying the number or percentage of patients. The results reveal that there is insufficient evidence to suggest increased odds of developing conjunctival hyperaemia with either treatment option.

Much of the data obtained for clinical signs was continuous in nature, with variable methods of recording, and so a meta-analysis was not possible for these other signs. A qualitative analysis had to be conducted which overall, did not draw out many significant differences between treatments.

Corneal staining appeared to either show no differences between treatments, or results of this were low or unclear (Lee et al., 2017, Shedden et al., 2010, Aptel et al., 2016, Baudouin and de Lunardo, 1998, Rouland et al., 2013). Similarly for punctate keratitis, between preserved and unpreserved treatments, there were either no differences or insignificant differences (Goldberg et al., 2014, Hamacher et al., 2008, Shedden et al., 2010). Day and colleagues (2013) found that punctate keratitis grading of 1 or more was more likely in those receiving preserved treatment than PF (Day et al., 2013). Likewise, Schirmer test results were unremarkable on the whole for both, except for Mastropasqua and colleagues (2013) who found that Schirmer test results to be significantly worse from baseline for the preserved treatment only (Mastropasqua et al., 2013).

TBUT tests do highlight some differences between treatment types, but the extent of these findings are hard to extrapolate when the studies are so different to each other, and so few studies conducted these tests. Interestingly, two studies found that the TBUT was reduced significantly for both preserved and PF treatments (Manni et al., 2005, Lee et al., 2017). Gómez-Aguayo et al (2018) found that TBUT was maintained throughout for both treatments (Gómez-Aguayo et al., 2018). Three studies indicated some benefits with PF treatment over preserved (Kumar et al., 2018b, Mastropasqua et al., 2013, Baudouin and de Lunardo, 1998).

Uusitalo et al (2008) produced confidence intervals that were quite large, particularly at the upper end, when looking at conjunctival hyperaemia. This suggests some uncertainty about the outcomes and is possibly linked to the methodology of the study. In this study, 16 healthy volunteers were used with an average age of 29.2 years. The treatment period was 16 days, including a crossover to the alternative treatment type. This is not very representative of a typical glaucomatous population, who are generally much older and on long-term treatment. The subjects were divided into classifications of mild, moderate and severe conjunctival hyperaemia in this study. For the odds ratio calculations, moderate and severe values were taken as showing the presence of conjunctival hyperaemia, whilst mild signs of this were grouped with no presence of conjunctival hyperaemia. This may have led to some underrepresentation of the real number of subjects who exhibited red eyes, and may account for the large confidence intervals (Uusitalo et al., 2008). However, as the summary mean is the best estimate, it includes the variability inherent in all the component studies, and so such a small study would be relatively uninfluential.

Evaluation of the signs and symptoms would be easier and more comparable with the use of standardised tests and a universal grading or scoring system in place. This would not only

make comparisons easier between studies, but also, enable collation of results from lots of RCTs. Many studies included in this review involved small sample sizes. If the data was reported more consistently between studies, it could be pooled, enabling more clinically relevant conclusions to be drawn, with greater statistical significance.

The measures of clinical signs also showed some inconsistencies with recording, as well as differences in the time points at which they were recorded, which could have contributed to the poor correlations found in this review. For example, Manni and colleagues (2005) investigated TBUT at regular intervals following the start of treatment (Manni et al., 2005), whereas Duru and Ozsaygili (2020) and Baudouin and de Lunardo (1998) looked at TBUT at baseline and endpoint only (Duru and Ozsaygili, 2020, Baudouin and de Lunardo, 1998). These changes over time might be a better indication of tear film status, rather than a stationary measure of such at the end of treatment. Similarly, Easty and colleagues (2006) evaluated symptoms at regular intervals throughout the course of the study (Easty et al., 2006). It has previously been shown that diurnal variations exist in the signs and symptoms of dry eye, and future studies should take this into consideration when conducting clinical trials (Walker et al., 2010).

Most of the included studies were carried out over a period of less than 12 months. The lowest trial period was in the crossover study by Baudouin and de Lunardo (1998), where subjects were exposed to each therapy for three days before crossover to the other (Baudouin and de Lunardo, 1998). The study by Mohammed and colleagues (2020) was the only one where the trial period ran over 24 months; all other studies were carried out for less than 12 months with the exception of Lee and colleagues (2017), whose study ran for 12 months (Mohammed et al., 2020, Lee et al., 2017).

Glaucomatous patients are mostly on lifelong treatment, and such short study periods are not reflective of the changes which may occur over the years with long-term treatment. Signs and symptoms may be comparable at week 12 of treatment, but perhaps not so after many years of treatment. For conditions such a glaucoma and OSD which are chronic, longitudinal assessment is required to analyse the true relationship. The cellular studies discussed later in this review demonstrate that there are microscopic changes which take place on exposure to both preserved and PF hypotensive drugs. Nevertheless, such changes may not manifest themselves into appreciable signs or symptoms until years of exposure to the drugs.

In the current review, there is also evidence of PF drops causing signs and symptoms of OSD, even after short study periods. Intolerance may therefore be loosely related to the active

compound too, and not just the presence of preservatives. Again, longer studies and further investigations are needed to decipher the reasons behind this effect.

Recent meta-analyses with similar aims mimic some of the outcomes of the current study in that PF drops are just as effective as preserved drops in the treatment of glaucoma, however, more concrete evidence is needed in terms of tolerability (Hedengran et al., 2020, Skov et al., 2022). Much of the current literature discusses the detrimental effects of preservatives on the ocular surface and related structures (Chang et al., 2015, Baudouin et al., 2010, Heijl et al., 2002). There is also evidence that signs and symptoms of DED are less prevalent with PF drops than preserved (Pisella et al., 2002). Though the short term studies in this systematic review highlight this to an extent, much is yet left to be uncovered.

2.6 Cellular studies

2.6.1 Laser scanning confocal microscopy

Four studies were identified in the literature search which fulfilled the eligibility criteria and looked at differences between preserved and PF glaucoma eye drops at a cellular level using confocal microscopy. One of these studies was by Ciancaglini and colleagues (2008) where subjects were randomised to either preserved levobunolol hydrochloride or PF levobunolol hydrochloride. Confocal microscopy was then used to image the ocular surface and observe any changes between the two drug formulations, as well as from baseline. The results of this investigation showed significant changes for both groups over the course of the treatment. There was a significant reduction in the density of goblet cells from baseline to month 6; 61% cell density decrease for the preserved group and 17% decrease in cell density for the PF group ($p<0.001$). Epithelial regularity (assessed as a cumulative score) revealed a significant increase from baseline to month 6 for both formulations, though it was higher for the preserved group (from 3 to 34) than for the preservative-free group (from 4 to 8) (Ciancaglini et al., 2008).

Furthermore, Impression Cytology (IC), another minimally invasive technique, was employed in this study to assess goblet and epithelial cells, according to Nelson's method (Nelson, 1988, Nelson et al., 1983). Cumulative grading revealed a score which was significantly higher in both groups from baseline, but again, more so for the preserved group than for PF ($p<0.001$). The difference between groups at 6 months was also statistically significant ($p<0.001$) (Ciancaglini et al., 2008).

IC was also used in the study by Mohammed and colleagues (2020), who investigated the link between the type of preservative (BAK or PQ) and the presence of inflammatory markers. The BAK preserved group showed increased levels of IL-6, IL-8 and IL-1β, whereas PQ only showed a 2.92-fold increase in IL-1β at month 24, and PF showed a 1.5-fold increase from month 1 to 24 for IL-10 only. It is evident then, that hypotensive treatment in glaucoma has some inflammatory effect, regardless of the presence or absence of preservatives (Mohammed et al., 2020).

The downfall of this study was the inconsistent treatment during the study duration. If a drop was insufficient in lowering the IOP, another was added with the same type of preservative. Therefore, some individuals may have been on more than one drop, which could ultimately have affected the outcome. Different classes of drugs were also used in each group, and again, the active ingredients could have influenced the inflammatory results. That being said, it is interesting that the study found a significant correlation between OSDI results and the markers IC IL 1β, IC IL10. Inflammation occurring at a cellular level may present symptoms in individuals, and this may occur within 2 years, but more likely, it could manifest after prolonged treatment (Mohammed et al., 2020).

Both of these powerful diagnostic tools help with the understanding of changes occurring at a cellular level, which may not be evident as signs or symptoms yet. What is interesting is that, though preserved treatment clearly impacts the goblet and epithelial cell density the most, there is no doubt that even PF treatment has some impact (Ciancaglini et al., 2008). Ciancaglini and colleagues (2008) suggested that this might be due to effects on the tear secretion system (De Saint Jean et al., 2000, Chiou et al., 2006, Ciancaglini et al., 2008). The drug itself, in their case, levobunolol, may also contribute to these changes.

Mastropasqua and colleagues (2014) also utilised laser scanning confocal microscopy (LSCM) in their investigation, specifically looking at mean microcyst density (MMD, cysts/mm2) and mean microcyst area (MMA, μm2) of the bulbar conjunctiva. Comparisons were made between preserved and PF latanoprost formulations, preserved and PF timolol formulations as well as one group of healthy individuals exposed only to the vehicle of latanoprost (including 0.02% BAK) and another group of healthy individuals administered with a physiological buffered saline (PBS) (Mastropasqua et al., 2014b).

LSCM findings indicate that MMA was significantly higher in both the preserved and PF latanoprost groups at month 3 compared to baseline ($p<0.001$), with the preserved group being

significantly higher of the two groups still ($p<0.001$). MMA did not change remarkably for the other sets. MMD on the other hand, was fairly static in all groups when comparing to baseline measures (Mastropasqua et al., 2014b).

These findings suggest that PGAs increase the trans-conjunctival/aqueous humour outflow in glaucomatous patients who have not been treated prior, since microcysts are regarded as stable structures unless exposed to medical or surgical stimuli. The fact that MMA increased by a half and two-fold (PF and preserved groups, respectively) without impacting the MMD, it suggests that outflow is enhanced through existing pathways rather than the formation of new ones (Mastropasqua et al., 2014b).

Nonetheless, careful consideration should be taken as this was only a short-term study and so long-term effects on MMA or MMD cannot be ruled out. The exact cause for these findings cannot be determined since they may suggest an inflammatory response rather than changes to the aqueous outflow. As aqueous humour outflow is dynamic in nature, and MMA is a static measure, the two are difficult to correlate (Mastropasqua et al., 2014b). Further investigation would be needed to distinguish causative factors, perhaps with the aid of other supporting tests.

Mastropasqua and colleagues (2013) combined LSCM and IC to examine changes at such microscopic levels. Subjects were randomised to either PF tafluprost or preserved latanoprost, with two control groups exposed either to PBS or the vehicle of latanoprost including 0.02% BAK. Goblet Cell Density (GCD) was measured at baseline, month 1 and month 6. Initially, GCD appears to increase for both preserved and PF hypotensive drops. This change was significant from baseline measures for the preserved group ($p<0.05$) and PF group ($p<0.001$), with both methods of testing. Surprisingly, this elevation was maintained only for the PF group at month 6 (Mastropasqua et al., 2013).

This phenomenon has been explained as possibly being linked to PGA derivatives' ability to stimulate mucin secretion and cell proliferation (Mastropasqua et al., 2013). This purports a potential protective property of PGAs, which has been suggested by previous studies. Pisella and colleagues (2004) used IC to look at pro-inflammatory markers and used cultured cell lines to explore the proapoptotic effects of preserved latanoprost, preserved timolol and unpreserved timolol. Though both preserved drug formulations resulted in higher pro-inflammatory and proapoptotic changes than unpreserved timolol, latanoprost caused less toxicity out of the two

drugs, and both caused less toxicity still when compared with BAK alone. Such results mimic the suggestion that PGAs play a protective role (Pisella et al., 2004).

However, the results of the Mastropasqua and colleagues (2013) study have to be considered with care, as this was a pilot study, with a small sample size and short study duration. The effects of BAK may counteract the protective role of PGAs in chronic treatment. Also, it would have been clinically better to compare the preserved tafluprost version to its PF counterpart, rather than latanoprost, to ensure more homogeneity between the drugs (Mastropasqua et al., 2013).

As with the other confocal studies, there are certain limitations to these findings. Confocal microscopy requires interpretation by an observer and some structures can prove difficult to examine (Mastropasqua et al., 2014a). Thus, confocal microscopy is more useful, when supported by clinical data from signs and symptoms, over a longer investigative period. This would provide a more complete picture of the impact of hypotensive eye drops on the ocular structures of chronically treated individuals.

2.6.2 Liquid chromatography/ mass spectrometry

Some of the involved studies investigated the pharmacokinetics of preserved and PF treatment using the method of high-performance liquid chromatography and mass spectrometric detection. Such was done by Uusitalo and colleagues (2008) where participants were exposed to preserved and PF formulations of tafluprost 0.0015% and plasma concentrations of tafluprost acid were then measured. The maximum concentration (Cmax) and time to maximum concentration (tmax) were also determined, as well as the area under the curve (AUC0–last). The problem with such method is that tafluprost acid is only detectable in plasma for up to an hour after instillation of the drops, and so effects over a few hours were not possible (Uusitalo et al., 2008).

The results of this study demonstrate that both the preserved and PF formulations show similar pharmacokinetic safety profiles. The plasma concentration peaked at 10 minutes before dropping off to unquantifiable levels, and the difference in mean concentrations of tafluprost acid were insignificant between the treatments. The outcomes of the aforementioned parameters (Cmax, tmax, AUC0–last) were alike in both cohorts, after single and repeat dosing (Uusitalo et al., 2008).

Similarly, Aptel and colleagues (2016) also conducted plasma analysis by liquid chromatography–mass spectrometry. Blood samples were taken and centrifuged for days 42 and 84, at pre-instillation, 5,10,15 and 30 minutes post instillation of drops. As in the study by Uusitalo and colleagues (2008), plasma concentrations were quite low on the whole, making it difficult to quantify latanoprost concentrations. Below the level of quantification (BLQ) calculations at 0 pg/mL, 20 pg/mL, and 39 pg/mL were needed to quantify results where they were less than the lower quantifiable limit of 40 pg/mL. Again, it was not possible to calculate the halftime, $t_{1/2}$ .The AUC0–30 was significantly lower for PF latanoprost than for preserved latanoprost for BLQs of 20 pg/mL and 39 pg/mL ($p < 0.05$). In addition, Cmax was significantly lower ($p < 0.05$) for PF latanoprost than for preserved latanoprost treatment at each calculated BLQ. The results of this have to be interpreted with some caution however, as the high incidence of BLQs cast a shadow on the findings. Though there were some pharmacokinetic differences between the two treatments, this was not reflective in the overall efficacy or tolerability of the treatments (Aptel et al., 2016).

Easty and colleagues (2006) also aimed to look at the pharmacokinetic properties of preserved and PF timolol gel. Plasma levels were assessed in 27 patients at week 12. As with the other studies looking at plasma concentrations, the levels were very low. The data was unquantifiable except in two cases, one for each treatment. Though this does not aid with the comparison between preserved and PF formulations, the results demonstrate that such low concentrations in the plasma would ensure a lower incidence of systemic side effects (Easty et al., 2006).

2.6.3 Miscellaneous measures

Two studies investigated safety measures from a slightly different perspective to the above examples. One of these studies was by Manni and colleagues (2005) where inflammatory cytokines were explored, as their presence can indicate ocular surface inflammation. In order to investigate such cytokines, IL-1β specifically for this study, a tear sample of 20 µl was required, which was then analysed using an enzyme-linked immunosorbent assay. It was found that IL-1β tear concentrations were significantly higher for the preserved therapy both at 30 days (53.2±5.8 ($p=0.018$)) and 60 days (88.5±9.8 ($p=0.012$)), compared to baseline. These results were echoed in both treatment sequences of this crossover study. PF treatment also showed a slight increase in IL-1β tear concentrations over the course of the treatment, though this was not significant (Manni et al., 2005).

IL-1β tear concentrations were specifically chosen for this study because this subgroup of cytokines is part of a myriad of cytokines involved in the regulation of ocular surface inflammation (Li and Tseng, 1995). The results confirm an inflammatory response with preserved medication, and to some extent, with PF treatment too. A study duration of more than 2 months may be required for such findings to manifest as clinical signs and symptoms for both treatments (Manni et al., 2005).

Mohammed and colleagues (2020) looked at inflammatory markers as described previously, using IC. In this study, tear samples were also analysed to look at such markers. It was found that BAK containing drops resulted in increases of IL-6, IL-8 and IL-1β. For IL-6, this elevation was significant at month 24 ($p=0.0368$). Likewise, IL-1β was also significantly increased from month 3 ($p=0.0243$), and significantly higher compared to PF at month 24 ($p=0.0187$). PQ preserved drops also resulted in some elevation of the inflammatory markers but this was insignificant throughout. It is unfortunate however, that this sampling of tears was inadequate from some patients, and eight out of the 35 tear samples produced too low a volume to be analysed. This does implicate the accuracy of the findings. Similarly, of the IC samples, 11 out of the 35 could not be used to their low quality/quantity (Mohammed et al., 2020).

Stevens and colleagues (2012) took a different approach entirely and measured flare intensity using the Laser-Cell-Flare-Meter. This was based on the assumption that BAK can impact anterior eye structures and consequently lead to some ocular inflammation. Indeed, the investigation confirmed that exposure to BAK preserved timolol caused a significant rise in flare compared both to the baseline and PF treatment. In fact, both treatments caused a significant increase in flare from baseline, with an increase of 1.51 ph/ms for PF treatment ($p = 0.008$), and 2.37 ph/ms for the preserved treatment ($p<0.001$) (Stevens et al., 2012).

It has been proposed that this increase could be accounted for by the mechanism of action by timolol itself. It works by reducing aqueous humour production, while protein filtration remains the same, and so increasing the flare within the eye (Stur et al., 1986). It has been suggested that it is BAK which is responsible for the difference between the groups, by contributing to an inflammatory response. Though this study was short, lasting only a month, it highlights some interesting findings of inflammation, exacerbated by the presence of preservatives (Stevens et al., 2012). As glaucoma treatment is chronic, it would be important to look at long-term effects of treatment, both for preserved and PF options.

2.7 Drops vs gels

Three studies were excluded in the final stages of screening due to the comparisons being made between drops and gels. One of these was a French study, and so it did not make the stages of translation. The remaining two have been explored for the purposes of this review. Frezzotti and colleagues (2014) compared PF timolol maleate gel drops to preserved timolol maleate drops. Schirmer test was significantly reduced at 12 months in the preserved group compared to the PF and control groups ($p<0.0001$) and TBUT was also significantly lower in the BAK preserved group than in the PF and control group at 12 months ($p < 0.0001$). This was backed up by conjunctival morphological changes for the preserved group at the cellular level, which was not exhibited by the unpreserved group (Frezzotti et al., 2014).

Delval and colleagues (2013) looked at PF timolol gel and preserved latanoprost eye drops. Signs and symptoms significantly improved with timolol gel compared to preserved latanoprost, while maintaining a stable IOP level throughout. However, this study recruited patients who already had some pre-existing ocular intolerance (Delval et al., 2013).

The results of these studies may well have been impacted by the type of medium that the preserved and unpreserved formulation was in, and so these results were not considered in this review. Although both studies show promising advantages of unpreserved gels over preserved drops, there is some bias to these findings as gels may remain in the eye for longer periods than drops. This adds a confounding variable between the two test groups, and a fair comparison cannot be made.

2.8 Conclusion

To summarise, preserved and PF hypotensive drops are equally effective at lowering IOP. This makes PF treatment a viable option for those with a compromised ocular surface, or those at risk of developing OSD. In terms of tolerability, the current review suggests that preserved medication increases the odds of developing ocular symptoms of discomfort. Therefore, PF therapy would be a better choice for patients with glaucoma or OHT.

This review looked at the multifaceted relationship between OSD and glaucoma drops. There are too many different variables to permit their combination into a meaningful assessment of the quantitative relationship between the presence or absence of preservatives and the incidence of signs and symptoms of OSD. However, in order to get a real sense of the effects

of preservatives on the ocular surface, one cannot only investigate measurable variables such as conjunctival hyperaemia or the occurrence of irritable eyes as these are not resolute. Overall, it is reasonable to deduce that, from the list of variables assessed, none were worse with PF treatment than preserved treatment. Though the data is insufficient to reach statistical significance, it is persuasive that PF treatment is an option that is at least as safe, and effective as preserved treatment.

Where quantitative comparisons were possible, there is a clear relationship between preservatives and increased chances of developing red irritable eyes, albeit this is only slightly significant. It is appreciated that the heterogeneity between studies in terms of methods and recording, may have disguised some findings and ultimately be the reason for the small correlation.

Moreover, the cellular studies indicate inflammatory changes in the early stages of glaucoma treatment. They could therefore be an early indicator of those patients who are at risk of developing OSD in the long-term. They provide valuable information to accompany the clinical results, and suggest some inflammation is present with both preserved and unpreserved glaucoma drops.

The association between glaucoma therapy and OSD is a complex one, and one that requires further investigation. Glaucoma is an insidious disease, and its treatment has the potential to cause both symptomatic and asymptomatic ocular surface problems. With glaucoma being a mostly asymptomatic disease, the side effects of the prescribed drops could result in symptoms which deter patients from using them properly. This lack of compliance could consequently lead to worsening of the glaucoma.

Being able to identify ‘at risk’ individuals who have predispositions to developing dry eyes may be the best simultaneous management of OSD and glaucoma. Such patients could be placed on the most appropriate treatment from the beginning, so as to prevent complications in the future.

From the results of the current systematic review, it is advised that longitudinal studies are carried out over several years, in order to fully appreciate the effects of glaucoma treatment on the ocular surface. Many of the inclusive studies were of short study durations, the majority under 12 months, and there is a possibility that such short periods may have disguised the apparent differences of the therapies on the ocular surface. The cellular studies indicate that

there may be subclinical changes to the ocular surface in the short term, which subsequently could present as clinically relevant signs and symptoms over the course of treatment. Changes such as these may not come to light until there has been sufficient treatment exposure.

Combining standardised tests looking at signs, symptoms, IOPs and cellular effects, with long term analysis, would allow for a full picture of the effects of both preserved and PF treatment on glaucoma and OHT patients. There appears to be much variability between studies in grading, recording and the choice of independent variables which are tested, which again may have influenced the lack of statistical differences between preserved and PF treatment.

Consistent methods are needed when assessing both signs and symptoms of OSD, and sometimes looking at changes over time provide more crucial evidence than stagnant measures in time. By approaching the issue of OSD in glaucoma in a more structured way, it should help to highlight the association of the two conditions better. Further research is welcomed, using a consensus-driven approach in the methodologies used to investigate the differences between preserved and unpreserved glaucoma treatment.

With the results of this review indicating equal efficacy, and better tolerability of PF hypotensive drops, it would be insightful to investigate current clinical prescribing habits in glaucoma clinics, to see if such benefits of PF therapy are applied in practice.

Chapter 3

Survey to determine current clinical approaches to ocular surface disease in UK glaucoma clinics

3.1 Introduction

As described in Chapters 1 and 2, there appears to be a link between certain glaucoma treatments and OSD. Therefore, the medical management of glaucoma can shape the fate of the ocular surface in treated patients. In order to understand how glaucoma management might be improved to achieve best results both in terms of controlling the glaucoma, whilst also maintaining a healthy ocular surface, there is a need to identify current clinical approaches in UK clinics. It is important to know what topical medication clinicians are prescribing and what thought processes are helping to shape their management. Furthermore, there is a need to establish the current views on the prevalence of OSD amongst glaucoma patients. Such insights will allow for a better understanding and highlight areas of improvement in the medical management of glaucoma and OSD.

According to the Royal College of Ophthalmologists, the prevalence of glaucoma in the United Kingdom is projected to rise by an estimated 22% from 2015 to 2025, and by 44% from 2015 to 2035. (Bruce and Tatham, 2018, The Royal College of Ophthalmologists, 2017). Glaucoma is one of the leading, chronic ocular conditions, which requires regular follow-ups in eye clinics (Foot and MacEwen, 2017, Tuck and Crick, 2003). Therefore, this coupled with an aging population, has undoubtedly contributed to outpatient eye care increasing in the UK by 40% in the last 10 years or so (Foot and MacEwen, 2017, Bruce and Tatham, 2018). This high demand has attracted a system of so called 'Virtual clinics'; clinics led by ophthalmic trained staff, which are virtually overseen, reviewed and essentially managed by glaucoma consultants (Wright and Diamond, 2015). A recent survey found that 50% of UK NHS trusts already have virtual glaucoma clinics (VGCs) in place (Gunn et al., 2018). Following the onset of the COVID-19 pandemic, a further push towards such clinics arose to meet the growing demands of reviewing the backlog of patients (Gunn et al., 2022, Powell et al., 2022). Figure 3.1 demonstrates the typical patient pathway through a VGC at Corbett Hospital (Dudley NHS, UK) in the West Midlands.

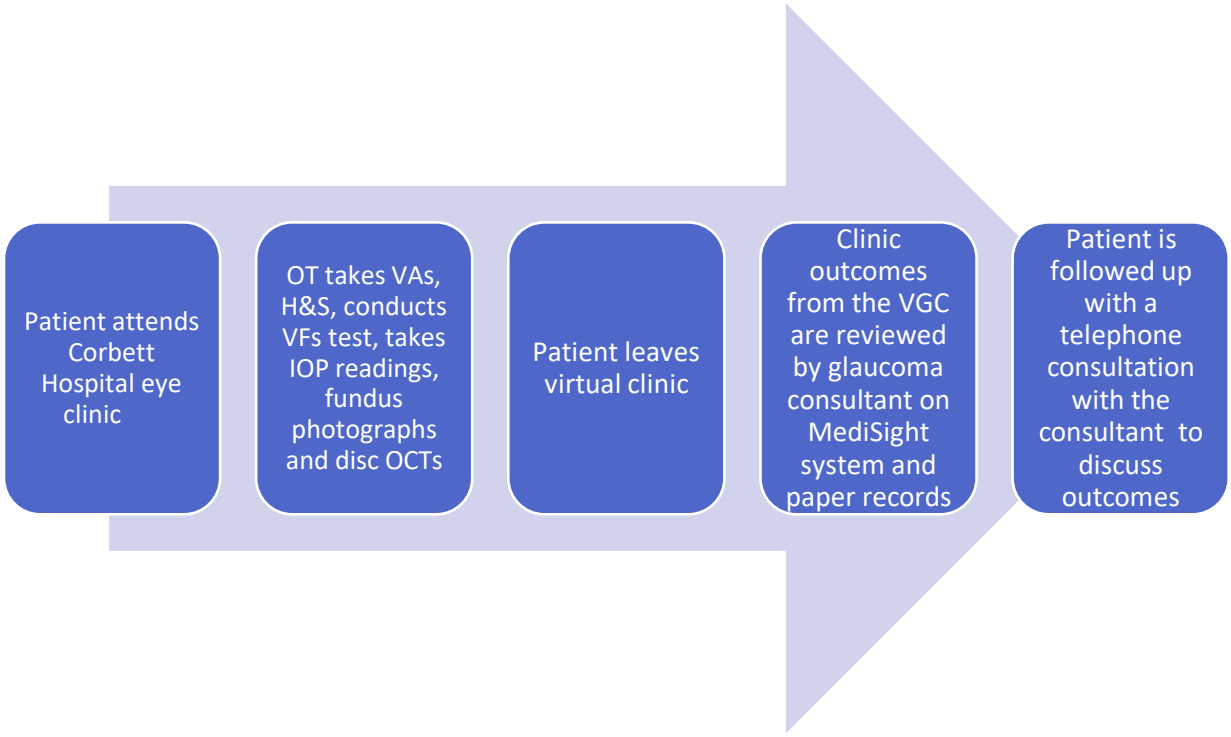


Figure 3.1: Pathway of the virtual glaucoma clinic (VGC) at Corbett Hospital (Dudley NHS, UK) in the West Midlands. Following the telephone consultation, patients are either called in to a face-to-face clinic with a clinician or informed of the stability of the results and advised of a routine future appointment. A letter is then sent to the GP and patient, outlining the management post-VGC. OT=ophthalmic technician, H&S=History and Symptoms, VFs=Visual Fields, IOP=Intraocular pressure, OCT=Optical coherence tomography

3.1.1 Guidelines to glaucoma management

Intraocular pressure is the most important modifiable factor in controlling the progression of glaucoma (Ting et al., 2014). By lowering and managing the IOPs of patients, the possibility of disease progression is reduced. When comparing treated and untreated patients, progression occurs later in those who have had their IOP controlled early on in the pathway (Heijl et al., 2002). The reduction of IOPs can be achieved through various means, including topical glaucoma medication, laser therapy and surgery (National Institute for Health and Care Excellence, 2017).

The NICE guidelines are pivotal in the management of glaucoma patients both in primary and secondary care. As of January 2022, NICE guidelines suggest that 360° selective laser trabeculoplasty (SLT) is to be offered to all newly diagnosed POAG (apart from cases of Pigment Dispersion Syndrome (PDS)) and OHT patients (IOP ≥24mmHg with a risk of vision loss). Where a patient declines this procedure, is unsuitable for it, is awaiting SLT or surgery or

in cases where SLT did not achieve the desired IOP reduction, the guidelines advise pharmacological treatment with a generic PGA.

Currently, NICE guidelines recommend generic PGAs as the first line pharmacological therapy for cases of POAG and OHT. If this does not achieve the desired results, it is recommended to swap to another generic PGA, before trying a drug from a different class. In cases of advancing glaucoma, surgical intervention is advised, with PGAs to be used in the interim period. PF drops are recommended for those patients who have allergies to preservatives or intolerances, or suffering from 'clinically significant and symptomatic' OSD (National Institute for Health and Care Excellence, 2017).

The presence of preservatives in drops is a widely debated topic in glaucoma treatment as the sight-threatening risk of blindness through glaucoma appears to overshadow the OSD related side effects of the preservatives. However, the signs and symptoms of OSD should not be overlooked, and should instead, dictate treatment choices in the management of glaucoma and OHT. The effect of this can be demonstrated by quality of life (QoL) studies, which show that the QoL appears to be worse in those with poorer OSD, which in turn is worse in those with more severe glaucoma (Skalicky et al., 2012). Consequently, the presence of OSD can affect compliance when it comes to managing the glaucoma (Stringham et al., 2018).

3.1.2 Patient Instruction

As well as the need for glaucoma drops to be comfortable, patients must be taught how to instil them. Firstly, to ensure that the drops are administered correctly and so that the active ingredients are reaching the target, and secondly, for patient confidence in their treatment. Adherence in glaucoma is of upmost importance especially as immediate complications from the disease may not be perceived by individuals, and so the consequences of poor drop technique or poor compliance may not be instantly evident to individuals.

Tatham and colleagues (2013) found that 54.1% of patients have a poor drop technique, with 11.8% missing the eyes completely and so failing to administer the needed drugs. Education on drop instillation dramatically improved the odds of good technique by 8.17 fold (Tatham et al., 2013). Thus, this highlights the importance of drop instillation education in clinics for best management of glaucoma and OHT both by the consultants and the patients alike. Poor drop technique could contribute to disease progression and subsequent changes in medication or surgical intervention, which may not be needed if the drops are used as intended. It is also

noteworthy that good compliance does not necessarily mean that drop technique is good. Recent changes to the NICE guidelines have added a statement insisting that patients are shown the correct drop instillation technique and examined attempting the technique, on first prescription of their drops (National Institute for Health and Care Excellence, 2017).

3.2 Aims

To establish current clinical practice in the medical management of glaucoma amongst a group of specialist clinicians in the UK.

3.3 Method

3.3.1 Ethics

This survey followed the tenets of the Declaration of Helsinki. NHS Ethical approval was obtained under the IRAS PROJECT ID 173203. This ethics allowed the use of questionnaires as part of dry eye investigations and observations. The data was collected via an online survey application. Prior to starting the survey, participants were provided with a small introductory paragraph outlining the aims of the survey, highlighting anonymity in participation and an approximate length of time to completion. As no identifiable data was collected, completing and submitting the survey was taken as informed consent.

3.3.2 Development of questionnaire

An anonymous questionnaire was developed on an online survey application. The survey was divided into 3 main sections: a) about you, b) the glaucoma clinics you work in and c) the use of PF medicine in glaucoma. These sections formed the basis of the questionnaire as each one provided a platform for the questions. The questionnaire was subdivided into these categories both for ease of use, as well as to separate important sections of interest.

Questions were initially distributed for content to two leading glaucoma specialist consultants, two academics at the University of Aston and to an industry led medical affairs specialist. Amendments were made as identified to aid clarity and scope.

After the finalisation of 17 questions, the survey was then uploaded onto the online survey application, structured into the three sections. The survey was then re-distributed to the aforementioned clinicians to provide their knowledge and feedback on both the quality and

content of the final survey. Once approval had been made, the survey was made live in August 2019.

3.3.3 Participants

The survey was distributed to UK and Eire consultants, optometrists, ophthalmic technicians, orthoptists and nurses specialising in glaucoma through mailing lists. The survey was sent out as an embedded email with a hyperlink to the web-based survey, which was accessible from mobile devices as well as computer systems.

3.3.4 Survey Questions

The questionnaire used in this survey is attached in Appendix 3. The rationale behind each question in each section is outlined below.

All about you

Firstly, it was important to establish the age of the clinician. This was an important factor to consider since age could potentially influence the clinician's decision making in practice (Baquedano et al., 2007).

As with the first question, the number of years qualified could affect how diseases are managed in practice. Although you would expect some consistencies amongst clinicians due to the training, if someone has been qualified longer, their experience and wisdom over the years may determine the final decision on management. Equally, someone who is either younger, or more recently qualified, may be more up to date with current practices and best management procedures.

It was also important to establish the job title of the clinician, as certain professionals may deal with the same problem differently depending on their experience, training and role.

Furthermore, the questionnaire was designed to obtain details of specialisms, since there could be some disparity in management of OSD and glaucoma depending on the professional's expertise. Glaucoma consultants may be familiar with problems in their clinics already and perhaps have a better understanding of the role that OSD plays in glaucoma, than someone who specialises in oculoplastics, for example.

The glaucoma clinics you work in

To determine the most popular first line therapy amongst UK clinicians, a list of drugs was formulated with the Dudley NHS Trust Formulary and with reference to the review by Steven and colleagues (2018) for clinicians to select from. Since this list was not exhaustive of all drugs available to clinicians, an 'other' option was also added (Steven et al., 2018, Joint Formulary Committee, 2022).

Next, it was vital to determine who has their ocular surface assessed in practice. It is easy to overlook the ocular surface in a busy clinic, especially when patients do not necessarily present with ocular surface problems or complaints. It also provides an insight into current practices which may benefit from changing. For instance, someone may not be assessed for OSD routinely and symptoms may not be evident at this stage. However, if they are at risk of OSD, or are in pre-disposition to the disease, then later OSD problems may be avoided if they are put on PF medication to begin with, rather than waiting for the problems to present themselves. This would only be established in asymptomatic patients by assessment of the ocular surface.

Further to this, another question was added to get an idea of clinicians' thoughts on OSD prior to prescribing. The aim was to highlight if there is a certain attitude towards OSD in glaucoma clinics. If this view is negative, it may indicate the need for further education and training to raise awareness of the concomitant issue of OSD and glaucoma.

Thereafter, a question specific to the methodology of investigating the ocular surface was added. The aim of this question was to look at current clinical practices. Perhaps the ocular surface is not checked comprehensively enough, and maybe early signs of OSD are being missed. The list was taken from the TFOS DEWS II Diagnostic Methodology report for the main clinical techniques available for assessing the ocular surface (Wolffsohn et al., 2017). Again, an 'other' option was added since the list was limited to the most common techniques.

The next few questions focussed on patient education in glaucoma clinics. The first of which, was the education of drop instillation. This is an essential factor in compliance of medication, as patients can struggle with instilling drops especially if they have never had to use eye drops before. If they are unaware how to instil drops, not only is there a risk they may not be doing it right and so threatening the progression of glaucoma, but it will also affect their confidence in their carer for not providing all the information (Carpenter et al., 2016). This question was

included to see if all patients are taught about drop instillation, and if not, it raises the question as to why not.

Moreover, there is only so much information patients, or anyone for that matter, can take in from one conversation. The drop instillation technique would be better backed up by a leaflet. Tatham and colleagues (2013) reported that 80% of patients in their study were not educated about drop instillation, though this could be related to poor recall too (Tatham et al., 2013). Carpenter and colleagues (2016) found that the most common drop instillation education provided to patients was through verbal communication, which did not help to improve instillation techniques at future visits (Carpenter et al., 2016). As a result, an insight on whether written information is provided in clinics regarding the glaucoma drops would allow for an understanding on whether such patient education is adequate or whether improvements are to be made in this area.

The remaining two questions of this section were aimed at getting the clinician's view on the matter of OSD in glaucoma clinics. The first question sought to investigate the current prevalence of OSD in glaucoma clinics in the UK from the clinician's perspective. It was also included to investigate current awareness of OSD in glaucoma settings amongst clinicians. The other question aimed to investigate the proportion of patients prescribed ocular lubricants in the glaucoma clinics. As such, this was an indirect way of checking the prevalence of OSD in glaucoma clinics, since ocular lubricants will generally be prescribed to those suffering from dry eyes.

The use of preservative-free medicine in glaucoma

The final section concentrated on the use of PF eye drops in clinical practice. In order to understand whom clinicians would be inclined to prescribe PF ocular hypotensive drops to, a question was added in this section to evaluate the circumstances under which clinicians would consider PF medication. If future research was to identify patients at risk of DED who would benefit from PF drops from the very start of treatment, this may well change the approach in glaucoma management.

Next, the questionnaire looked at whether PF drops would be prescribed without the presence of OSD. This formed an important question, as there is much literature backing PF glaucoma medication over preserved medication as discussed in Chapters 1 and 2. The objective of this

question was to see if clinicians would still opt to prescribe preserved medication when there are no overt signs or symptoms of OSD present.

For clinicians who selected no to the previous question, the next one aimed to look at the reasons for this. Perhaps one of the most important questions in the survey, it was vital to establish the barriers deterring clinicians from prescribing PF drops.

Additionally, determining whether age was an important factor when prescribing PF medication was also of significance, since it is known that the incidence of DED increases with age (Moss et al., 2004). The inclusion of this question was to uncover prescribing patterns with regards to the age of the patient.

The last question was included to see if OSD is being picked up later in glaucoma clinics, perhaps after medication has been started. This would potentially highlight a link between glaucoma drops and the need for ocular lubricants. As a result, clinicians were asked to estimate the number of patients complaining from intolerance, allergy or discomfort from the hypotensive drops on follow up visits.

3.4 Results

The survey was distributed over a period of 8 weeks. A total of 62 responses were collected within this timeframe. An interim analysis was performed during this period, and the results of this were used to draft an abstract which was submitted to the UK and Eire Glaucoma Society (UKEGS). The abstract was accepted and the results of the survey were subsequently presented as a poster presentation at the UKEGS conference in 2019. Appendix 4 includes the abstract submitted to UKEGS, and Appendix 5 includes the poster presented at the UKEGS conference.

3.4.1 Survey Distribution and Responses

3.4.1.1 ‘About you’-Demographics of the survey

The majority of participants were 41-50 years old (40%), followed by 51-60 years old (26%) and then 31-40 years old (19%). Smaller numbers made up over 60-year-olds (11%) and 21-30 year olds (3%).

In terms of number of years qualified, the vast majority of participants had been qualified over 15 years (69%). Newly qualified clinicians (0-5 years qualified) formed a small percentage of the overall respondents at 6%. There were slightly more participants qualified 11-15 years (13%) and 6-10 years (11%).

Most participants were consultant ophthalmologists (79%). Optometrists made up a smaller percentage at 10%, followed by middle grade ophthalmologists (5%), trainee ophthalmologists (3%). The minority were nurse prescribers (2%) and 'other' (2%), which in this case was a specialist optometrist.

A large proportion of participants were glaucoma specialists (90%). Other responses making up 5% of the total were 'undecided', 'general ophthalmologist with interests in medical retina' and 'refractive surgery'. Few participants were corneal specialists (3%) and medical retina specialists (2%).

3.4.1.2 'The glaucoma clinics you work in'- The management of glaucoma and OSD

What is your first line treatment for Glaucoma/Ocular hypertension in a new patient? Please select your top 3 preferences in order from below.

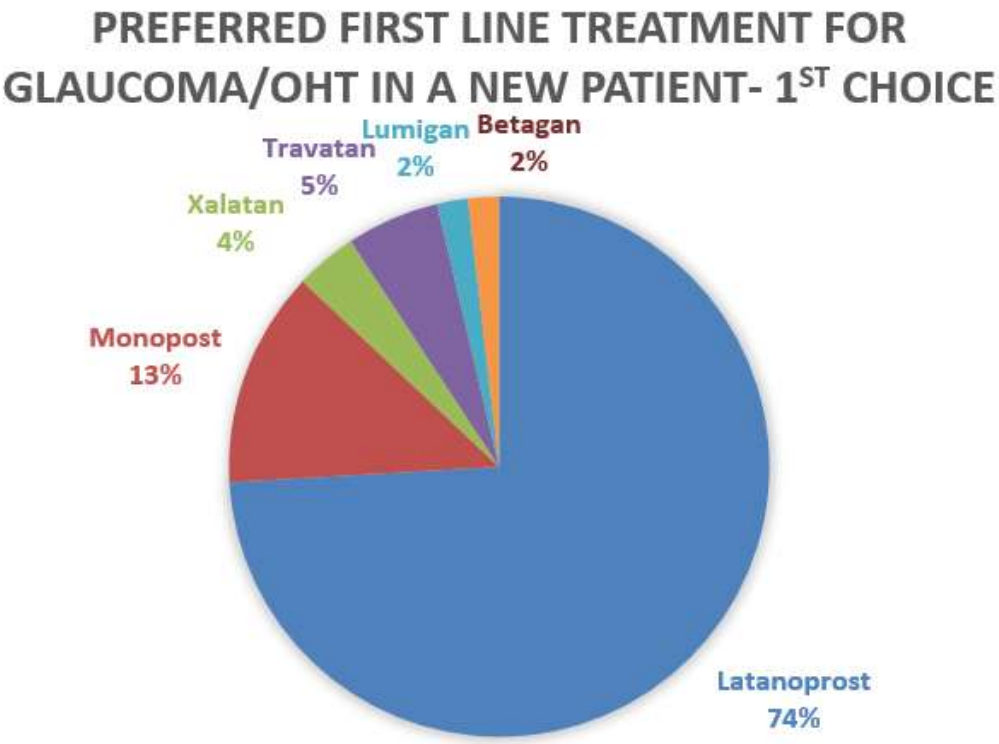


Figure 3.2: Preferred first line therapy: choice 1.

Fifty-four out of 62 participants responded to this question. The most popular choice in first line treatment was Latanoprost with 78% of participants favouring this drug overall. Xalatan is the brand name for Latanoprost, and it was suggested by one of the lead consultants at Russells Hall Hospital to add both options to the list so that participants could pick either the branded version or the generic version.

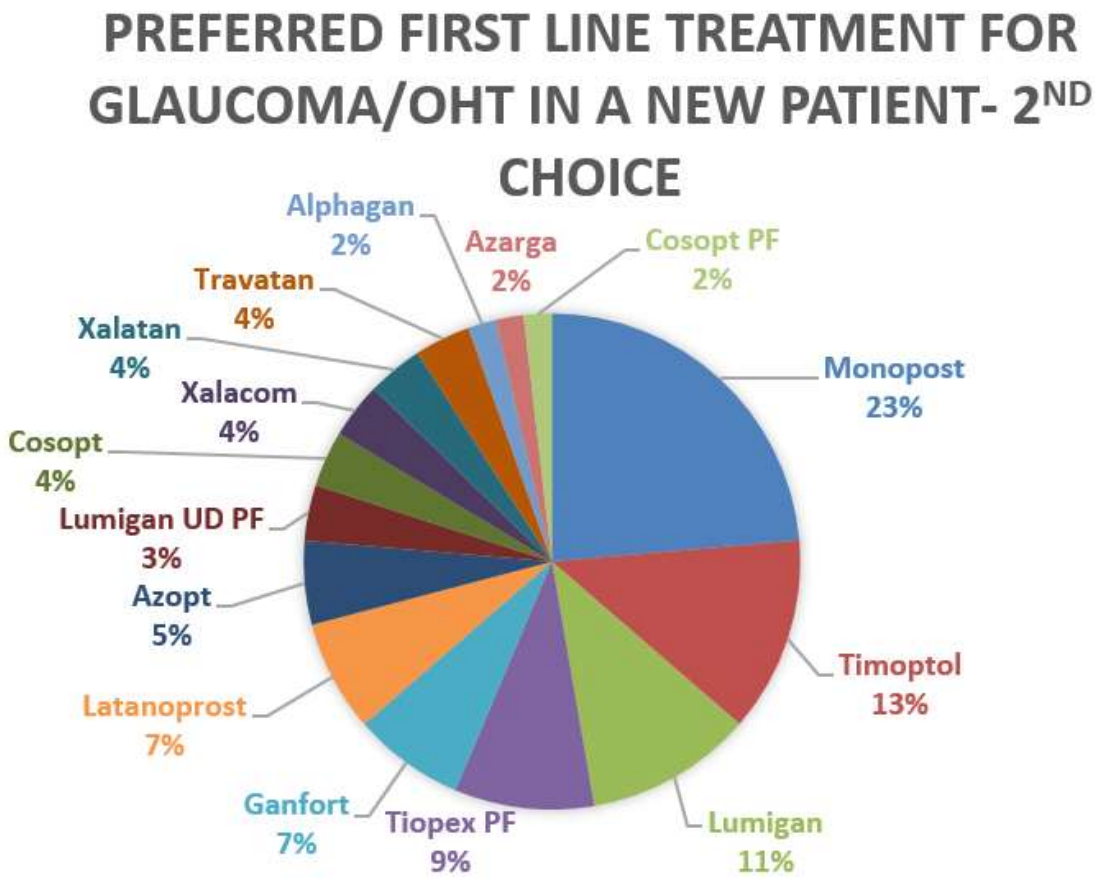


Figure 3.3: Preferred first line therapy: choice 2.

There was much more diversity in the second choice of first line treatment. Though Monopost was the preferred choice overall with 23% backing this, there was much more spread amongst clinicians for their 2nd option, than their 1st option. Timoptol followed with 13% and Lumigan with 11%, for overall preference.

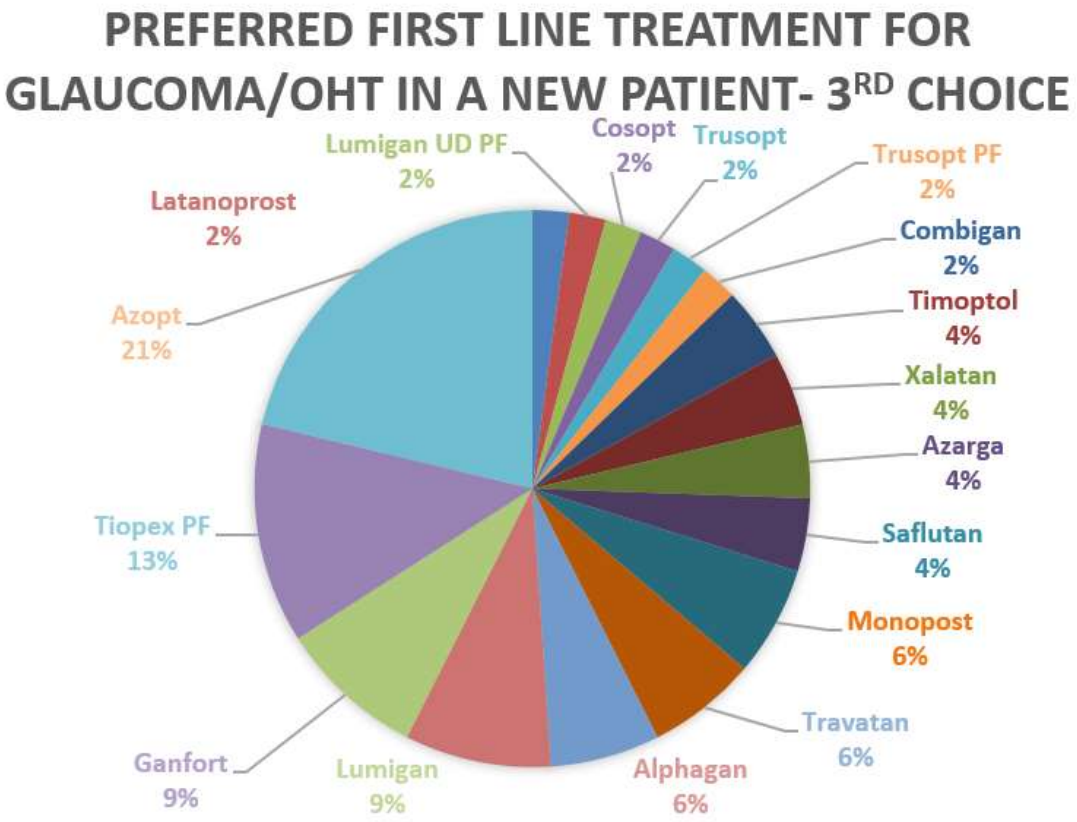
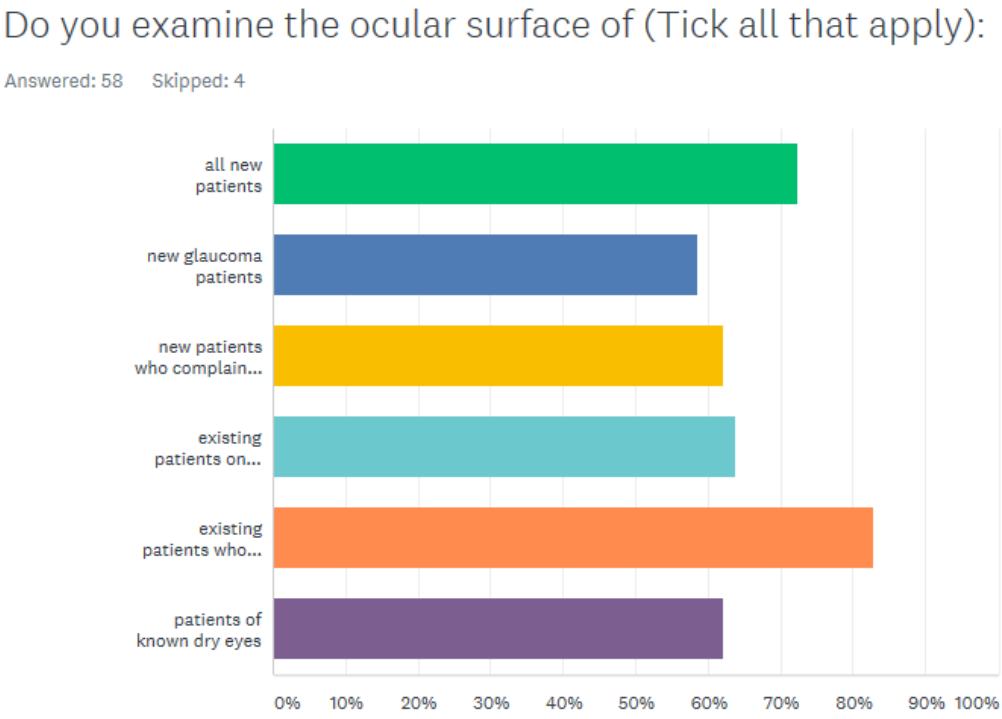


Figure 3.4: Preferred first line therapy: choice 3.

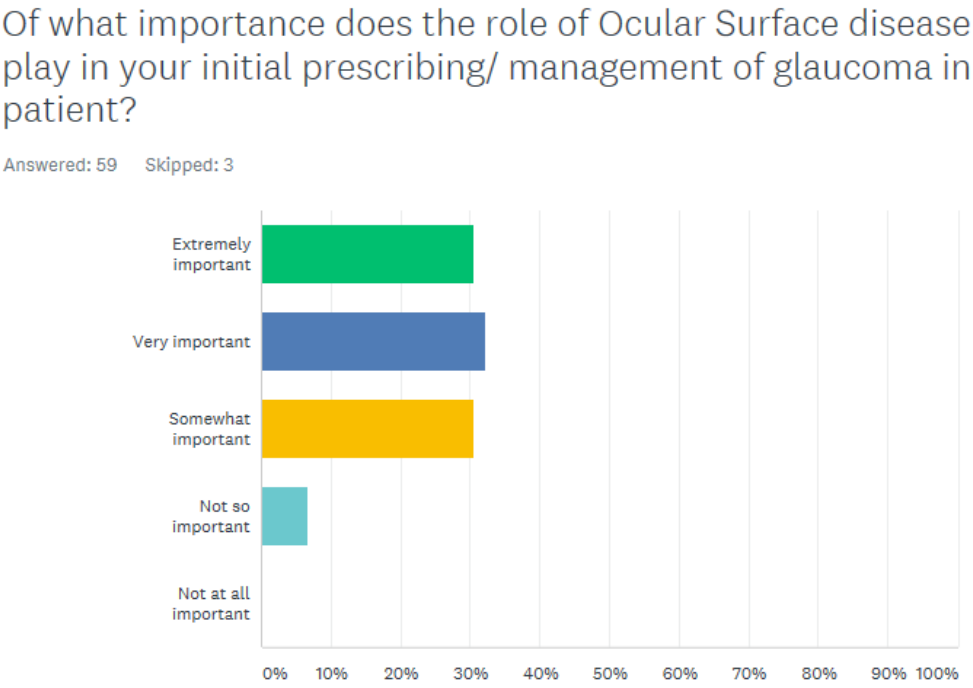
The third most popular choice of first line therapy was Azopt (21%), followed by Tiopex PF (13%). However, as with the second option, there was a lot of spread amongst clinicians as to their preferred choice for treatment option 3. The thirteen 'other' responses to this question were as follows: 10 participants commented that SLT should be the first line therapy for a new patient presenting with glaucoma or OHT, one response quoted 'observation or laser', another quoted 'generic latanoprost then generic timolol' and lastly, another quoted '3rd choice would be combination of latanoprost and brinzolamide'.



ANSWER CHOICES	RESPONSES	
all new patients	72.41%	42
new glaucoma patients	58.62%	34
new patients who complain of dryness symptoms	62.07%	36
existing patients on glaucoma drops	63.79%	37
existing patients who complain of dryness symptoms	82.76%	48
patients of known dry eyes	62.07%	36
Total Respondents: 58		

Figure 3.5: Ocular surface checks of patients.

According to the responses, clinicians mostly check the ocular surface of existing patients who complain of dryness symptoms (83%) and all new patients (72%).



ANSWER CHOICES	RESPONSES	
Extremely important	30.51%	18
Very important	32.20%	19
Somewhat important	30.51%	18
Not so important	6.78%	4
Not at all important	0.00%	0
TOTAL		59

Figure 3.6: How important is OSD in first time prescribing?

Ninety-three percent of clinicians felt that OSD plays an important part of initial prescribing, whether that is extremely important, very important or somewhat important. Only 7% of clinicians felt that OSD is not an important factor in first time prescribing.

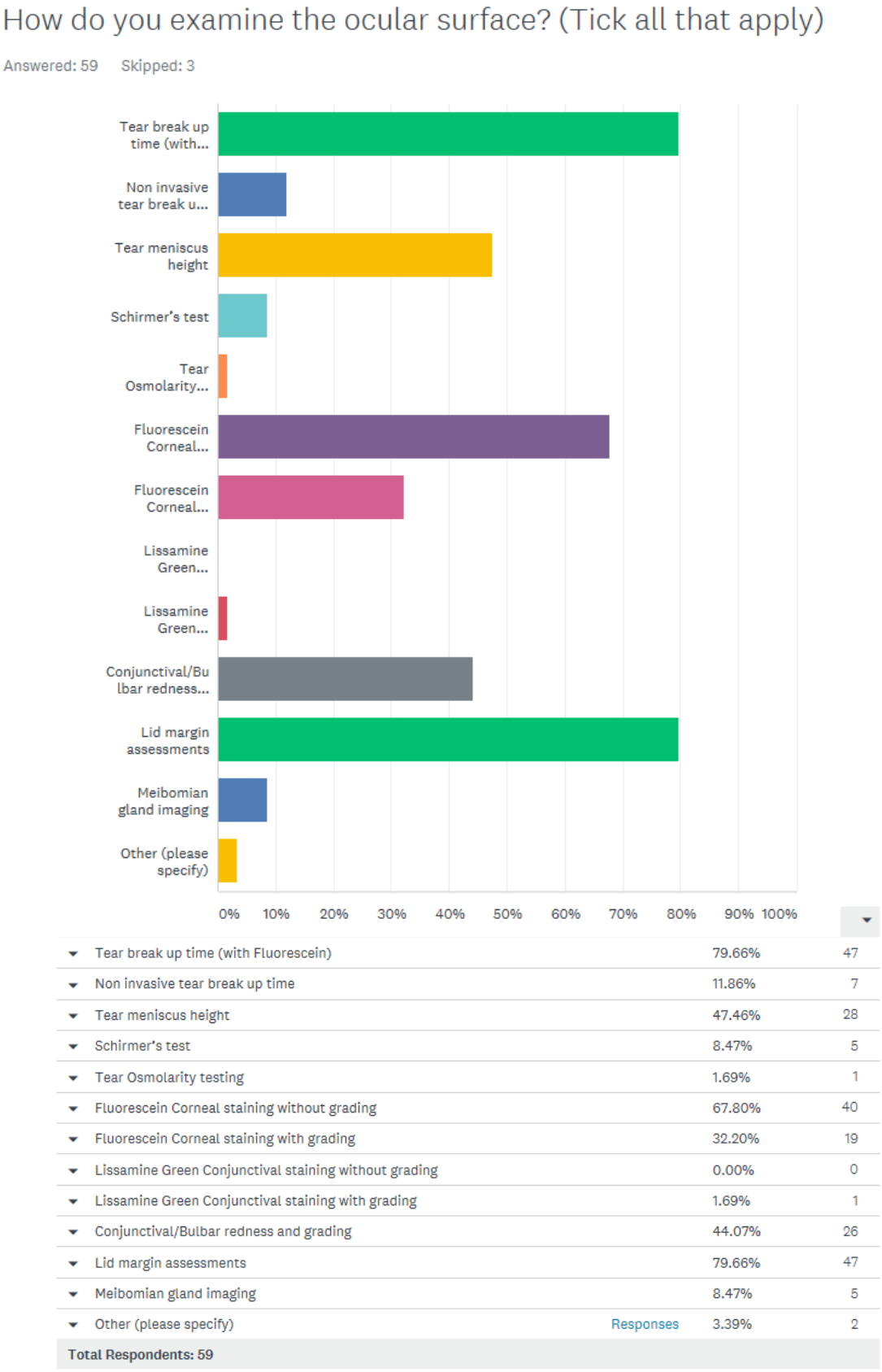
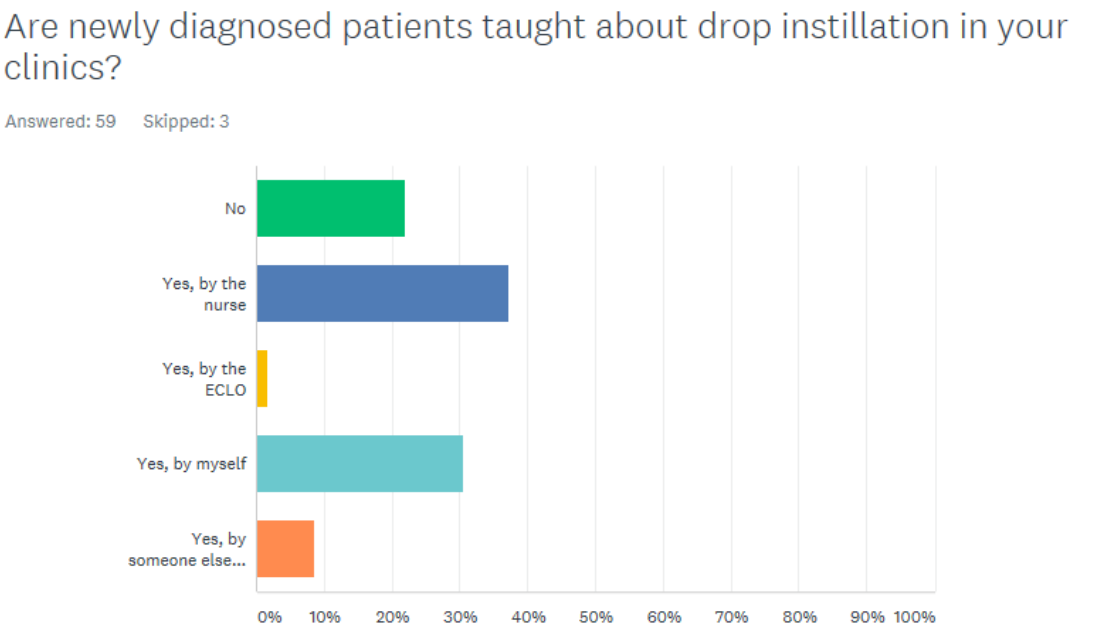


Figure 3.7: Assessment of ocular surface.

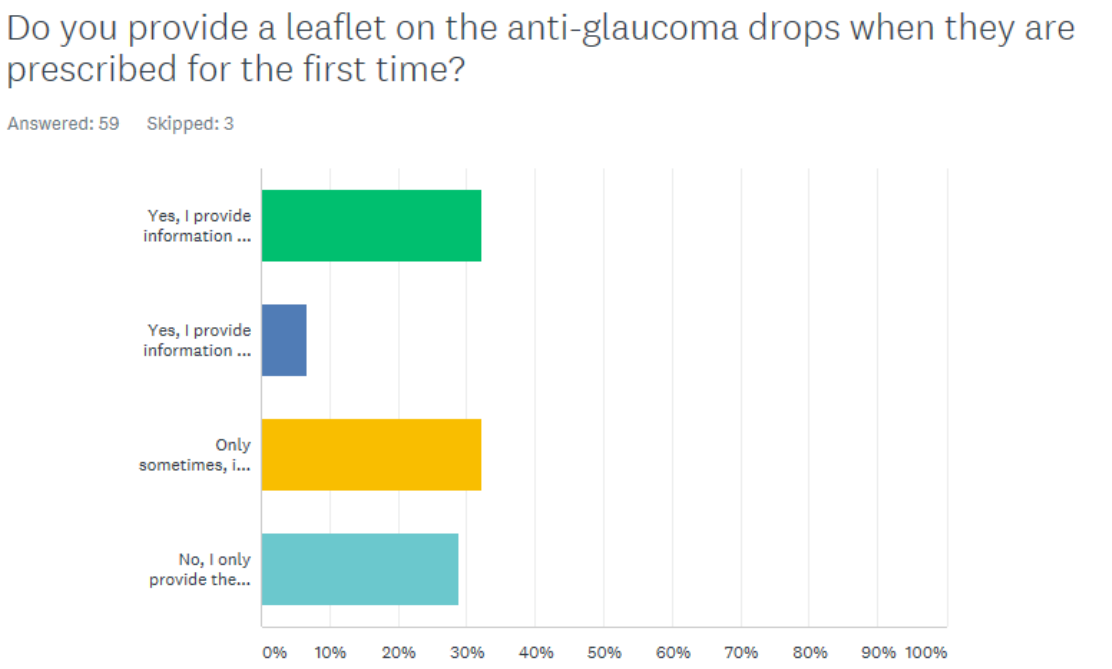
Tear break up time with fluorescein, lid margin assessments and fluorescein corneal staining without grading, were the most common ways clinicians checked the ocular surface (80%, 80% and 68%, respectively). Lissamine green staining and osmolarity testing appeared to be the least popular methods used to check the ocular surface. The respondents who selected other stated ‘fascial skin’ and ‘slit lamp’ as answers.



ANSWER CHOICES		RESPONSES	
No		22.03%	13
Yes, by the nurse		37.29%	22
Yes, by the ECLO		1.69%	1
Yes, by myself		30.51%	18
Yes, by someone else (please specify)	Responses	8.47%	5
TOTAL			59

Figure 3.8: Drop instillation education.

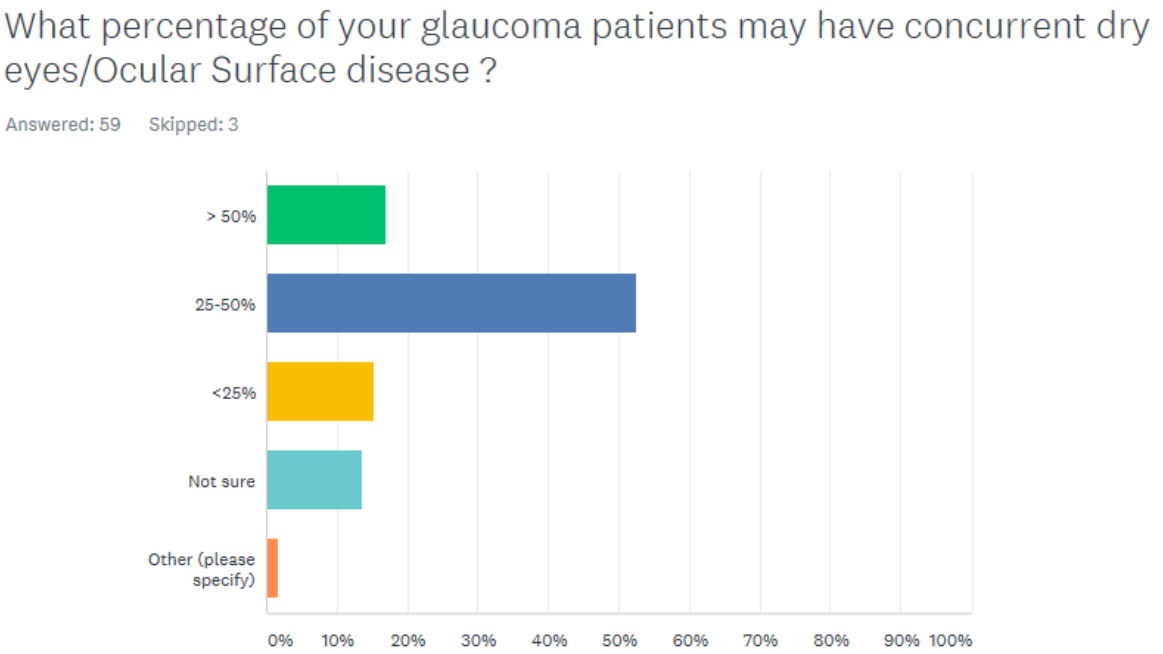
It appears that the majority of patients are taught about drop instillation technique either by the nurse (37%) or by the clinician themselves (31%). However, 22% of patients are not taught how to instil their eye drops. Five respondents stated that the drop instillation education was provided by ‘someone else’. Their answers were as follows: ‘prescribing clinician’, ‘technician’, ‘shared care optometrist’, ‘by the optometrist who sees them’ and ‘pharmacy’.



ANSWER CHOICES	RESPONSES	
Yes, I provide information on the drops and how to instill them	32.20%	19
Yes, I provide information on the drops, how to instill them and how often to instill them	6.78%	4
Only sometimes, if one is available	32.20%	19
No, I only provide the prescription to obtain the drops	28.81%	17
TOTAL		59

Figure 3.9: Issuing of leaflets on eye drops.

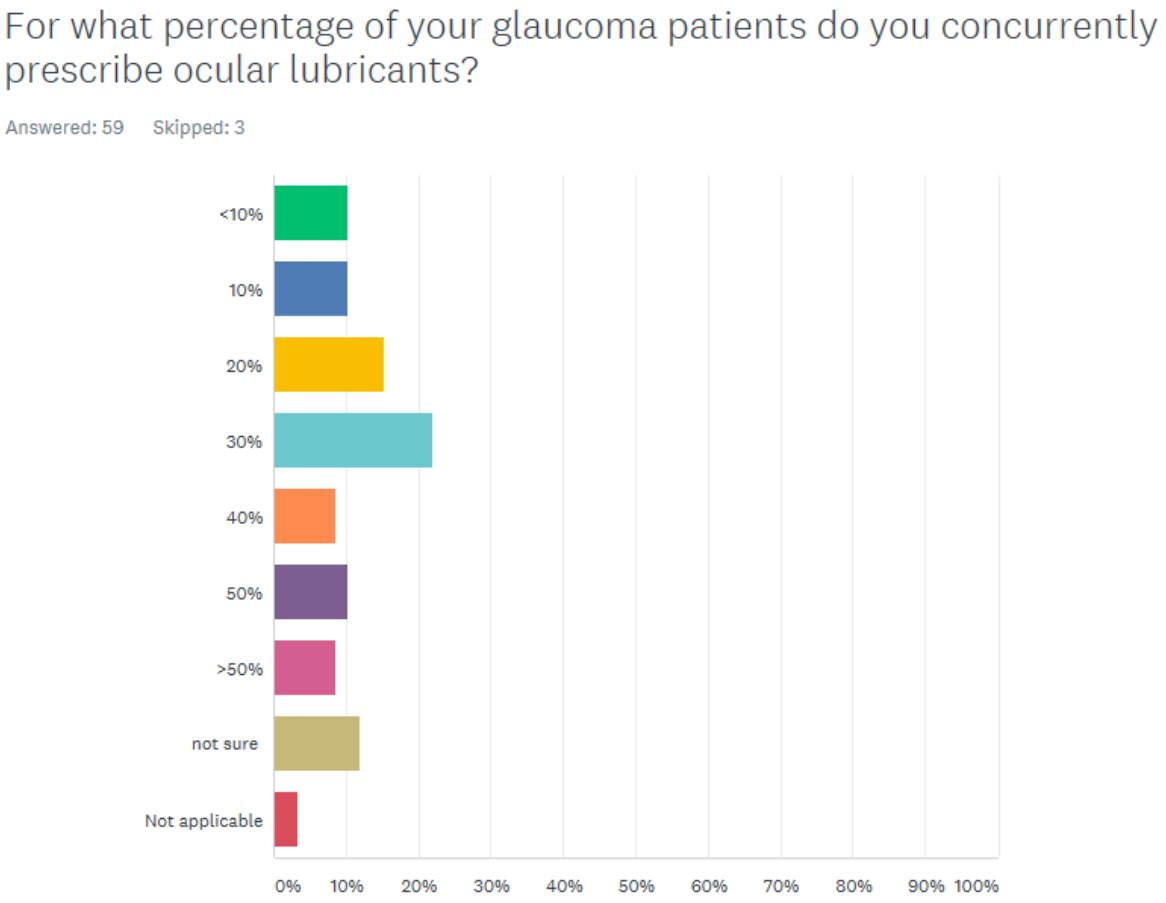
Thirty-two percent of clinicians provide information on the drops and how to instil them. However, only 7% provide additional information to patients in terms of how often to instil their drops. A large proportion of clinicians do not provide any information at all, or only if a leaflet is available (61%).



ANSWER CHOICES		RESPONSES	
> 50%		16.95%	10
25-50%		52.54%	31
<25%		15.25%	9
Not sure		13.56%	8
Other (please specify)	Responses	1.69%	1
TOTAL			5

Figure 3.10: Concurrent dry eye in glaucoma clinics.

Fifty-three percent of clinicians stated that 25-50% of their patients may have concurrent dry eyes or OSD. The only ‘other’ respondent stated that ‘no one knows’ the answer to this. Of those who answered this question, 17% did think the prevalence of dry eyes in their clinics is more than 50%, though the remainder thought it was much less (15%) or were not entirely sure (14%).

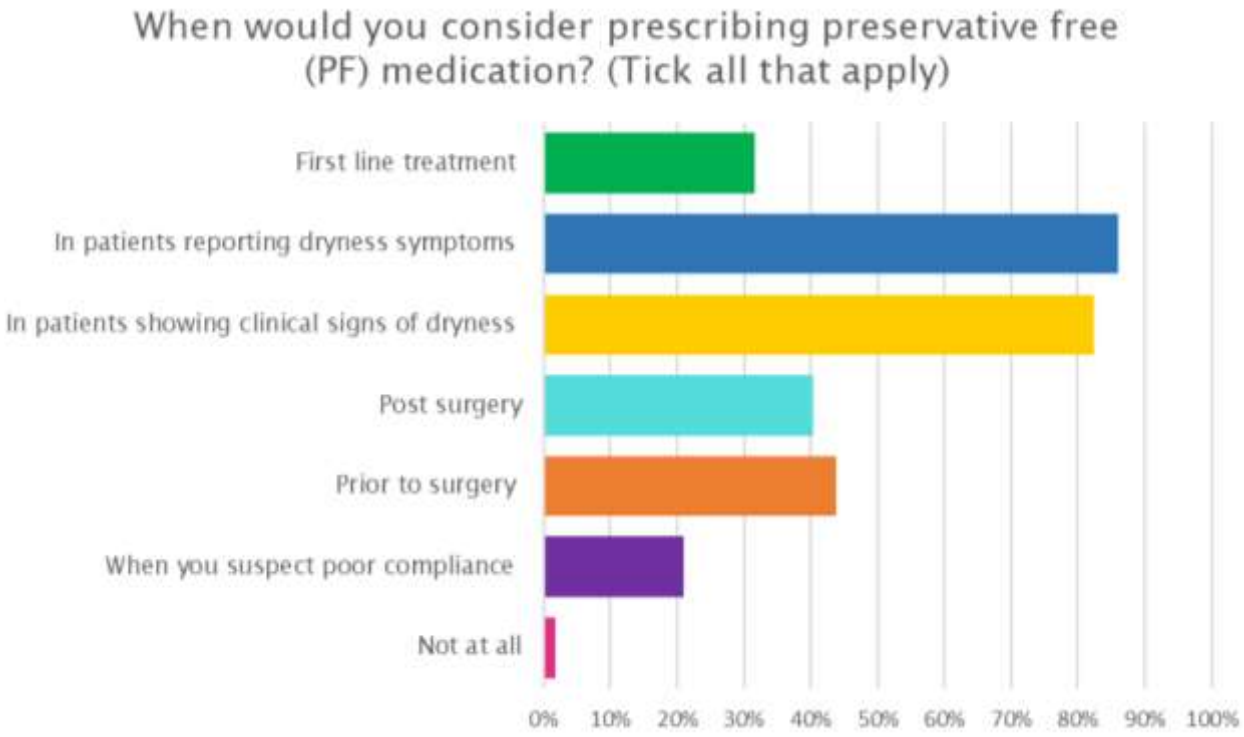


ANSWER CHOICES	RESPONSES	
<10%	10.17%	6
10%	10.17%	6
20%	15.25%	9
30%	22.03%	13
40%	8.47%	5
50%	10.17%	6
>50%	8.47%	5
not sure	11.86%	7
Not applicable	3.39%	2
TOTAL		59

Figure 3.11: Prescription of ocular lubricants.

There was a broad spread of responses, with a small majority (22%) of clinicians concurrently prescribing ocular lubricants to 30% of their patients. The prescribing of ocular lubricants amongst clinicians appears to be widely distributed.

3.4.1.3 'The use of preservative-free medicine in glaucoma'- Approaches and attitudes to PF medication



ANSWER CHOICES	RESPONSES	
First line treatment	31.58%	18
In patients reporting dryness symptoms	85.96%	49
In patients showing clinical signs of dryness	82.46%	47
Post surgery	40.35%	23
Prior to surgery	43.86%	25
When you suspect poor compliance	21.05%	12
Not at all	1.75%	1
Total Respondents: 57		

Figure 3.12: Prescription of PF medication.

The majority of clinicians would opt to prescribe PF drops in cases where there are either signs (82%) or symptoms (86%) of DED present. Prior to and post-surgery were the next most common reasons to prescribe PF drops. One respondent felt there was never a need to prescribe PF drops.

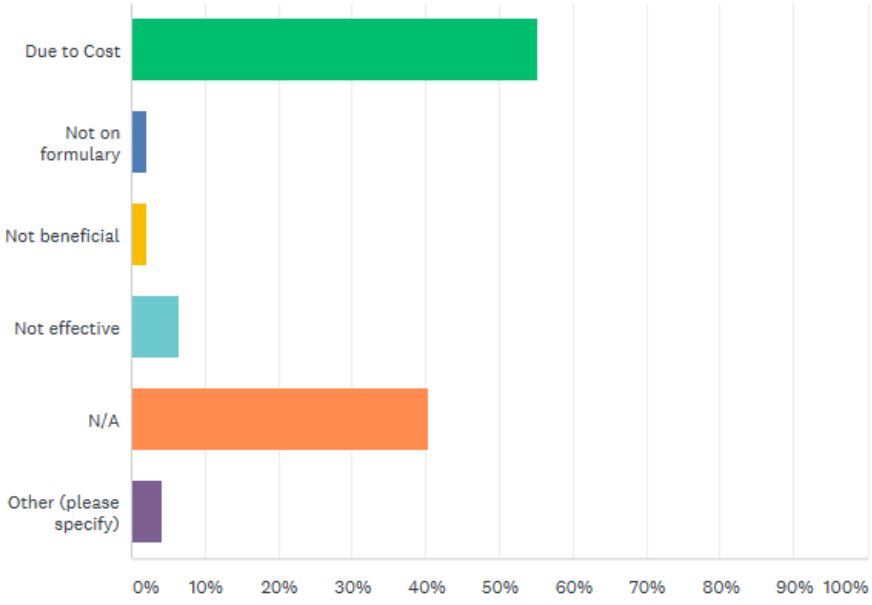
Would you consider PF drops in a patient without Ocular surface disease?

Answered: 57 Skipped: 5

Fifty-seven participants answered this question. Of the total responses, 56% said they would consider PF drops in a patient without OSD.

If no, why not? (Tick all that apply)

Answered: 47 Skipped: 15



ANSWER CHOICES		RESPONSES	
Due to Cost		55.32%	26
Not on formulary		2.13%	1
Not beneficial		2.13%	1
Not effective		6.38%	3
N/A		40.43%	19
Other (please specify)	Responses	4.26%	2
Total Respondents: 47			

Figure 3.13: Reasons for not prescribing PF.

The leading reason as to what would deter clinicians from prescribing PF drops without OSD present was cost (55%). Forty percent of respondents felt this was not applicable to them. The two individual 'other' responses stated that it is 'rarely appropriate' or 'rarely reported by patients' to require PF drops in such a situation.

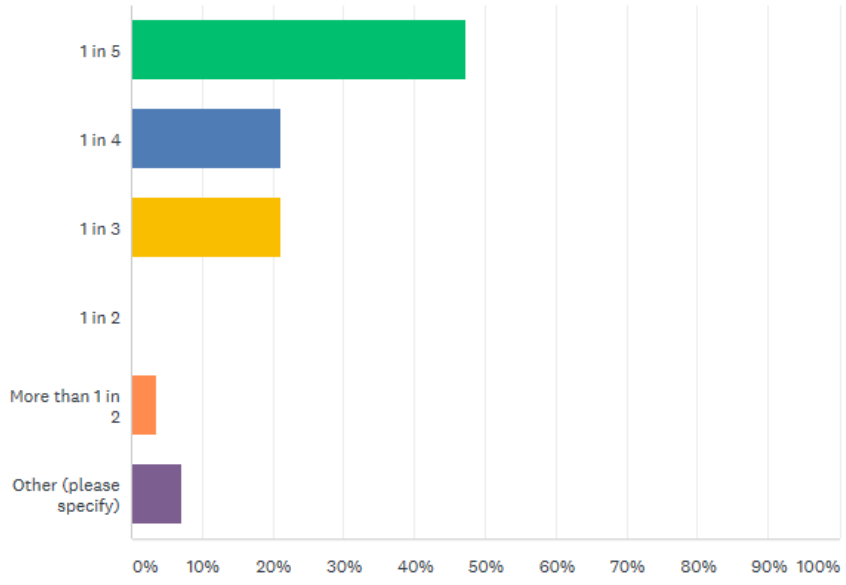
Do you consider age an important factor when prescribing PF medication?

Answered: 57 Skipped: 5

Most clinicians (56%) felt age is not important when prescribing PF medication, whilst 44% of clinicians felt that age does play an important part.

Roughly how many of your patients on average complain of intolerance/allergy/discomfort to drops on a follow up appointment?

Answered: 57 Skipped: 5



ANSWER CHOICES		RESPONSES	
1 in 5		47.37%	27
1 in 4		21.05%	12
1 in 3		21.05%	12
1 in 2		0.00%	0
More than 1 in 2		3.51%	2
Other (please specify)	Responses	7.02%	4
TOTAL			57

Figure 3.14: Intolerance on follow up.

Most clinicians (47%) are finding that at least 1 out of 5 patients complain of ocular discomfort symptoms at follow up appointments. Forty-two percent of clinicians find that 1 in 4 or 1 in 3 patients are symptomatic at follow up appointments. The ‘other’ responses were as follows: 1 in 10, less than 10%, less than 1 in 5 and 1 in 15.

3.4.1.4 Filtered Results

The data obtained from the survey was then filtered to provide a more in-depth analysis of the responses. Filters were applied to see what approaches in clinics were taken by different groups of responders. The results of such filters are described in the following section.

Group 1: Respondents who selected Latanoprost as their first choice for first line therapy

Of those that selected latanoprost as their first choice in the first line therapy of glaucoma or OHT, 65% thought that OSD was either extremely important or very important in first time prescribing, with an additional 28% classing it as 'somewhat important'. Eight percent thought it was not so important.

Fifty percent of this group of respondents felt that 25-50% of their patients may have concurrent OSD whilst 15% thought coexisting dry eyes was probably present in more than 50% of their patients. Thirty-five percent thought either it was common in less 25% of their patients, or they were unsure.

Twenty-five percent of this group of clinicians also stated that 30% of their patients are concurrently prescribed ocular lubricants. Twenty-eight percent stated that 40% to over 50% of patients were concurrently prescribed lubricating drops. Thirteen percent of clinicians were unsure of how often they prescribe ocular lubricants in their clinics.

Group 2: Respondents who did not think that OSD is important in first time prescribing of drops

For this group, information on the glaucoma drops was never issued, only the prescription was handed to the patients. The ocular surface was checked in all existing patients who complain of dryness symptoms, in 67% of new patients complaining of dryness issues, and in 33% of existing patients on glaucoma drops.

In terms of awareness of concurrent OSD being present in glaucoma patients, 25% felt this was in less than 25% of patients whereas the remainder were not sure.

Group 3: Respondents who have been qualified 0-5 years

In this group, 67% of clinicians checked the ocular surface of all new patients. The ocular surface was also checked in patients of known dry eyes (33%), existing patients on glaucoma

drops (33%) and existing patients complaining of dryness symptoms (33%).
Sixty-seven percent of this group felt OSD was ‘extremely important’ in initial prescribing, and 33% thought it was ‘somewhat important’.

100% of these clinicians teach their patients about drop instillation themselves.

Also in this group, 50% were optometrists, 25% nurse practitioners and 25% trainee ophthalmologists.

Group 3: Respondents who have been qualified over 15 years
This group consisted of 91% consultant ophthalmologists, 2% middle grade ophthalmologists, 5% optometrists and 2% specialist optometrists.

Of these, 62% think that OSD plays an ‘extremely important’ or a ‘very important’ part in initial prescribing in a new patient. Twenty-eight percent thought that it is ‘somewhat important’, while the remaining 10% thought it is not so important.

In terms of drop instillation, 29% of clinicians do not teach newly diagnosed patients how to administer them. Thirty-six percent delegate the teaching to nurses, 2% delegate to the ECLO (Eye Clinic Liaison Officer) and 21% teach patients themselves. The remainder of clinicians delegate this task to others (pharmacist, optometrists, technician, shared care optometrist and to the prescribing clinician).

3.5 Discussion

The aim of this study was to investigate current clinical approaches to OSD in glaucoma clinics in the UK. Much of the present and previous literature looking at OSD in glaucoma has been from a ‘signs or symptoms’ perspective or modelled at a cellular level (as described in Chapters 1 and 2). There does not appear to be any literature available at present, investigating the prevalence of OSD in glaucoma from a clinician’s point of view, with emphasis on the current clinical practice, through the use of a survey. Thus, the current study aims to highlight issues that may previously have been overlooked.

Ninety-three percent of clinicians feel that OSD is important to some extent, but preserved latanoprost was still the most preferred choice for first line therapy. In fact, 85% of the first choice in first line therapy was some form of a PGA. The results of this seem to be in line with

NICE guidelines, recommending PGAs primarily due to their efficacy and safety (National Institute for Health and Care Excellence, 2017). There is much more variation in second and third choices of first line therapy, and the preferred drugs are much more diverse amongst clinicians. Though PGAs seem to be the preferred choice for glaucoma and OHT treatment, when given the option to look at alternatives, clinicians are more likely to consider PF options. It appears that PF drops are considered by clinicians, but maybe not in the first instance.

Those who preferred latanoprost as their first choice in the first line therapy of glaucoma and OHT treatment did have an awareness of the issues of OSD within their clinics. This can be demonstrated by the filtered analysis, which revealed that 50% of such clinicians felt that 25-50% of their patients may have OSD as well as glaucoma, and 53% of the clinicians in this sub-group concurrently prescribe ocular lubricants in 30% to over 50% of their patients.

It should be noted that SLT was a popular suggestion in the 'other' comments for first line therapy. Many felt it should be considered as first choice in the treatment of glaucoma and OHT. In current literature, SLT has been shown to be as effective as latanoprost in reducing IOPs (McIlraith et al., 2006). This is a viable option and one to be considered in wider practice, especially in patients where compliance and intolerance to drops is an issue, or where large diurnal fluctuations may deteriorate the glaucoma (Asrani et al., 2000). Since this survey was distributed and analysed, NICE guidelines have amended their recommendations to reflect SLT as a primary option to those patients requiring intervention for Chronic Open Angle Glaucoma (COAG) and OHT (National Institute for Health and Care Excellence, 2017).

In terms of checking the ocular surface, corneal staining with fluorescein, lid assessments and tear break up time (TBUT) were the methods most commonly employed in clinics. Goldmann application tonometry (GAT) is widely used in glaucoma clinics to check the IOPs, for which fluorescein instillation is essential (Cook et al., 2012). Thus, it appears to be practical to check the ocular surface at the same time, with the fluorescein in place. However, though staining is checked, it is not graded by all clinicians. It would be beneficial to record the amount of staining for comparative reasons both across time, and between consultants, to monitor the ocular surface in the course of the treatment journey. Generally, the ocular surface of most patients appears to be checked in clinics, though there is some bias towards existing patients who complain of dryness symptoms.

There is also a difference in prescribing patterns depending on 'number of years qualified'. Those who were more newly qualified (0-5 years), tended to be more aware of the problem of

OSD in glaucoma. Sixty-seven percent of the newly qualified clinicians felt OSD played an ‘extremely important’ role in first time prescribing, whereas the rest felt it was ‘somewhat important’. No newly qualified respondent felt OSD was of no importance in first time prescribing.

The clinicians who were more than 15 years qualified also generally agreed there was some importance of OSD in initial prescribing. However, a small proportion (10%), felt it was not so important.

Such differences can be further reflected in drop education questions. The newly qualified clinicians teach their patients about drop instillation themselves, one hundred percent of the time. Whereas for the clinicians qualified over 15 years, the task tended to be delegated to the nurse in the majority of cases (36%). Astonishingly, 29% of clinicians in the longer qualified group, do not educate their patients about drop administration at all, be that by themselves or by delegation.

It is also interesting that those who fall into the ‘newly qualified’ group are all either trainee ophthalmologists, optometrists or nurse prescribers, whereas 91% of those qualified for more than 15 years are consultant ophthalmologists. This highlights the different perspectives amongst clinicians, depending on job roles within ophthalmology.

Good practice would be to issue leaflets at the first diagnosis of glaucoma, particularly as forgetfulness tends to be a recurring reason for poor adherence (Lacey et al., 2009). Thirty-two percent of clinicians provide information on the drops and how to instil them, but only 7% provide further detail as to how often to instil them. A large number of clinicians do not provide any information at all (29%), with the remainder only providing information if it is available to hand. This emphasises the inconsistencies within care; there will be some patients better educated on drop administration and regime, which will in turn allow for better glaucoma management, compared to others who are under those clinicians who do not deem such patient education necessary, or where it is overlooked in busy clinics.

Glaucoma and OSD positively correlate with age (Stapleton et al., 2017, Le et al., 2003). It is surprising to see then, that the majority of clinicians (56%) do not feel that age plays a factor when prescribing PF treatment. Of course, the risk of OSD should play a role across all ages, but particularly in those at a heightened risk through their age. Extra care should be taken in

older patients as they have an increased chance of having OSD. If they can be prescribed PF drops sooner, before symptoms arise, then future problems could be avoided.

By filtering the respondents who did not feel that OSD is important in first time prescribing, a certain attitude towards OSD in glaucoma can be seen. None of this group provides any written pamphlets on first time prescribing. Also, this group checks the ocular surface mainly of existing patients who complain of dryness symptoms (100%) and new glaucoma patients with complaints of dry eyes (67%). Only 33% checked the ocular surface of existing patients already on glaucoma drops. No clinicians in this group checked the ocular surface of all new patients coming into the clinic. There is a need to change such perspectives in practice and raise awareness of long-term problems associated with a poor ocular surface within the realm of glaucoma management.

Referring to the total responses, 47% of clinicians state that at least one in five of their follow up patients complain of some discomfort or intolerance to drops. The remainder stated that more than one in five patients had complaints on follow up (46%), and only 7% thought this occurred less than in 1 in 5 patients. The presence of non-tolerance appears to be common in glaucoma clinics. Perhaps this would occur less often if PF drops were issued sooner, especially in those groups of patients at risk of OSD, to prevent potential forthcoming problems.

Though this study has highlighted some novel insights into the prescribing patterns and attitudes in UK glaucoma clinics, it does have its limitations. The main limitation of this study is the small sample size. Although the data provides some good understanding into the approaches currently employed in UK clinics, a large-scale survey involving clinicians from various NHS trusts would allow for statistically significant conclusions to be drawn.

Future studies could investigate current clinical approaches in different NHS trusts, to explore the disparities and similarities in prescribing habits and clinical methods amongst clinicians in differing hospitals. Other design improvements could consider the volume of glaucoma and OHT patients seen by the clinician, to reflect if such variable influences management. It would also be useful to add the option of a dry eye questionnaire such as DEQ-5 (5-Item Dry Eye Questionnaire) or OSDI (Ocular Surface Disease Index) for assessments, to see if such a tool is used in glaucoma clinics to assess symptomatic OSD, and whether those clinicians using this routinely, are more aware of dry eye problems within their clinics.

Nonetheless, the limitations do not detract from the results of the current study, which give a unique insight into the management of OSD in glaucoma, from a clinician's perspective.

3.6 Conclusion

There appears to be widespread knowledge that OSD and glaucoma are linked and often appear simultaneously in glaucoma clinics. However, the extent of this knowledge is not consistent amongst clinicians of different roles and different ages. There is a lack of uniformity amongst clinicians when it comes to management, both in terms of therapy as well as patient education. There is a need to raise awareness of the problem of OSD within glaucoma amongst clinicians. Changes in the approaches to managing OSD in glaucoma clinics could potentially evade problems later on such as intolerance, frequent drop changes, more frequent visits to the eye clinic, adherence issues and unnecessary surgery. Although cost is the main reason for avoiding PF drops as first line therapy, it is important to investigate the potential savings in the long term by choosing PF therapy to begin with, which could evade ocular surface problems in susceptible patients. It would be interesting to see if there are any predicting factors of OSD in treated glaucoma patients; 'at risk' patients could then be screened and put on PF free drops at point of diagnosis.

Furthermore, with the insights obtained from clinicians as part of the current survey, it would be of great interest to see how such attitudes and prescribing habits reflect in the glaucoma clinics. Conducting a survey in a similar manner but addressing patients instead to get their perspectives on patient education, symptoms of OSD and drop instillation techniques, would help to provide a fuller picture of the multifaceted issue of OSD within glaucoma for both patients and their clinicians.

Chapter 4

Patient survey investigating adherence to glaucoma treatment

4.1 Introduction

Adherence has been described as the action of a patient taking their medication just as it has been prescribed (Schwartz and Quigley, 2008). A patient who is compliant is one who takes their medication exactly as has been advised by their health care professional. Though adherence and compliance are frequently and interchangeably used in medical settings these days, the terms have both been criticised for their lack of consideration of a patient's contribution to their medical management, as well as creating a stigma for these patients and subsequently affecting patient-healthcare provider relationships (Osterberg and Blaschke, 2005, Steiner and Earnest, 2000). It has been suggested that these facile terms be replaced by a more holistic definition, with more emphasis on description and analysis of individuals, to fully understand and change the behaviours of patients (Steiner and Earnest, 2000).

Though it may not be ideal to class patient compliant behaviour as adherence, it is a term which is universally understood and widely used in the literature. For this reason, it has been used in this study when investigating patient behaviours. However, a holistic and open-minded approach has been taken in this study to dismiss the negativities associated with the term. Recently, the term adherence has been accepted over compliance as it assumes a partnership between the patient and physician when it comes to treatment. On the other hand, compliance assumes that patients passively follow orders given by their physician (Robin and Muir, 2019, Brown and Bussell, 2011). Since both of these terms are used in current literature, both are referred to in the present study.

Adherence to glaucoma treatment is a topical issue and one that is heavily discussed in current literature (Friedman et al., 2007, Tsai et al., 2003, Olthoff et al., 2005, Cate et al., 2014, Rotchford and Murphy, 1998, Norell and Granström, 1980). As glaucoma can be a symptomless condition on the whole, particularly in its early stages, it is vital that hypotensive drops are taken regimentally by patients as to prevent progression of a blinding eye disease. However, as patients do not feel or see any immediate benefit from taking topical pharmacotherapy, there is a risk of poor adherence.

Tsai and colleagues (2003) developed a systematic approach to classifying barriers experienced by patients to adhering to their glaucoma medication. These were grouped into situational/environmental factors, medication regime, patient factors and health factors. This study was the first of its kind in addressing the issues into a taxonomy-based system. Forgetfulness, complexity of treatment regime and side effects were just a few of the reasons

patients missed instilling their drops (Tsai et al., 2003). It is clear that non-adherence is a complex and multifactorial area, and patients cannot simply be pigeonholed into singular reasons for non-adherence.

Hahn (2009) proposed a 4-step assessment of adherence through an interview process with patients. The objective of such was to engage patients in their glaucoma management and follow the 'ask-tell-ask' practice to decipher the patient's understanding and misunderstanding of their condition and medication, as well as allowing the healthcare professional to address any misconceptions (Back et al., 2005, Hahn, 2009). Such patient-centred communication is regarded crucial in glaucoma care, as patients want to please their physician and be seen as a 'good' patient, and so may not reveal the true extent of their non-adherence (Hahn, 2009).

Poor adherence has been discussed in various medical fields and 'physician pleasing' appears to be a common problem. For instance, Simmons and colleagues (2000), found that 30 out of 101 patients activated their inhalers in excess of 100 times within a 3-hour window prior to being reviewed by a clinician, in their study looking at subject characteristics of predictive value for such inhaler 'dumping'(Simmons et al., 2000). Similarly, in a hypertensive study of patients believed to be treatment resistant, a significant improvement occurred in blood pressure by month 2, returning to normal levels in one third of patients, once an electronic monitoring system was deployed (Burnier et al., 2001). Such is also the case in glaucoma treatment. It appears that patients like to be perceived as obedient by their healthcare professionals and often disguise poor compliance.

4.1.1 Measuring adherence

The percentage of patients demonstrating non-adherence to glaucoma medication ranges from ~5% to 80%. Such variance can be attributed to the differing methods used to assess adherence, as well as what individual studies class as non-adherence (Olthoff et al., 2005). One of the most common methods used for measuring deviations by patients to prescribed procedures is through the use of questionnaires. An example of such is by Welge-Lussen and colleagues (2015), who used two questionnaires across a timescale of two months to assess knowledge of glaucoma, refill of medication and instances of missed drops. They found that forgetfulness, inattentiveness and multiple daily drops were the top three reasons for missing doses. However, overall, no significant association was found between glaucoma knowledge, demographic data or clinical characteristics and the likelihood of non-adherence (Welge-Lussen et al., 2015).

The problem with such questionnaire-based assessments is the potential of misreporting by patients who may give presumed right answers rather than honest answers. In this particular study, the second questionnaire at month two happened to fall around the time of most patients' follow up appointments with their ophthalmologist. As found by Kass and colleagues (1986), patients are likely to be more adherent prior to their follow up appointments, which could inevitably have influenced the results of the second questionnaire (Kass et al., 1986). Patients were also selected from a university hospital, with 90% having a sound knowledge of their condition. This may not be entirely representative of the wider population of glaucoma patients, and may demonstrate why there was such a weak correlation between knowledge of glaucoma and non-adherence (Welge-Lussen et al., 2015).

Similarly, other self-reporting methods such as the use of diaries and interviews have also shown to overestimate adherence levels. Djafari and colleagues (2009) found a subjective adherence of 88.3% according to patients who were interviewed about their drops, the number of missed doses and knowledge about their condition. Such levels were not resonated by drug database analysis and physician reported adherence, which were 71.8% and 74.6%, respectively (Djafari et al., 2009). Overall, adherence seemed to be much higher in this study compared to others, which could be explained due to the retrospective nature of drug dispensary data, coupled with participants who have been on long-term glaucoma treatment.

Due to the great variance in quantifiable data from adherence studies, many have opted to look at more objective methods to assess compliance. Electronic monitoring devices have become a popular addition to the traditional questionnaires and interviews in such studies. An example of such device is the Travatan® dosing aid by Alcon, which administers travoprost drops to patients. The bottle fits within the device and a lever is pressed to allow drop instillation. The device uses a microchip to record the date and time each time the lever is depressed (Okeke et al., 2009b).

Okeke and colleagues (2009) used this device to conduct a two-phase study. The initial phase consisted of measuring adherence in individuals using travaprost with the dosing aid (DA), whilst the second phase focussed on improving adherence in those with poor compliance in phase one. The initial phase was conducted in conjunction with a patient questionnaire, a depression survey and an independent assessment by the physician (Okeke et al., 2009b).

They found an adherence level of 71% using the DA calculation, which was similar to the physician-based estimate of 77%. Patients were still found to overestimate adherence, even

with the monitoring device employed in this study of which they were aware of, with a rate of 95%. The correlation between the DA and physician estimate, and between the DA and patient reported adherence, was poor overall. This suggests that physicians are unable to accurately identify adherent patients from non-adherent patients (Okeke et al., 2009b).

The DA was found to be quite accurate on the whole, with adherence figures reflecting findings from previous studies such as that by Kass and colleagues (1986), who investigated compliance to topical pilocarpine using an eye drop monitoring device and found adherence levels of 76.0±24.3%. Similar to the Okeke and colleagues' (2009) study, patient reported figures were about 20% higher in this study, at 97.1±5.9% (Kass et al., 1986, Okeke et al., 2009b).

Kass and colleagues (1987) also investigated whether a more complex regime influenced adherence levels, by comparing timolol use only, to timolol use in conjunction with pilocarpine, using an eye drop-monitoring device. Patients on just timolol had adherence levels of 82.7±19.0%; those on timolol and pilocarpine had adherence levels of 84.3±14.0% and 77.7±18.7% for each drug, respectively (Kass et al., 1987). This seems comprehensible, since patients have reported they would prefer once daily drops for convenience as opposed to multiple instillations of drops (Buller et al., 2007).

Variations to the above electronic monitoring devices include electronic caps, which record each time the container is opened to access the medication, as well as a more recent wireless development, which uses a sensor to establish when the drops are opened, closed, the number of drops leaving the container and how the drops are instilled (Boland et al., 2014, Thompson et al., 2018, Gatwood et al., 2017).

Another method used to assess patient compliance is through direct observation. Though patients may be adherent, in that drops are instilled as prescribed and at timely intervals, the instillation technique may be poor and so treatment will be ineffective though the individual themselves is compliant. Stone and colleagues (2009) investigated this concept by firstly, questioning patients about their hypotensive drops and technique, and secondly, by video recording them whilst they administered sterile solutions from bottles similar to the ones used for common glaucoma drops (Stone et al., 2009).

They found that overall, patients reported positively about their drop instillation technique, with 92.8% stating that they had no problems with drop administration, whilst 61.9% reported that

they never missed the eye on instillation. However, these figures did not correlate well with the video recordings which found that only 21.9% of the patients using the 15mL bottle, and 30.8% of patients using the 2.5mL bottle, were able to instil the drops without touching the eye or ocular adnexa. Furthermore, 61.9% of patients reported that they washed their hands prior to handling the eye drops, when in reality, video recordings confirmed that only 1.7% of patients did this (Stone et al., 2009). This emphasises the importance of observing patients during consultations to check the drop instillation technique. Poor technique may therefore disguise adherent patients. Recent changes to the NICE guidelines encourage clinicians to observe patients instilling eye drops to check their technique at the primary point of prescribing ocular hypotensive drops (National Institute for Health and Care Excellence, 2017).

The use of pharmacy data has also been used in some adherence studies. It is another objective method to monitor not only adherence, but also persistence. Persistence is the term used to describe the time between starting medication to discontinuation by the patient (Schwartz and Quigley, 2008). Persistence provides insightful information along with adherence on patient behaviours and discontinuation rates.

Several studies have found that persistence with glaucoma medication to be relatively low, with figures ranging from 20% to 64% according to a recent literature review by Schwartz and Quigley (2008) (Spooner et al., 2002, Dasgupta et al., 2002, Schwartz and Quigley, 2008).

Pharmacy data provides information on refill rates and prescription collections, which would ultimately indicate whether patients are adherent by replenishing their hypotensive drops at a timely manner. Tse and colleagues (2016) looked at prescription records at a UK GP practice to establish adherence rates, which were calculated by averaging the difference between annual ‘actual’ collected prescriptions and ‘expected’ prescription collections, across the course of treatment. Analysis was made in age groups, and showed adherence to be poorest in 20–59-year-olds, with collections on average being 2.3 fewer than the 12 expected over a 12-month period. Surprisingly, collections were 1.3 more than the expected 12 for the 90-99 year old age group (Tse et al., 2016).

The latter could perhaps be explained by poor handling of drops by the older population, which would waste drops and result in a higher refill rate (Lacey et al., 2009, Tatham et al., 2013, Tse et al., 2016). On the contrary, the younger group may struggle to adhere to their drops due to their busy lifestyles (Patel and Spaeth, 1995). The differences in refill rates amongst the different age groups emphasises the importance of educating patients on both drop instillation

techniques, as well as the reasons why hypotensive eye drops are so crucial in the treatment of glaucoma and OHT (Lacey et al., 2009, Tatham et al., 2013).

Pharmacy records are reasonably easy to access and analyse, and allow classification into subgroups depending on patient age and drug class. However, they do not provide an insight into reasons for non-adherence, and though prescriptions may be collected, it does not mean that patients are retrieving their medication from the chemist.

Friedman and colleagues (2007) employed a different metric when looking at adherence for analysing pharmacy claims data. They used Medication Possession Ratio (MPR), a value calculated as follows:

$$\text{“Sum of ‘days supply’ of all glaucoma medications during observation period*} \;\Big/\; \text{Sum of ‘days of medication required’ during observation period*”}$$

*Observation period: days from index prescription until end of study, first surgery, or disenrollment (Friedman et al., 2007)

To calculate the ‘days supply’, expected drop count from bottles must be determined. MPR has advantages in that the single value takes into consideration combination-therapy. It provides a metric for adherence which acknowledges that patients may be adherent to one of their drops but no to the other. It also reflects patients who stop and recommence their treatment, and so captures any gaps in the observation period (Friedman et al., 2007).

In this particular study, MPR was combined with data from patient interviews, physician interviews and patient charts to assess adherence. It was found that the mean MPR was 0.64 for the 13 956 patients included in the pharmacy claims data analysis. Fifty-four percent of patients who were followed up at 12 months had a gap in refilling their initial prescribed drug. Of these, 22% persisted once they restarted their medication after the gap, whereas 78% lapsed at least once more. At the end of the year, 59% of patients had hypotensive drops available to them. Only 10% of the 10260 patients actually persisted with their eye drops during the course of the year (Friedman et al., 2007).

Though MPR provides valuable additional information, it is at risk of sampling errors which can overestimate or underestimate the true value. For example, patients may use more than the

one expected drop per instillation, either to ensure the drop goes into the eye, or due to handling difficulties, which in turn will overestimate the MPR. On the other hand, if second- or third-line therapy was commenced but then stopped by the clinician over a short period of time, the results of the MPR can be liable to underestimation (Friedman et al., 2007).

Cate and colleagues (2015) set out to compare the different methods used to assess adherence to glaucoma medication through the use of a randomised controlled trial (RCT). The data used for this study was taken from the original RCT, the 'Norwich Adherence Glaucoma Study', which looked at interventions to potentially improve adherence (Cate et al., 2014, Cate et al., 2015). The adherence measures which were compared were the Travalert DA, patient self-report data from a questionnaire consisting of questions covering 'Frequency of Missed Dose' (FMD) and Morisky Measure of Adherence Scale (MMAS) (Morisky et al., 1986), and finally, the MPR using prescription records (Cate et al., 2015).

All methods produced some gaps in datasets due to missing data. The self-reporting questionnaires produced the most complete dataset over the 8 months, with the DA and pharmacy data showing similar gaps over this period. Data from prescription records was lacking in places as it was not provided by health centres. For the Travalert DA, data was missing either due to tampering of the device or device malfunction over the 8 month period (Cate et al., 2015).

Overall, the Travalert DA measured a mean adherence level of 77% over the 8 months. Once the data was dichotomised into adherent and non-adherent categories, adherence levels stood at 54% for the DA, 60% for the MMAS and 57% for the FMD. Prescribing practices made MPR data unreliable to draw accurate conclusions from. Patients were prescribed more than the required amount of drops for the month on some occasions, and this seemed to be for a variety of reasons such as previously running out of drops too soon, holiday supply, misplacing the drops or in cases where patients received the same amount of drops for unilateral cases as for bilateral cases. It is evident that there is poor correlation between different measuring methods, and this coupled with missing data, makes it difficult to measure adherence accurately over a long period (Cate et al., 2015).

Glaucoma medication adherence is a complex field to investigate, and as no biologic metabolite is available to be measured, there is no 'gold standard' in terms of assessing adherence (Muir and Lee, 2011). The aforementioned methods all have their pros and cons,

and perhaps the best way to assess adherence is through a combination of the different techniques available.

4.1.2 Factors affecting adherence

Many factors have been attributed to poor adherence. These have been explored in various studies, using an assortment of the methods mentioned above. The following highlights the most commonly discussed factors affecting adherence to glaucoma medication and some corresponding studies demonstrating this.

1. Frequent and complex dosing regimes

Searches of the current literature often return complex dosing regimes as one of the primary factors affecting adherence. Cohen Castel and colleagues (2014) used both subjective and objective methods to investigate this, by conducting telephone interviews and using these in conjunction with prescription data to calculate MPR. The questionnaire used for the telephone interviews was structured using the previous work by Tsai and colleagues (2013), with sections divided into patient based factors, situational/environmental factors, medication based factors and physician based factors (Tsai et al., 2003). They found that adherence was better for those who used a greater number of drops to use per day. It is assumed that this may be as a result of better patient education, as those on increased dosing may have more advanced glaucoma and so the counselling by the physician may be better in these cases (Cohen Castel et al., 2014).

However, such results are not reflected in other studies. Robin and colleagues (2007), compared adherence in two groups of patients; those on monotherapy using a prostaglandin analogue (PGA), and those on multi-therapy, whereby another drug was used alongside the PGA. Assessment was made using an electronic monitoring device, with measurements taken for dosing errors, coverage, inter-dose intervals and the percentage of doses taken (Robin et al., 2007).

Dosing errors leading to over or under adherence were present in 20% of the study participants. Only 3.3% of the PGA monotherapy group fell into the ‘poor’ dosing category, whereas for the multi-therapy group, 10% of poor dosing occurred for the PGA drug, and 30% of poor dosing occurred for the additional therapy. Coverage, defined as ‘the proportion of time for which the interval between doses was no more than two hours more than the nominal dosing interval…’ (Robin et al., 2007), was also poorer for the multi-therapy group when

combining data for both the PGA and adjunctive therapy (85.6±12.6), compared to PGA monotherapy alone (97.5±3.9) (Robin et al., 2007).

On the whole, adherence to PGAs was good in both the monotherapy and multi-therapy groups. Essentially, a more complex routine appears to lead to poorer adherence, however, once-a-day drugs within a complex regime still show good adherence from patients (Robin et al., 2007).

2. Forgetfulness

Forgetfulness is one of the most commonly reported reasons for non-adherence (Patel and Spaeth, 1995, Olthoff et al., 2009, Newman-Casey et al., 2015). Olthoff and colleagues (2009) conducted a questionnaire to investigate the determinants of non-adherence in a Dutch population of glaucoma patients. They found that 26.7% of patients admitted that they had forgotten to use their drops on one or more occasions, which made it one of the most significant contributors to missed doses. This is in line with other studies, which also state forgetfulness as a leading factor of poor compliance in glaucoma patients (Konstas et al., 2000, Bour et al., 1993, Taylor et al., 2002).

3. Poor Knowledge

A lack of knowledge about the disease and the poor understanding of the ill effects of not taking hypotensive eye drops also form a proportion of non-adherent cases. Stryker and colleagues (2010) used interview questions to make comparisons between adherent and non-adherent patients. They found that it was only a small selection of study participants who felt that there was no benefit in taking their medication (12.5%). However, non-adherent patients were less sure of any benefits in taking their glaucoma drops than adherent patients (20.8% vs 3.1%, $p<0.05$) (Stryker et al., 2010).

On the contrary, McClelland and colleagues (2019), found no significant association between adherence and knowledge of glaucoma. However, they did find that some patients who started to use their medication more regularly in the last 6 months, claimed this was due to better knowledge and understanding of the disease (McClelland et al., 2019).

4. Age

Some studies have reported that adherence improves with increasing age. Cohen Castel and colleagues (2014) combined telephone interviews with MPR data from pharmacy records to

assess adherence in a large group of Israeli glaucoma patients. An MPR of <0.8 was classed as non-adherence and that of >0.8 was classed as good adherence. The multivariate analysis of this study found 'older age' was a factor that supported good adherence (Cohen Castel et al., 2014).

Similarly, Olthoff and colleagues (2009) also found non-adherence to be more prevalent amongst the younger participants of their study. Of the patients aged 55 years or younger, 44.7% were non-adherent compared with 18.9% of non-adherent patients in the 74 years and older age group. This difference in adherence amongst different age groups was significant in this study (p=0.01) (Olthoff et al., 2009).

Of course, these findings are offset by cognitive and memory problems associated with older glaucoma patients, which may negatively affect adherence. Yochim and colleagues (2012) investigated cognitive and mental health prevalence amongst glaucoma patients. Cognitive impairment was highly prevalent amongst glaucoma patients aged over 50, with 44% of the included patients demonstrating some cognitive deficiency on one or more of the measures. Furthermore, memory problems were found amongst ~20% of this study population. Such results indicate that adherence may be influenced by the neurological changes associated with older age (Yochim et al., 2012).

5. Side effects

Side effects from glaucoma medication are common (Inoue, 2014, Wolfram et al., 2019). When investigating common barriers to non-adherence, the occurrence of side effects to glaucoma medication was linked to higher odds of non-adherence with an odds ratio (OR) of 2.1, and 95% Confidence Intervals (CI) of 1.0–4.3 (p= 0.04) (Newman-Casey et al., 2015). Patel and Spaeth (1995) on the other hand, found that side effects did not significantly affect adherence (Patel and Spaeth, 1995). Another study using subjective methods of focus groups and interviews with patients, found that though patients suffer from side effects, they do not report these to limit their compliance. This study also found that side effects only appear to be reported to clinicians if they are intolerable to the patient (Taylor et al., 2002).

6. Instillation technique

Difficulties with instilling hypotensive drops appears to be a common barrier to glaucoma medication adherence. Newman-Casey and colleagues (2015) found higher odds for non-adherence associated with drop instillation problems (OR = 2.1, 95% CI 1.0–4.3, p= 0.04).

Eighteen percent of the sampled subjects also reported an interest in drop instillation aids in this study (Newman-Casey et al., 2015).

Likewise, Stryker and colleagues (2010) also found an association between difficulties in administering drops and adherence, albeit this was non-significant. When classified into groups, 22.9% of non-adherent patients and 9.4% of adherent patients reported that drop instillation problems posed a barrier to using their drops (Stryker et al., 2010).

7. Other factors

Several other factors have been mentioned in the current literature to have an impact on adherence amongst treated glaucoma and OHT patients. Such barriers are cost, poor health literacy and the belief that the drops are ineffective (Tsai et al., 2003, Lacey et al., 2009, Muir et al., 2006).

4.1.3 Patient education

Friedman and colleagues (2008) investigated factors which drive patients to adherence or non-adherence using a combination of retrospective data, prospective patient surveys, physician and patient telephone interviews and chart reviews. The results of the study highlight the crucial role clinicians play in patient education. They found that 86% of patients were aware that not taking their medication as prescribed could lead to loss of vision. The 14% who did not think that they would lose their vision if they did not take their glaucoma drops, showed significantly lower adherence levels (Friedman et al., 2008).

Current NICE guidelines encourage a discussion between healthcare professionals and patients about the diagnosis, prognosis, drop instillation techniques, treatment and management of their glaucoma. It is also suggested that such conversations are backed up with information in ‘accessible format’, at both the first visit as well as future follow-ups. In patients with insufficient IOP control despite topical treatment, the guidelines advise that adherence is assessed, as well as checking the patient’s drop instillation technique, prior to considering alternative management options (National Institute for Health and Care Excellence, 2017).

Interestingly, ophthalmologists themselves have differing attitudes and behaviours towards adherence in their clinics, which in turn could influence patient compliance. Gelb and colleagues (2008) investigated this by interviewing 103 physicians who were involved in

treating patients included in the Glaucoma Adherence and Persistency Study (GAPS) (Friedman et al., 2007). Physicians were divided into 3 categories depending on their attitudes and behaviours: 'reactive' physicians, 'sceptical' physicians and 'idealistic' physicians. Idealistic physicians actively try to improve and address adherence, sceptical physicians feel that they cannot influence adherence and so do not invest efforts into this, and reactive physicians are less proactive about adherence, and more reactive to the situation (Gelb et al., 2008).

Results from the original GAPS indicate that patients are indeed influenced by their interaction with their physicians (Friedman et al., 2008). MPR was significantly better for patients who stated that their physicians ''explained what to expect in the future from glaucoma,'' compared to others. Such an explanation was more likely to have been provided by 'idealistic' physicians. MPR was also higher in those individuals who were contacted by their physicians with telephone reminders, and again, this type of action was significantly more prevalent amongst the group of idealistic physicians. Lastly, MPR was higher in those individuals who were aware that glaucoma could lead to vision loss (Gelb et al., 2008, Friedman et al., 2008). In turn, it is evident that the communication provided by physicians can positively affect adherence in glaucoma patients, and perhaps education amongst physicians is required to create better behavioural habits in managing adherence in the glaucoma clinics.

Non-adherence is a topical issue in the medical management of glaucoma and OHT. While several attempts have been made to quantify adherence rates amongst treated glaucomatous patients, results are not always an accurate reflection of reality, since objective and subjective methods of assessment are not synonymous in their rates. This current chapter aims to illuminate on this pressing issue, through the use of a survey to assess not only adherence rates in a UK hospital glaucoma clinic, but to also investigate adherence rates specifically related to patient education and symptoms of OSD.

4.2 Aims

- To investigate which factors influence adherence
- To measure adherence in a UK hospital glaucoma clinic
- To investigate the link between side effects to glaucoma medication and adherence
- To investigate the link between patient education and adherence
- To compare adherence at a UK hospital glaucoma clinic with a national cohort of glaucoma and OHT patients

4.3 Methods

Originally, a prospective study was proposed with both objective and subjective methods to measure adherence and the aforementioned secondary aims. However, due to the COVID-19 pandemic and with consequential restrictions, such a study could not be carried out as initially planned. It was decided then, that a survey be carried out instead to allow adequate data collection and to provide some scope on the topic.

The questionnaire itself was originally designed with a total of 19 questions divided into three sections: 'All about you', 'Medical information' and 'Drop instillation information'. The questions covered a variety of areas including the names of the hypotensive drops used, the number of years patients have had glaucoma and whether sufficient information was provided about the drops and the condition, whether verbal or written, at the start of the treatment. This first draft was then reviewed, both by academics and consultants with specialities in glaucoma, and any necessary adjustments were made based on the feedback to form a final version of the questionnaire.

The final questionnaire was printed out for distribution at Corbett Hospital (Dudley NHS Trust, UK) based in the West Midlands. This site is a sister hospital to Russells Hall Hospital (Dudley NHS Trust, UK) in the West Midlands, and is the location of the Virtual Glaucoma Clinics (VGCs). Here, new and follow up glaucoma patients attend appointments with ophthalmic technicians to have their auxiliary tests completed such as visual fields, IOPs and fundus photos, prior to a phone consultation with their consultant to discuss the outcomes as per COVID-19 protocol.

The questionnaire was also uploaded on to an online survey platform to allow for digital data collection alongside the paper version distributed at Corbett Hospital (Dudley NHS Trust, UK). The online survey consisted of the same questions, presented in the same order as the paper version of the questionnaire. An introduction was added to a welcome page and the survey was formatted to a user-friendly setup. Such changes allowed the option to skip certain questions and the selection of 'not applicable' in some instances.

The final questionnaire as printed and distributed at Corbett Hospital (Dudley NHS Trust, UK) is attached in Appendix 6. The consent form and Patient Information Sheet (PIS) are attached in Appendix 7.

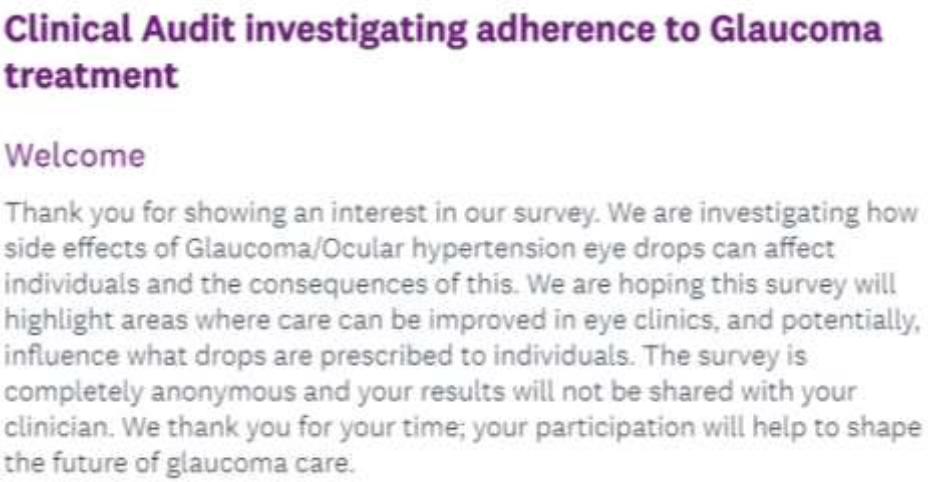


Figure 4.1: Introduction page of the online survey

4.3.1 Ethics

The project was reviewed by the University Research Ethics Committee (UREC) and a favourable decision issued alongside granted permission from the Russells Hall Hospital Research and Development department.

For paper-based surveys, participants were issued patient information leaflets and given time to consider all information before consenting to complete the survey. For the online version, consent was assumed if the patient followed the link and completed the survey. Both the online and physical versions of the questionnaire were anonymous, and no personal data was required from the patient.

The survey was distributed over a four-month period from March 2021 to June 2021 at Corbett Hospital. The online version was advertised and live for the same duration.

4.3.2 Sample size determination

Power calculations, made using GPower (version 3.1.9.7), showed that 88 participants were required to enable Chi-square tests for 2 x 2 matrices to detect statistically significant medium size effects at the 5% significance level ($\alpha = 0.05$) with 80% power. This is using Cohen's standards of effect size and employing a medium effect.

4.4 Results

By the close of the survey, 67 responses were received via the online link, and 63 responses were collected at Corbett Hospital. The results have been classified into two groups depending on where data collection occurred. These cohorts are A) National and B) Hospital. Hereinafter, the results will be discussed separately for each group.

4.4.1 Demographics and Adherence

National Cohort

The majority of participants were aged 65 years and over (70%, n=47). The remaining proportion of participants were aged 55-64 years (22%, n=15), 45-54 years (4%, n=3) and 35-44 years (3%, n=2) in descending order. None of the participants were aged 34 years or under.

Of all the participants, many fell into the Caucasian/White/English/Welsh/ Scottish/Northern Irish/British/Irish group (96%, n=64), with the remainder making up a small percentage of Black/African/Caribbean/Black British (3%, n=2) and Asian/Asian British/Indian/Pakistani/Bangladeshi/Chinese/Any other Asian backgrounds (1%, n=1).

The average duration of using glaucoma and OHT drops was 10 years amongst this group, with figures ranging from 1 year to 38 years.

Hospital cohort

As with the national demographics, the majority of participants fell into the 65 and over age group (90%, n=57), followed by the 55-64 years (5%, n=3), then 45-54 years (3%, n=2) and lastly 35-44 years (2%, n=1). No participants fell into the categories of 34 years or under.

Again, Caucasians formed much of the participant base, with 94% (n=59) falling in this category. Mixed/Multiple ethnic group/White and Black Caribbean/White and Black African/White and Asian made up 3% (n=2) of participants, and 3% (n=2) fell into the Black/African/Caribbean/Black British ethnicity group.

The average duration of glaucoma/OHT treatment was 11 years, with figures ranging from 1 year to 50 years.

Adherence rates

Adherence in this study was classed as never missing a dose of glaucoma/OHT medication in line with a previous adherence studies (Tamrat et al., 2015, Rajurkar et al., 2018). Therefore, for question 14, an answer of 0 times per week would equate to good adherence. Any missed doses would equate to non-adherence or poor adherence.

National cohort

Fifty-five participants answered question 14, whilst 12 decided to skip it. Forty-two patients reported that they missed zero doses of their medication a week. This equates to an adherence rate of between 63% and 76%, with the former percentage assuming that those who skipped the question did so due to non-adherence.

Hospital cohort

All participants completed question 14 at Dudley. Of the 63 respondents, 50 reported that they missed no doses a week, equating to an adherence rate of 79%.

4.4.2 Most commonly prescribed drops

National cohort

The three most commonly prescribed hypotensive drops for the national group were Latanoprost (29%, n=19), Bimatoprost (27%, n=18) and Monopost (20%, n=13).

Hospital cohort

The three most commonly prescribed hypotensive drops for the hospital group were Latanoprost (37%, n=23) and Monopost (22%, n=14). 'Other' came up at 22% (n=14) as well, however, due to the varied responses for this, with some not being hypotensive eye drops, this proportion cannot be solely attributed to a certain drug or class of drugs. The other responses were as follows:

- Hyloforte, Clinitas gel
- Dorzolamide+Timolol fixed combination
- Brinzolamide
- Latanoprost+Timolol fixed combination
- Brinzolamide

- Clinitas, Vitapos
- Liquifilm tears
- Brinzolamide, Thealoz duo
- Brimonidine, Brinzolamide
- Fixapost, Simbrinza, Thealoz duo
- Simbrinza
- Brimonidine
- Brimonidine
- Coqun tablets

4.4.3 Factors affecting adherence

The options presented as answers for question 15 had been based on the most common reasons for non-adherence as shown in the literature. An option of 'other' was added in case a participant's reasons differ to the presented options. This question allowed multiple responses per participant.

National cohort

Fifty-five participants responded to this question, and 12 skipped it. Inapplicability of this question was expressed by 53% (n=29) of participants. 'Forgetfulness' was the most common reason for missed doses (36%, n=20). 'Running out of drops' was the next most popular answer (11%, n=6) followed by 'complicated routine/too many drops to take' (7%, n=4). 'Difficulty handling the bottles/vials of medication to squeeze out the drops' and 'side effects of drops e.g. 'stinging, burning' were only reported by a small percentage of individuals (5%, n=3 each). No participant reported missing their drops due to not understanding the reason for taking them. The 'other' responses have been added to Appendix 8.

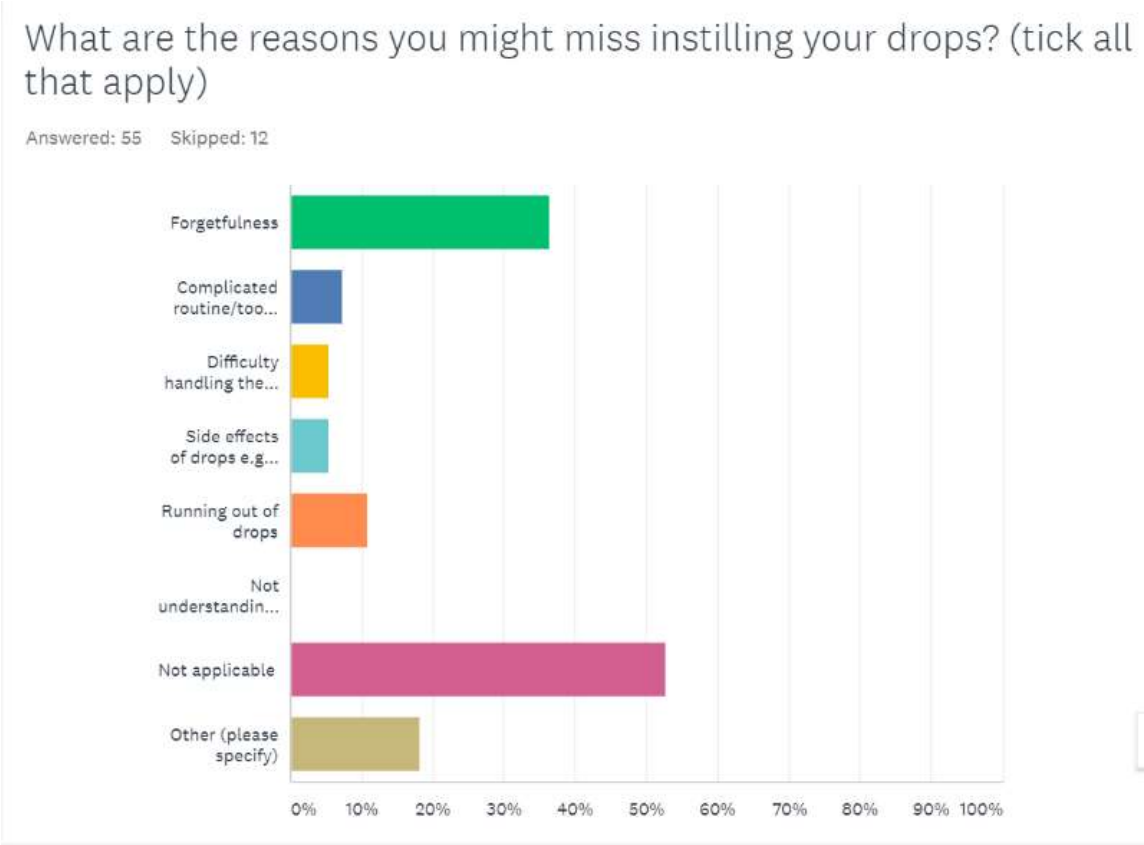


Figure 4.2: Reasons for missed doses of glaucoma and OHT eye drops.

Hospital cohort

All 63 participants answered this question. As in the national results, 'Forgetfulness' was the most common reason for missing drops (24%, n=15). 'Not applicable' was selected by 67% (n=42) of participants. All other reasons made up very small percentages of responses, with 'side effects of drops' and 'running out of drops' at 5% (n=3) each, 'difficulty handling the bottles/vials of medication to squeeze out the drops' at 3% (n=2) and 'not understanding why you have to take the drops' at 2% (n=1). No participant reported that missed doses due to a 'complicated routine/too many drops to take'. There was only one 'other' response which stated 'once in 6 months'.

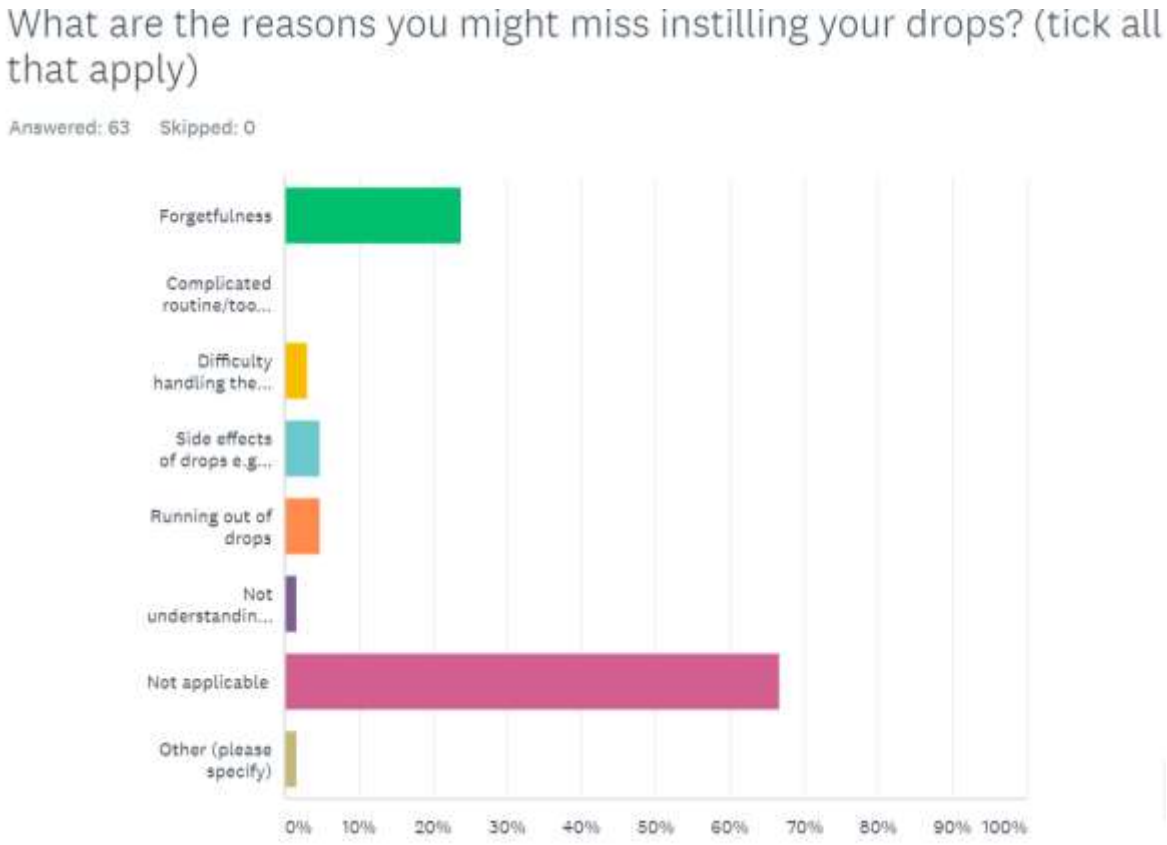


Figure 4.3: Reasons for missed doses of glaucoma and OHT eye drops.

4.4.4 What proportion of patients have side effects to medication?

National cohort

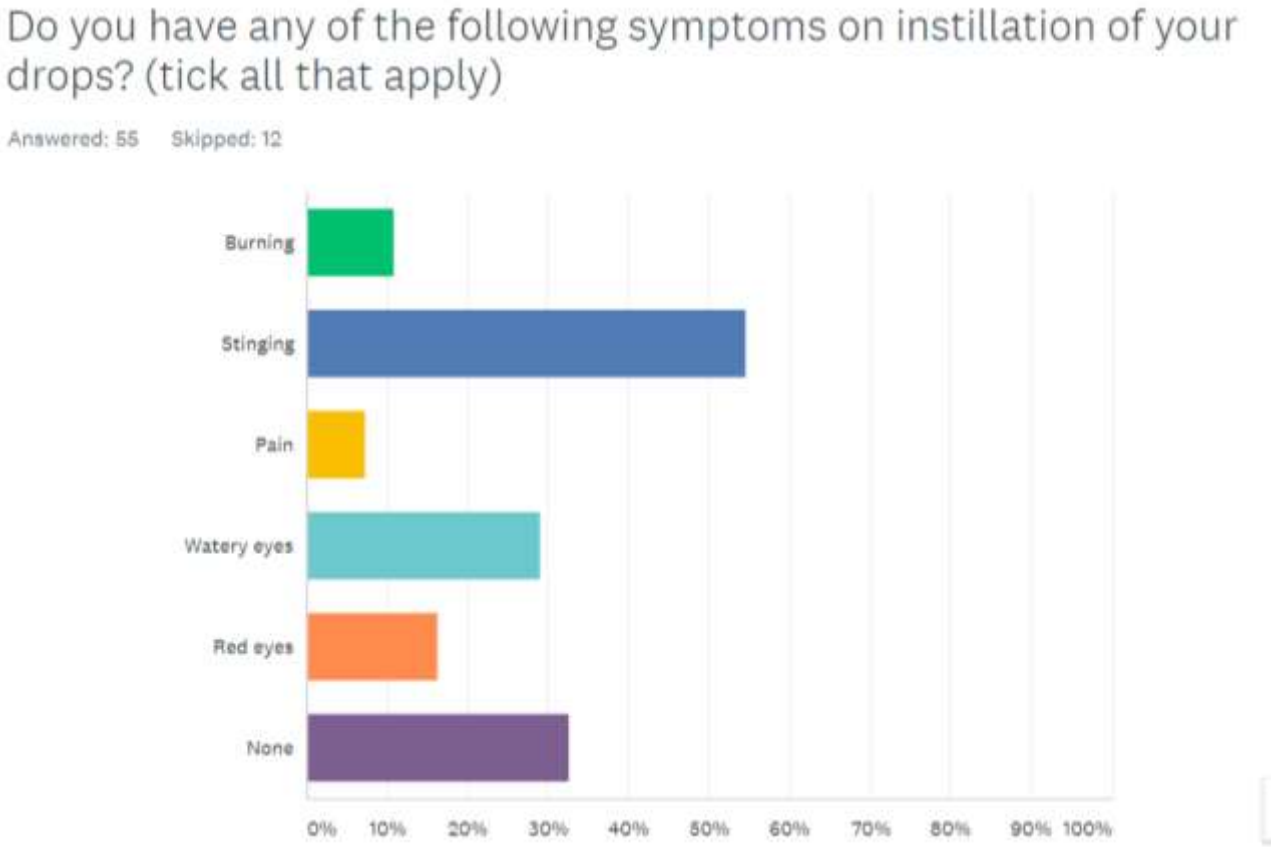


Figure 4.4: Symptoms experienced on instillation of hypotensive eye drops.

Fifty-five participants answered this question and 12 skipped it. Stinging was the most common side effect on instillation of glaucoma/OHT drops, with 55% (n=30) of participants reporting it as a symptom. Watery eyes and red eyes were the next most common symptom on instillation, making up 29% (n=16) and 16% (n=9) of the results respectively. 'Burning' sensation was experienced by 11% of participants (n=6) and pain by 7% (n=4). Thirty-three percent (n=18) reported no symptoms on instillation, and so 67% (n=37) of patients experienced one or more symptoms on instillation.

Hospital cohort

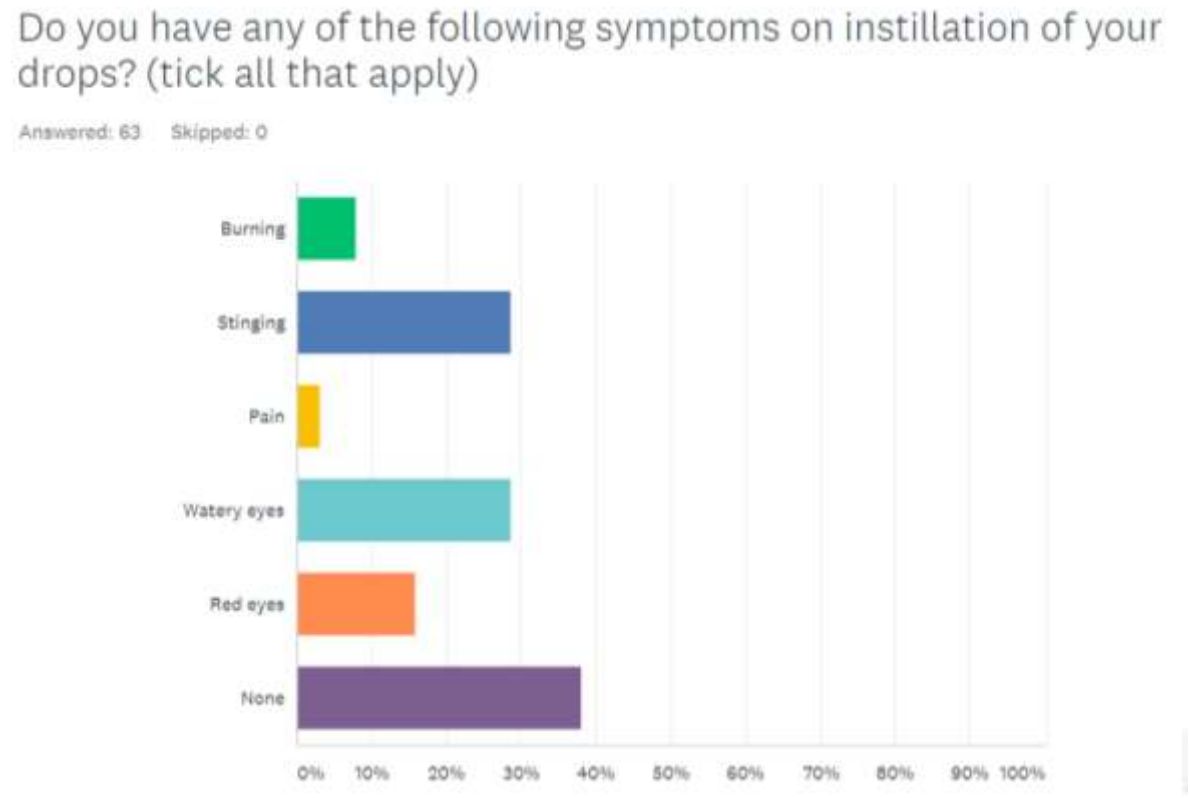


Figure 4.5: Symptoms experienced on instillation of hypotensive eye drops.

All 63 participants answered this question for the Dudley hospital cohort. Stinging and watery eyes were equally as prevalent on instillation of drops (29% each, n=18). Red eyes were reported as the next most frequent side effect on instillation of hypotensive drops (16%, n=10). 'Burning' sensation and pain made up smaller percentages, at 8% (n=5) and 3% (n=2), respectively. Of all the respondents, 24 did not report any side effects to the drops. So, 62% (n=39) of all participants at Corbett hospital experienced at least one or more of the symptoms mentioned above.

4.4.5 Does the occurrence of side effects affect adherence?

Question 12 was filtered to form a subgroup of all patients who experienced one or more symptoms on instillation of their drops. Question 14 was then analysed to see how many of these symptomatic patients miss using their drops at least once a week. Since more than one response could be selected on Question 12 (regarding symptoms), analysis was made on Excel to avoid any over-counting of participants for Question 14 (regarding number of times drops missed a week).

National cohort

Of the total 67 participants for this group, 18 reported no symptoms on instillation of the eye drops. Twelve participants skipped this question entirely. Of the remaining 37 participants reporting side effects to the eye drops, 10 missed taking their medication at least once a week. Using the definition of adherence in this study then, 27% (n=10) of participants having side effects on instillation of their drops were non-adherent. Since 12 participants skipped this question, one must consider the worst-case scenario and assume these were symptomatic, non-adherent participants. Therefore, the adherence rate for this symptomatic group lies between 41% to 73%

Since the adherence rate overall ranged from 63% to 76% for the national cohort, results indicate that those suffering from side effects of the eye drops may be less adherent, though it is difficult to ascertain without the true numbers.

	Symptoms	**No Symptoms**	**Total**
Adherent	27	15	42
Non-adherent	10	3	13
Total	37	18	55

Table 4.1: Contingency table illustrating the number of patients falling into each category for the National cohort.

Considering only those participants who answered the question, the chi-square (X^2) statistic for this data is 0.720. The p-value is 0.396, demonstrating no significant association between side effects and non-adherence (Table 4.1).

Hospital cohort

For the hospital cohort, 24 participants reported no side effects to their medication. Thirty-nine participants reported at least one symptom on instillation. Of these 39 participants, nine missed their drops at least once a week. Therefore, 23% of patients suffering with side effects from their eye drops were non-adherent. The adherence rate for symptomatic patients was 77% for the hospital cohort.

The overall adherence for the hospital cohort was 79%, so symptomatic respondents appear less adherent, albeit this difference is small.

	Symptoms	No Symptoms	Total
Adherent	30	21	51
Non-adherent	9	3	12
Total	39	24	63

Table 4.2: Contingency table illustrating the number of patients falling into each category for the Hospital cohort.

The chi-square (X^2) statistic for this data is 1.078. The p-value is 0.300, demonstrating no significant association between side effects and non-adherence (Table 4.2).

4.4.6 Does the duration of glaucoma/OHT treatment influence the incidence of side effects?

The responses were filtered depending on the duration of treatment, and the responses to Question 12 investigating symptoms were analysed in each subgroup for comparison.

National cohort

Forty-one of the included participants had been on ocular hypotensive drops for more than 5 years. Of these, 33 answered question 12, whereas eight skipped this question. Twelve of the 33 participants did not report any side effects on instillation of their drops. Of those that had been treated for glaucoma/OHT for more than 5 years, 64% (n=21) experienced some symptoms on instillation of their drops (Figure 4.6).

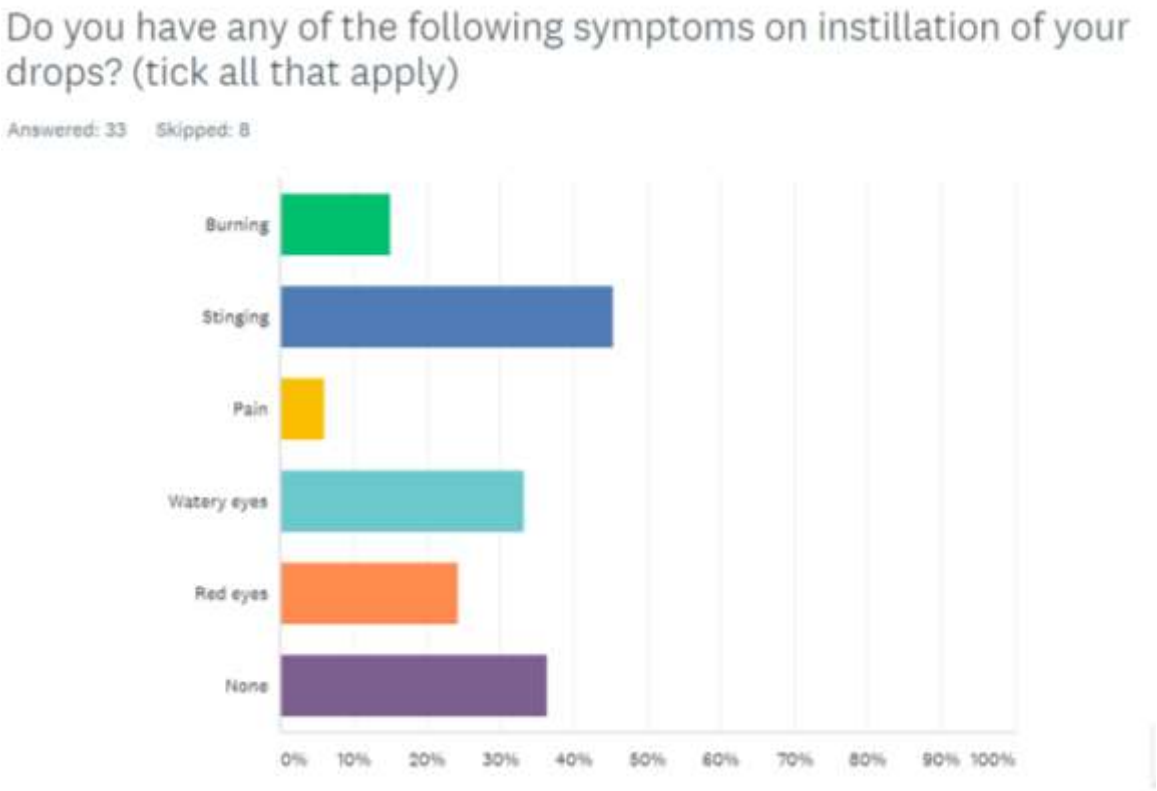


Figure 4.6: Symptoms experienced on instillation of hypotensive eye drops for patients on treatment for more than 5 years.

Filtering for individuals who had been on treatment for less than 5 years, 26 of the included participants fell into this category. Twenty-two of these patients answered question 12 about symptoms. Twenty-seven percent (n=6) of respondents did not complain of any symptoms on instillation, but 73% (n=16) did experience some form of side effect on instillation. Stinging was the most reported symptom, with 68% (n=15) of this subgroup experiencing this (Figure 4.7).

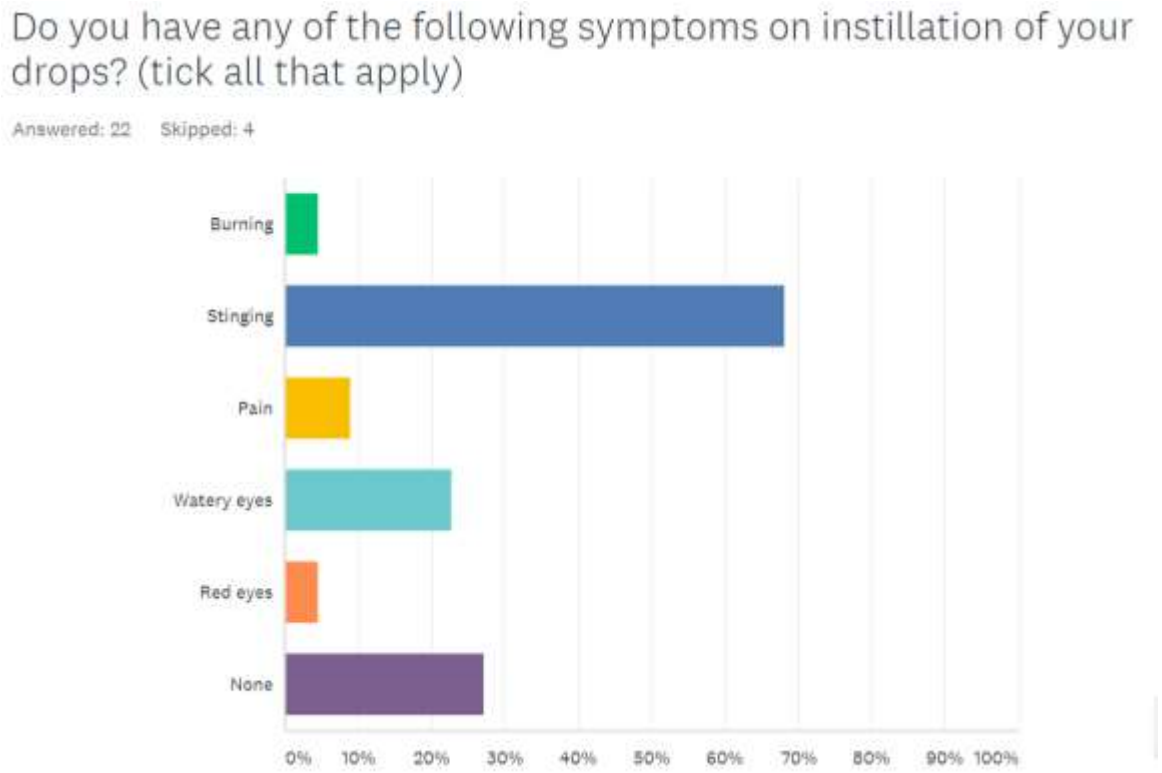


Figure 4.7: Symptoms experienced on instillation of hypotensive eye drops for patients on treatment for less than 5 years.

	<5years	>5years	Total
Symptoms	16	21	37
No Symptoms	6	12	18
Total	22	33	55

Table 4.3: Contingency table illustrating the number of patients falling into each category for the National cohort.

With the national results indicating that 67% of patients experienced some symptoms on instillation of their drops, the filtered results suggest that those who have been on treatment for a shorter duration (<5 years) are more likely to experience side effects than those on long-term treatment (>5 years), with symptom rates of 73% for those on treatment less 5 years, and 64%

for those on treatment more than 5 years. However, the chi-square (X^2) statistic for this data is 0.496 and with a p-value of 0.481, demonstrates no significant association (Table 4.3).

Hospital cohort

For the Dudley hospital cohort, 40 participants had been taking their ocular hypotensive drops for more than 5 years. Sixteen participants in this subgroup reported no problems on instillation. Stinging was the most commonly reported side effect (Figure 4.8). Overall, 60% (n=24/40) of patients on drops for more than 5 years experienced some symptoms on instillation.

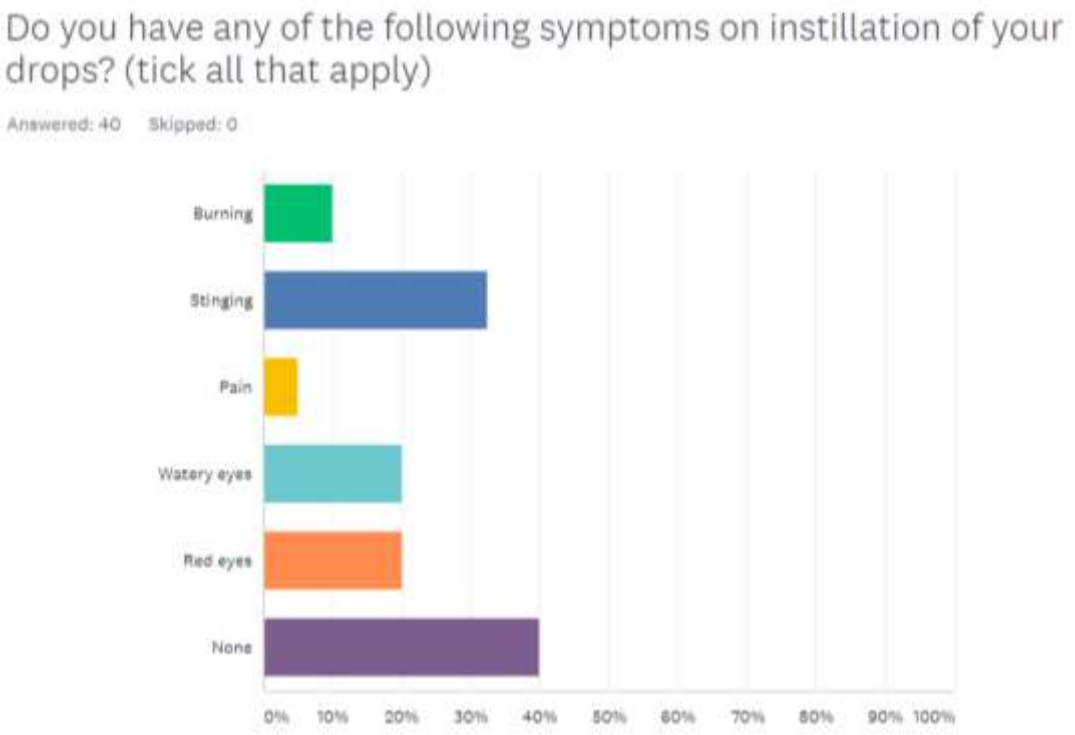


Figure 4.8: Symptoms experienced on instillation of hypotensive eye drops for patients on treatment for more than 5 years.

Nineteen patients had been on hypotensive drops for less than 5 years in the Dudley hospital group. All 19 patients answered question 12 in this sub-group. Of these patients, 63% (n=12) experienced symptoms on instillation. Watery eyes and stinging were the most reported symptoms at 37% (n=7) and 26% (n=5) respectively (Figure 4.9).

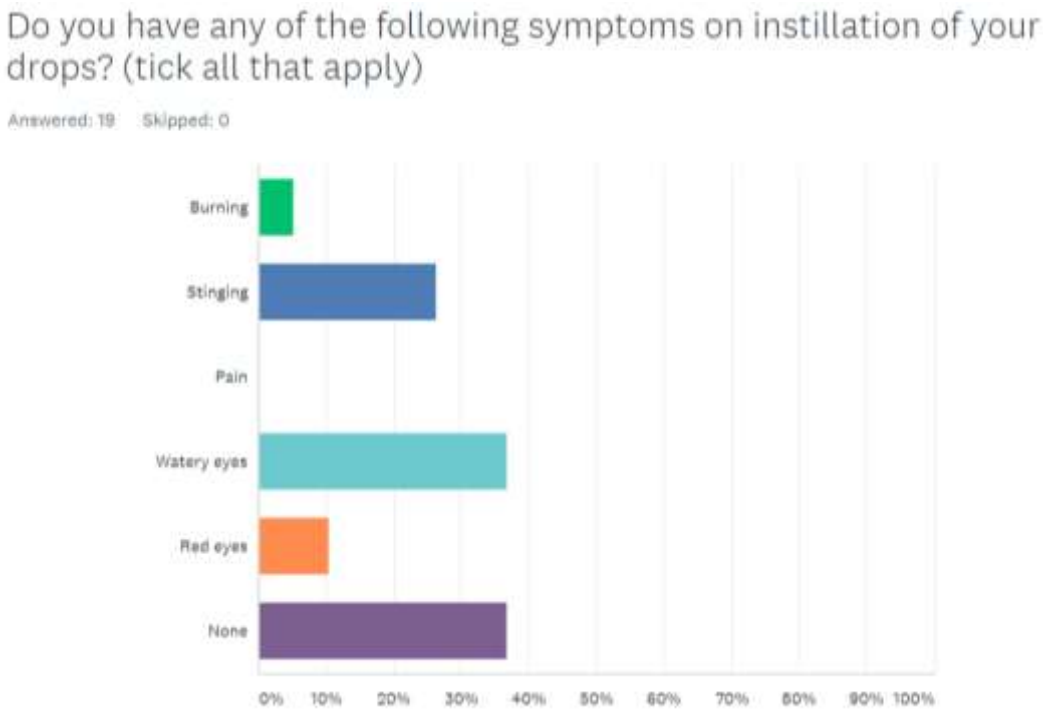


Figure 4.9: Symptoms experienced on instillation of hypotensive eye drops for patients on treatment for less than 5 years.

	<5years	>5years	Total
Symptoms	12	24	36
No Symptoms	7	16	23
Total	19	40	59

Table 4.4: Contingency table illustrating the number of patients falling into each category for the Hospital cohort.

With 62.0% of participants experiencing symptoms on instillation for the Dudley Hospital cohort, those on drops for less than 5 years were slightly more likely to experience symptoms compared to those on drops for more than 5 years, though this difference was small (63% vs. 60%). The chi-square (X^2) statistic for this data is 0.054 and with a p-value of 0.816, demonstrates no significant association between length of treatment and the occurrence of side effects (Table 4.4).

4.4.7 Patient Education

National cohort

Results from the survey reveal that 63% (n=40) of participants did not receive written information about their condition at the start of the treatment, with 57% (n=37) stating that they had insufficient information about their condition prior to starting treatment, in the national group.

Hospital cohort

The results starkly differed for the hospital group with 78% (n=47) of participants reporting that they were issued written information about their condition on commencing treatment. Furthermore, 87% (n=55) felt that they had sufficient information prior to starting their treatment.

4.4.8 Patient education vs Adherence

Filters were applied to allow subgroups to be formed within the hospital and the national groups, to investigate the relationship between patient education and adherence.

National cohort

The first filter applied grouped those patients together who felt that they had sufficient information from their consultant prior to starting their treatment. In this sub-group, 23 responded and five skipped this question. Of these, 18 did not miss any drops. The adherence rate was subsequently 78%.

The filter was then changed to group together those patients who felt that they did not have sufficient information before starting treatment. In this group, 31 answered while six skipped the question. Of the 31, 23 did not miss any drop instillations. The adherence rate for this sub-group was 74%.

	Sufficient Info	Insufficient Info	Total
Adherent	18	23	41
Non-adherent	5	8	13
Total	23	31	54

Table 4.5: Contingency table illustrating the number of patients falling into each category for the National cohort.

The chi-square (X^2) statistic for this data is 0.120. The p-value is 0.730, demonstrating no significant association between adherence and patient education at the point of starting treatment (Table 4.5).

Hospital cohort

When filtering for those patients who felt that they had sufficient information from their consultant prior to starting their treatment, 55 participants fell into this subgroup. Of these, 45 did not miss any drops. The adherence rate for this group was therefore 82%.

When the filter was changed to those patients who felt they had insufficient information before starting treatment, only eight patients fell into this sub-group. Six of these patients reported never missing their drops, resulting in an adherence rate of 75%.

	Sufficient Info	Insufficient Info	Total
Adherent	45	6	51
Non-adherent	10	2	12
Total	55	8	63

Table 4.6: Contingency table illustrating the number of patients falling into each category for the Hospital cohort.

The chi-square (X^2) statistic for this data is 0.211. The p-value is 0.6460, demonstrating no significant association between adherence and patient education at the point of starting treatment (Table 4.6).

4.4.9 Drop Instillation

National cohort

In this group, 86% (n=56) of participants instilled their drops themselves, and the remaining 14% (n=9) had them instilled by their partner.

Question 8 focussed on the ease of handling the drops on instillation. On a scale of 1 to 10 (with 1 being very easy and 10 being very hard), on average, ease of handling was scored at four.

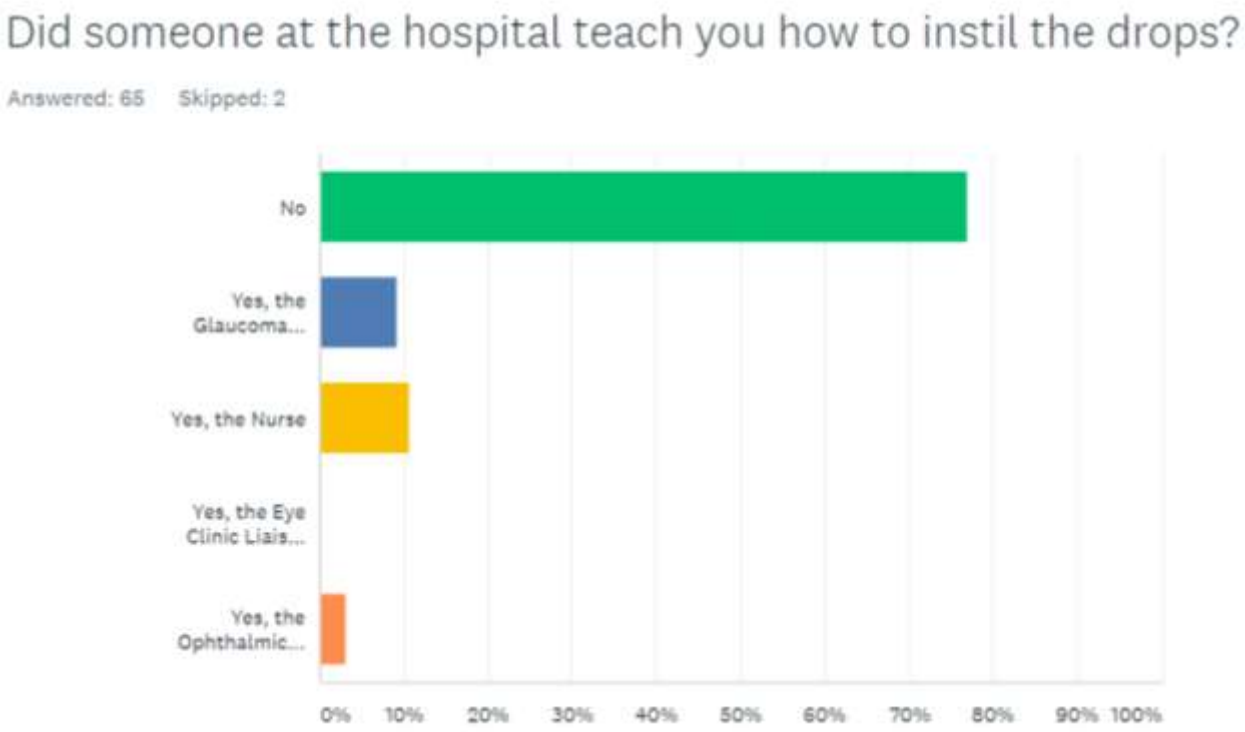


Figure 4.10: Details of who taught participants their drop technique, if at all.

Of the 65 participants that answered, 77% (n=50) were not taught how to instil their drops. The remainder were either taught by the nurse (11%, n=7), the consultant (9%, n=6) or by an ophthalmic technician (3%, n=2). In this national group, 74% (n=48) of respondents were not issued written instructions on drop instillation technique.

Hospital cohort

Of the 62 participants that responded, 84% (n=53) instilled their drops themselves. For some, their partners instilled them (10%, n=6), for others it was their carers (2%, n=1) or their nurses (2%, n=1). Two participants selected ‘other’, with the responses being ‘one myself, one my carer’ and ‘myself, my partner’.

In terms of ease of handling their drops on instillation, the average from the scale of 1 to 10 (with 1 being very easy and 10 being very hard) was also scored at four, as in the national group.

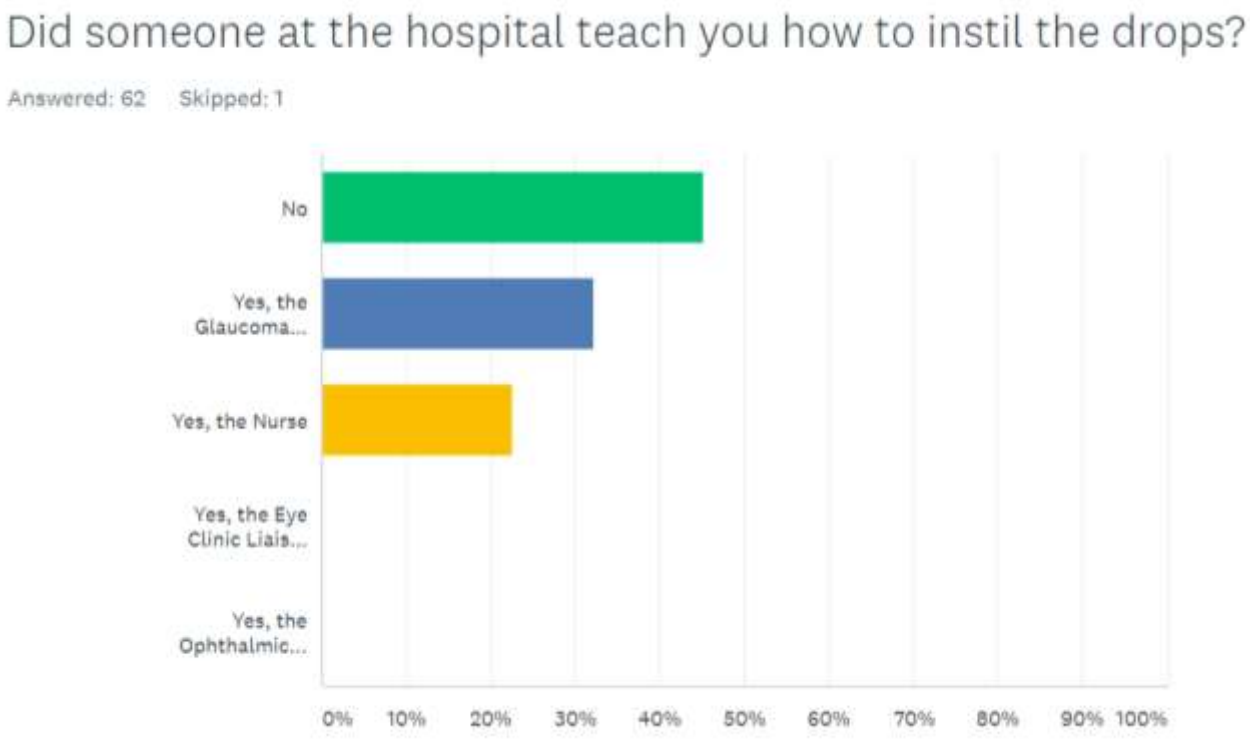


Figure 4.11: Details of who taught participants their drop technique, if at all.

In this group, 45% (n=28) of participants stated that they were not taught about drop instillation at the hospital, which is a smaller proportion than the national results (77%, n=50). The remainder were taught either by the consultant (32%, n=20) or the nurse (23%, n=14). Of the 61 that answered for the hospital group, 56% (n=34) reported that they were issued written instructions on drop instillation technique, which is higher than the national group.

4.4.10 Reminders

National cohort

Though forgetfulness was the most common reason for missing drops, the majority of patients do not have reminders in place prompting them to take their drops (49%, n=32). Some use an alarm (12%, n=8), some use app reminders (9%, n=6) and others use paper charts (5%, n=3). The 'other' responses (25%, n=16) have been added in Appendix 9.

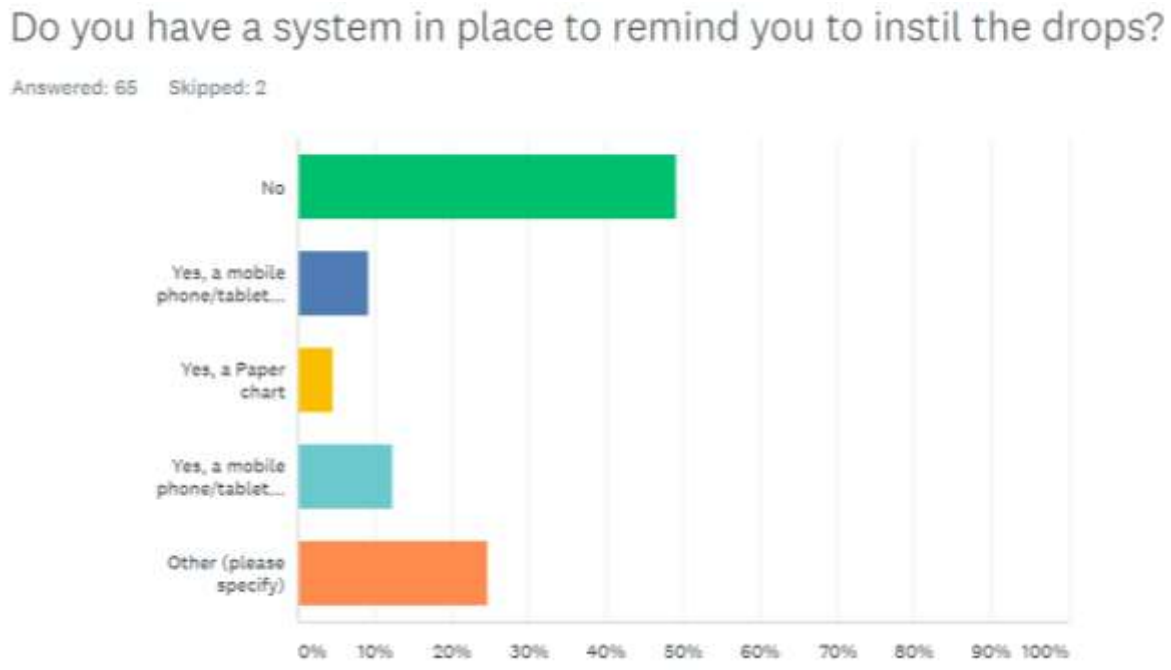


Figure 4.12: Percentage of patients with a reminder system in place to prompt drop instillation.

Hospital cohort

As with the national results, the vast majority of participants do not have reminders in place to prompt drop instillation (73%, n=46). A few use paper chart reminders (8%, n=5) whilst a fraction use app reminders (2%, n=1). The 'other' responses (17%, n=11) have been added in Appendix 9.

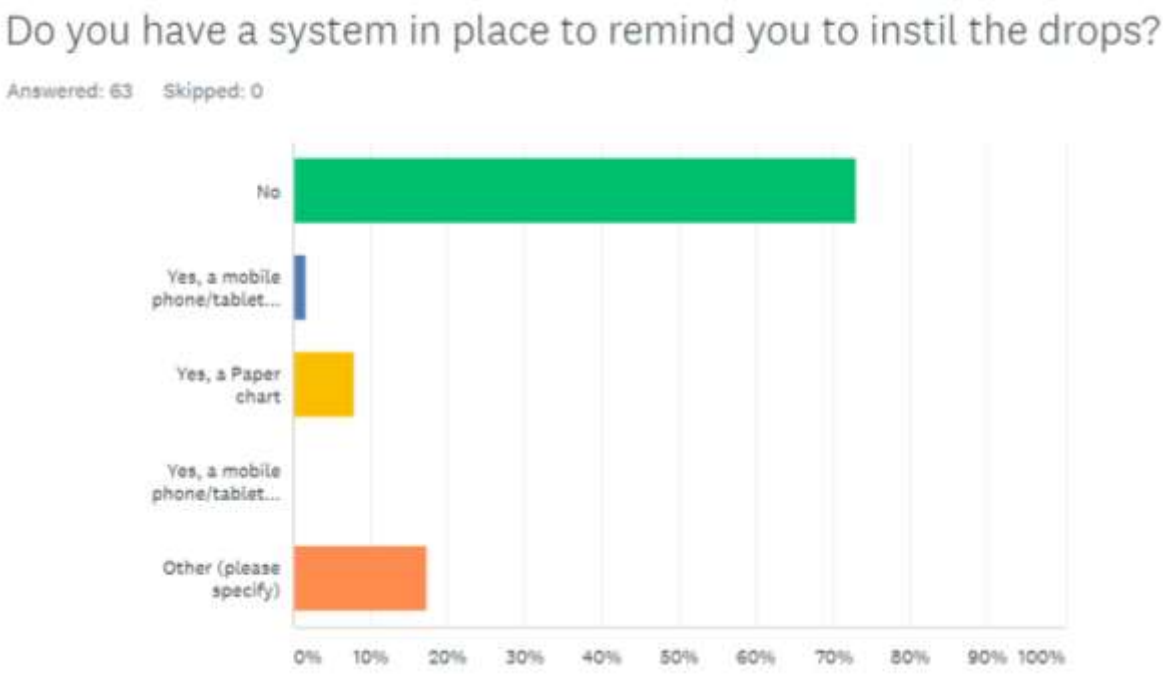


Figure 4.13: Percentage of patients with a reminder system in place to prompt drop instillation.

4.4.11 What proportion of symptomatic patients have had previous surgery or laser?

The results were filtered to show only those patients who are symptomatic on instillation on drops, and Question 19 was analysed.

National cohort

Of the 37 symptomatic patients, 65% (n=24) had prior eye surgery, 35% (n=13) did not.

	Symptoms	No symptoms	Total
Surgery	24	14	38
No Surgery	13	4	17
Total	37	18	55

Table 4.7: Contingency table illustrating the number of patients falling into each category for the National cohort.

The chi-square (X^2) statistic for this data is 0.946. The p-value is 0.331, demonstrating no significant association between prior surgery and symptoms (Table 4.7).

Hospital cohort

For the Dudley group, of the 39 patients who were symptomatic, 39% (n=15) had prior surgery, 62% (n=24) did not.

	Symptoms	No symptoms	Total
Surgery	15	10	25
No surgery	24	14	38
Total	39	24	63

Table 4.8: Contingency table illustrating the number of patients falling into each category for the National cohort.

The chi-square (X^2) statistic for this data is 0.064. The p-value is 0.801, demonstrating no significant association between prior surgery and symptoms (Table 4.8).

4.4.12 The use of dry eye drops

National cohort

Fifty-five participants answered the question about dry eye drops, 30 of which were not using any dry eye drops at all. For the remaining 25 who were using dry eye drops at the time of the survey, the vast majority of them only started using them after being diagnosed with glaucoma/OHT (92%, n=23).

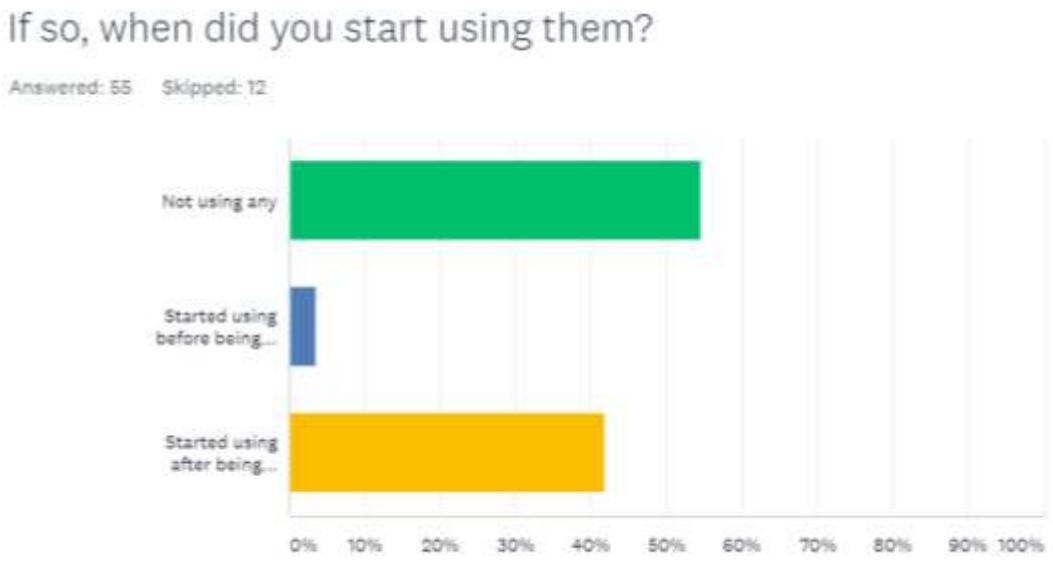


Figure 4.14: Percentage distribution of patients using dry eye drops. Those who were using dry eye drops were then divided according to when they were commenced, prior to or post diagnosis.

For the following question, on frequency of dry eye drops usage, 28 patients reported not using any dry eye drops at all compared to 30 for the question before. For the remaining participants, most used them either a ‘few times a day’ (24%, n=13) or ‘as and when’ (18%, n=10). Few used them ‘once a day’ or ‘few times a week’ (4%, n=2 each).

Hospital cohort

Of the 63 participants who answered the question about the use of dry eye drops, 34 were not using any. The remaining 29 participants were using dry eye drops, with the majority of them commencing these drops after being diagnosed with glaucoma or OHT (79%, n=23).

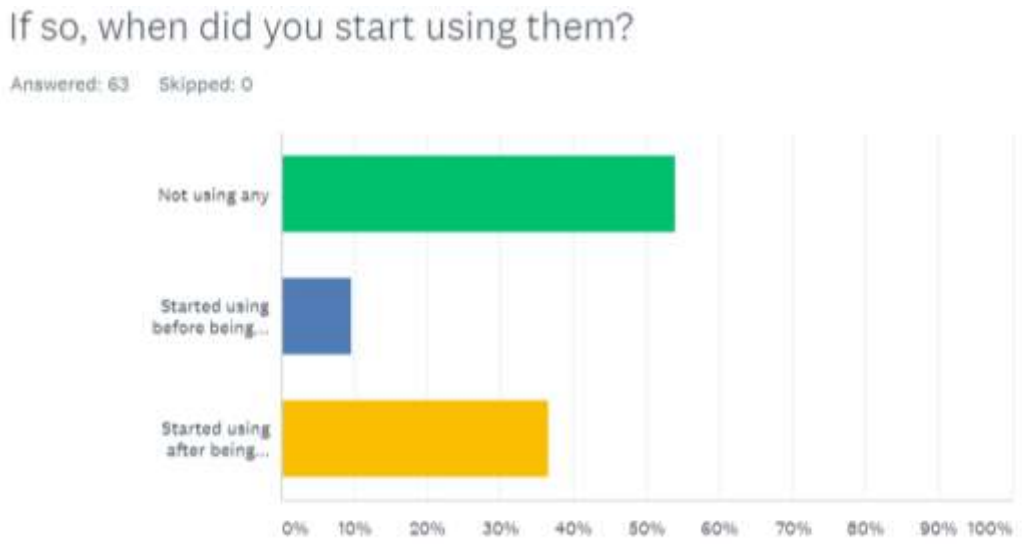


Figure 4.15: Percentage distribution of patients using dry eye drops. Those who were using dry eye drops were then divided according to when they were commenced, prior to or post diagnosis.

In terms of frequency of dry eye drop usage, 34 stated they did not use any at all. For the remainder, much of the use was a 'few times a day' (32%, n=20), some 'as and when' (8%, n=5), and a fraction 'once a day' or 'few times a week' (4.8%, n=3 and 2%, n=1, respectively).

4.5 Discussion

Adherence rates in this study were in line with those found in previous studies (Kass et al., 1987, Kass et al., 1986, Okeke et al., 2009b, Rossi et al., 2010, Tamrat et al., 2015). It is interesting that the adherence rates found in this survey-based study are similar to those found previously using electronic monitoring devices. Self-reported measures, such as through patient interviews, have been shown to overestimate adherence by ~20% (Okeke et al., 2009b, Kass et al., 1986). This may indicate either, that the responses have been accurate and honest in this study, or, that adherence rates amongst the participants might in fact be ~20% less than what has been found.

It may not surprising that the adherence levels were higher for the hospital cohort (79%) compared to the national cohort (63%-76%). Questionnaires handed out at Corbett hospital had the advantage that a clinician was available in the waiting area, where participants were enrolled and carried out the survey. The clinician was on hand to help clarify the questionnaire, explain the aims and help to assist with any stuck points. This may in turn have created some participant bias. Those participants carrying out the survey online, in their own time, would not have been exposed to such bias.

This could explain the results of question 15, when asked about the reasons for missed doses. For the national group, 53% (n=29) reported that this was not applicable to them (58% with the additional three patients reporting no missed doses in the 'other' section). In contrast, 67% (n=42) of the hospital group stated that this was inapplicable to them. The presence of a clinician may have influenced such outcomes, where the patient may have been more reluctant to reveal non-adherence.

Furthermore, Questions 5 and 6 regarding written information and the sufficiency of information provided at diagnosis also demonstrate some differences between the groups. In terms of patient education, 63% (n=40) of patients in the national group did not receive written information about their condition at the start of the treatment, and 57% (n=37) stated they had insufficient information about their condition prior to starting treatment. On the contrary, for the hospital group, 78% (n=47) of participants reported that they were issued written information about their condition on commencing treatment and 87% (n=55) felt that they had sufficient information prior to starting their drops. Such differences again may be accounted for by social desirability bias in the hospital setting for the group who completed the survey at Corbett Hospital (Dudley NHS Trust, UK) (Grimm, 2010). However, it may also be suggestive of the differences in care and patient education across the country in glaucoma clinics. The latter would explain the higher adherence rates found amongst the Corbett Hospital cohort compared to the national cohort.

Patient education appears to be an important element in glaucoma medication adherence. Okeke and colleagues (Okeke et al., 2009a) conducted a randomised controlled trial (RCT) to investigate whether educational interventions helped to improve adherence. Patients were observed for a period of three months prior to such intervention to establish baseline adherence. For the intervention group, there was a significant improvement in adherence rates from baseline to month three, from 54±17% to 73±22% ($p<0.01$). The control group, who received no extra educational interventions, showed insignificant changes from baseline to month three. The difference in the rates of improvement between the two groups at month three was also remarkable ($p= 0.01$) (Okeke et al., 2009a).

Similarly, a RCT by Konstas and colleagues (2009) also looked at intense interventions focussing on patient education on glaucoma and adherence. Adherence rates were significantly superior in the intervention group across months 1, 3 and 6 ($p<0.001$) when comparing to the group receiving non-specific education (Konstas et al., 2009). Such results reflect the direct benefit of education in treated glaucoma and OHT patients.

The Norwich Adherence Glaucoma Study conducted by Cate and colleagues (2014) found conflicting results to the aforementioned RCTs. Here, Glaucoma Support Assistants (GSAs) were employed to deliver interventions of glaucoma education and support using behaviour change counselling to newly prescribed glaucoma and OHT patients, whilst a comparison group received the standard care. No significant benefit was found from the tailored support package in the intervention group, and with an average cost of £10.35 per patient, such intervention was deemed ineffective. However, this study did highlight that patient satisfaction was much higher amongst the intervention group compared to the control group, and with relatively low costs to achieve this, it may provide benefit in the long run (Cate et al., 2014).

The current survey sought to investigate the link between patient education and adherence. Filtered analysis does indeed show that adherence levels were higher amongst those patients who felt they had sufficient information from their consultant prior to starting their treatment, compared to those that did not. This was the case for both the national cohort (78% adherence in those with sufficient information, 74% adherence in those with insufficient information) and the hospital cohort (82% adherence in those with sufficient information, 75% in those with insufficient information). According to the current survey, such association between adherence and patient education, however, is non-significant for the hospital cohort [X^2 (1, N = 63)=0.211 (p=0.646)] and for the national cohort [X^2 (1, N = 54)=0.120 (p=0.730)]. Interpretation must be made with caution, since the subgroups resulted in low and unequal numbers, which makes it difficult to draw concrete conclusions. This is an area which would warrant further investigation, since patient education may be of great benefit both from an adherence and from an economic point of view.

Though NICE guidelines encourage patient education with information to be provided in accessible formats to support this, it is inevitable that in busy eye clinics, this may not occur consistently. Being well informed and having a good relationship with the clinician, has been linked to better adherence levels (Friedman et al., 2008, Nordmann et al., 2011). A collaborative approach in this area would ensure that patients are given all the required information highlighting future consequences, which is especially important for those who rely solely on their clinician for all their knowledge (Friedman et al., 2008). Perhaps, as in other fields, a tailored approach for individuals would ensure maximising patient education and better adherence (Strecher et al., 2008, Spencer et al., 2011, Newman-Casey et al., 2015).

As with previous studies, forgetfulness was the leading reason for missed drops in both groups (Newman-Casey et al., 2015, Patel and Spaeth, 1995). The prevalence of glaucoma increases

with age and this is clear to see with over 90% of participants being aged 65 and over in this study (Tuck and Crick, 1998). With increasing age come cognitive changes and memory loss (Yochim et al., 2012) .It is not surprising then, that forgetfulness is so common amongst glaucoma patients. Though we look at adherence in terms of missed doses, such cognitive problems may also translate into the wider glaucoma and OHT care, with patients being susceptible to forgetfulness, there is the possibility the suggested drop instillation technique or details about the condition are also being forgotten. In this study, patients may have forgotten if they received written information or sufficient information before starting treatment, especially if they have been on treatment for many years. Such remarks were made by some participants to the clinician at Corbett hospital.

It has been said that patients remember as little as 25% of medical information immediately after having the discussion, and this further decreases with time (McGuire, 1996). A more recent study looking at medical recall in newly diagnosed cancer patients found that patients recalled about 60% of information, with increasing age being negatively associated with this (Nguyen et al., 2019).

This emphasises the need for regular reminders, whether in clinics or over the telephone, to glaucoma and OHT patients. Assessing drop instillation techniques at each visit, providing information about the condition and having a healthy discussion about new developments, may nurture better patient-physician relationships, keep patients informed and involved in their treatment, as well as re-iterate important points, all of which may improve adherence.

Furthermore, though forgetfulness is a leading cause of non-adherence, this survey has found that the majority of patients do not appear to have a system in place to serve as a reminder to instil their drops. A randomised controlled trial (RCT) by Lai and colleagues (2020) found that a reference chart with a tele-reminder significantly improved adherence to glaucoma medication. They suggest a multifaceted approach to tackling the multifactorial problem that is non-adherence (Lai et al., 2020).

The COVID-19 pandemic has brought about many changes in the way clinics run within the NHS. Particularly, the implementation of telephone appointments for screening, diagnosis and follow-ups replacing some of the usual face-to-face (F2F) clinics, has become a new norm. The VGCs at Corbett Hospital are short consultations, with ophthalmic technicians who take a quick history as well as carrying out a battery of glaucoma tests. These results are fed back to the consultants who appropriately triage the patient either to be called into a F2F clinic, or to

continue with treatment/monitoring. Patients have a telephone consultation with the consultant to discuss the outcomes of the VGC appointment, and this has received positive praise from both clinicians and patients as being an efficient method of managing patients in the inter-rim between F2F consultations, with a recent internal hospital audit reflecting such findings. Such clinics have been welcomed across the country (Gunn et al., 2022, Gunn et al., 2018).

Drop instillation and handling difficulties are common barriers to adherence in glaucoma/OHT clinics (Newman-Casey et al., 2015). On a 10-point scale, ascending from 1 to 10 with increasing difficulty in drop instillation, both groups scored 4 on average. It is evident that patients struggle somewhat with drop instillation. Moreover, in the Corbett hospital cohort, many patients complained to the available clinician about the drop bottles and the difficulty in squeezing them. This issue must be especially concerning for elderly patients or those with arthritis or weakness in their hands. Perhaps this area needs to be investigated further and presents as an opportunity for pharmaceutical companies to invest in better packaging and innovations to help with the administration of hypotensive drops.

Though side effects only make up a small fraction of reasons for missed doses, results suggest that adherence is poorer amongst patients who are symptomatic on drop instillation. The adherence rate for symptomatic patients was 41-73% for the national cohort (the former percentage assuming those who skipped the question were symptomatic and non-adherent) and 77% for the hospital cohorts. Compared with the overall adherence rates at 63%-76% and 79% for the national and hospital cohorts, respectively, symptomatic patients do appear less adherent. Unfortunately, numbers are too small to deduce exact causative relationships between the two variables, but this does warrant further investigation. Chi square (X^2) analysis shows no significant association between symptoms and adherence for the national cohort [X^2 (1, N = 55)=0.720 (p=0.396)], or the hospital cohort [X^2 (1, N = 63)=1.078 (p=0.300)].

Although patients may not report side effects as a barrier to taking drops, it can still affect adherence. Taylor and colleagues (2002) used qualitative research methods to investigate reasons for non-compliance. Side effects were reported by patients in this study, though they were not classed as a reason to missing drops. Patients were reluctant to report side effects to their clinicians unless they are intolerable (Taylor et al., 2002). This corroborates the findings in this current survey, which highlights that over 60% of patients suffered one or more symptoms on instillation of their drops in both groups, with the vast majority reporting it not to deter them from using their drops.

Apart from forgetfulness being the leading reason for missed doses in both groups, the other top three reasons were ‘running out of drops’ and ‘complicated routine’ for the national cohort, and ‘side effects’ and ‘running out of drops’ for the hospital cohorts which is in line with other studies (Chawla et al., 2007, Patel and Spaeth, 1995, Tsai et al., 2003).

Though the current study does not raise significant associations between the duration of glaucoma medication use and the occurrence of side effects, it is reasonable to deduce that symptoms on instillation are apparent regardless of the length of treatment. It is crucial that newly diagnosed patients are properly educated on their condition and the imperative use of the drops to avoid vision loss, especially since side effects may out balance any perceived benefits particularly at the start of treatment.

4.5.1 Limitations and future work

The current literature indicates that adherence is not simple and straightforward to measure. The choice of tool and the delivery can both impact the adherence rates achieved (Cate et al., 2015, Grimm, 2010). Initially, the present study was designed to measure adherence by combining different tools such as electronic devices, as well as introducing an enhanced education service around glaucoma and drop instillation. Due to the emergence of the Covid-19 pandemic, such plans were hindered. It was decided to measure adherence in the only way possible at the time, through the use of a questionnaire. This may be the reason why the results fail to show significance in their patterns, being limited by the constraints of questionnaires.

The current questionnaire was susceptible to non-responders and missing data. Attempts were made to take this into account during analysis, and so adherence rates were given as a range. For the national cohort, the adherence rate ranged between 63% and 76%, with the former percentage assuming that those who skipped the question did so due to non-adherence. Since all participants answered the question for the hospital cohort, the adherence rate was 79%. Perhaps for the national results, 63% is the best estimate, although this might be a floor value. Such interpretation might be susceptible to some inaccuracy since it lacks precision.

Delivery of the online questionnaire was replicated from the paper version issued at the hospital. The online version had the possibility to skip questions which participants did not feel were relevant to them. There is a possibility though, that adherence rates may be liable to some discrepancies since non-adherent participants may have skipped adherence related

questions. An improved platform which permits logical pathways and ensures compulsory questions are answered, would ensure that relevant questions are answered by the right individuals.

If the questionnaire in this study is used for future work, it may be beneficial to revise the questions. Participants were asked ‘How often a week do you miss instilling your eye drops?’. As some patients may not miss drops on a weekly basis but still do so on occasion, the question regarding reasons for non-adherence was answered by more participants than those who admitted to missing weekly drop instillations. This may have undercounted to number of patients missing drops. A revision of the current questionnaire could try to account for missed doses not just on a weekly basis, but also consider monthly, quarterly, or sporadic missed doses.

It is advised that future work combines quantitative and qualitative measures of adherence to draw a full picture of the situation. One suggestion is the possibility to follow two groups of newly treated patients in parallel. One group would receive the usual care and education as is routine (control group) and the other group would receive enhanced education. It would then be interesting to measure adherence at different time periods amongst both groups to see if such interventions have any effect on adherence. Adherence rates could be measured using quantitative (e.g. electronic monitoring device) and qualitative (e.g. questionnaires or focus groups) methods to investigate if there is a preferred adherence tool. Additionally, it would be interesting to study such groups over the years to see if poorer adherence rates do indeed correlate with worsening glaucoma.

4.6 Conclusion

This survey has highlighted that the occurrence of side effects to ocular hypotensive drops is a prominent issue, with 67% of the national cohort and 62% of the hospital cohort experiencing at least one symptom on instillation of the drops, with stinging being the most common complaint. This could lead to patient dissatisfaction and so addressing such symptoms of ocular surface disturbance should therefore be a primary target in the management of adherence to glaucoma eye drops.

The proper implementation of patient education, through leaflets, videos, consultations with GSAs and telephone follow-ups could provide not only patient satisfaction, but potentially contribute to better adherence in the long run. There is a need for long-term observations to

assess this, particularly as much of the current literature focusses only on short time periods of observation (Cate et al., 2014, Okeke et al., 2009b).

The current survey has also highlighted the complexities of measuring adherence in glaucoma clinics. Many participants for the national cohort skipped the question about missed doses entirely, and this poses a question as to why. If this was due to non-adherent patient non-disclosure, the true problem might be underrepresented.

Although the study met the minimum sample size required, trends did not show in the results, suggesting that a larger sample size may be needed for future investigations.

Adherence to glaucoma and OHT medication is an ongoing problem. Poor adherence is associated with higher rates of vision loss (Stewart et al., 1993, Schwartz and Quigley, 2008). With a lack of overt symptoms, glaucoma poses a great risk to individuals who are not informed about the benefits of their medication. Better patient and physician relationships, and tailored patient education, could help to tackle some barriers to adherence. The multifactorial problem of adherence requires a multidimensional approach to fully understand and address the underlying issues that patients face.

Chapter 5:

Retrospective audit looking at demographics and predicting factors of ocular surface disease in glaucoma

5.1 Introduction

The previous chapters have discussed some connections between the preservatives in hypotensive eye drops and the occurrence of ocular surface disease (OSD). There are, however, some gaps in knowledge as to the chances of an individual developing OSD. Patients may not show symptoms of OSD despite using preserved drops for a significant time, whilst others may exhibit signs and symptoms even when prescribed preservative-free (PF) medication (Pisella et al., 2002). This raises the question as to whether some people are more prone to developing OSD whilst being treated for glaucoma or OHT. By predicting which elements increase the chances of a patient developing OSD in the course of their glaucoma treatment, it would enable those 'at risk' individuals to receive PF treatment from diagnosis. This would ultimately allow for better long-term management due to improved compliance and reducing the costs of additional outpatient appointments, since PF drops are better tolerated (Economou et al., 2018, Misiuk-Hojlo et al., 2018).

In order to investigate this notion of predictive factors, a retrospective audit of patient records was conducted at an ophthalmology unit in the West Midlands (Dudley NHS Trust, UK) to determine if there are any risk factors for OSD in patients under medical treatment for glaucoma or OHT.

5.1.1 Current demographics of glaucoma patients in the UK

The National Institute for Health and Care Excellence (NICE) states that Primary Open Angle Glaucoma (POAG) affects around 2% of the UK population aged 40 and over. This statistic rises with increasing age, affecting approximately 1% of people aged 40, 3% of people aged 60 and 8% of people aged 80 (National Institute for Health and Care Excellence, 2022, Hollands et al., 2013).

Furthermore, NICE states that POAG is equally prevalent amongst males and female (Bowling, 2015, National Institute for Health and Care Excellence, 2022). However, a recent longitudinal study by Kreft and colleagues (2019) using German data found that the incidence of POAG was significantly higher amongst women than men (Kreft et al., 2019). This is contradictory to a study carried out by Khachatryan and colleagues (2019), who found that men were more likely to have POAG than women across all age groups. Furthermore, around the ages of 50-55 years, both men and women were equally as likely of having POAG, and this may be related to hormonal changes within this age range due to menopause (Khachatryan et al., 2019). This

study only investigated gender and risk in an African-American population and so prevalence of POAG amongst males and females is likely to be influenced by ethnicity, which therefore highlights limitations within such studies.

There does appear to be some racial disparity amongst POAG sufferers. People of African descent are more likely to suffer from POAG than those of European descent (Tham et al., 2014). In a meta-analysis carried out by Kapetanakis and colleagues (2016), a prevalence of 5.2% at 60 years and 12.2% at 80 years was found amongst Black populations. The rise in prevalence per decade also disproportionately affects Hispanics the most, followed by Caucasians (Kapetanakis et al., 2016).

Though these statistics demonstrate global trends, the UK Biobank report confirms such findings with their study. The self-reported, voluntary, cross-sectional study found that those of black and Asian ethnicities had significantly higher rates of glaucoma than Caucasians. Of the 112,690 participants for whom ocular statistics were provided, 1916 confirmed a diagnosis of glaucoma. Of these, 3.3% of participants of Black ethnicities, 2.1% of participants of Asian ethnicities, and 1.6% of Caucasian ethnicities stated the presence of glaucoma (Shweikh et al., 2015).

However, these statistics must be interpreted with some caution, as the overall response rate was only 5.5%, relying on patients to self-report on their conditions. The subgroups of glaucoma could not be classified, and so it is difficult to know whether the responses relate to POAG or Closed Angle Glaucoma (CAG). There is also a possibility that such self-reporting methods may lead to miscounting, as patients who have OHT or those who are suspected glaucoma cases, could possibly have mistakenly declared the presence of glaucoma. Nonetheless, the results of this study provide valuable information about the UK glaucoma trends, which mirror those found globally (Shweikh et al., 2015).

These demographics differ for people suffering from CAG, otherwise known as Primary Angle Closure Glaucoma (PACG). Day and colleagues (2012) report the prevalence of PACG to be 0.4% in people aged 40 years or more, when considering a European population. As with POAG, the prevalence of PACG increases with age, with those aged 70 and older having a prevalence of 0.94%. Women are 3 times more likely to suffer from PACG than men. At the time of publication, 130,000 people in the UK had a confirmed diagnosis of PACG, and it was estimated that this number increased by 19% by 2022 (Day et al., 2012).

Globally, the prevalence of POAG is about 3.1%, whilst the prevalence of PACG is 0.5%. Overall prevalence of glaucoma stands at around 3.5% in those aged 40-80. This is influenced by the location and ethnicities of the population, with POAG being most prevalent in Africa (4.2%), whilst PACG is predominant within Asia (1.1%) (Tham et al., 2014, Jonas et al., 2017).

5.1.2 Prevalence of OSD in Glaucoma

Garcia-Feijoo and Sampaolesi (2012) investigated the occurrence of OSD in glaucoma patients, with an international study recruiting 600 patients from Argentina, Australia, China, Colombia, Germany, India, Mexico, and Spain. Of these, 448 patients were used in the final analysis. OSD was assessed with the use of Ocular Surface Disease Index (OSDI) questionnaires in this study. Similar to findings by Leung and colleagues (2008), a prevalence of 59.2% was found in this group of individuals (Garcia-Feijoo and Sampaolesi, 2012, Leung et al., 2008).

Furthermore, those patients with a longer history of glaucoma had significantly worse OSDI scores than those with a shorter history ($p=0.03$). There was also a clinical difference in scores between those patients using one or two drops, compared to those using three or four drops, to treat their glaucoma, albeit this difference was non-significant (Garcia-Feijoo and Sampaolesi, 2012). Previous studies also echo this finding, with prevalence of OSD in glaucoma patients being dose dependent. Those on more drops appear to be more likely to have OSD, and that too, of greater severity (Pisella et al., 2002, Baudouin et al., 2012b).

Currently, there appears to be a lack of research into the prevalence of OSD amongst glaucoma patients prior to commencing hypotensive treatment. Knowledge of this statistic would be helpful, as it would provide insight on the proportion of patients having prior OSD, as opposed to treatment induced OSD. Such knowledge would provide key information to clinicians when managing treatment-naïve patients. It could influence first line therapy in glaucoma clinics, as well as potentially aiding the long-term management of patients who would otherwise develop problems to preserved drops.

5.1.3 Implications of OSD in glaucoma clinics

The presence of OSD within a glaucomatous or ocular hypotensive population can have many consequences, both clinical and financial, and it is for this reason that management of both conditions concurrently is of such importance. The main implications are outlined below.

5.1.3.1 Cost

Glaucoma and suspected glaucoma jointly make up one of the largest NHS outpatient attendance sectors in England, with around 20% of new referrals to the hospital eye service (HES) being classed as suspect glaucoma cases (Davey et al., 2011, Lash, 2003). Monitoring patients with chronic glaucoma has been estimated to burden the NHS financially at £22.5 million a year (Ratnarajan et al., 2013, Forbes et al., 2019, National Institute for Health and Care Excellence, 2022). Likewise, Dry Eye Disease (DED) has been estimated to cost the healthcare system annually about $1100/~£807per person in the UK (Clegg et al., 2006). The two occurring in conjunction can therefore have severe economic consequences.

OSD occurring in patients being treated for chronic glaucoma can result in more frequent visits to the eye clinic (Nordmann et al., 2003), as well as more frequent changes to the medication (Zimmerman et al., 2009). In patients symptomatic of DED, clinicians may have to issue lubricating drops alongside the hypotensive eye drops used to treat the glaucoma or OHT, as found in Chapter 3 (the clinician survey) and Chapter 4 (the patient survey). DED in glaucomatous patients may impact the efficiency of treatment, whether that is through adherence issues or due to compromise of the ocular surface, potentially leading to the need for glaucoma surgery or laser treatment. Furthermore, research shows that a compromised ocular surface through long-term preserved treatment can negatively affect the success rates of trabeculectomy (Broadway and Chang, 2001, Baudouin et al., 1999). All of these factors are contributors to cost implications in patients being treated for glaucoma or OHT.

5.1.3.2 Adherence

OSD is highly prevalent amongst medicated glaucoma patients. Leung and colleagues (2008) found that 59% of treated glaucoma patients complained of dry eye symptoms in at least one of their eyes, with 27% complaining of severe symptoms (Leung et al., 2008). Furthermore, OSDI scores appear to be significantly worse for those on two or more hypotensive drops compared to monotherapy (Fechtner et al., 2010). Clinically, the odds of abnormal lissamine green staining are two times higher for each additional BAK-preserved drop added to the regime (Leung et al., 2008).

As well as the number of drops used to control the glaucoma or OHT, the duration of treatment is also associated with higher rates of OSD (Rossi et al., 2012). Prolonged therapy, as is common in glaucoma and OHT, exposes the ocular surface to more preservatives and

excipients of hypotensive drops over a longer duration, both of which can induce cellular toxicity (Fukuchi et al., 2010)

Such symptoms of OSD when taking hypotensive drops can have detrimental effects on patient adherence. In a small study by Chawla and colleagues (2007), side effects to medication was one of the top three reasons for non-adherence (Chawla et al., 2007). Moreover, Zimmerman and associates (2007) found 97% of physicians believed that adverse events from glaucoma medication were an obstacle to adherence. Conjunctival hyperaemia was the most commonly noted side effect to prostaglandin analogues in this study, and those patients who felt that such adverse events were problematic, had significantly poorer adherence (p=0.04) (Zimmerman et al., 2007b).

5.1.3.3 Quality of life

The implications of adverse reactions on the quality of life of glaucoma patients are well documented in current literature (Nordmann et al., 2003, Rossi et al., 2013a). An example of such study by Skalicky and associates (2012) set out to explore the relationship between OSD and quality of life (QoL) amongst a glaucomatous cohort. OSD and QoL were assessed using OSDI and Glaucoma Quality of Life-15 (GQL-15) questionnaires. These statistics were analysed in parallel with glaucoma severity amongst the inclusive patients as well as the number and type of drops administered by the individuals. The GQL-15 used in this study comprises of 15 items linked to visual disability from visual field loss and was originally piloted by Nelson and colleagues (1999) (Nelson et al., 2003, Nelson et al., 1999). By combining these outcome measures, they found a positive correlation between OSD and glaucoma severity, and in turn, poorer QoL scores on GQL-15. In fact, it was found that the GQL-15 score was a direct predictive indicator of OSDI scores (odds ratio [OR] 4.14, 95% confidence interval [CI] 2.59–6.63, P <0.001) (Skalicky et al., 2012).

Similarly, a survey carried by Nordmann and colleagues (2013), found that 62.4% of the patients suffered from at least one ocular side effect to their glaucoma medication. This in turn translated to poorer QoL scores as reflected by the results of the National Eye Institute Visual – Function Questionnaire (NEI-VFQ-25), a condensed form of the 51 item questionnaire assessing vision and health related quality of life (Mangione et al., 1998a). Burning, blurred vision and tearing were the most reported side effects in this survey. Furthermore, dry eyes was one of the six side effects related with over half of the measures of the NEI-VFQ-25. Patient satisfaction was also strongly associated with QoL; those who were not satisfied with

their treatment had a poorer QoL and more frequent appointments with their clinicians (Nordmann et al., 2003).

5.1.4 Current risk factors for developing OSD

5.1.4.1 Aging

Increasing age has been positively attributed with developing DED. There is some variance amongst available studies as to the exact figures of prevalence of DED across different age brackets, depending on what measures were used to classify dry eye. The meta-analysis carried out by TFOS DEWS II indicates little change in signs and symptoms of DED under 50 years of age, with increasing DED from 50 years onwards, with a more prominent increase amongst 80+ years (Stapleton et al., 2017).

Several studies indicate that older age is a risk factor to developing DED (Schaumberg et al., 2003, Schaumberg et al., 2009, Ahn et al., 2014, Viso et al., 2009). An example of such by Moss and colleagues (2000) found that the prevalence of DED was 8.4% in those under 60 years of age, increasing significantly to 19% in those over 80 years ($p<0.001$) (Moss et al., 2000). Similarly, when Moss and colleagues (2004) investigated the incidence of dry eyes amongst a cohort of patients in the Beaver Dam study, they also found a significant association between increasing age and the incidence of dry eyes. The incidence of DED over a 5 year study period was 10.7% in those aged 48-59, compared to 17.9% in those aged 80 and over (Moss et al., 2004).

There has been particular interest in the older population and the presence of dry eyes. Several studies have specifically looked into DED in the elderly population, such as that by Uchino and colleagues (2006) carried out in Japan, where only those aged 60 and over were recruited. Within this population, 73.5% of eyes displayed definitive signs of dry eyes (Uchino et al., 2006). Similarly, studies carried out globally in Spain and China with adult populations echo similar findings; dry eye was significantly linked to aging ($p<0.001$) (Viso et al., 2009, Jie et al., 2009).

Such findings are not surprising given the complex biological changes which occur with aging. Morphological lid changes, decreased tear film production and comorbidities are all associated with older patients which in turn could expose them to increased risks of developing DED (Obata, 2002, Vehof et al., 2021, Arita et al., 2008, Bozek et al., 2016).

There has been some criticism that many studies investing DED risk factors have only considered samples of older populations, and thus, overlooking potential trends within a younger population. In an effort to address this, Paulsen and associates (2014) set out to explore the prevalence of DED amongst a predominantly middle-aged cohort, with participants ranging from 21 to 84 years old. Diagnosis of DED was purely subjective, with the use of self-report methods or interviews. Results showed that the prevalence of DED was indeed higher amongst those aged 50 and older, compared to those aged 2-49 years (15.2% vs 14.1%), albeit this difference was not clinically significant (p=0.06) (Paulsen et al., 2014).

A recent large-scale study involving 79,866 participants and investigating the risk factors of DED, found that 20-30 year olds were particularly symptomatic of dry eyes. Specifically, this age group showed the highest prevalence of DED in men compared to other decades when basing analysis on symptoms alone. Although clinical diagnosis of DED and the use of ocular lubricants do suggest a positive correlation with age, this study highlights the overlooked younger population who may be symptomatic due to an ever-evolving digital lifestyle (Vehof et al., 2021).

5.1.4.2 Female Sex

The TFOS DEWS II Epidemiology report lists ‘Female sex’ as one of the top, consistent and non-modifiable risk factors for developing DED (Stapleton et al., 2017). Much of the current literature supports the notion that dry eye disproportionately affects women more than men (Ahn et al., 2014, Viso et al., 2009, Hashemi et al., 2014). Epidemiological studies provide the best insight into this, by eliminating potential discrepancies with sexes in clinical based care settings.

An example of such large-scale population-based epidemiology study by Schaumberg and colleagues (2003) found an overall prevalence of around 7.8% in women (Schaumberg et al., 2003). In comparison, a similar large-scale study carried out amongst a male population of physicians found a prevalence of about 4.4% (Schaumberg et al., 2009). Both studies made age-based adjustments, and these prevalence values reflect the rates amongst those aged 50 and older. Comparing these in parallel, the prevalence of DED is significantly higher in women than in men, translating to around a 70% increased risk amongst women of developing DED (Sullivan et al., 2017). Interestingly, both studies reflect an increase in prevalence of DED with increasing age (5.7% in women under 50 years old vs 9.8% in women aged 75 and over, and

3.9% for men aged 50-54 vs 7.7% for men aged 80 and over) (Schaumberg et al., 2003, Schaumberg et al., 2009).

These findings are corroborated by results from the Beaver Dam Study and the Beaver Dam Offspring Study (BOSS), both of which investigated the risk factors and prevalence of DED. Significant differences were found between sexes, with higher rates of dry eye amongst women. In the Beaver Dam Study, prevalence of DED was 16.7% in women and 11.4% in men ($p<0.001$) which equates to almost 50% higher rates for women once corrected for age (Moss et al., 2000). Similarly, for BOSS, figures also echoed such disparity between sexes; prevalence of dry eye was 17.9% for women and 10.5% for men ($p< 0.0001$) (Paulsen et al., 2014).

Furthermore, there is substantial evidence from studies conducted in Asian populations, which also show such differences between men and women (Hua et al., 2014, Uchino et al., 2013, Han et al., 2011, Tan et al., 2015). An example of such, the Beijing Eye Study, found the odds of developing symptomatic dry eye were significantly linked with female gender ($P<0.001$; OR1.56, 95% CI 1.23-1.98) (Jie et al., 2009).

Several factors have been attributed to this difference found between sexes. Hormones, specifically the sex steroids of oestrogen, progesterone and androgens, can influence the homeostasis of the ocular surface by altering tear film composition (Krenzer et al., 2000, Truong et al., 2014, Suzuki et al., 2008). Oestrogen, primarily produced by the ovaries in females, can act as an antagonist to androgen, both of which influence the meibomian glands and their contribution to a healthy tear film (Sullivan et al., 2009, Suzuki et al., 2008, Truong et al., 2014). While androgen promotes lipid production and secretion, oestrogen counteracts this by reducing lipid production (Sullivan et al., 2000, Suzuki et al., 2008). When this balance is disrupted, as in postmenopausal women on hormone replacement therapy (HRT) or in cases of androgen deficiency, meibomian gland dysfunction (MGD) and DED can become apparent (Krenzer et al., 2000, Schaumberg et al., 2001).

Sex specific differences have also been detected at an anatomical level. As outlined by the TFOS DEWS II report, such differences occur with the cornea, the conjunctiva, the lacrimal gland, the nasolacrimal duct, the meibomian gland and the tear film (Sullivan et al., 2017). Suzuki and colleagues (2009) explored this by examining gene expression in human corneal epithelial cells. They found sex related differences in over 600 of these genes *in vivo* and, to a slightly lesser extent, *in vitro* using cultured human epithelial cells. Interestingly, females

showed elevated levels of gene expressions associated with the enzyme transglutaminase 1, which is involved in protein cross-linking. Increased levels of this enzyme correlate with dry eye and corneal keratinisation (Nakamura et al., 2001, Chen et al., 2008, Suzuki et al., 2009).

5.1.4.3 Systemic medication

Several medications have been associated with developing DED. In the longitudinal Beaver Dam Study, a strong link was found between four classes of drugs, which increased the odds of developing dry eyes: antidepressants, anti-anxiety drugs, antihistamines and oral steroids. To a lesser extent, diuretics were also positively associated with dry eye. Moreover, those taking or previously having taken vitamins also showed an increased incidence of dry eyes, once adjusted for age (Moss et al., 2008).

Schaumberg and associates (2009) investigated the prevalence and risk factors of DED amongst older, male participants from the Physician's Health Studies. In this population, risks of DED were almost 2-fold higher in men being medically treated with antidepressants. Those who were on medication for benign prostatic hyperplasia also showed a significant link to DED (Schaumberg et al., 2009).

Polypharmacy is very common in the elderly population (Slabaugh et al., 2010). Antecedent-consequent relationships are difficult to ascertain when a combination of drugs can interact with each other and perhaps increase the odds of DED, which would otherwise go undetected if only treated with a single drug. Furthermore, it is challenging to associate a single drug to DED, and so the association is made with drug groups instead. Lastly, drugs may solely increase the risks of DED, they could do so in combination through polypharmacy, or indeed the main causative agent in developing DED could lie with the comorbidity rather than the treatment for it (Fraunfelder et al., 2012).

TFOS DEWS II classifies drug classes into three categories of possible risk. These are described as consistent, probable and inconclusive, depending on the supporting evidence available. From this, antihistamines, antidepressants, anxiolytics, isotretinoin fall into the consistent category and so form a strong risk to DED (Galor et al., 2012, Stapleton et al., 2017, Neudorfer et al., 2012). Probable risks are associated with anticholinergic, diuretics, beta-blockers (Ozen Tunay et al., 2016, Moss et al., 2008, Fraunfelder et al., 2012, Fraunfelder FT, 2008). Lastly, inconclusive links are associated with multivitamins and oral contraceptives (He et al., 2021, Moss et al., 2000).

5.1.4.4 Comorbidities

Systemic

Several systemic conditions have also been linked to DED. Of these, the main one that presents itself repeatedly in literature is diabetes. A case control study by Manaviat and colleagues (2008) found the prevalence of DED within a diabetic population of 54.3%. Furthermore, this association between DED and diabetes appears to be significant depending on the duration of diabetes ($p=0.01$), as well as the presence of diabetic retinopathy (DR) ($p=0.02$) (Manaviat et al., 2008).

Similarly, Najafi and colleagues (2013) also mimicked this association between DED and DR and found this relationship to be significant ($p=0.01$). However, unlike Manaviat and colleagues (2008), Najafi and colleagues (2013), found the prevalence of DED to be much lower amongst their diabetic participants, at 27.7% (Najafi et al., 2013).

The reason for such discrepancies between studies could lie with the measures used to diagnose DED. Diabetes can lead to morphological corneal changes which ultimately lead to a reduction in the sensitivity of the cornea (Rosenberg et al., 2000). Thus, the prevalence of DED amongst diabetics may be underestimated, when relying on subjective self-report measures for diagnosis of DED (Stapleton et al., 2017).

Another consistent risk factor for dry eye is Sjögren's Syndrome. Sjögren's Syndrome is an autoimmune disorder affecting the endocrine glands, with particular effects on the salivary and lacrimal glands leading to xerostomia and dry eyes (Borchers et al., 2003). An investigation looking into the occurrence of Keratoconjunctivitis Sicca (KCS) using an international Sjögren's Syndrome registry found that 85% of patients reported symptomatic dry eye, with roughly half of these experiencing such symptoms for over five years (Whitcher et al., 2010).

Sjögren's Syndrome is typically classified into two categories, Primary Sjögren's Syndrome and Secondary Sjögren's Syndrome, with the latter associated with connective tissue diseases such as Rheumatoid Arthritis (RA) whilst the former is not. In one study evaluating patients diagnosed with DED, around 26% had some form of underlying rheumatic disease, with 10.9% of them being diagnosed with PSS and 11.4% with RA (Akpek et al., 2009).

Ocular

MGD is regarded as a pivotal factor in contributing to dry eyes. The International Workshop on MGD defines it as:

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

The obstruction of the meibomian glands has been closely linked to the evaporative branch of dry eye (Bron and Tiffany, 2004). In a study by Lemp and associates (2012), Schirmer testing and MGD scoring were used to evaluate the distribution of patients falling into the aqueous deficient and evaporative DED categories. Subsequently, it was found that 86% of dry eye patients who presented with aqueous deficient dry eye, evaporative dry eye or a combination of the two, showed signs of MGD (Lemp et al., 2012).

Similarly, Viso and colleagues (2011) also found a strong association between both symptomatic and asymptomatic dry eye and the presence of MGD in their study looking at a random sample from a Spanish population. DED diagnosis was made using both subjective and objective measures, with participants being classed as such only at the concurrent presentation of dry eye symptoms and evidence of at least one positive sign. The prevalence of DED was found to be 11% within this population and 30.5% for MGD. Moreover, 45.8% of those diagnosed with DED also had MGD. The odds of MGD in DED were highly associated with both symptoms (OR=2.26) and signs of DED (Tear Break Up Time OR=1.97, Fluorescein staining OR=2.09) (Viso et al., 2011). On the whole, MGD appears to present asymptomatically more than symptomatically, a point which requires noting when investigating MGD (Viso et al., 2012).

5.1.4.5 Asian Race

It is well documented that Asian race is a significant risk factor for DED (Stapleton et al., 2017). Disparities in the rates of dry eye appear to be apparent between Asians and Caucasians and are probably due to the physiological differences between the races (Craig and Wang, 2019, Craig et al., 2019). Asians appear to be predisposed to incomplete blinking, which may be linked to amplified eyelid tension, exhibit higher levels of MGD and show increased lid wiper epitheliopathy, when compared to age and sex matched Caucasians (Craig et al., 2019, Yamamoto et al., 2016, Kim et al., 2019). Such differences may account for the three-fold

increased risk of DED, when basing diagnosis on the TFOS DEWS II diagnostic criteria (Craig et al., 2019).

Furthermore, MGD appears to be highly prevalent amongst Asians (Siak et al., 2012). Significantly greater levels of Meibomian gland dropout and poorer quality secretions were observed amongst Asian participants in a study by Craig and colleagues (2019), who looked at ethnic differences in the pathophysiology of dry eye (Craig et al., 2019). This tendency to MGD as well as incomplete blinking, may be the crucial reason to the increased prevalence of DED in Asian populations (Craig et al., 2016, Guo et al., 2010).

5.1.4.6 Additional factors

Several other factors have also been associated with increased risks of developing DED. These are categorised depending on the body of literature supporting their contribution, as well as classing them as non-modifiable or modifiable, by TFOS DEWS II (see Table 5.1) (Stapleton et al., 2017). Such risk factors include contact lens wear (Uchino et al., 2008, Paulsen et al., 2014), use of a visual display unit (VDU) (Uchino et al., 2013) and laser-assisted in situ keratomileusis (LASIK) procedures (De Paiva et al., 2006).

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

Table 5.1: Adapted from TFOS DEWS II Epidemiology report. A summary of risk factors associated with OSD and their probable influence (Stapleton et al., 2017).

5.4.2 The overlap of risk factors for OSD and Glaucoma

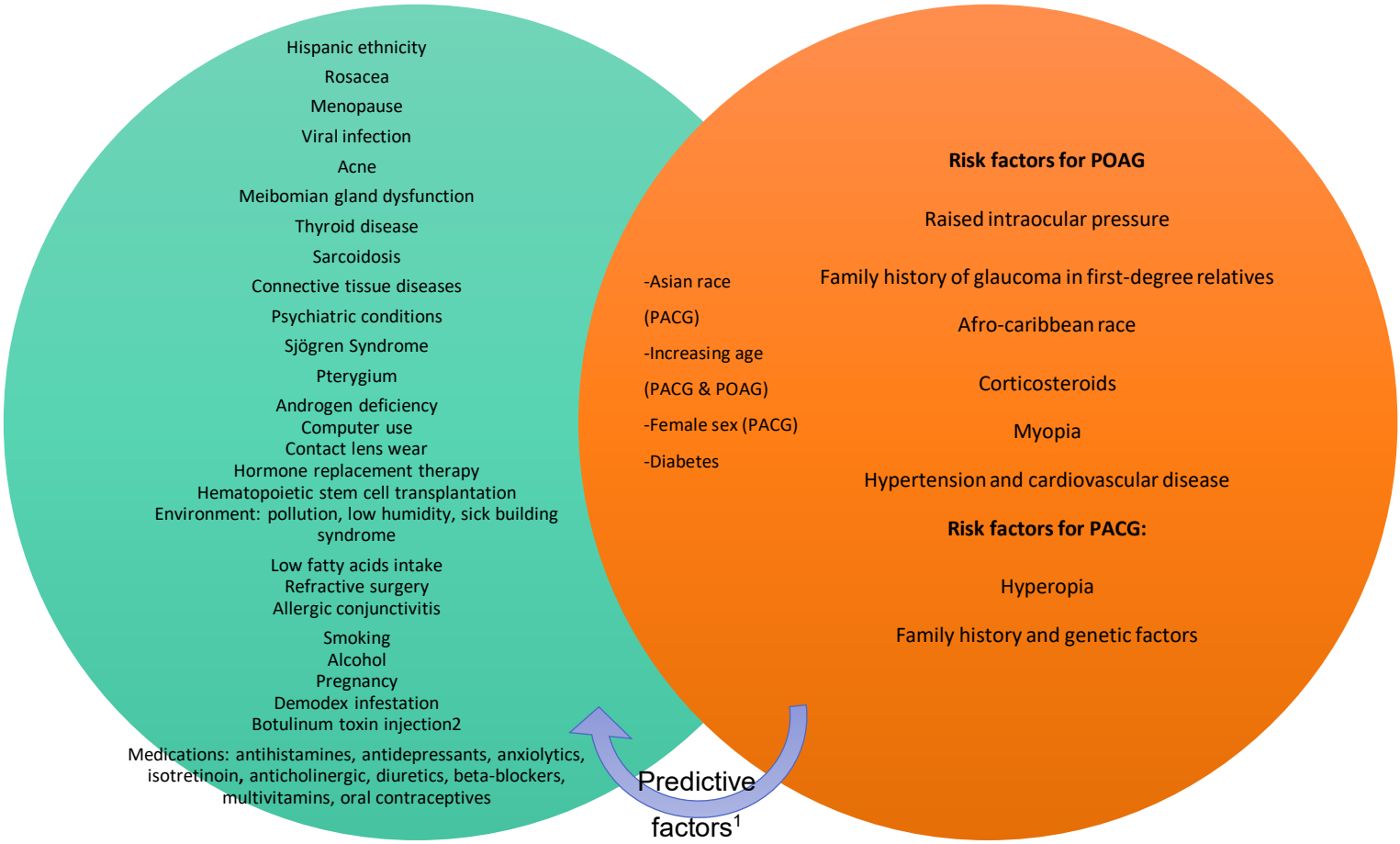


Figure 5.1: Venn diagram outlining the risk factors of OSD and glaucoma. [1]A potential link of predictive factors, which may increase the risk of developing OSD in those who are diagnosed and treated for glaucoma. Sources for these risk factors are from the TFOS DEWS II Epidemiology report and from NICE (National Institute for Health and Care Excellence, 2022, Stapleton et al., 2017).

Glaucoma and OSD coexist in clinics. There is also some overlap of risk factors, which simultaneously occur in both glaucoma and OSD (Figure 5.1). OSD is highly prevalent amongst glaucoma sufferers, and so there is a possibility that there are further risk factors or predictive factors which exist, that would make one susceptible to developing dry eye whilst being treated for glaucoma. Therefore, this retrospective audit set out to investigate such correlations, by looking at the demographics and clinical metrics of patients presenting to the glaucoma clinics,

following their glaucoma journey to examine the indicators which heighten a person's risk to developing OSD.

5.2 Aims and Objectives

- To investigate the demographics of the glaucoma patients presenting at Russells Hall Eye Clinic, (Dudley NHS Trust, UK), in the West Midlands
- To identify risk factors associated with developing OSD during medical glaucoma treatment

5.3 Methods

The retrospective audit was undertaken at Russells Hall hospital (RHH) (Dudley NHS Trust, UK) based in the West Midlands. The audit department at RHH use the 'Audit Management and Tracking' (AMaT) software for the purposes of hospital audits and service evaluations. This software enables the creation of official audits, from the design of the Pro-forma through to implementing action plans on completion. As the audit was undertaken at RHH, official procedures were employed and the process was carried out through AMaT.

The initial audit was registered on AMaT in 2019. However, due to the COVID-19 pandemic and redeployment of hospital staff, data collection did not commence until September 2020. Records for the audit were selected by the audit department at RHH, with the criteria that patients had visited the glaucoma clinic in the timeframe of July 2018 to July 2019. In particular, these patients were required to have attended the 'New Glaucoma Clinic' on a Friday afternoon; a clinic dedicated to new patients who have been referred as suspect glaucoma or OHT cases. This clinic also uses a pre-set consultation template designed by the lead glaucoma consultant at RHH for recording purposes. Each visit therefore includes all relevant data on previous history, current personal information (including medication, comorbidities and lifestyle details) as well as all the necessary clinical information required as advised by NICE guidelines. The Pro-forma for this audit was based predominantly on this template for two reasons: a) to ensure that all the necessary information was available for each patient at each visit and b) it covered all the necessary information that was needed to look at predictive factors retrospectively.

Ideally, records were only selected if they had used this set clinic templates. This was not always possible, since certain consultants use a blank sheet for their consultations as a personal preference, rather than the provided clinic templates. In addition, the clinic templates only came into action a few years ago. Any records of patient visit before this time would rely on freehand note taking from the clinician. Those records which were obtained from the audit department but were unsuitable for the study, were classed into four main categories of rejection: diagnosed earlier in pathway before seeing the glaucoma consultant, unsuitable records, illegible handwriting and incomplete notes/old notes missing. This formed the basis of the exclusion criteria.

Inclusion criteria

- Seen in the RHH glaucoma clinic as a suspect glaucoma/OHT patient, and subsequently treated with either hypotensive drops or laser/surgery after a positive diagnosis, or continued to be monitored as a suspect case
- Treatment-naïve on arrival into the RHH glaucoma clinic
- Information available on patient history, medication, comorbidities, lifestyle, ethnicity and clinical data

Exclusion criteria

- Diagnosed and commenced treatment earlier in pathway in other ophthalmic clinic/hospital before seeing glaucoma consultant and so lacking the required baseline measures
- Unsuitable records-discharged/no signs of glaucoma/patient missed appointments so discharged/missing baseline information
- Illegible handwriting
- Incomplete or missing notes

5.3.1 Ethics

As this was a retrospective study, an audit application was made to both RHH and Aston University for permission to commence this study as an audit.

Furthermore, Good Clinical Practice (GCP) had to be undertaken by all participating researchers before any collection of data at the hospital.

5.3.2 Pro-forma

A provisional Pro-forma was drafted and then distributed to two leading optometry academics at Aston University, as well as the lead glaucoma consultants at RHH. It was modified according to the feedback received. The final version was then designed on AMaT. The order of the Pro-forma followed the template used in clinics to allow for easier data collection by enabling information to be located in the right order. Forty-six items were identified for the Pro-forma. The final Pro-forma, as set out on AMaT, has been attached in Appendix 10.

5.4 Results

The initial audit had to be completed on AMaT by March 2021 due to internal hospital deadlines, and so an interim analysis was performed on the 46 records obtained between October 2020 to March 2021. A re-audit was then submitted in May 2021, which allowed for further data collection. No changes were made to the original Pro-forma on resubmission. The timeframe of patient visits was changed from 01/04/2014 to 19/05/2021, to allow for a larger range of suitable records to be used. The audit was completed in October 2021, with an additional 55 suitable records added incorporated into the analysis. In total, 331 records were screened for this audit. Of these records, 101 were suitable and met the inclusion criteria. The remaining 230 records were excluded as they fell into one of the four categories of exclusion.

5.4.1 Demographics

The audit comprised of 54% females and 46% males. The majority of patients were aged 65 and over (63%), followed by those aged 55-64 (20%) and 45-54 (13%). A smaller minority fell into the age bracket of 35-44 (3%) and 18-24 (1%).

The most common ethnicity in the audit was Caucasian (89%). Asian and Black ethnicities made up a smaller percentage of patients at 5% each. Only 1% of the patient base belonged to a mixed ethnic group.

In terms of social status, 30% of patients lived alone while the remainder lived with someone else. Most of the included patients were retired (62%), and most were married (57%). The remainder were either widowed (13%), single (9%), had a partner (5%) or were divorced (3%). The information on marital status was unavailable for 12% of the patients.

Non-smokers made up the biggest proportion of patients (94%), the rest being smokers. Seventy-three percent of patients were non-drinkers, 23% casual drinkers, and the remaining 4% alcohol dependent.

The vast majority of patients did not have a family history of glaucoma (FHG) (67%). Mother was the most common relation in terms of FHG (16%) followed by sister (10%). Grandparents, father and brother make up smaller proportions of FHG links at 6%, 4% and 4% respectively.

5.4.2 1st Visit Baseline information

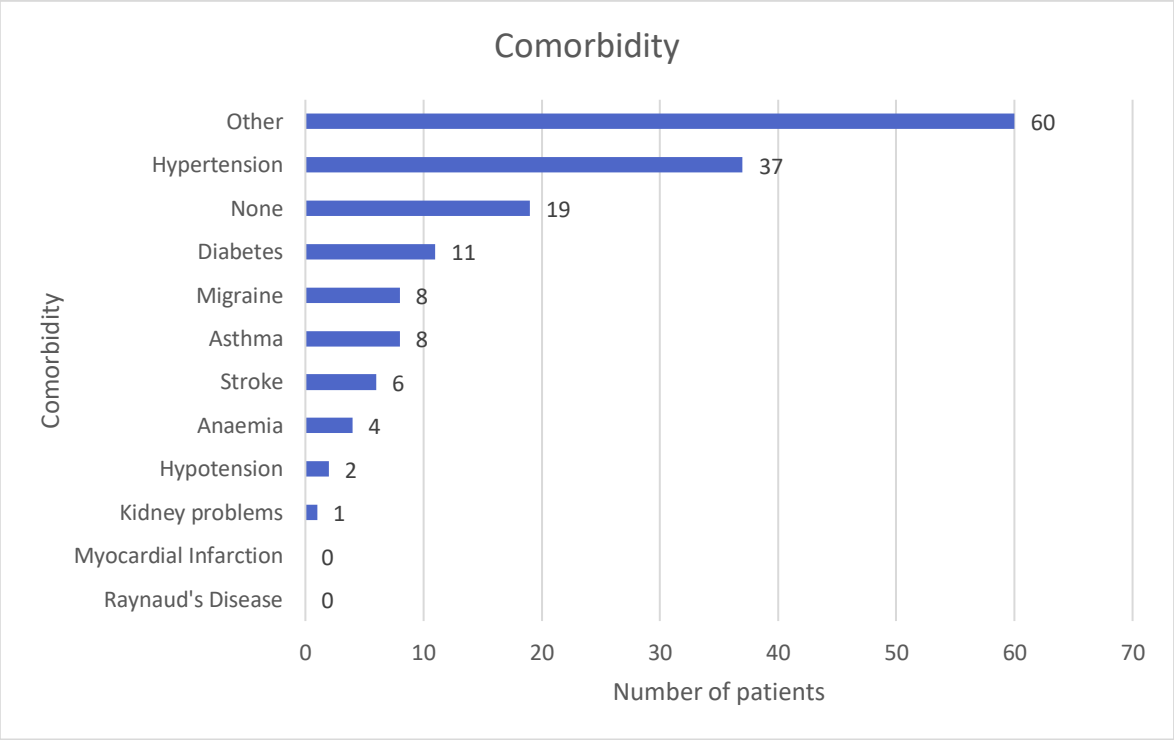


Figure 5.2: Common comorbidities presenting in the RHH glaucoma clinics at the initial visit

The most common comorbidity presenting at the initial visit in the glaucoma clinics at RHH was hypertension, with 37% (n=37/101) of patients having this condition. Diabetes, asthma, migraine and stroke were the next most commonly reported comorbidities with 11% (n=11/101), 8% (n=8/101), 8% (n=8/101) and 6% (n=6/101) of patients suffering from these conditions, respectively.

Nineteen percent of patients did not suffer from any other conditions at all. The vast majority of patients were classed as having 'other' comorbidities (59%). Unfortunately, due to the AMaT system of recording, it is not possible to know what these other conditions were specifically.

The AMaT list followed the clinic template listing only common conditions associated with glaucoma, or those which would be implicated by potential treatment options.

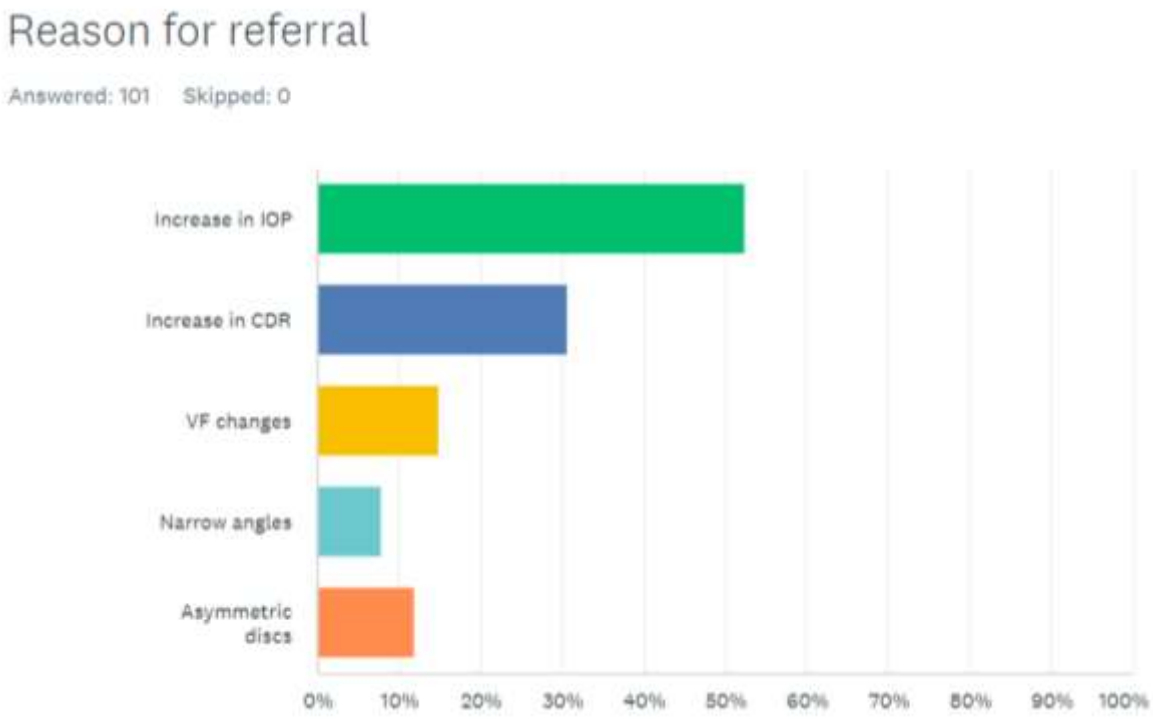


Figure 5.3: Reasons for referral into the glaucoma clinic as noted on the first visit.

The most common reason for referral was made based on elevated IOPs (52%, n=53), followed by increases in the cup-to-disc ratio (CDR) (31%, n=31/101) and visual field (VF) changes (15%, n=15/101). A smaller proportion were referred for asymmetric discs (12%, n=12/101) and narrow angles (8%, n=8/101).

5.4.3 Most common Medication

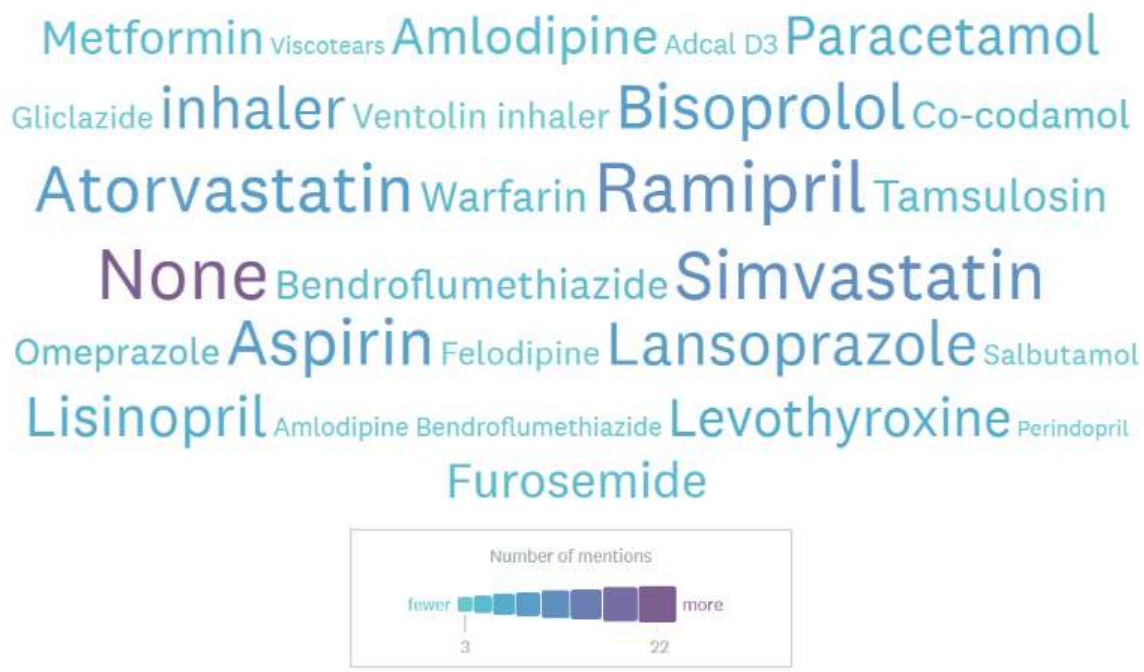


Figure 5.4: Word cloud demonstrating the most commonly mentioned medications

The top medications taken by patients were Ramipril (14%, n=14/101), Simvastatin (14%, n=14/101), Atorvastatin (12%, n=12/101), Aspirin (12%, n=12/101), Bisoprolol (11%, n=11/101), Lansoprazole (11%, n=11/101) and inhalers (11%, n=11/101). At the first visit, around 1 out of 5 patients did not take any medication at all.

5.4.4 Allergies

The vast majority of patients did not suffer from any allergies (80%, n=81). Penicillin was the most commonly reported allergy (9%, n=9). Thirteen percent (n=13) of patients had some form of allergy other than penicillin.

5.4.5 1st Visit- Baseline clinical data

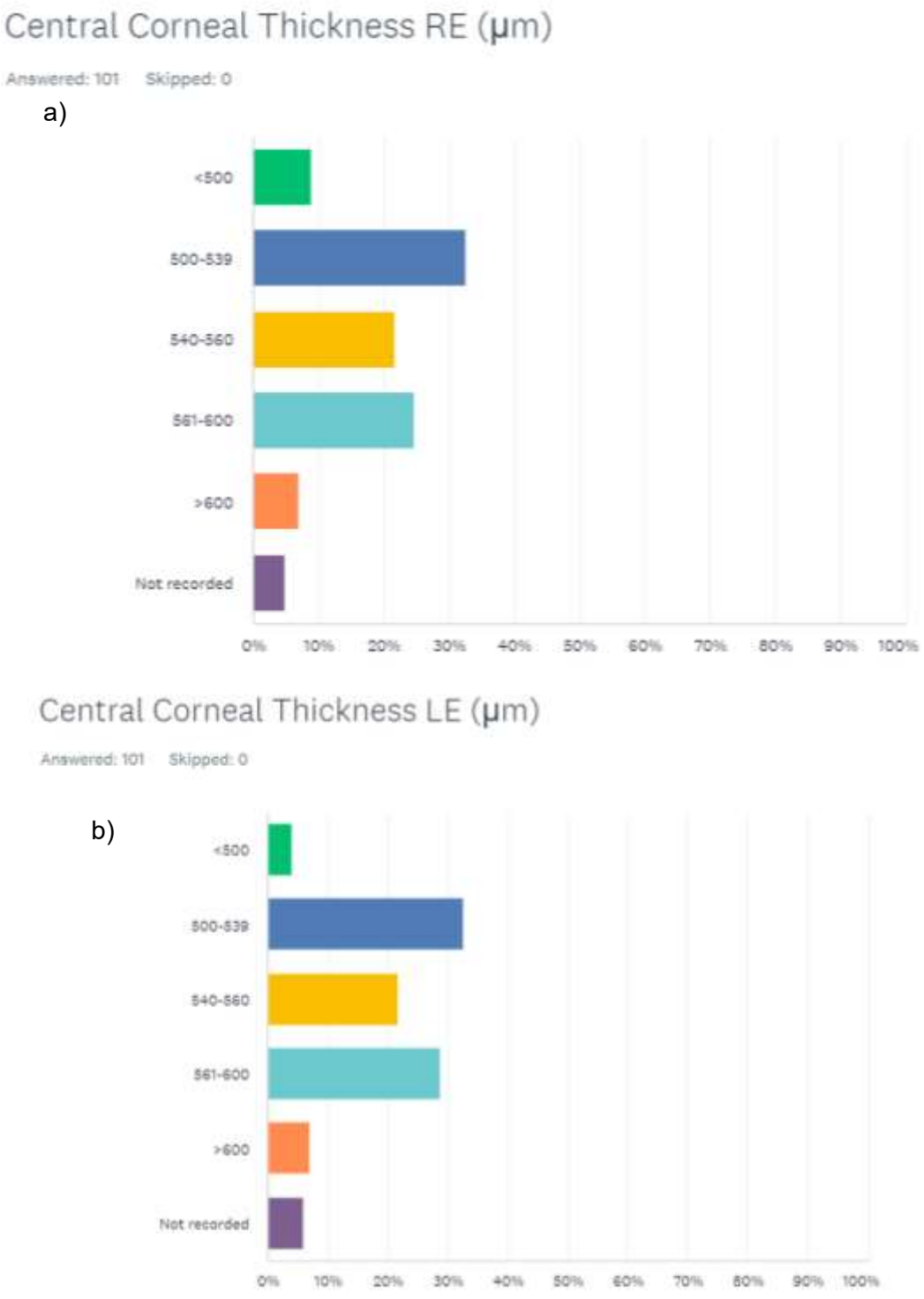


Figure 5.5 Range of CCT of patients presenting to the glaucoma clinics at the first visit for a) the right eye and b) the left eye.

Most patients had a central corneal thickness (CCT) on the slightly thinner side, with 33% having a CCT of 500-539μm for both the right eye (RE) and left eye (LE). Slightly thicker than average CCT was observed in 25% of patients for the RE and 29% for the LE. Patients falling into the average range of 540-560 μm were so for 22% of REs and 22% of LEs. The remainder had very thin CCT (9% RE, 4% LE), very thick CCT (7% RE and LE), or did not have this measurement taken at all (5% RE, 6% LE).

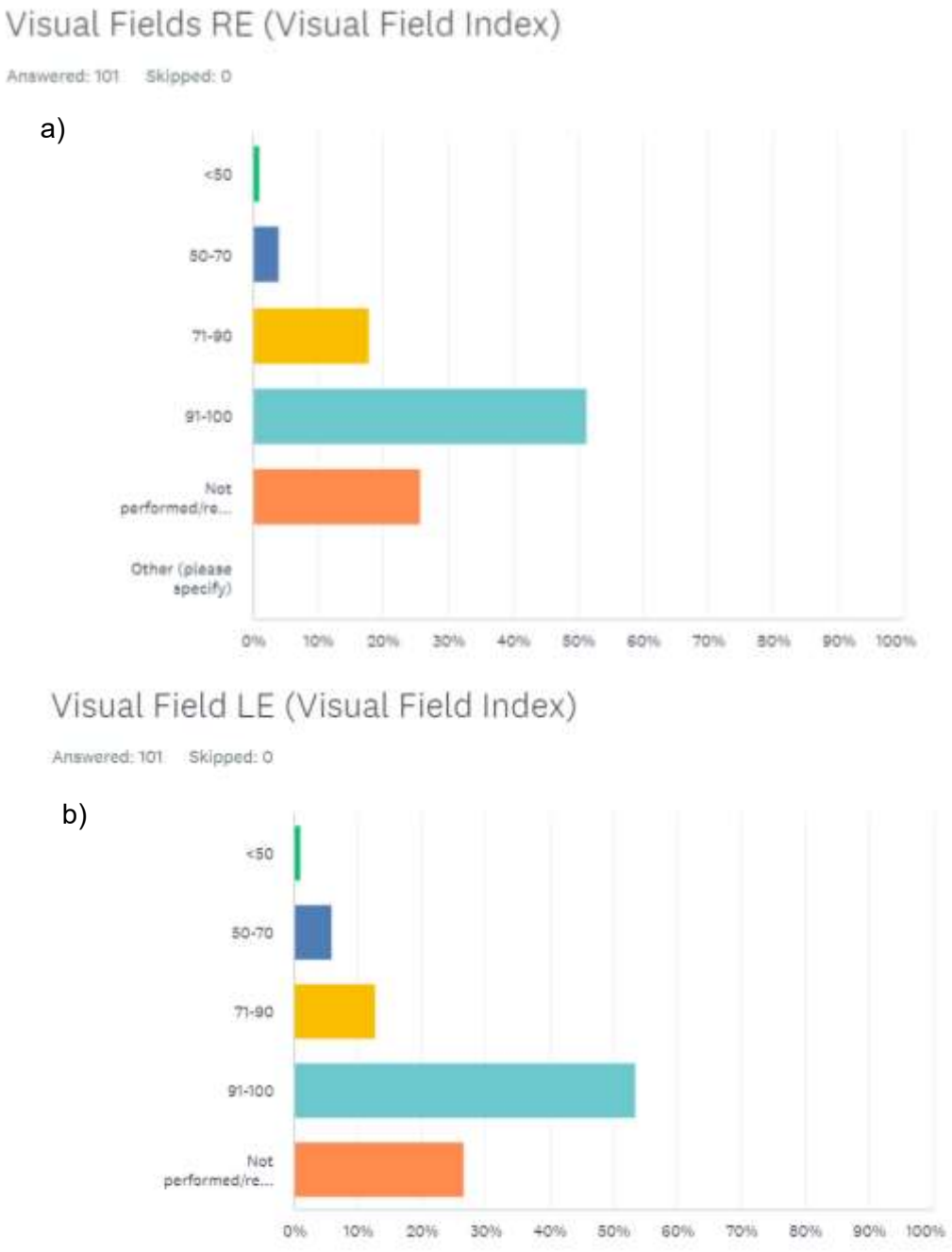


Figure 5.6: The spread of visual field indices for patients at the first visit for a) the RE and b) the LE.

The majority of patients had a visual fields index (VFI) of 91% to 100% for the RE (51%) and the LE (53%). To a lesser extent, patients had indices of 71-90% (18% RE, 13% LE), 50-70% (4% RE, 6% LE) and 1% had a VFI of less than 50% (RE and LE). This statistic was missing for many of the audited records (26% RE, 27% LE).

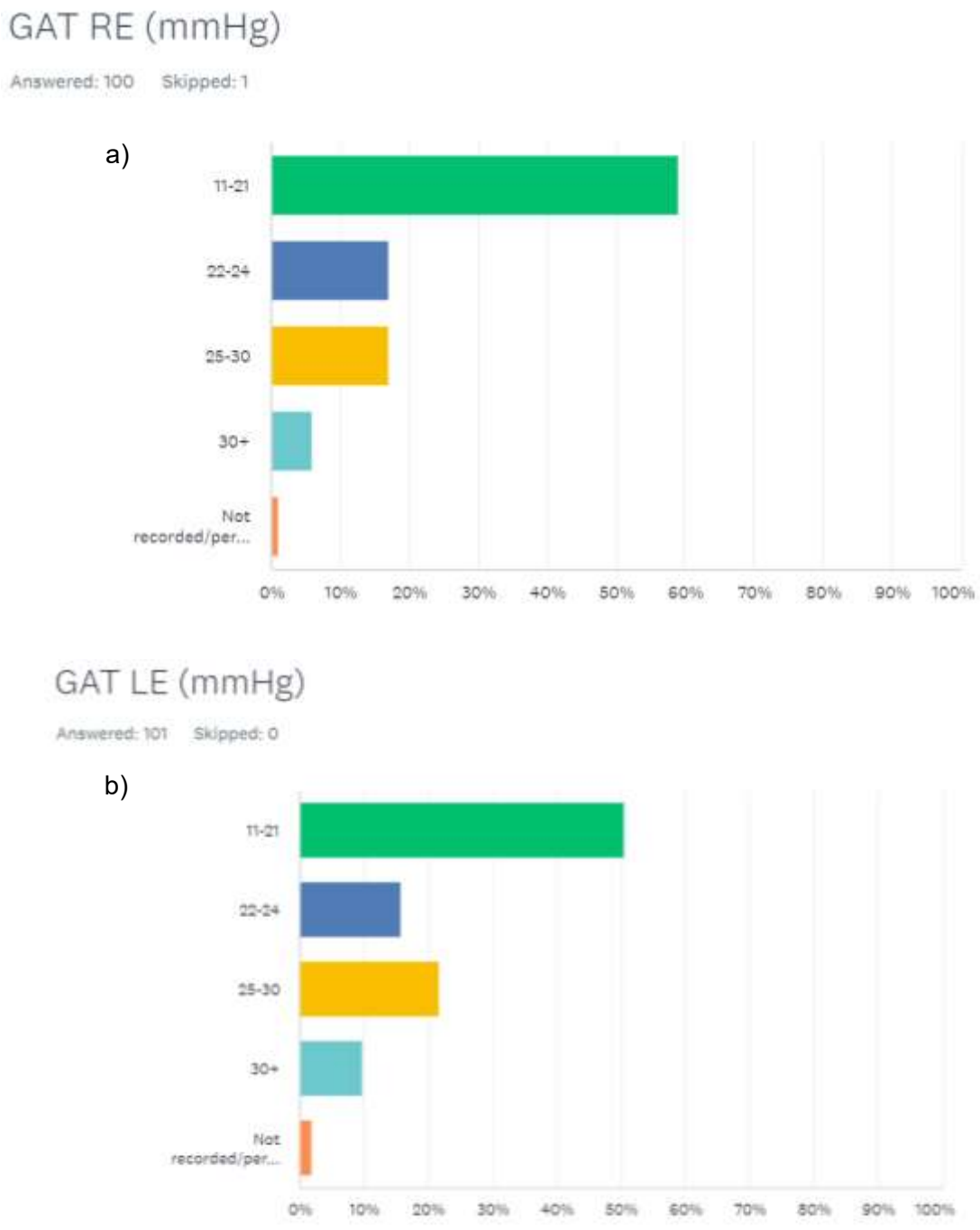


Figure 5.7: Range of IOPs encountered on the first visit for a) the RE and b) the LE.

Most patients presented with IOPs in the normal range of 11-21mmHg (59% RE, 51% LE). The number of patients with IOPs of 22-24mmHg and 25-30mmHg were similar for the RE (17% in each category), but slightly higher for the LE in the range of 25-30mmHg (22%) compared to 22-24mmHg (16%). An IOP of 30mmHg and higher was observed in 6% of REs and 10% of LEs.

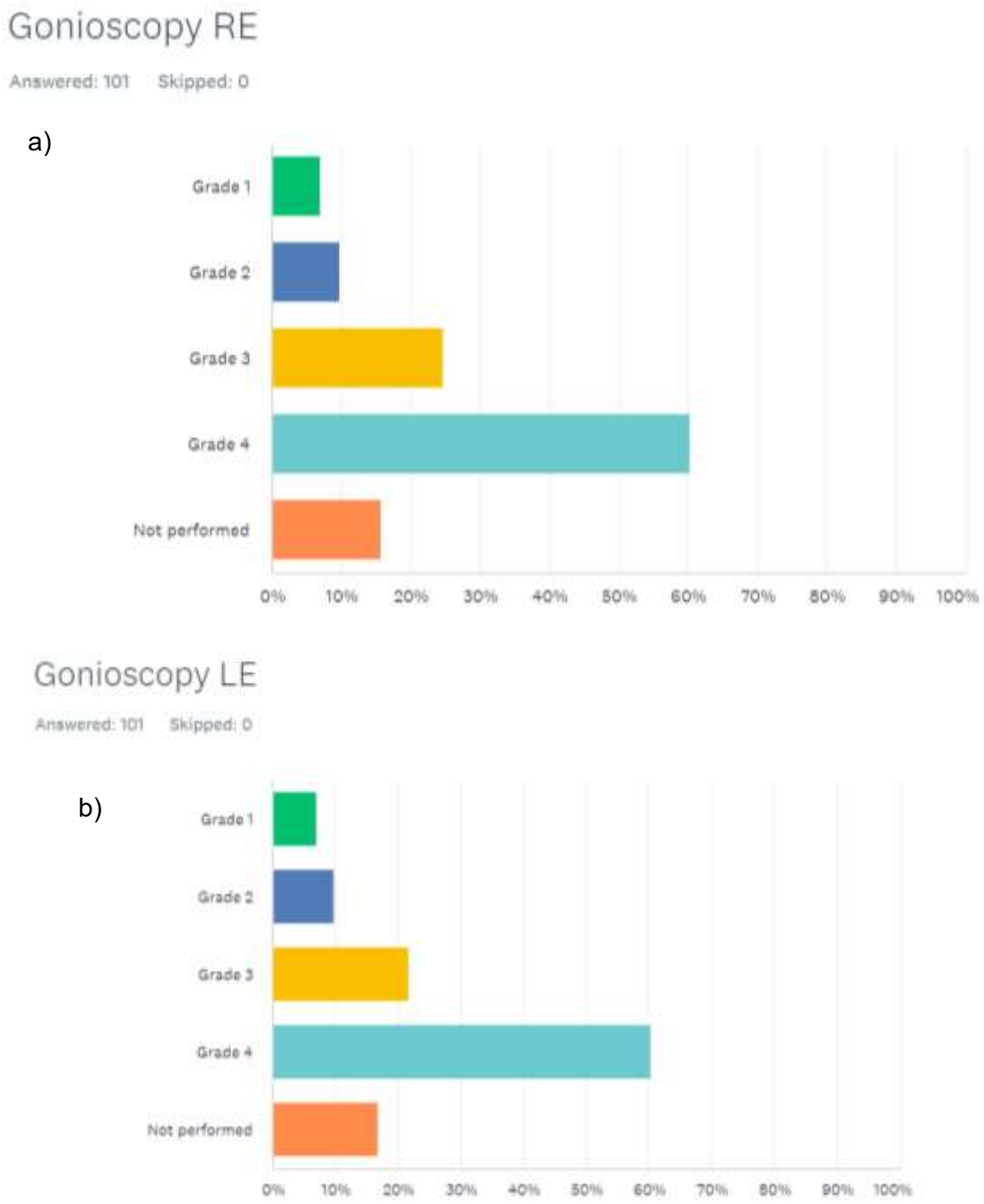


Figure 5.8: Range of Gonioscopy angles observed on the first visit for a) the RE and b) the LE.

For the majority of patients on visit 1, the angle appeared to be wide open at grade 4 (60% RE and LE). Grade 3 was the next most common grading, with 25% of patients falling into this category for the RE, and 22% for the LE. Grade 2 and grade 1 were the least common angles on presentation, with only 10% and 7% of patients having such narrow angles for the RE and LE, respectively. It should be noted that as gonioscopy angles are graded for four quadrants per eye, a patient may present with differing grades per eye. This overlap is the reason for the total responses exceeding the expected 101 in this case, however, percentages have been calculated out of the total number of patients, N=101.

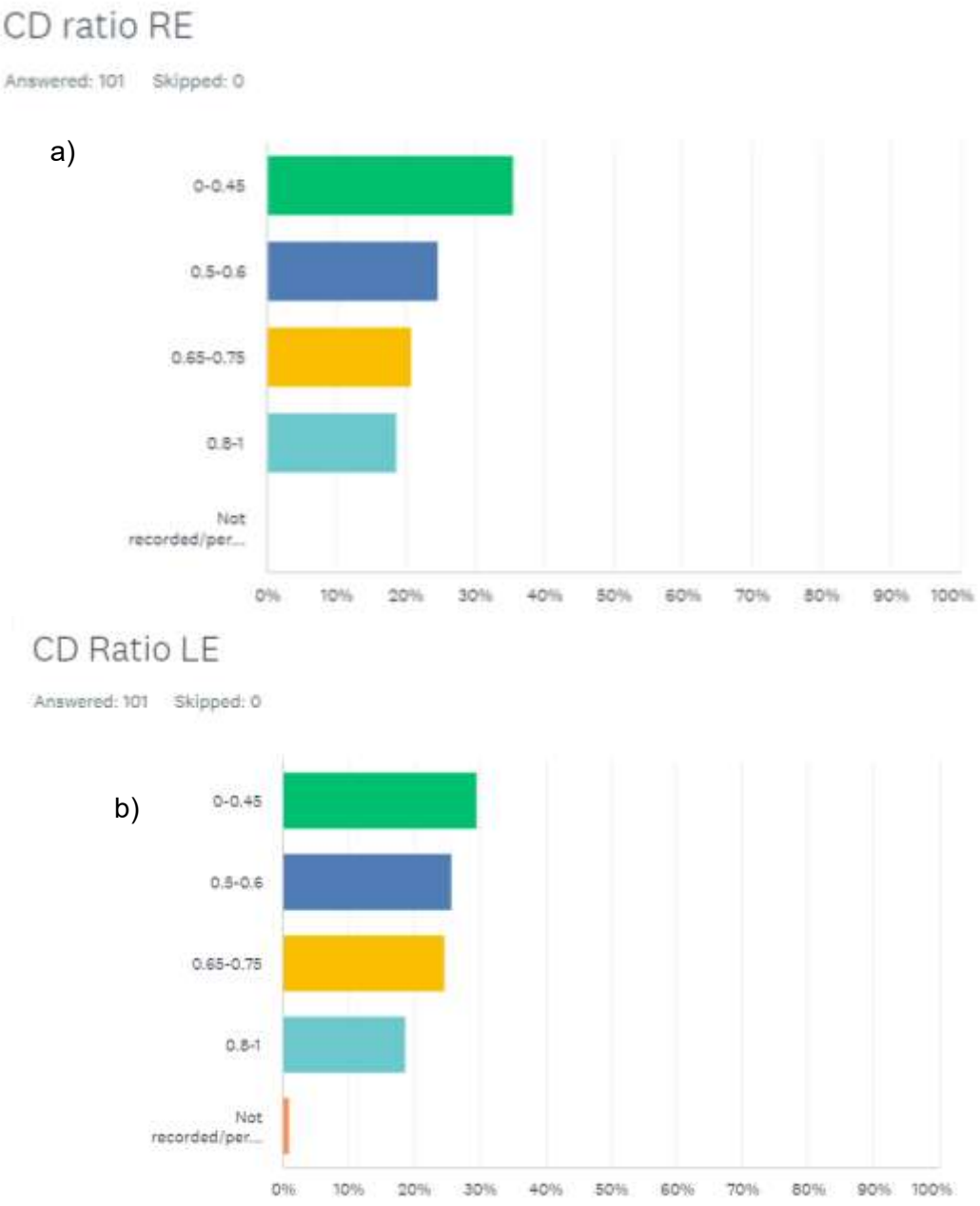


Figure 5.9: Bar chart of the distribution of CDRs for a) the RE and b) the LE, on the first visit.

A CDR of 0-0.45 appeared to be the most common presentation, with 36% of patients showing this for the RE, and 30% for the LE. For the RE, a CDR of 0.5-0.6 was the next most common, followed by 0.65-0.75 and 0.8-1, with 25%, 21% and 19% of patients falling into these categories, respectively. For the LE, a similar progressive pattern was followed with 26% of patients presenting with CDRs of 0.5-0.6, 25% with CDRs of 0.65-0.75 and 19% with CDRs of 0.8-1. This data was missing for one person for the LE only.

5.4.6 Diagnosis and management

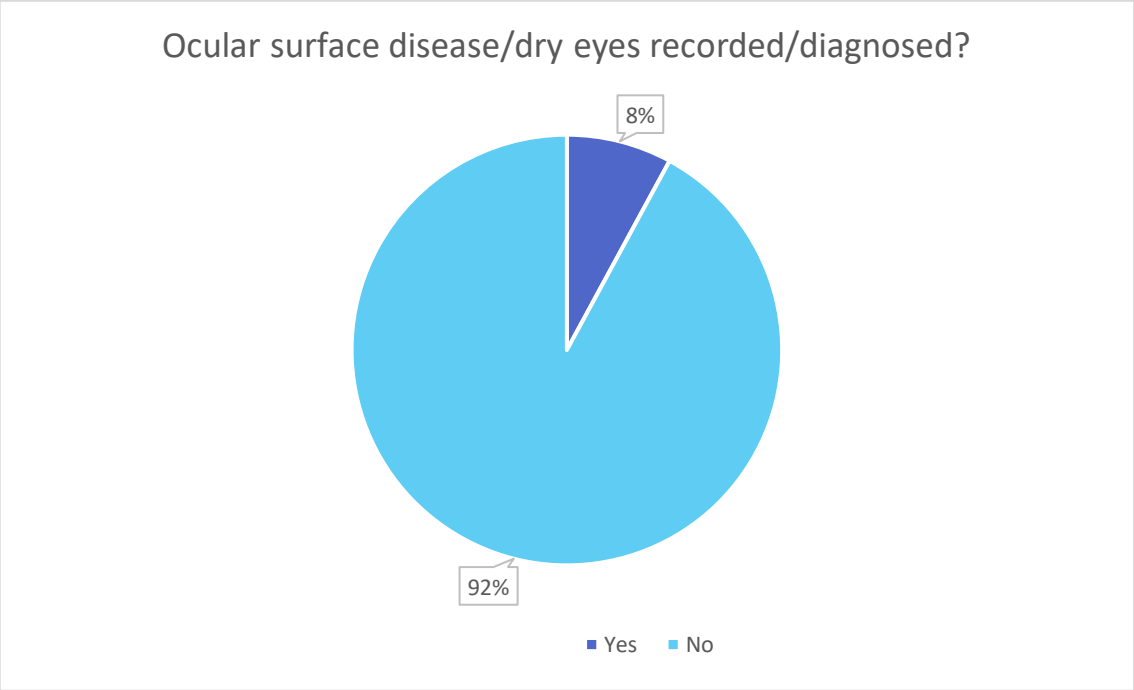


Figure 5.10: The percentage of patients who were recorded as having OSD on the first visit to the glaucoma clinic at RHH.

Out of the 101 patients screened for this audit, 92% were either not diagnosed with OSD or this information was missing from their records. Only 8% had OSD recorded on their first visit.

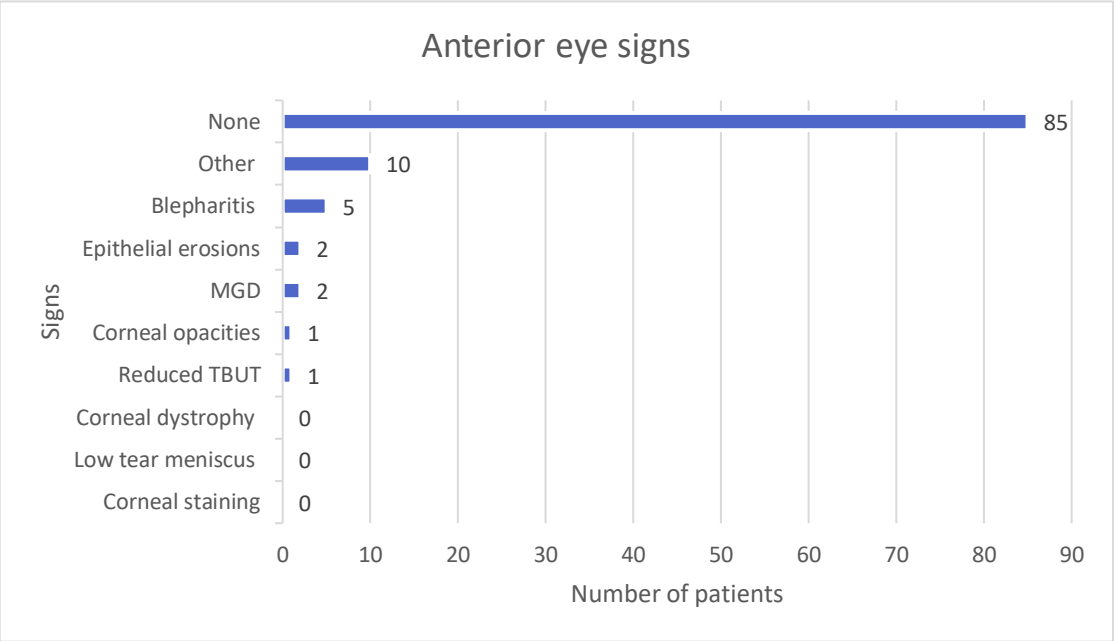


Figure 5.11: Anterior eye signs observed and noted at the first visit.

Figure 5.11 demonstrates the anterior eye signs noted at the first visit by the clinicians. The vast majority of patients did not have any stated anterior eye signs (84%, n=85/101), with 10% (n=10/101) showing 'other' ocular signs not listed. The remainder were recorded as having blepharitis (5%, n=5/101), MGD (2%, n=2/101), epithelial erosions (2%, n=2/101), corneal opacities (1%, n=1/101) and reduced tear break up time (TBUT) (1%, n=1/101).

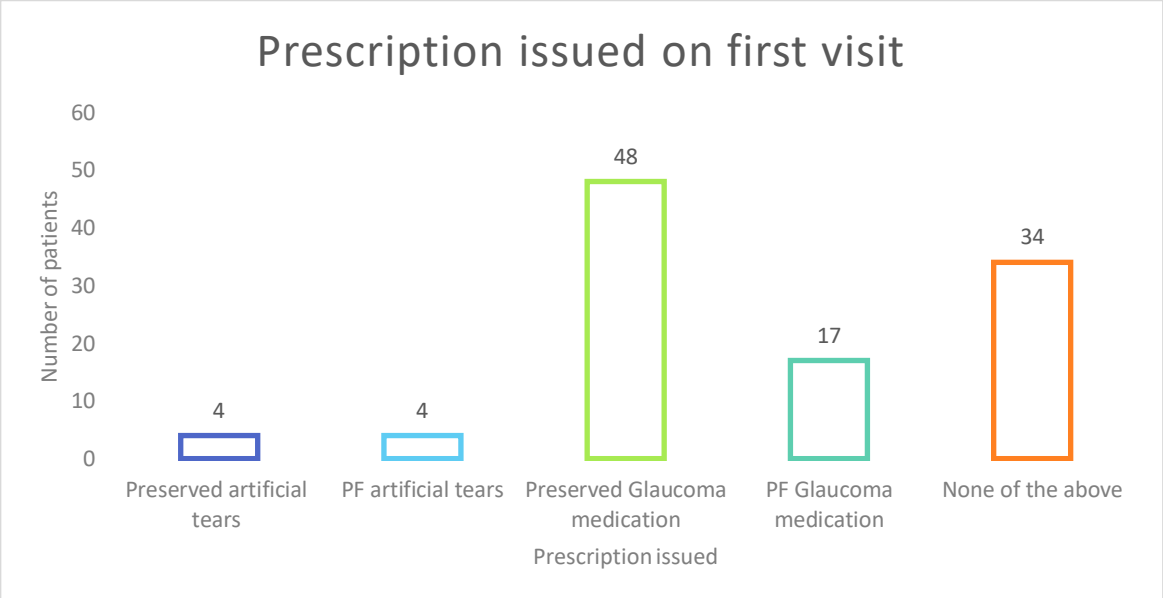


Figure 5.12: Outcomes of the first visit in terms of the drops prescribed by the clinician.

Most patients were prescribed preserved hypotensive drops at the first visit (48%, n=48/101), and the next biggest proportion of patients were not prescribed any artificial tears or

hypotensive drops (34%, n=34/101). Artificial tears were prescribed in 8% (n=8/101) of patients in total, with preserved and PF making up equal proportions of this. PF glaucoma drops were prescribed to 17% (n=17/101) of patients at this baseline visit.

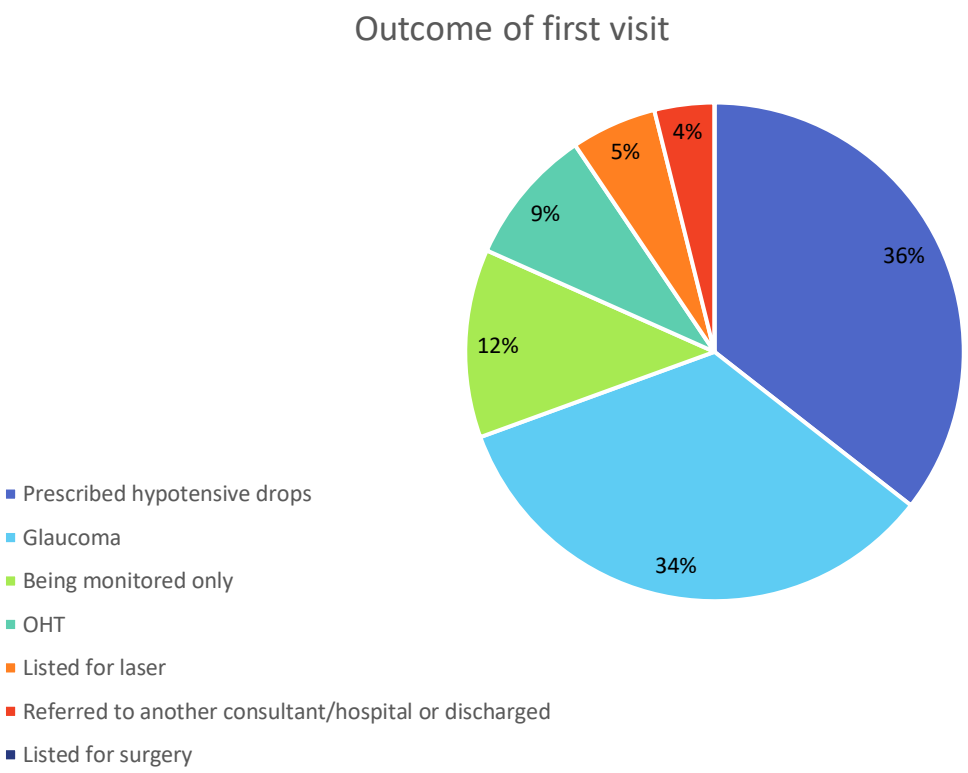


Figure 5.13: Percentage distribution of the outcomes of the first visit to the glaucoma clinic at RHH of newly referred patients, as a proportion of the total outcomes (N=180)

Outcome of visit	**Number of patients**
Prescribed hypotensive drops	64
Glaucoma	61
Being monitored only	22
OHT	16
Listed for laser	10
Referred to another consultant/hospital or discharged	7
Listed for surgery	0

Table 5.2: The main outcomes of the first visit and the number of patients within each outcome group.

Glaucoma and OHT was diagnosed in 60% (n=61/101) and 16% (n=16/101) of patients respectively. Subsequently, 63% (n=64/101) were prescribed some form of hypotensive drop, whilst 22% (n=22/101) were being monitored only without any treatment. A smaller proportion

of patients were either listed for laser therapy (10%, n=10/101) or they were referred to another consultant or discharged (7%, n=7/101).

5.4.7 Second visit/diagnosis visit

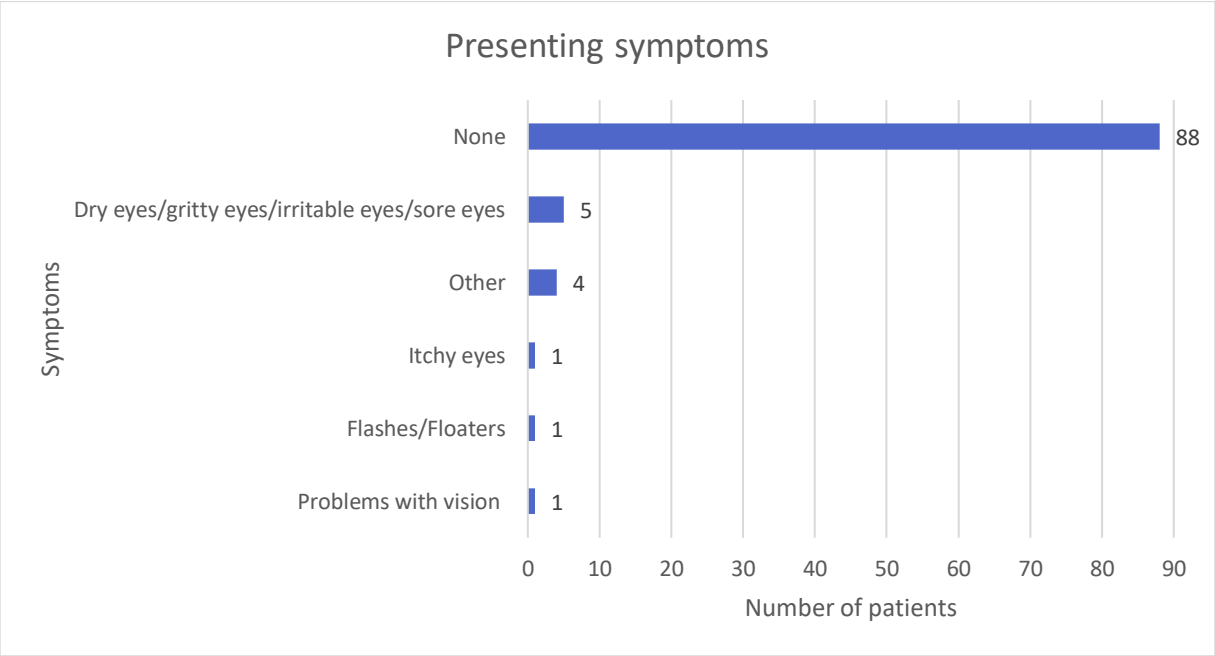


Figure 5.14: Symptoms of the patients at their second visit to the glaucoma clinic, or the visit at which they had been diagnosed with glaucoma or OHT.

Most patients did not have any symptoms recorded at their second visit or diagnosis visit (87%, n=88/101). It should be noted that this could either mean that they had no symptoms, or that this question was unanswered so may not have been asked in the first place. Therefore, it is not possible to differentiate between no symptoms reported and no symptoms recorded. Few patients reported dry or irritable eyes (5%, n=5/101), and a minority reported visual problems (1%, n=1/101), flashes and floaters (1%, n=1/101) and itchy eyes (1%, n=1/101). Diplopia, illegible handwriting and cataracts were the 'other' items noted during the audit (4%, n=4/101).

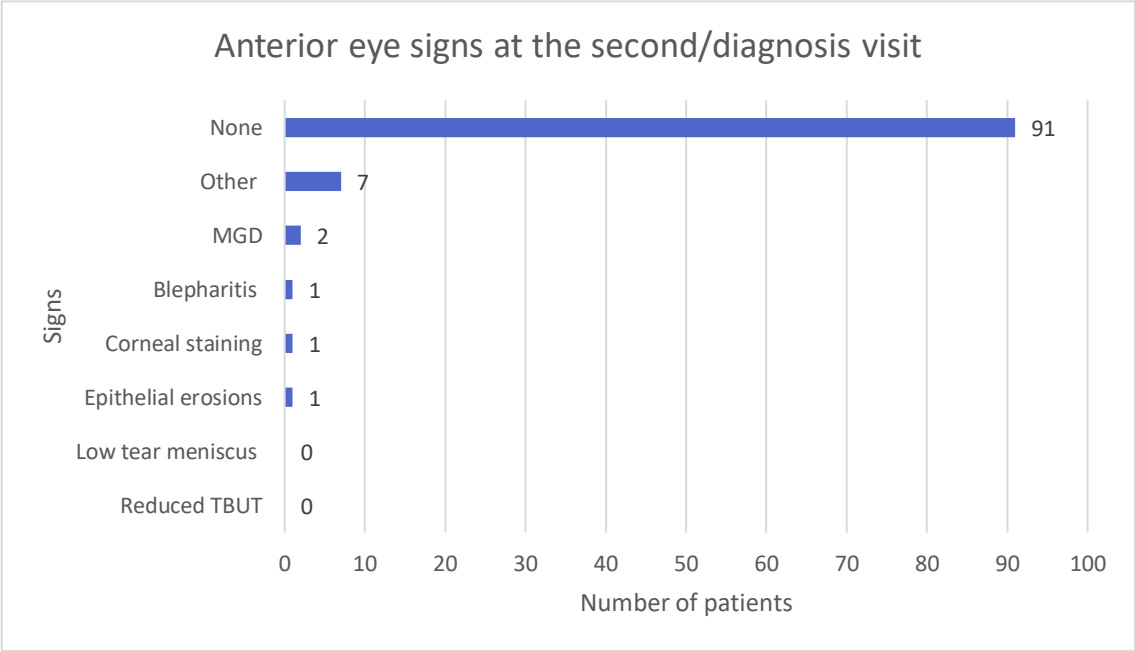


Figure 5.15: Anterior signs recorded at the second visit/diagnosis visit in the glaucoma clinic at RHH.

Most patients showed no ocular signs at presentation on their second/diagnosis visit (90%, n=91/101). 'Other' anterior signs were noted in 7% (n=7/101) of patients. MGD (2%, n=2/101), blepharitis (1%, n=1/101), corneal staining (1%, n=1/101) and epithelial erosions (1%, n=1/101) made up smaller minorities of anterior signs at the follow up visit.

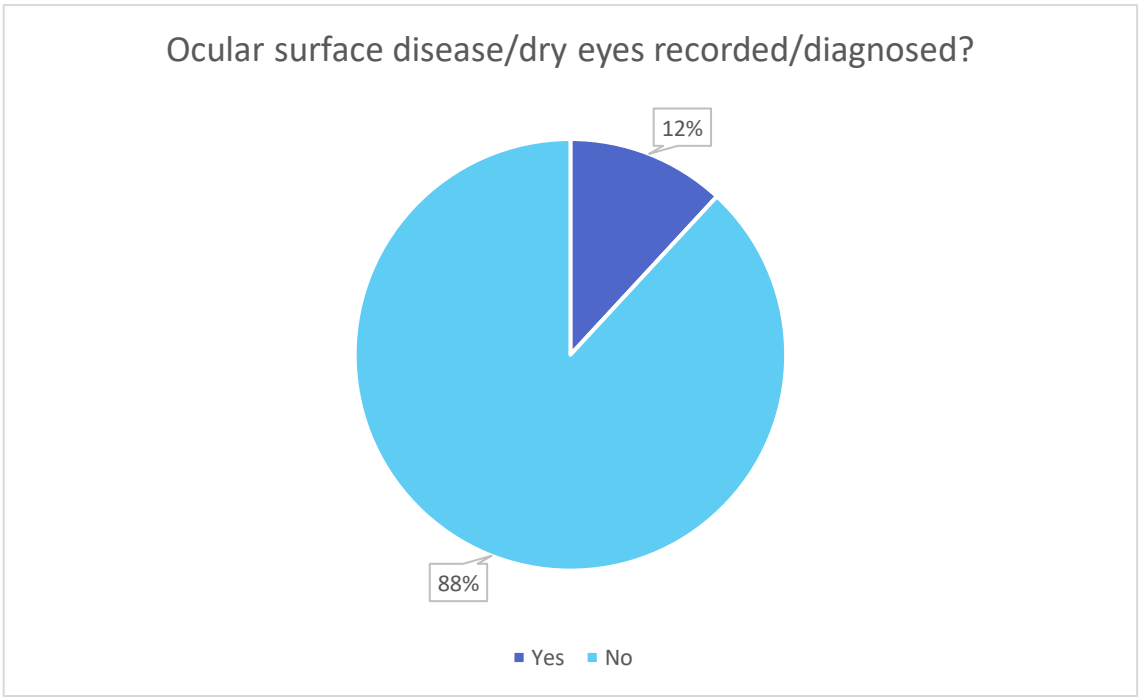


Figure 5.16: The percentage of patients who were recorded as having OSD on the second/diagnosis visit.

OSD was recorded for 12 patients and was absent for 89 patients. Though 89 records did not have it noted, it is not possible to decipher whether there was no diagnosis of OSD or whether this was just not checked and therefore not recorded.

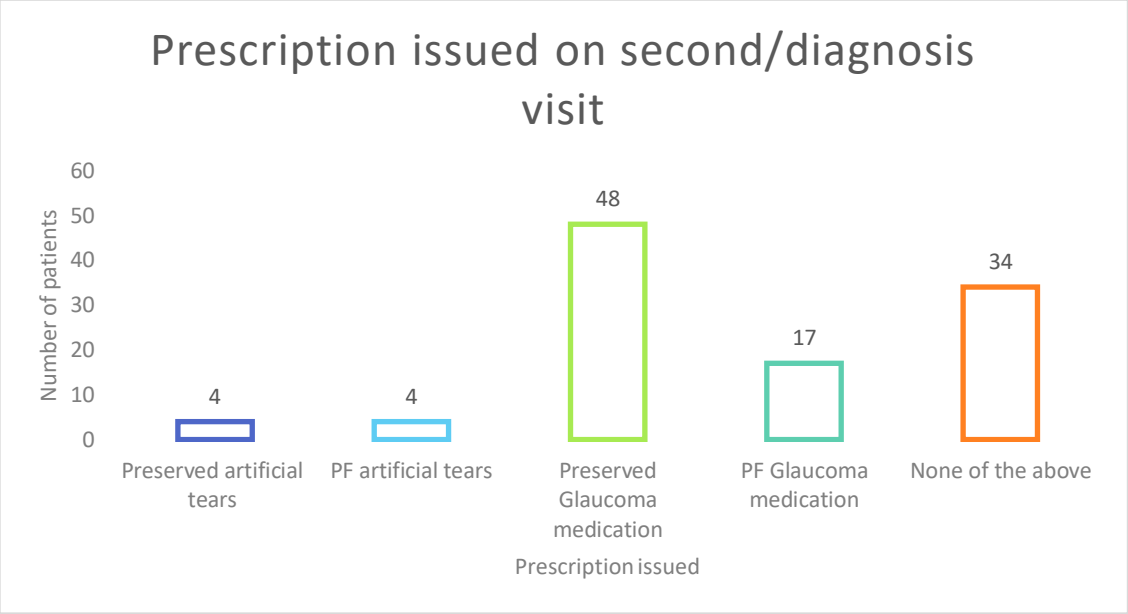


Figure 5.17: Prescription issued on the second visit or the diagnosis visit of patients presenting to the glaucoma clinic at RHH.

For the vast majority of patients following their second/diagnosis visit into the clinic, resulted in the issuing of preserved glaucoma drops (48%, n=48/101). In comparison, a much smaller proportion were issued PF drops at this visit (17%, n=17/101), whilst a modest proportion were not issued any drops at all (34%, n=34/101). Few patients were issued artificial tears in both preserved and PF formulations (4%, n=4/101, each).

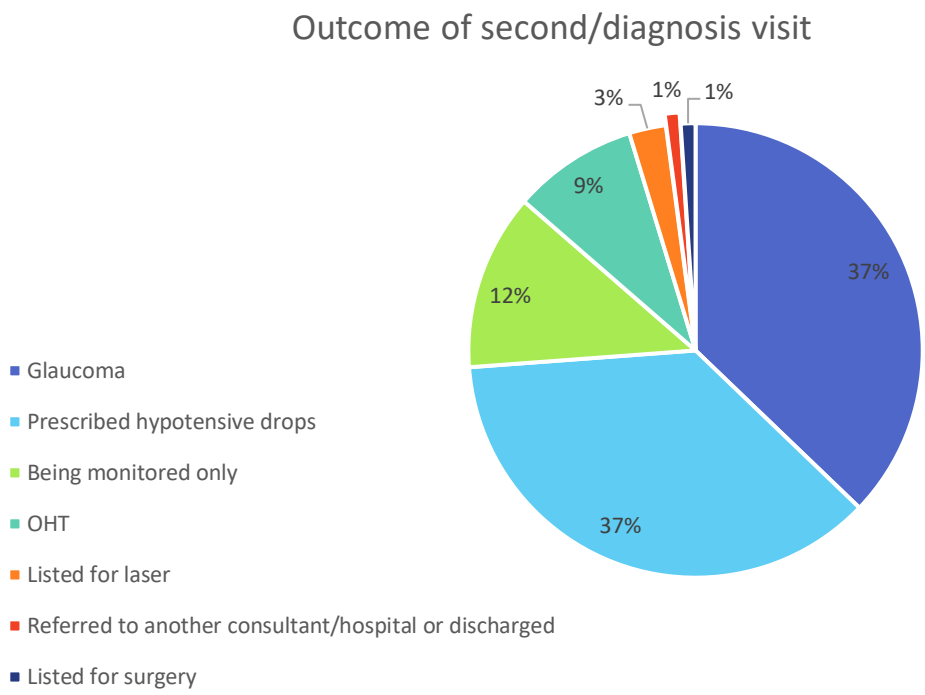


Figure 5.18: Percentage distribution of the patient outcomes on the second/diagnosis visit, as a proportion of the total outcomes (N=191).

Outcome of visit	**Number of patients**
Glaucoma	71
Prescribed hypotensive drops	70
Being monitored only	24
OHT	17
Listed for laser	5
Referred to another consultant/hospital or discharged	2
Listed for surgery	2

Table 5.3: The main outcomes of the second/diagnosis visit and the number of patients within each outcome group.

The main outcome of this second/diagnosis visit resulted in diagnosis of glaucoma (70%, n=71/101) and the issuing of hypotensive drops (70%, n=70/101). Twenty-four percent (n=24/101) of patients were continued to be monitored without any intervention. OHT was diagnosed in a smaller proportion of patients (17%, n=17/101). Few patients were subsequently listed for laser (5%, n=5/101), listed for surgery (2%, n=2/101), referred or discharged (2%, n=2/101).

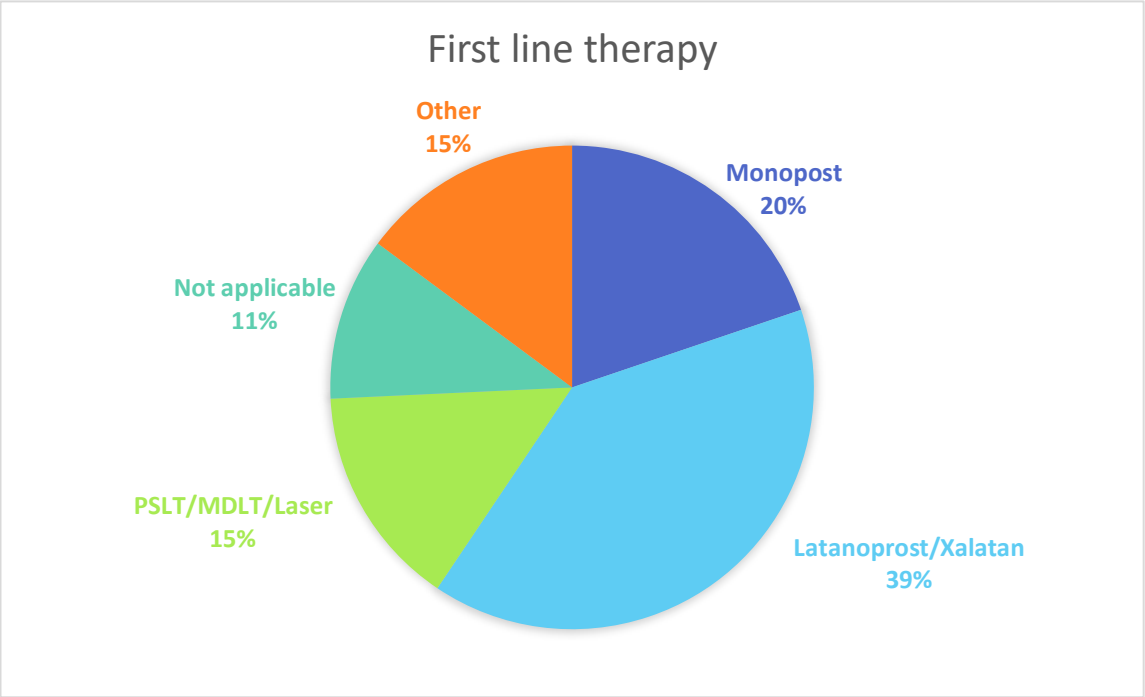


Figure 5.19: First line therapy for patients on the first visit or the diagnosis visit. PSLT= Pattern Scanning Laser Trabeculoplasty, MDLT= Micropulse Diode Laser Trabeculoplasty

First line therapy	**Number of patients**
Monopost	20
Latanoprost/Xalatan	40
PSLT/MDLT/Laser	15
Not applicable	11
Other	15

Table 5.4: The number of patients per first line therapy.

The vast majority of patients were prescribed latanoprost (sold under the brand name Xalatan) as their first line therapy (40%, n=40/101). Monopost, the PF version of Latanoprost, was the next most issued first line therapy at 20% (n=20/101). Some patients were not prescribed pharmacological treatment and were offered alternative laser treatment instead (15%, n=15/101). In 11% (n=11/101) of patients, neither medical or laser therapy was offered. In such cases, clinicians were only monitoring the patients in the glaucoma clinics. The 'other' options (15%, n=15/101) included the following:

- Azarga
- Travatan
- Betagan
- Duotrav

- Betoptic
- Cosopt
- Pilocarpine
- Propine
- Simbrinza
- Timolol/Timoptol
- Dry eye drops

5.4.8 Final visit

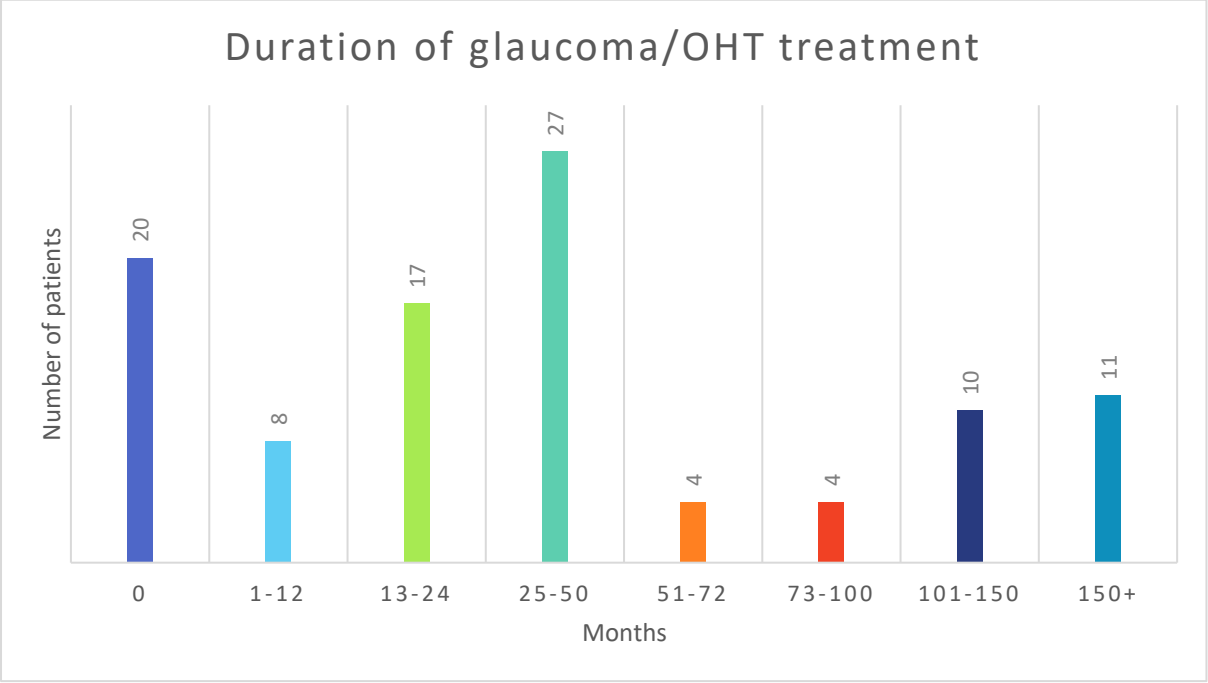


Figure 5.20: Duration of medical therapy for glaucoma and OHT for patients attending the glaucoma clinics at RHH.

The duration of medically managed glaucoma/OHT varied greatly in clinics. Whilst the majority had been on medication between 25-50 months (27%), 25% of patients had been on treatment for less than 25 months whilst 29% had been on treatment for more than 50 months. These statistics only take into account those patients who had been treated with hypotensive drops. Those classed as receiving 0 months of treatment represent those patients who only had laser treatment or surgery, or those who were just being monitored, so this group was not medically managed (20%).

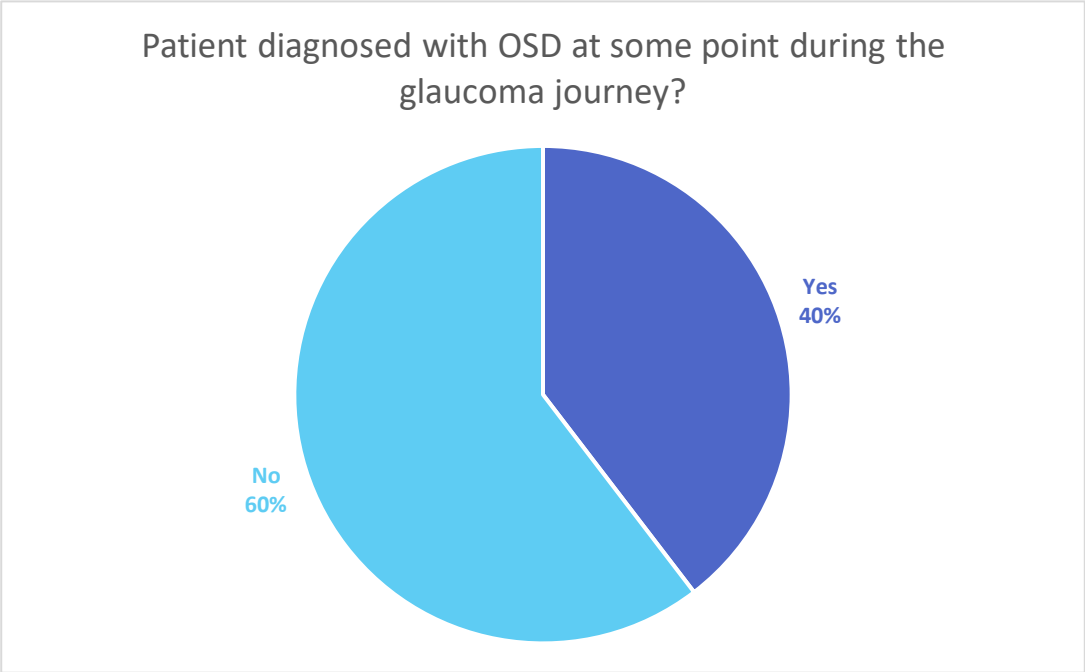


Figure 5.21: Percentage of patients diagnosed with OSD during the glaucoma/OHT journey.

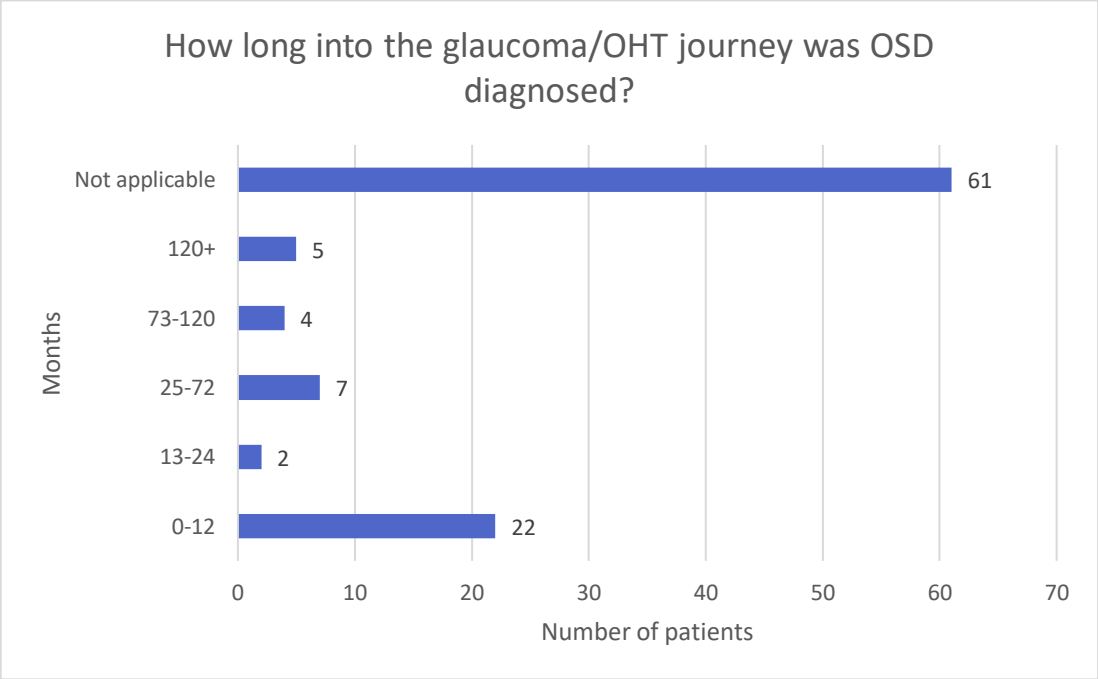


Figure 5.22: The point in time at which OSD was diagnosed in patients.

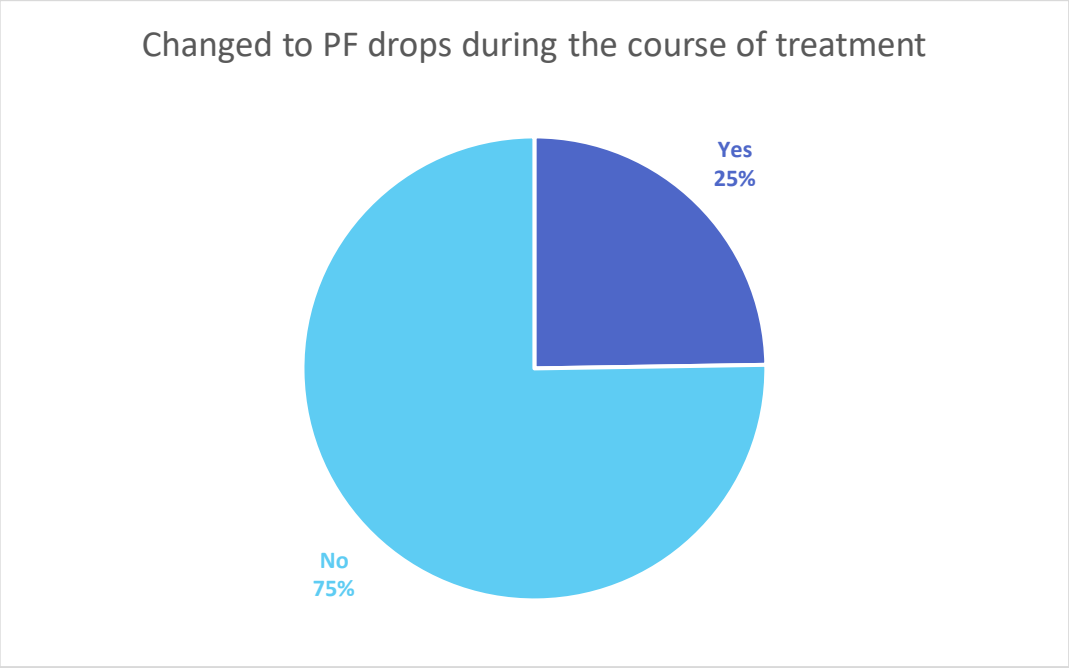


Figure 5.23: Percentage of patients changed to PG treatment in the course of their glaucoma/OHT journey.

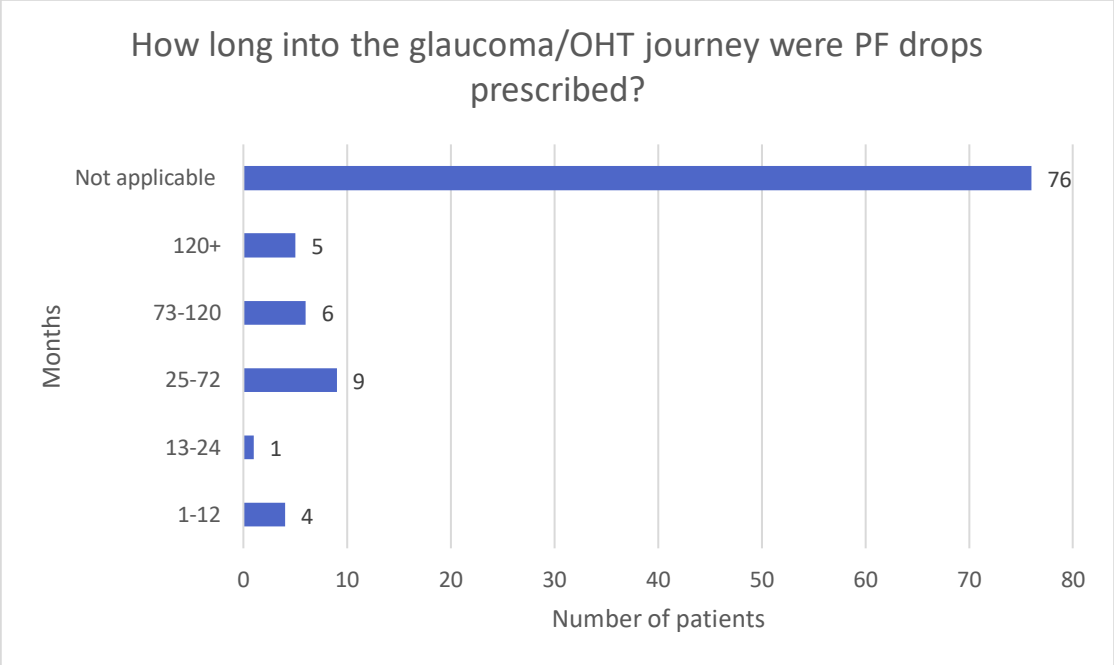


Figure 5.24: The point in time at which patients were prescribed or switched to PF treatment.

Figures 5.21 and 5.22 demonstrate the number of patients diagnosed with OSD during their glaucoma/OHT journey at RHH, and the time-point of diagnosis. Forty percent were diagnosed with OSD, with the majority being diagnosed within the first 12 months (22%). Fewer people were changed to PF treatment during their glaucoma/OHT journey (25%), as illustrated by figures 5.23 and 5.24. Most patients were changed to PF treatment between 25 to 72 months into their treatment (9%).

During the Glaucoma/OHT journey at RHH, 27% (n=27/101) of patients required some form of laser surgery, whilst 9% (n=9/101) required glaucoma surgery.

5.4.9 Known and predictive risk factors for OSD in glaucoma clinics

Factor	Changed to PF in the course of the Tx (n=25) (n/%)		Not changed to PF in the course of the Tx (n=59) (n/%)		On PF from Day 1 (n=17) (n/%)	
Age >65	13	52.0%	38	64.4%	13	76.5%
Female	14	56.0%	32	54.2%	9	52.9%
Asian	0	0.0%	4	6.8%	1	5.9%
Smoker	2	8.0%	3	5.1%	1	5.9%
Alcohol consumer	9	36.0%	15	25.4%	3	17.6%
Allergies	5	20.0%	11	18.6%	4	23.5%
MGD	2	8.0%	0	0.0%	0	0.0%
Diabetes	2	8.0%	6	10.2%	3	17.6%
HRT	1	4.0%	0	0.0%	1	5.9%
Tamsulosin	1	4.0%	2	3.4%	2	11.8%
Antidepressants/ Anti-anxiety medication	2	8.0%	9	15.3%	2	11.8%
Afro-Caribbean	2	8.0%	3	5.1%	0	0.0%
3 or more systemic drugs	9	36.0%	26	44.1%	11	64.7%
5 or more systemic drugs	3	12.0%	18	30.5%	7	41.2%
Asthma	1	4.0%	5	8.5%	2	11.8%
Migraine	2	8.0%	5	8.5%	1	5.9%
Inhaler	2	8.0%	5	8.5%	4	23.5%
Hypertension	10	40.0%	21	35.6%	7	41.2%
Blepharitis	2	8%	2	3%	1	6%
Other anterior eye signs (other than Bleph or MGD)	4	16%	6	10%	3	18%

Table 5.5: Table of known risk factors (highlighted in blue) as evidenced in the current literature and TFOS DEWS II, and potential predictive risk factors (highlighted in orange). Conditional formatting allows identification of which risk factors were most prevalent within each group. All factors are as noted on first visit unless otherwise stated. Tx=Treatment

The 101 records audited for this study were ultimately divided into three groups; those that were changed to PF treatment in the course of the glaucoma/OHT journey, those who were not changed to PF, and those who were prescribed PF drops from the first visit. Essentially, such categorisation allows most prevalent risk factors for developing OSD amongst each group to be identified.

Of the known risk factors for OSD, increasing age and female sex appear to be the most prevalent in all three groups (Table 5.5). Alcohol consumption and allergies affects a smaller, but noticeable nonetheless, proportion of patients presenting to the glaucoma clinic at RHH.

In terms of predictive risk factors, being on 3 or more systemic drugs, being on 5 or more systemic drugs, hypertension and 'other' anterior signs (other than blepharitis or MGD) appear to be predominant characteristics amongst patients presenting to the clinic.

Though female sex prevailed in all three groups relatively evenly, alcohol consumption appeared to be more common amongst those patients requiring changes to PF treatment than those who were not switched to PF treatment (36.0% vs 25.4%). Furthermore, hypertension and 'other' anterior signs were also more prominent factors in those patients who required changing to PF treatment than those who did not (40.0% vs 35.6% and 16.0% vs 10.0%, respectively).

Clinicians appeared to issue PF drops more readily to patients on the first visit if they had allergies, had diabetes, were on Tamsulosin or HRT, or those who were of an older age. The issuing of PF drops on the first visit also seemed to be influenced by an increasing number of drugs, hypertension and 'other' anterior eye signs, though the latter two show smaller percentage differences between the groups.

Metric	Changed to PF in the course of the Tx (n=25)		Not changed to PF in the course of the Tx (n=59)		On PF from Day 1 (n=17)	
IOP >21mmHg*	68% (17)		51% (30)		35% (6)	
average IOP RE	24.2mmHg		20.4mmHg		19.4mmHg	
average IOP LE	24.8mmHg		21.5mmHg		18.5mmHg	
CDR >0.5*	76% (19)		63% (37)		100% (17)	
average CDR RE	0.58		0.58		0.68	
average CDR LE	0.57		0.56		0.65	
Gonio angle ≥Gd3 RE	25	100%	45	76%	16	94%
Gonio angle ≤Gd2 RE	3	12%	14	24%	0	0%
Gonio angle ≥Gd3 LE	24	96%	45	76%	14	82%
Gonio angle ≤Gd2 LE	3	12%	14	24%	0	0%
CCT ≥561µm RE	10	40%	14	24%	8	47%
CCT ≤539µm RE	9	36%	25	42%	8	47%
CCT ≥561µm LE	13	52%	16	27%	8	47%
CCT ≤539µm LE	7	28%	23	39%	7	41%
Average CCT RE	558µm		544µm		543µm	
Average CCT LE	560µm		546µm		546µm	
VFI ≥90% RE	11	44%	36	61%	7	41%
VFI ≤80% RE	2	8%	6	10%	1	6%
VFI ≥90% LE	12	48%	34	58%	10	59%
VFI ≤80% LE	4	16%	7	12%	0	0%
Average VFI RE	93%		91%		90%	
Average VFI LE	90%		91%		95%	

Table 5.6: Clinical metrics at first visit of patients presenting to the RHH glaucoma clinic for each group.
* in either eye Tx=Treatment

Referring to Table 5.6, those patients who presented to the clinic with an increased IOP on visit one were more prevalent in the ‘changed to PF hypotensive drops’ group. The average IOP on visit one was also higher for those in the ‘changed to PF’ group compared to those ‘not changed to PF’, or those ‘on PF from day’ (24.5mmHg, 21.0mmHg and 19.0mmHg respectively, when averaged across the two eyes).

Patients who had a CDR of >0.5 were more likely fall in the ‘prescribed PF drops from the first visit’ group. Those that were not prescribed PF on the first visit but had a CDR of >0.5 at baseline, were likely to be in the group requiring ‘switching to PF drops’ during their treatment period. The average CDR was highest amongst those put on PF treatment from day one.

Overall, most patients presenting to the eye clinic had a Gonioscopy angle of grade 3 or more. There was a slightly greater percentage of patients with Gonioscopy angles of grade 2 or less in the group not requiring switching to PF. It should be noted that patients could be classed as

having Gonioscopy grades of 2 and 3 simultaneously, since the angles are graded in quadrants per eye.

In terms of CCT, for patients in the 'PF from day 1' group, nearly half had thicker than average corneas, and the other half had thinner than average corneas. Those with thinner than average corneas were more prevalent in the group not requiring changing to PF drops, and those that had thicker than average corneas appeared more prevalent in the group requiring changes to PF treatment (Table 5.6).

For the majority of patients presenting to the clinic, the visual field index (VFI) was 90% or more, regardless of group classification.

Metric	Changed to PF in the course of the Tx (n/%) (N=25)		Not changed to PF in the course of the Tx (n/%) (N=59)		On PF from Day 1 (n/%) (N=17)	
Required laser Tx	8	32%	17	29%	0	0%
Required glaucoma surgery	6	24%	5	8%	0	0%
OSD diagnosed at some point	17	68%	20	34%	3	18%
Currently on preserved drops	2	8%	29	49%	0	0%
Currently on PF drops	16	64%	6	10%	15	88%
Currently on combination of preserved and PF drops	7	28%	5	8%	2	12%

Table 5.7: Final visit outcomes for each group. In total, 37 patients were on PF treatment by the final visit, 31 were on preserved treatment, 14 on combined treatment of preserved and PF and 19 patients did not have any medication by the final visit.

By the time of the final visit, those who were prescribed PF drops from day 1 did not require any laser or surgical intervention in the course of their treatment. Moreover, 88% of patients in this group remained on PF drops throughout. The remaining 12% were on combined treatment of PF and preserved hypotensive drops by the final visit, and no patient in this group had to be changed solely to preserved drops.

For the group who was changed to PF treatment during their glaucoma or OHT journey, 68% of patients were diagnosed with OSD at some point, with 64% of patients on PF treatment by the final visit into the glaucoma clinic. Only 8% remained on preserved drops by the final visit, with the remaining 28% being on combined treatment. About a third of this group had laser surgery at some point during their treatment journey and 24% required glaucoma surgery.

In the group where patients were not changed to PF treatment, 34% were diagnosed with OSD during the course of the treatment, but only 10% were on PF drops by the final visit. Patients in this category may not have been treated at the first visit and monitored for a while, eventually being put on PF treatment, which explains this subgroup of PF treated patients who had not been switched to this treatment. In addition, a small proportion of patients who were not switched to PF treatment, did require laser intervention (29%), and some required glaucoma surgery (8%).

5.5 Discussion

OSD remains a prevalent comorbidity in patients presenting to the glaucoma clinic. In this current study, 40% of patients were diagnosed with OSD at some point during their glaucoma or OHT management at RHH. Of these, most patients were diagnosed with OSD within the first 12 months of their care. Though OSD appears to be a prevailing issue in these clinics, its management appears to be mismatched, and only 25% of patients were changed to PF hypotensive drops during their glaucoma or OHT journey, with the majority of them being switched after 25 months of treatment.

As quoted by Skalicky and associates (2012), OSD in glaucoma clinics is ‘under-recognised and undertreated’ (Skalicky et al., 2012, Brewitt and Sistani, 2001). The current audit supports this statement; though only 8% of patients were diagnosed and recorded as having OSD on the first visit, 84% of patients had no anterior eye signs recorded, and subsequently 17% patients were prescribed PF hypotensive drops. By the second visit, 12% of patients were diagnosed with OSD, 22% were prescribed PF hypotensive drops, yet 90% of patients had no anterior signs noted on their records.

The absence of noted anterior eye signs does not negate OSD. It appears that OSD is not at the forefront of investigations in glaucoma clinics, and whilst the more important measurements of GAT, CCT and CDR are routinely performed and recorded, anterior segment assessment is, on the whole, omitted from records of glaucoma and OHT patients, even though NICE guidelines advise such examinations (National Institute for Health and Care Excellence, 2017). Perhaps clinicians record only negative signs, and omission could equate to a healthy ocular surface. However, this does not explain the rationale behind prescribing PF treatment in this study.

According to the NICE guidelines, PF treatment for glaucoma and OHT should only be offered in cases of 'clinically significant and symptomatic' OSD (National Institute for Health and Care Excellence, 2022). On the basis of this, and recommendations from the consultants at Russells Hall Hospital (Dudley NHS Trust, West Midlands), it was accepted that switching to PF treatment is an indicator that the patient has developed OSD. As the data on anterior eye signs and symptoms and diagnosis of OSD was inconsistent and sparse, for the purposes of this study, switching to PF treatment was regarded as the best measure of OSD.

5.5.1 Known risk factors

5.5.1.1 Female and older age

Table 5.5 summarises the known risk factors and the number of patients falling into each group of prescription pattern. Female sex and ages over 65 were prime characteristics of patients presenting to the glaucoma clinic at RHH. This is not surprising, since several studies have shown increasing age to be a risk factor for both PACG and POAG (Day et al., 2012, Kapetanakis et al., 2016). Women are known to be at an increased risk from PACG, which is thought to be associated with their shallower anterior chambers (Quigley and Broman, 2006, Aung et al., 2005). The disparity between men and women and their health-seeking behaviour, as well as the longevity of women over men, could also account for this trend picked up in the RHH glaucoma clinics (Thompson et al., 2016, Vajaranant et al., 2010).

Female sex and increasing age are also principle risk factors to developing OSD (Vehof et al., 2014a). Since such a high percentage of patients presenting to the glaucoma clinic are females and of older ages, a thorough anterior examination would provide crucial information, and a diagnosis of OSD at baseline would establish which patients would benefit from PF treatment from the first visit. Though not all females and older patients will necessarily develop OSD, there is a chance that patients presenting to the glaucoma clinics already have, or have a predisposition to developing, OSD. Referring back to Figure 5.1, female sex and older age are known risk factors, overlapping both glaucoma and OSD. With such a high proportion of referrals to the clinic of such patients, baseline ocular surface assessments would be fundamental in treating the two conditions in conjunction.

5.5.1.2 Alcohol

Alcohol consumption appears to be positively associated with developing OSD and requiring changes to PF treatment. In the current study, 36.0% of patients who were alcohol drinkers

were switched to PF drops in the course of their glaucoma or OHT journey, as opposed to 25.4% who were not. A slightly smaller proportion (17.6%) were placed on PF treatment from the first visit. There appears to be some correlation between alcohol consumption and the chances of requiring medication changes to PF alternatives in the course of the treatment, and perhaps this link is considered by clinicians which is reflected by the number that are put on PF treatment on day one.

A recent large population-based study by Magno and colleagues (2021) investigated the link between alcohol consumption and symptomatic dry eye, taking into account several potential confounding variables, as well as making sex-based stratifications. Alcohol drinkers were more likely to report symptomatic dry eyes compared to non-drinkers, although much of the weight of this rested on females. Increased risks were significantly associated between alcohol consumption and OSD, however, this risk appeared to be sex specific, with females showing such patterns whilst males did not. On the contrary, in males, increased alcohol intake was associated with a reduced risk of symptomatic dry eye, suggesting some protective benefit (Magno et al., 2021). It has been suggested that the lack of symptoms of DED in heavy drinkers could be down to peripheral neuropathy (Julian et al., 2019, You et al., 2016).

In this present study, only about a quarter of patients declared themselves as alcohol drinkers. There is a possibility that the real figures are underrepresented since the clinic template states ‘alcohol dependency’ with a ‘yes’ and ‘no’ tick box answer option. Whilst some clinicians record casual drinking under this heading, or rephrase ‘alcohol dependency’ to ‘alcohol consumption’, there is a chance that unless someone declares alcohol dependency, less frequent drinkers are overlooked.

Alcohol consumption has been shown to negatively affect both the ocular surface and tear film, with evidence of orally consumed alcohol being present in the tear-film at a concentration half of that found in blood, 4 hours after the first intake (Kim et al., 2012). Alcohol consumption increases tear hyperosmolarity, reduces TBUT and increases corneal staining, all of which are significant compared to no alcohol consumption (Kim et al., 2012). Although the current audit lacks the strength of numbers, it highlights a real potential predictive factor which should be considered in glaucoma clinics.

5.5.1.3 Smoking

TFOS DEWS II places smoking as an inconclusive and modifiable risk factor of OSD (Stapleton et al., 2017). In the current study, smokers were slightly more likely to be consigned to the group that needed to be switched to PF treatment (8%), than the group that did not require PF changes (5.1%).

Thomas and colleagues (2012) reported the detrimental effects of smoking on the ocular surface and tear film. A questionnaire was carried out by participants by means of the OSDI, and ocular measurements were taken of TBUT, Schirmer's II test, corneal staining and ocular esthesiometry. Compared to the control group of non-smokers, smokers had significantly lower TBUT, significantly lower corneal and conjunctival sensitivity and significantly higher corneal punctate staining. Evidently, smoking contributes to pre-corneal tear film alterations, leading to tear film instability, and this coupled with decreased corneal sensitivity, results in insidious consequences (Thomas et al., 2012).

Similarly, a more recent report by Bhutia and associates (2021) reverberated these findings by Thomas and colleagues (2012). Again, both subjective and objective assessments were made, and notable differences were found between smoker and non-smokers. Smokers displayed significantly lower TBUTs, Schirmer's test values and tear meniscus heights (TMH), as well as significantly higher scores on OSDI (Bhutia et al., 2021).

It has been suggested that these changes are induced by mechanisms at a cellular level. A reduced goblet cell density, lipid layer abnormalities and elevated levels of neutrophils have all been attributed to such differences (Matsumoto et al., 2008). Though the present study includes only a small number of smokers, the data suggests predispositions to developing OSD in smokers, as is indicated by the proportion of smoking patients that had to be switched to PF treatment in the course of their management.

5.5.1.4 Diabetes

In this audit, the majority of diabetics appeared to be placed on PF treatment from the initial visit (17.6%). There was not much discrepancy in proportions of patients who did require PF changes and those who did not (8% vs 10.2% respectively). Diabetes was the second most commonly reported comorbidity in these clinics, and so forms an important element to consider when prescribing hypotensive drops.

Diabetes is classed as a ‘probable’ risk factor of OSD according to the TFOS DEWS II epidemiology report (Stapleton et al., 2017). Assessing OSD in diabetic patients can be difficult, since diabetes is associated with decreased corneal sensitivity and so relying on subjective measures alone can lead to an underestimation of the actual scope of the problem (Stapleton et al., 2017, Misra et al., 2014). This could explain the insignificant differences between diabetic patients requiring changes to PF treatment and those not needing changes to PF treatment. If clinicians in the glaucoma clinics rely on self-reported measures alone, patients may not declare symptoms of OSD and so would not be changed to PF treatment. However, this does not mean that OSD is not prevalent amongst this subgroup, rather that there needs to be a heightened focus on anterior eye signs over symptoms alone in these glaucoma clinics.

Perhaps clinician awareness of the compromised ocular surface of diabetics explains why a higher percentage of diabetic patients were placed on PF hypotensive drops from day one.

5.5.1.5 Medication

HRT/Tamsulosin

Medications which influence hormones, such as HRT and Tamsulosin, are known to be linked to OSD (Schaumberg et al., 2001, Galor et al., 2011). In the present study, a higher percentage of patients on HRT and Tamsulosin were prescribed PF drops from the first visit (5.9% and 11.8% respectively), compared to those changed to PF (4.0% for both), and those not changed to PF (0.0% and 3.4% respectively). Though the numbers are small, it appears that drugs altering hormone levels may ultimately contribute to patients receiving PF drops from the initial visit.

Antidepressants/Antianxiety medication

Antidepressants and anxiolytics are classed as ‘consistent and modifiable’ risk factors of OSD according to TFOS DEWS II (Stapleton et al., 2017). Although previous studies have shown a positive association of these medication classes with OSD, the current audit does not reflect such patterns (Galor et al., 2012). Most patients did not require changes to PF treatment (15.3%), or were issued PF treatment on day one (11.8%). Only a small number required changes to PF treatment (8%).

5.5.2 Predictive risk factors

5.5.2.1 Systemic drugs

From the current audit, two main trends are picked up. A high proportion of patients presenting to the glaucoma clinics at RHH are on at least 3 or more systemic drugs, and those on 3 or more systemic drugs are more likely to be prescribed PF treatment at the initial visit. This same pattern is seen for those on five or more systemic drugs, but to a slightly lesser extent. For 3 or more and 5 or more systemic drugs, a higher proportion of patients fall into the 'not changed to PF' group than the 'changed to PF' group (44.1% vs 36.0% and 30.5% vs 12.0%, respectively). Yet the biggest proportion of patients in both categories of risk factors, fall into the 'PF from day 1' group (64.7% for 3 or more systemic drugs and 41.2% 5 or more systemic drugs).

A study published by Schein and colleagues (1999) looked into the effects of medications as probable risk factors to developing dry eyes and a dry mouth. A dose-dependent risk was found; every addition of systemic medication increased the odds of developing dry eyes and dry mouth. The odds ratio for one systemic drug stood at 1.7 (CI 0.7-4.0), increasing to 2.9 (CI 1.2-6.9) for three and 7.0 (CI 2.7–18.0) for five, highlighting not only the detrimental effects of systemic medication on the ocular surface, but the complexities of polypharmacy and drug interactions as a risk factor to developing OSD (Schein et al., 1999, Fraunfelder et al., 2012).

5.5.2.2 Comorbidities

Respiratory conditions

A history of respiratory illness is routinely obtained in glaucoma clinics, since care must be taken when prescribing in such patients due to the increased risks of bronchoconstriction with beta-blockers (Nelson et al., 1986).

Literature on the association between asthma and respiratory illness with dry eye is sparse. Few studies have found increased risks of asthmatics developing OSD (Huang et al., 2018, Chia et al., 2003, Huang et al., 2021). Asthma can fall under the atopic triad, with eczema and allergies, and with these variables falling under the same umbrella, it can be difficult to ascertain a direct association of asthma to OSD. The medication for the treatment of asthma and respiratory illnesses, such as the use of corticosteroid inhalers, can also increase the risks for developing DED (Chia et al., 2003).

Perhaps due to this multifaceted issue, and the restrictions of beta-blockers in such patients, it might explain the higher proportion of asthmatic patients being prescribed PF drops from day one (11.8%). However, those that were not prescribed PF treatment from day one, were less likely to require changes to PF treatment in the course of the therapy (8.5%).

Ocular conditions

Blepharitis is closely associated with DED, since recurring episodes of the former can lead to the latter. It is classed as a comorbidity of OSD rather than diagnostic element of it (Wolffsohn et al., 2017). Though the numbers are small, the current audit shows that patients with blepharitis signs were either placed on PF drops from day one (6%), or they required changes to PF treatment (8%).

These findings are echoed by 'other' anterior eye signs; patients with any other anterior eye comorbidities were either placed on PF treatment from day one (18%), or required switching to PF treatment in the course of their journey (16%). Fewer patients did not need to be switched to PF treatment throughout the course with blepharitis (3%) and 'other' anterior eye signs (10%).

This is indicative that the anterior eye must be assessed thoroughly at baseline, since early signs could act as predictive indicators for the development of OSD.

5.5.2.3 IOP

Interestingly, IOP patterns in this audit indicate that patients who presented with IOPs greater than 21mmHg on their first visit, were more likely to require changes to PF treatment in the course of their journey (Table 5.6). Furthermore, the mean IOP of patients in the group 'changed to PF' was higher for both eyes (24.2mmHg RE, 24.8mmHg LE), compared with the groups 'not changed to PF' (20.4mmHg RE, 21.5mmHg LE) and 'PF from day 1' (19.4mmHg RE, 18.5mmHg LE). This suggests that increased IOP at baseline could act as a predictive indicator for OSD.

It is already well documented that increased IOP at baseline is a risk factor for developing POAG (Jiang et al., 2012, Leske et al., 2008). However, to date, the association between increased IOP and the risk of developing DED are yet to be investigated.

In this current audit, patients presenting with higher IOP levels may have had more advanced glaucoma or OHT, which could explain the need for more frequent prescription changes, and hence, a higher proportion of these patients switching to PF treatment. This does not account for changes specifically to PF treatment though.

5.5.2.4 CCT

Interestingly, there was a higher proportion of patients with thicker than average corneas (40% RE, 52% LE) in the group 'changed to PF treatment', than patients with thinner than average corneas (36% RE, 28% LE). Additionally, there was also a greater fraction of patients with thicker than average corneas in this group when compared to the group that were 'not changed to PF' (24% RE, 27% LE). In contrast, for the group not requiring changes to PF treatment, a greater percentage of patients had thinner than average corneas (42% RE, 39% LE). Not only was this percentage of patients greater than those in the same cohort with thicker corneas, but the percentage of patients with thinner corneas also outweighed those in the group requiring changes to PF treatment. It therefore appears, that those with thinner corneas tend not to require PF changes to treatment, whereas, those with thicker corneas do. Although this concept has not been studied before, it is most certainly an area that requires further exploration and could form an important predictive factor.

It has been suggested that ocular hypotensive therapy is less effective in patients with thicker corneas, which may in part explain why a higher CCT than average was positively associated with the group 'changed to PF' (Johnson et al., 2008). It may be that those with thicker CCTs required more frequent medication changes due to ineffectiveness to treatment. However, this assumption is one that would need further investigation as ineffectiveness to treatment does not fully explain why patients would be switched to PF treatment as opposed to a different preserved treatment altogether.

5.5.3 Limitations

The current audit does have some limitations. The COVID-19 pandemic not only limited the number of records retrieved for this audit, but impacted the glaucoma clinics as well. The process at RHH was re-assessed due to the rapidly evolving pandemic, with the introduction of virtual clinics for the ophthalmology department. Patients presented to the sister site at Corbett Hospital (Dudley NHS trust, UK) in the West Midlands, for screening tests of IOP measurements, VFs testing, visual acuities and fundus photography. The results were then

reviewed remotely by consultants, to establish which patients require face-to-face consultations. Due to this, some of the records included in the audit lacked the extensive tests needed for possible medication changes. If the IOP, visual fields and CDRs were consistent, the patient may have been overlooked and offered continuation of the current medication with a review in the foreseeable future. However, a lack of thorough history taking and anterior eye checks in such patients may indicate an oversight of patients with OSD, leading to an underestimation of the actual number of patients who would have required a change to PF treatment.

The same applies to patients presenting to the glaucoma clinics for the first time. If such referral was made during the pandemic and patients attended the virtual clinic, unless there was immediate threat to vision due to most probable OHT or glaucoma, patients would be screened at Corbett Hospital with the most important tests and reviewed in a face-to-face clinic at a later date. The anterior eye is not assessed unless in a face-to-face clinic with a glaucoma clinician.

Furthermore, a modest number of records were suitable and included in the current audit, compared to the total number screened. Obtaining records during the pandemic was difficult due to the priority of COVID-19 related work in the hospital departments. Additionally, many records fell into the exclusion criteria outlined previously. Numerous records lacked the thorough history required at baseline, with patients being prescribed hypotensive drops earlier in the pathway or at other hospitals, making it difficult to extract all the necessary information as per clinic template. There was a large number of records which had missing notes, missing tests, and patients who were monitored only. The consequences of this meant that the number of patients falling into the groups ‘changed to PF’, ‘not changed to PF’ and ‘PF from day 1’ were limited and unequal within each group.

Though the tables (Tables 5.5, 5.6 and 5.7) provide some indication of the distribution of patients within each group and reflect these as frequencies amongst each known and predictive risk factor, such observations are lacking in strength due to their inability to show significance of these associations. As record keeping was inconsistent and poor on the whole, it is difficult to ascertain which patients presented with, or developed OSD, and so symptomology was not taken as the target variable. Instead, uptake of PF treatment was taken as a surrogate for developing OSD. Although this does not permit calculation of predictive risk factors, the associated factors found in this study should be explored further.

The eye clinic at Russells Hall Hospital (Dudley NHS Trust, West Midlands) has recently employed a digital system for record keeping. With this in place, records are easier to screen during audits, with all information in one place and previous patient histories fully legible. There are also sections with prompts for clinical checks including anterior eye signs. This should in theory make future audits easier to conduct, and the data more robust. If symptoms and signs indicating OSD are recorded, it will be possible to identify those with glaucoma who also have a positive diagnosis of OSD, and then using linear regression, allow analysis to determine which risk factors predict membership to this group.

5.5.4 Future work and suggestions

The current study has highlighted some interesting predictive factors for OSD in glaucoma clinics. A higher than average CCT, increased IOP at baseline, alcohol consumption and ocular comorbidities are a few of the factors which appear to predispose patients to requiring changes to PF treatment. It would be insightful to extrapolate the current study and obtain larger numbers of patients within each group to draw conclusions of statistical significance.

In addition, in the current audit, only patients who were prescribed PF from the first visit were considered in the analysis. For many patients, diagnosis and prescribing may not occur until several visits have been made to the glaucoma clinic. It may, therefore, be beneficial to investigate first line therapy, regardless of onset of treatment.

Since the start of this audit, several changes have been made to the department in terms of data collection. RHH has implemented the use of 'MediSIGHT', an Electronic Medical Records system (EMR). The use of this has allowed easier location of patient data, with templates built into the system and available to use for the recording of a thorough history, the necessary anterior and posterior tests required in ophthalmology clinics as well as easy identification of management and drug prescriptions. This digital record keeping could be the key factor in allowing many more records to fall into the inclusion criteria for future audits.

A suggestion made to the RHH glaucoma clinic since the completion of this audit was to add a tick-box alongside the anterior eye signs section for OSD. This simple prompt could alert clinicians to specifically look for OSD both prior to starting treatment, as well as through the course of the glaucoma or OHT journey.

Finally, this audit illuminates the many facets to developing OSD in a glaucoma/OHT patient's lifetime. These factors are not singular, and there is some overlap and interactions between these aspects. There is scope for the development of an algorithm, or a 'risk calculator', which could process the cumulative risks and compute an overall risk ratio for each individual presenting to the glaucoma clinic. Such screening would enable clinicians to easily identify those patients who would benefit from PF treatment from day one, and to avoid unnecessary changes to PF treatment further down the line. Much like the OHTS-derived predictive risk models, this could pave the way for the future of OSD in glaucoma clinics (Medeiros et al., 2005).

5.6 Conclusion

The current study has allowed an insight into the journeys of glaucoma and OHT patients at Russells Hall Hospital (Dudley NHS Trust, West Midlands). The information acquired indicates that those presenting to the glaucoma clinic are mostly over the age of 65. Women are more likely to attend the glaucoma clinic than men, albeit this disparity is small. The vast majority of patients in the audit were Caucasian, and this may be related to the overall demographic of Dudley. Interestingly, of the records that were audited, a high proportion had no family history of glaucoma, which is contradictory to the risk factors of POAG (National Institute for Health and Care Excellence, 2022, Jonas et al., 2017).The most common genetic predispositions were related to mother and sister, respectively. The audit revealed that over 9/10 patients were non-smokers. Hypertension is the leading comorbidity that is present in glaucoma clinics, which may be the reason why Ramipril was one of the most commonly prescribed medication.

Although the current study is not powered to make statistically significant associations of risk factors for developing OSD in the course of glaucoma treatment, it has highlighted associations and trends that warrant further exploration. Taking patients who were either prescribed PF treatment from diagnosis or those who were switched to PF as indicators for the development of OSD, associations such as polypharmacy, raised baseline IOP, alcohol consumption, ocular conditions, thicker than average CCT and CDR>0.5 appear to be most prevalent for these groups than the group not requiring PF switches. These associations are weak at this stage but could be of value if investigated further.

In conclusion, OSD remains a prevalent issue in glaucoma clinics. There is a predisposition for certain individuals to develop OSD in the course of their glaucoma/OHT treatment. There are however inconsistencies in diagnosing OSD and prescribing PF treatment. It has come to light

that anterior eye signs may be overlooked by clinicians, resulting in an underestimation of the real problem of OSD in these clinics. Investigations looking at anterior signs and measuring the prevalence of OSD in glaucoma clinics prior to starting treatment are welcomed, as they would provide crucial baseline information and help identify patients who would benefit from PF treatment in the long-term. Identifying risk factors at the baseline visit could help form predictive-risk models and shape the future of the concomitant care of OSD and glaucoma.

Chapter 6

The prevalence of ocular surface disease at glaucoma diagnosis

6.1 Introduction

The previous chapters have discussed the intricacies of glaucoma clinics, and the multitude of factors which must be considered before a patient commences treatment. Glaucoma is a life-long condition, and with that, requires meticulous monitoring from consultants to ensure that the treatment is matched to the clinical need. This may mean changes to medication during the course of treatment, the need for glaucoma surgery or laser therapy and in some cases changes to preservative-free (PF) alternatives. The latter forms the basis of Chapters 6 and 7.

It was noted during the retrospective audit of chapter 5, that the diagnosis of OSD during the course of the treatment did not align well with the anterior eye signs and symptoms recorded during the first and follow up visits. The lack of recording of OSD and anterior signs led to some obfuscation; it is unclear why some patients were switched to PF treatment whilst others were not. In fact, recording of anterior eye signs was omitted in a substantial number of records which suggests that the prevalence of OSD in glaucoma clinics may well be highly underestimated.

The prevalence of dry eye disease (DED) has been estimated to lie anywhere between 5% to 50% (Stapleton et al., 2017). The literature outlines the cumulative risk factors for patients treated with hypotensive drops for glaucoma and OHT. The number of drops, the duration of treatment and the total benzalkonium chloride (BAK) exposure all increase the risk of patients developing OSD during the course of their treatment (Rossi et al., 2012). Though much of the current literature looks at the prevalence of OSD within a treated glaucoma and OHT population, there is a lack of evidence of the prevalence of OSD within such a population prior to commencing hypotensive treatment. This chapter aims to illuminate on the latter and bridge this gap in knowledge through patient evaluation in a clinical setting.

6.1.1 Prevalence of OSD in glaucoma

The prevalence of OSD in glaucoma has been discussed at lengths in the current literature, with Leung and colleagues (2008) approximating this to be around 59%, whereas Tsai and colleagues (2006) looked at the prevalence of glaucoma with a population of patients with severe OSD and found levels of 65.7% (Leung et al., 2008, Tsai et al., 2006). The prevalence of OSD in glaucoma is discussed in more detail in Section 5.1.2.

6.1.2 Diagnosing OSD

The TFOS DEWS II Diagnostic Methodology report is a comprehensive account detailing the appropriate tests and their correct order, to allow for diagnosis and monitoring of DED (Wolffsohn et al., 2017). The terms OSD and DED are often used interchangeably in literature, and the main differentiating factor between the two is the apparent presence of symptoms in DED. DED is therefore a subset of OSD. In this chapter both terms are referred to.

In order to fully appreciate which diagnostic tests are required to class an individual as having DED, it is important to revisit the definition of it as stated by the TFOS DEWS II report.

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

The tests used to diagnose DED must therefore reflect the individual aspects as outlined by the definition. A number of tests are recommended by the TFOS DEWS II report (Wolffsohn et al., 2017). To summarise, these are as follows:

- Triaging questions
- Risk factor analysis
- Ocular Surface Disease Index (OSDI)/Dry Eye Questionnaire (DEQ)
- Non-invasive tear film breakup time
- Corneal, conjunctival and lid margin staining using lissamine green and fluorescein
- Tear hyperosmolarity

6.1.3 Triaging questions and risk factor analysis

Differential diagnosis plays an important role in the hierarchy of DED diagnosis and management. Many ocular conditions can mimic symptoms and signs of DED and so triaging questions are vital to funnel information down to the most probable cause. The DEWS II report highlights a series of questions which should be employed at the beginning of an assessment to differentiate true DED cases from other conditions (Figure 6.1).

'How severe is the eye discomfort?'	•Dry eye tends to be described as an irritation/grittiness/dryness •Pain would indicate non-DED related problems such as trauma, infection or ulceration
'Do you have any mouth dryness or enlarged glands?'	•A positive response to this is suggestive of Sjögren's syndrome
'How long have your symptoms lasted and was there a triggering event?'	•DED is a persistent and chronic condition •Any sudden symptoms, or symptoms initiated by an event, could indicate trauma, infection or ulceration
'Is your vision affected and does it clear on blinking?'	•DED related visual blur should largely resolve on blinking once the ocular surface is replensished with a fresh tear film. Reduced vision not improving on blinking could indicate more sinister causes requiring urgent investigation.
'Are the symptoms or redness worse in one eye than the other?'	•DED tends to affect both eyes, so unilateral redness or symptoms require further assessment to rule out other ocular conditions.
'Do they eyes itch, is there any discharge or crusting and are they swollen?'	•Bilateral, itchy eyes indicate an allergic response •Discharge which is mucopurulent is linked to infection
'Do you wear contact lenses?'	•Contact lens wear can trigger or worsen DED and so contact lens wearers require appropriate management in such cases.
'Have you been diagnosed with any general health conditions and/or are you taking any medications?'	•Certain medications and general health conditions can trigger or exasberate dry eye •Patients should be encouraged to discuss their ocular symptoms with their GP

Figure 6.1: Triaging questions as suggested by TFOS DEWS II: Diagnostic Methodology report. Such questions aid in the differential diagnosis of DED. Triaging questions suggesting conditions other than DED would require a full follow up investigation including slit lamp examination to decipher primary cause (Wolffsohn et al., 2017).

Triaging questions should be followed by appropriate risk factor analysis. Referring back to Chapter 5 investigating the risk factors of OSD, it is apparent that there are many elements

which heighten the probability of developing DED. Such risks should be considered not only for informed diagnosis, but also to enable best management in cases of confirmed DED.

6.1.4 Symptoms

Both the old and the new revised definition of DED refer to the presence of ocular symptoms (Craig et al., 2017, Report of the International Dry Eye Workshop, 2007). The correlation between signs and symptoms of DED is low and inconsistent (Bartlett et al., 2015). In some cases, symptoms can precede ocular signs in DED, and so, appropriate questioning of patients is crucial for diagnosis. Assessment of patient symptoms of DED is also vital for monitoring purposes and to establish the effectiveness of treatment (Wolffsohn et al., 2017). A study by Begley and associates (2003) found a better association between symptoms and clinician grading of DED than that between signs and clinician grading (Begley et al., 2003). Thus, symptomology appears to be an important factor for clinicians when diagnosing DED and has been found to be the leading diagnostic tool used in clinical practice (Nichols et al., 2000).

The DEWS report recommends the use of a validated questionnaire to assess symptoms of DED. Though most clinical consultations entail a patient report of their medical history and symptoms, such information is difficult to collate and analyse quantitatively. The use of standardised questionnaires allows translation of visual dysfunction and ocular symptoms into numerical information that can easily be evaluated (Wolffsohn et al., 2017).

The most commonly used questionnaires in the assessment of DED according to the DEWS report are outlined in Table 6.1 below.

Questionnaire title	Reference	Category assessed
5-Item Dry Eye Questionnaire (DEQ-5)	(Chalmers et al., 2010)	Symptoms
Dry Eye Epidemiology Projects (DEEP)	(Oden et al., 1998)	Symptoms
Dry Eye Questionnaire (DEQ)	(Begley et al., 2002)	Symptoms
Dry Eye-Related Quality-of Life Score (DEQS)	(Sakane et al., 2013)	Symptoms and HRQL
Impact of Dry Eye on Everyday Life (IDEEL)	(Abetz et al., 2011)	Symptoms and HRQL
McMonnies' Questionnaire (MQ)	(McMonnies and Ho, 1987)	Symptoms and risk factors
National Eye Institute Visual Function Questionnaire (NEI-VFQ)	(Mangione et al., 1998b)	Visual functioning; HRQL
Ocular Comfort Index (OCI and OCI-C)	(Johnson and Murphy, 2007)	Symptoms
Ocular Surface Disease Index (OSDI)	(Schiffman et al., 2000)	Symptoms and HRQL
Standard Patient Evaluation of Eye Dryness (SPEED)	(Blackie et al., 2009)	Symptoms
Symptom Assessment in Dry Eye (SANDE)	(Schaumberg et al., 2007)	Symptoms
Women's health study questionnaire (WHS)	(Schaumberg et al., 2003)	Symptoms

HRQL= Health related quality of life
Table 6.1: Commonly used DED questionnaires with their respective primary sources and assessment categories, as outlined by TFOS DEWS II (Stapleton et al., 2017, Wolffsohn et al., 2017)

The OSDI is a 12-item DED questionnaire which covers both the frequency of symptoms and the effects of such problems on visual function. The questions are divided into three sections: the first section consisting of five questions relating to ocular symptoms, the second section consisting of four questions relating to functional limitations, and the last section consisting of three questions assessing the impact of environmental factors on ocular discomfort. The assessments are made on a 5-point scale, with zero representing the problem occurring 'none of the time' and four representing the problem occurring 'all of the time'. Patients are required to score the OSDI based on their experience in the last week (Stapleton et al., 2017). The scores are analysed according to the overall sum of the responses versus the number of

questions answered. The severity of DED disease is determined on a linear scale from 0 to 100, with greater scores indicating more severe cases of DED (Schiffman et al., 2000).

Originally developed by the Outcomes Research Group at Allergan Inc (Irvine, Calif), the OSDI has become well established in the field of DED, with many other questionnaires determining their validity against it such as SANDE and SPEED (Walt et al., 1997, Schiffman et al., 2000, Wolffsohn et al., 2017, Finis et al., 2014, Asiedu et al., 2016, Amparo et al., 2015). Consequently, its use in diagnosis of DED is favoured by the TFOS DEWS II committee. The OSDI questionnaire has been attached in Appendix 11.

The other questionnaire recommended by the TFOS DEWS II report in the assessment of symptoms is the DEQ-5. A subset of the original 21-item DEQ, the DEQ-5 entails five questions about ocular discomfort, dryness and epiphora. The DEQ-5 also encompasses questions specific to the intensity of discomfort and dryness on an evening (Chalmers et al., 2010). The evaluation of evening symptoms is particularly relevant, since diurnal variation was indicated by the original DEQ, with marked increases in DED symptom severity on an evening (Begley et al., 2001). Assessment is made on a Likert scale, with scores ranging from 0-4 or 0-5, and the sum of the scores range from 0-22. Scores of six or greater indicate non-Sjögren's syndrome associated keratoconjunctivitis sicca (non-SS KCS), whereas scores of 12 or greater indicate Sjögren's syndrome associated keratoconjunctivitis sicca (SS KCS) (Chalmers et al., 2010). Due to its ability to distinguish between non-SS KCS and SS KCS, as well as identifying patients with and without DED, and its fairly short format, the DEQ-5 is favoured by the TFOS DEWS II committee in its use for screening DED (Chalmers et al., 2010, Wolffsohn et al., 2017).

6.1.5 Tear film

6.1.5.1 Tear break-up time

The definition of DED highlights the involvement of tear film instability in the aetiology of OSD (Craig et al., 2017). Several tests can be employed to assess the tear film (Sweeney et al., 2013). Perhaps the most commonly used test in clinical practice for the assessment of the tear film is the tear break-up time (TBUT). TBUT refers to the time elapsed between a complete blink and the point of interruption of the tear film (Wolffsohn et al., 2017).

Measurement of TBUT can be classified into two forms according to whether Sodium Fluorescein (NaFl) is instilled to make this assessment or whether a non-intrusive method is

employed. NaFl is commonly used to investigate TBUT due to its ability to enhance tear film visibility under slit lamp biomicroscopy against a cobalt blue filter (Akpek et al., 2019). Though its use has been recommended by the 'Dry Eye Syndrome Preferred Practice Pattern'®, NaFl threatens tear film stability which can ultimately affect the accuracy of the TBUT result (Akpek et al., 2019, Mengher et al., 1985a).

In a prospective study by Mooi and colleagues (2017), Fluorescein instilled TBUT (FBUT) was compared to non-invasive TBUT (NIBUT). Two NaFl concentrations were used via impregnated strips; a 1µl strip from the Dry Eye Test™ (Amcon Laboratories, St Louis, MO, USA), and a conventional strip (Haag-Streit, UK) using one drop of saline equating to 15–30µl. Results indicate that tear film stability may be correlated with the volume of NaFl used to make the TBUT assessment, rather than just its use alone. NIBUT and FBUT using minimal amount of NaFl displayed similar results, whereas conventional concentrations led to a reduced break-up time (Mooi et al., 2017).

Nonetheless, due to its potential to implicate tear film stability, TFOS DEWS II recommends TBUT measurements to be taken without NaFl where possible. Objective methods are preferred over subjective ones due to the variability in TBUT results using observer-based instruments alone (Elliott et al., 1998, Wolffsohn et al., 2017). Patients are required to blink naturally, then cease to blink until there are breaks in the tear film. In cases where a stare cannot be upheld before a break in the tear film, the time to that blink is taken as the TBUT. Three measures of TBUT are taken, where the median is recorded as the main result (Wolffsohn et al., 2017). A result of <10 seconds is suggestive of DED, and lower still when using an automated system (Wolffsohn et al., 2017, Hong et al., 2013, Mengher et al., 1985b)

Another vital tool in the diagnosis of DED is tear film osmolarity. As per the revised definition of DED, hyperosmolarity plays a major role in the aetiological processes of DED (Craig et al., 2017). Compared to other diagnostic tools, tear osmolarity appears to be superior in its ability to diagnose DED (Lemp et al., 2011). With a sensitivity of 73% and a specificity of 92%, a positive diagnosis can be made if the osmolarity reading is 308mOsm/L or greater, or with an inter-eye difference of more than 8mOsm/L (Jacobi et al., 2011, Lemp et al., 2011, Sullivan, 2014).

Anatomically, hyperosmolarity has been found to correlate with increased levels the pro-inflammatory cytokine IFN-y (Jackson et al., 2016). This cytokine has been shown to amplify conjunctival apoptosis when under desiccating stress (Zhang et al., 2011). The cells which

secrete such cytokines, namely, natural killer (NK) cells, appear to play an important role in the activation of DED (Chen et al., 2011).

6.1.5.2 Tear Volume

Although the tear volume is not explicitly stated as an element of DED in the definition by the DEWS II report, its assessment can provide vital information about the status of the tear film and possible tear film dysfunction (Mainstone et al., 1996). Reduced tear menisci have been found amongst aqueous deficient dry eye sufferers (Uchida et al., 2007, Yuan et al., 2010).

Being non-invasive and providing quantifiable information, meniscometry is the most commonly used method to assess tear volume in clinical practice (Nichols et al., 2000). Occupying 75-90% of the total tear film volume, the tear meniscus height (TMH) can provide a good insight of the tear volume (Holly, 1985, García-Resúa et al., 2009). Alternatively, tear meniscus width (TMW), radius of curvature (TMC) and the cross sectional area (TMA) can also be good indicators of tear volume, and such parameters show promising diagnostic and monitoring purposes in DED (Mainstone et al., 1996).

Typically, TMH measurements are made using the slit lamp beam, adjusting its height to match that of the tear meniscus. Such methods are susceptible to inter-visit repeatability issues and are dependent on the observer, which can cause some variability in the findings (Nichols et al., 2004a, Wolffsohn et al., 2017). More recently, digital methods have been employed for more accurate measurements. Such techniques have involved the use of Optical Coherence Tomography (OCT) as well as topography using a Keratograph, both showing good repeatability and reproducibility (Canan et al., 2014, Wang et al., 2009, Baek et al., 2015).

6.1.5.3 Interferometry

Interferometry is another method which can be employed to evaluate the tear film, specifically through observation and analysis of the pre-corneal tear film reflectivity (Wolffsohn et al., 2017). Photometry used for the assessment of the tear film initially led to the approximation of the thickness of the lipid layer of the tear film to be ~40nm (Olsen, 1985). Such methods are based on the fundamentals of wavelength dependent fringes (WDF), whereby reflections between the interface of the air and the surface of the tear film, and the interface between tear film and the cornea, result in interference waves (Hosaka et al., 2011, King-Smith et al., 1999).

Determination of the pre-corneal tear film thickness can be a useful tool in the diagnosis and management of DED. A case control study by Hosaka and colleagues (2011) found that the tear film of dry eye patients was significantly thinner than those who did not suffer from dry eye (2.0±1.5μm vs 6.0±2.4μm, P <0.0001), and the addition of punctal plugs led to a significant improvement in tear film thickness (Hosaka et al., 2011).

Furthermore, such interference also gives rise to interferometric fringe patterns, which can act as indicators to the stability of the lipid layer. Craig and colleagues (1997) investigated such fringe patterns in dry eye patients and controls. It was found that the rate of tear evaporation was closely associated with the configuration of the lipid layer. Those who showed fringe patterns which were suggestive of an abnormal lipid layer, or those lacking a lipid layer entirely, revealed significantly higher tear evaporation rates. Where the fringe patterns showed uniform and stable lipid layers, irrespective of thickness, the tear film was well preserved (Craig and Tomlinson, 1997).

6.1.6 Ocular surface staining

Ocular surface staining using impregnated strips of NaFl and lissamine green dyes can provide useful information regarding the status of the ocular surface. The use of such dyes allows visibility of dead and/or damaged cells on the cornea, conjunctiva and the eyelid margins (Bandamwar et al., 2014, NORN, 1973). Rose Bengal takes a lesser preference due to its associated stinging, its cytotoxicity resulting in staining of undamaged cells, and due to the difficulty in observing the staining against dark irides (Manning et al., 1995, Kim and Foulks, 1999, Feenstra and Tseng, 1992, Bron, 2001). Though on the whole, corneal staining is a latter feature of DED, its assessment is recommended by the DEWS II report (Wolffsohn et al., 2017).

It is common practice to use NaFl to assess the cornea, whilst lissamine green is used for conjunctival examination (Wolffsohn et al., 2017). A combination of 2% fluorescein and 1% lissamine green has demonstrated optimal staining ability and simultaneous patient comfort (Korb et al., 2008). The pattern of staining can be a good indicator of both the aetiological factors, and in cases of DED, provide insight into the severity of the disease (Bron et al., 2015).

Several ocular surface staining scales have been developed to allow for consistent measurements of corneal and conjunctival staining both between practitioners and across time. Examples of such scales include the Bijsterveld system, the National Eye Institute/Industry

Workshop guidelines and the Oxford Scheme, with interpretation being based on the frequency and distribution of punctate spots (van Bijsterveld, 1969, A. Lemp, 1995, Bron et al., 2003).

As well as mentioning ocular surface damage, which is evidenced through corneal and conjunctival staining, the DEWS II report definition refers to ocular surface inflammation as being a major component in DED (Craig et al., 2017, Wei and Asbell, 2014). Clinically, such inflammation of the ocular surface is demonstrated through conjunctival redness (Ferrari et al., 2015). Differential diagnosis plays an important role in this particular sign since conjunctival redness is not limited to DED (Wolffsohn et al., 2017, Leibowitz, 2000).

6.1.7 Lid margin analysis

Though lid margin disease is not necessarily a diagnostic feature of DED, its presence can act as an accompaniment to dry eye or indicate the subtype of DED. One of the major lid margin disorders which can give rise to DED is meibomian gland dysfunction (MGD) (see Section 5.1.4.4 ‘Comorbidities’ for a full definition of MGD).

The meibomian glands, residing within the tarsal plates of the eyelids, are responsible for the production and secretion of a concoction of lipids, cholesterol, fatty acids, triacylglycerol, phospholipids and wax esters. Once this secretion enters the tear film, it acts to protect and preserve. As the outermost layer of the tear film, it aids in conserving the aqueous layer by impeding evaporation. Hindrance of this system, can give rise to MGD (Nichols et al., 2011).

MGD has been recognised as a consistent factor for evaporative dry eye (EDE), and EDE as the most prevalent subtype of DED (Bron and Tiffany, 2004, Lemp et al., 2012). The presence of MGD has been closely linked to the signs and symptoms of DED (Viso et al., 2011, Uchino et al., 2006). Baudouin and colleagues (2016) state that MGD is the ‘most frequent cause of DED’, describing the relationship between DED and MGD as a ‘double vicious cycle’ due to the underlying mechanisms connecting the two (Figure 6.2) (Baudouin et al., 2016).

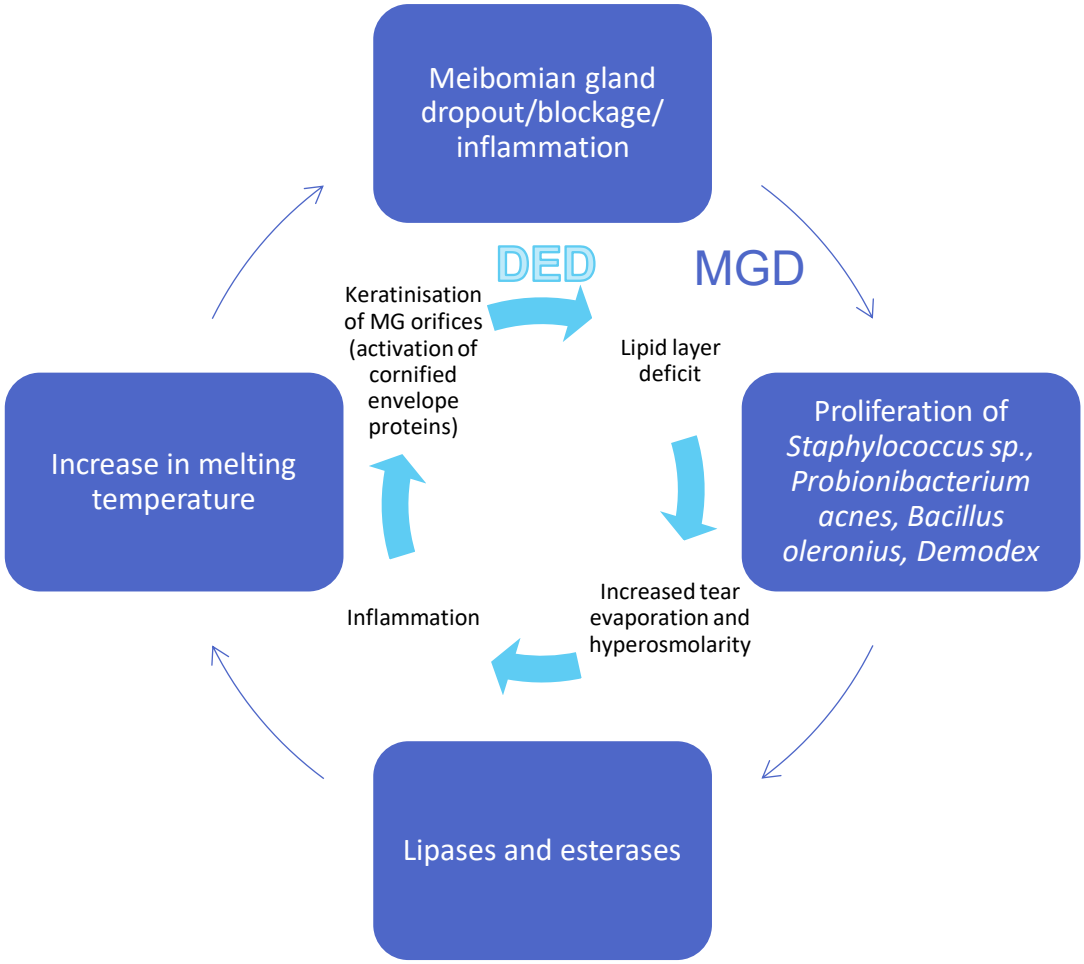


Figure 6.2: The 'double vicious circle' of DED and MGD. Figure adapted from the review by Baudouin and colleagues (2015) (Baudouin, 2014, Baudouin et al., 2016)

MGD is typically visualised using meibography; a system using transillumination to highlight the morphology of the meibomian glands. By everting the eyelids and presenting a luminous source, a silhouette of the glands is imaged, spotlighting any shortfalls in structure (Wolffsohn et al., 2017, Arita et al., 2008). Originally penned by Tapie in 1977, meibography has evolved over the years, with newer adaptations promoting non-invasive, *in vivo* approaches using infra-red imaging techniques, through the use of a slit lamp biomicroscope or handheld LED devices (Tapie, 1977, Arita et al., 2008, Arita et al., 2013).

Alternatively, meibum secretion by the ducts as well as their frequency and location can also be assessed for the grading of MGD (Korb and Blackie, 2008). Both the quality and the quantity of such secretions can indicate the functioning of the meibomian glands (Wolffsohn et al., 2017, Shimazaki et al., 1998, Shimazaki et al., 1995). Several grading scales have been developed to

quantify the severity of MGD through lid margin analysis (Arita et al., 2016, Bron et al., 1991, Shimazaki et al., 1998, Shimazaki et al., 1995).

Another frequent cofounding factor to DED is blepharitis; a chronic inflammatory response of the lid margin resulting in ocular irritation, lid swelling and redness (Wolffsohn et al., 2017, Amescua et al., 2019). Blepharitis is usually divided into its anterior and posterior form depending on the location of lid involvement, with the latter better known as MGD (Amescua et al., 2019).

DED and blepharitis are closely linked, with clinical features of the two often being congruent. DED and staphylococcal blepharitis have been reported to coexist in 50%-75% of cases (Amescua et al., 2019, McCulley et al., 1982, Baum, 1985). Assessment of the lid margin and careful observation of the features of blepharitis may help to distinguish the type of blepharitis. For more specific diagnosis, analysis of cultures obtained from the lid margin may be required (Amescua et al., 2019). Grading scales have been used to standardise blepharitis assessment in clinical practice (Bunya et al., 2013).

6.1.8 Protocol for dry eye diagnosis

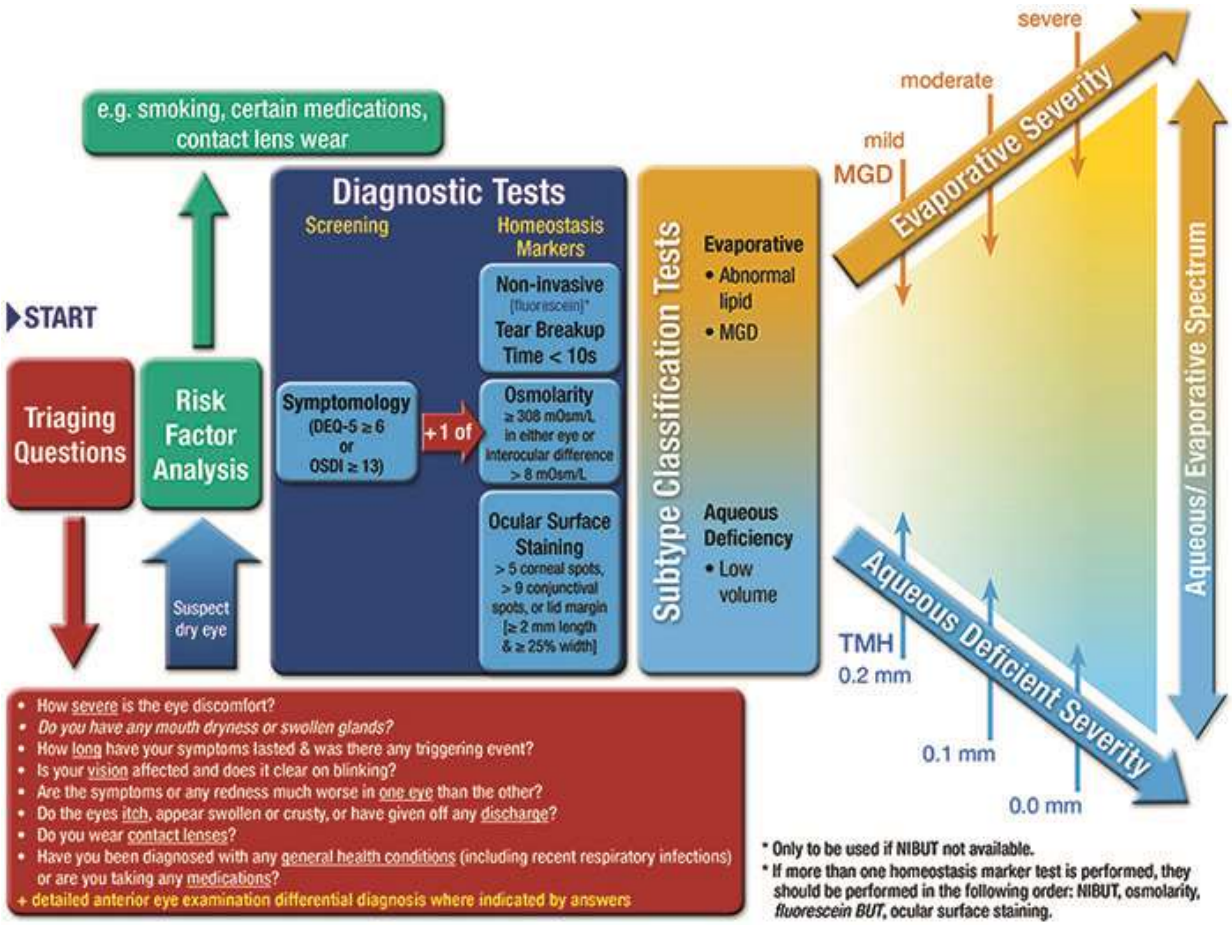


Figure 6.3: TFOS DEWS II recommended flowchart for the diagnosis of DED reproduced with permission (Wolffsohn et al., 2017).

The DEWS II report recommends a standardised protocol for the diagnosis of DED as outlined in figure 6.3. There are numerous tests available in the diagnosis, management and monitoring of DED as discussed above. Applying some of these tests as endorsed by the DEWS II report, this chapter aims to highlight the prevalence of OSD and DED at the point of arrival into the glaucoma clinic at Russells Hall Hospital (Dudley NHS Trust, UK) in the West Midlands.

6.2 Aims and Objectives

To investigate the prevalence of OSD and DED in a new glaucoma patient clinic at Russells Hall Hospital (Dudley NHS Trust, UK) in the West Midlands, comparing prevalence rates amongst untreated, suspect glaucoma and/or OHT patients with newly treated glaucoma and/or OHT patients

6.3 Methods

6.3.1 Glaucoma clinics at Russells Hall Hospital

Russells Hall Hospital (RHH) (Dudley NHS Trust, UK) in the West Midlands, conducts a variety of ophthalmology clinics. The glaucoma clinics run by the ophthalmology department can be divided into 'new' glaucoma clinics and 'follow up' glaucoma clinics. Patients are referred to the 'new' clinics by their optometrists, GPs or other consultants, if they are suspected to have glaucoma or OHT. Once a positive diagnosis has been made of glaucoma or OHT, or once patients are deemed as 'suspect' glaucoma/OHT cases requiring close monitoring, they are reviewed in the 'follow up' clinics. Though most patients are not started on treatment until they are reviewed in the 'new' clinic, there is a possibility that some may be started on topical treatment by other consultants prior to being referred to be seen in the glaucoma clinic in cases where immediate intervention is required to address the elevated intraocular pressures (IOPs).

The majority of the glaucoma clinics are run by specialist consultants, however, in cases where the glaucoma or OHT is stable or well controlled, and for those patients just being monitored without treatment, they are often booked in with Advanced Nurse Practitioners specialising in glaucoma (AGPs) or advanced ophthalmic technicians who have been trained in glaucoma. AGPs and advanced ophthalmic technicians will see patients in their follow up clinics, and escalate any patients to the glaucoma consultants, should signs or symptoms present to them which require further investigation.

The COVID-19 pandemic led to some disruption of these routine clinics at RHH. At the peak of the pandemic, only urgent appointments were kept in the glaucoma clinics. Patients requiring follow up appointments were reviewed through telephone consultations, with face-to-face consultations to be rearranged once restrictions would ease.

As the pandemic appeared to be a long-term issue, the creation of the 'Virtual Glaucoma Clinic' (VGC) came about to address the backlog of patients. Patients presented to these clinics at the sister site of Corbett Hospital (Dudley NHS, UK) in the West Midlands. The VGCs were ran by ophthalmic technicians who would see both new and follow up glaucoma and OHT patients. A battery of tests were conducted including measurement of IOPs, visual fields (VFs) testing, fundus photography, OCT scans and visual acuities. This was combined with a history and symptoms report. The outcome of these visits was then virtually reviewed by

glaucoma consultants, and the outcomes of this were discussed with the patient over the phone. Any patient requiring intervention or further assessment was then booked for a face-to-face appointment with a consultant at the earliest date, whereas patients who appeared to show normal or stable results, were scheduled for follow up appointments in the VGC in the future.

6.3.2 Enhanced Glaucoma Clinic

With the onset of the COVID-19 pandemic and the disturbance to the workings of the NHS, glaucoma consultants at RHH proposed the formation of an intermediate clinic, which would link VGCs and face-to-face glaucoma clinics. This clinic was named the 'Enhanced Glaucoma Clinic' (EGC) and would be led by an Optometrist working alongside the glaucoma consultants at RHH. Patients from the VGCs requiring intervention would be referred to the face-to-face EGC and the Optometrist would carry out a series of tests including Goldmann Applanation Tonometry (GAT), anterior chamber assessment using the Van Herick technique or gonioscopy, fundoscopy with particular focus on the optic disc, pachymetry, a detailed personal history and symptoms, OCT and VFs assessments.

The 'enhanced' element of this clinic was introduced following the findings of the retrospective audit (Chapter 5). The leading glaucoma consultants of RHH were keen to trial a new clinic which would introduce additional dry eye tests into the routine glaucoma consultation. This implementation would allow screening for DED at baseline as well as at follow up appointments. This clinic would therefore help to address the shortfalls highlighted in Chapter 5; anterior eye signs need to be checked more thoroughly and patients screened for OSD.

Referrals to the EGC were made internally via the VCGs and by other ophthalmology consultants. Patients presenting to the EGC were suspected to have glaucoma or OHT, and were likely to require treatment. Initially, only new patients presented to this clinic, however, with time, follow up patients were also referred to this clinic.

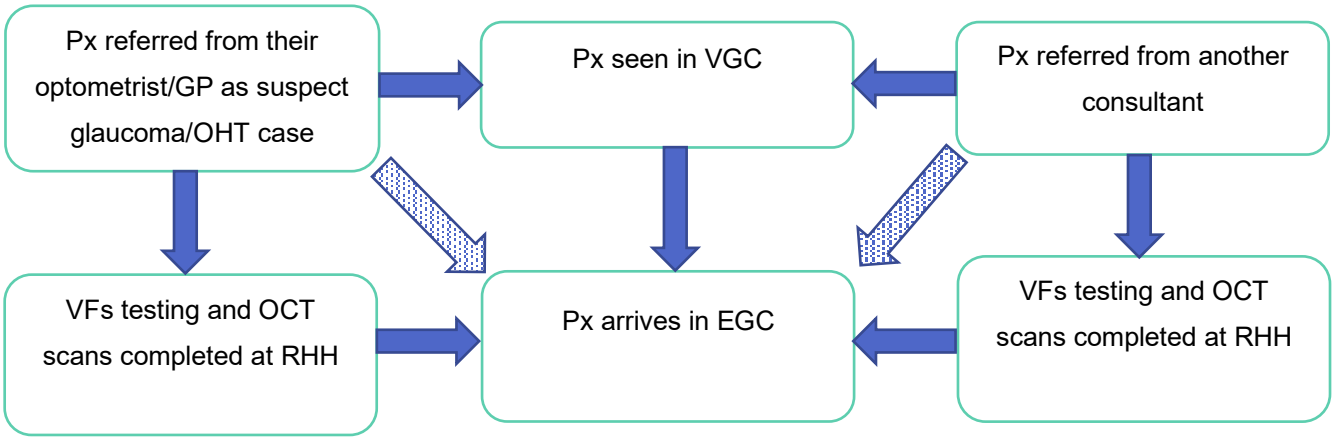
6.3.3 Data collection

The EGC began in June 2021. Patients arrived in this clinic via different pathways. New patients were primarily assessed in the VGCs first and then referred to the EGC if there was an indication that the patient required intervention, treatment or further assessment. Patients arriving in other ophthalmology clinics for their initial assessments, and who met the inclusion

criteria set out below (Section 6.3.6), were referred internally to the EGC directly. There were some exceptions where consultants chose to refer via the VGC, though this was clinician dependent.

Patients presenting to this clinic were assigned unique ID numbers, alongside their NHS numbers. This ID system was then used to access these records retrospectively for analysis.

6.3.4 Patient Journey



Px=Patient

Figure 6.4: Patient pathway for referral into the EGC at RHH. Dark arrows represent the most common pathways, whilst the lighter arrows depict less common routes. Ideally, patients arriving into the EGC have their supplementary tests performed beforehand, whether this is prior to the EGC appointment or on the day of the appointment. Patients arriving into the EGC from the VGC will already have had their VFs tests and OCT scans performed. Occasionally, patients are referred directly to the EGC without having their supplementary tests performed, resulting in a gap in this data.

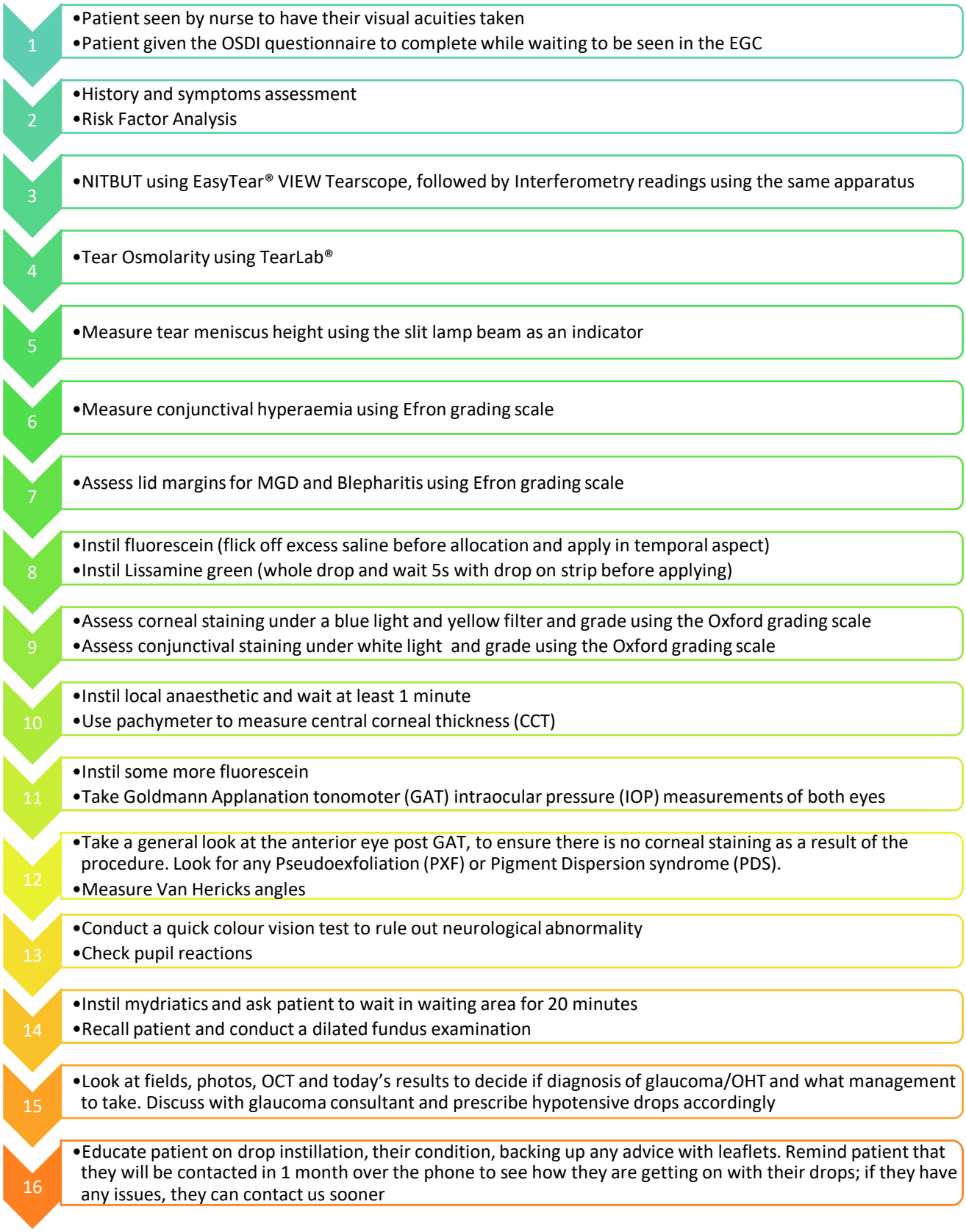


Figure 6.5: Patient pathway on arrival into the EGC. The steps highlight the preferred order of tests according to both the TFOS DEWS II report as well as instructions as per apparatus (Wolffsohn et al., 2017). Tests such as the TearLab® and EasyTear® VIEW tearscope must be conducted prior to any

invasive procedures requiring drop instillation. Dry eye tests are conducted first, followed by the routine tests required in the glaucoma clinic.

6.3.5 Dry eye tests

The following describes the tests used in the diagnosis of OSD in the EGC, in order of their use.

1. *Non-Invasive Break-Up Time*
   The NIBUT was the first diagnostic measurement taken since it relies on a non-invasive approach and could be influenced by instillation into, or manipulation of, the ocular surface. The EasyTear® VIEW device was fitted on to the slit lamp biomicroscope, with the settings at maximum luminance on the device. The addition of a grid insert into the tearscope allowed projection of the grid onto the front of the eye. Patients were then instructed to blink a few times, and then proceed to keep their eyes open for as long as possible, with the timer on the tearscope being activated on instruction of the stare. The grid projection was observed through the slit lamp viewing system, and on signs of first disruption of the projected grid, the timer was stopped. Three measurements were taken per eye. If a stare could not be upheld before disruption to the grid pattern, the timer was stopped on blink and that reading taken as the NIBUT, as per the TFOS DEWS II protocol (Best et al., 2013, Wolffsohn et al., 2017)

   Where NIBUT was not available, TBUT was carried out using fluorescein to aid observation. Fluorescein break-up-time (FBUT) measures in such instances were made just prior to ocular surface staining grading (step 7). Once the fluorescein was instilled, patients were instructed to blink a few times and proceed to hold a gaze. The time was noted between the initial point of gaze hold to the first point of tear film disruption as demonstrated by blank spots in the tear film. The measurement was repeated three times (Nichols et al., 2004a, Wolffsohn et al., 2017, Mooi et al., 2017).

2. *Interferometry*
   Fringe patterns were also observed with the EasyTear® VIEW tearscope, immediately after taking NIBUT readings. The grid insert was removed from the device and the system focussed on the tear film layer in front of the cornea. Patients were asked to blink naturally, and the fringe pattern was compared to the Guillon categories: Grade 1 Open Meshwork, Grade 2 Closed Meshwork, Grade 3 Wave and Grade 4 Coloured fringes. The amorphous category was omitted due to its uncommon nature, and thus, the lack of availability of

images to compare to this category (Bolón-Canedo et al., 2012, Guillon, 1998). The fringe pattern images used for comparison in the EGC clinic are from a study by Bolón-Canedo and colleagues (2012) (Bolón-Canedo et al., 2012), and are attached in Appendix 12.

3. *Tear Osmolarity*
   Tear osmolarity was taken using the TearLab® Osmolarity System. This system uses less than 50-nanoliters of tear fluid to generate an osmolarity reading. The device has to be calibrated and temperature stabilised prior to its use. A new osmolarity test card was attached to the device for each eye, and for each patient. The patient was instructed to look up and away, and the test card chip was gently rested on the outer edge of the lower lid, making brief contact with the lid margin but avoiding the globe, collecting enough fluid from the tear lake. Returning the device back on the main stand generated a reading (Wolffsohn et al., 2017, TearLab, 2022).

4. *Tear Meniscus Height*
   TMH was measured next in the battery of dry eye tests, using the beam of the slit lamp as an indicator of height. The patient was instructed to look ahead, whilst positioned at the slit lamp, and the beam was adjusted in height. The beam was then lined up with the top of the lower lid margin, at the centre of the lid, directly below the pupil. The beam was then adjusted to match the height of the tear lake at this point. Such variable beam height measurements have been employed successfully in the past (Nichols et al., 2004a).

5. *Conjunctival hyperaemia*
   Conjunctival hyperaemia was measured with the aid of the Efron grading scale. The five-point scale covers normal, trace, mild, moderate and severe categories. The patient was instructed to gaze in the four principal directions, and the hyperaemia score was made according to overall bulbar redness (Efron et al., 2001).

6. *Lid margin analysis*
   Next, blepharitis and MGD grading was conducted using images from the Efron grading scale to make a diagnosis. For MGD, assessment was made of the upper and lower lid margins and compared with the images depicted on the Efron scale. For blepharitis, patients were asked to close their eyes and the top lash line was assessed, followed by opening the eyes, and the lower lash line assessed. Both observations were made under bright light and medium-high magnification, and grading made based on comparisons to the scale (Efron et al., 2001).

7. *Corneal staining*
   A drop of saline was added to an impregnated fluorescein strip (1mg Sodium Fluorescein Bio Fluoro Ophthalmic Strips). The strip was shaken to remove any excess saline before allocation. The patient was asked to look up and away, and the strip was applied to the far, temporal aspect of the eye. Observation through the slit lamp was made after a few minutes post instillation, under cobalt blue light with a Wratten filter to aid viewing (Peterson et al., 2006). The Oxford grading scale was used to make comparisons and score the severity of staining (Appendix 13) (Bron et al., 2003, Wolffsohn et al., 2017).

8. *Conjunctival staining*
   Lissamine green was added at the same time as the fluorescein, so both ocular surface staining assessments could be made together (Korb et al., 2008). A drop of saline was added to an impregnated strip of Lissamine green I-Dew 1.5mg Lissamine Green Ophthalmic Strips), and the whole drop was allowed to be absorbed by the strip. After 5 seconds, the patient was asked to look up and away again, and the strip was applied to the far, outer temporal aspect of the eye. The Oxford grading scale was used to make comparisons and score the severity of staining (Appendix 13) (Bron et al., 2003, Wolffsohn et al., 2017).

6.3.6 Inclusion/Exclusion criteria

Inclusion criteria

- Patients suspected of having glaucoma or OHT but have not been commenced on topical hypotensive drops (for prevalence of DED and OSD in untreated patients)
- Patients who have started topical hypotensive treatment (for prevalence of DED and OSD in treated patients)
- Patients aged 18-100 years, with a sound understanding to be able to complete the OSDI questionnaire
- Patients able to sit at the slit lamp for at least 1 hour

Exclusion criteria

- Patients who have previously had glaucoma surgery or laser interventions
- Patients who are not able to comprehend the OSDI questionnaire

- Patients requiring immediate medical attention from a consultant due to complexities of their glaucoma or OHT
- Patients who are unable to sit at the slit lamp for their assessments

6.3.7 Ethics

This research followed the tenets of the Declaration of Helsinki. NHS Ethical approval was obtained under the IRAS PROJECT ID 173203. The EGC formed part of the routine glaucoma clinics at RHH and data collected in these clinics was analysed retrospectively.

6.3.8 Sample size determination

The prevalence of DED within glaucoma populations has been estimated to be around 59% (Leung et al., 2008, Garcia-Feijoo and Sampaolesi, 2012). Therefore, a minimum of 100 patients would be needed per subject group so each patient represents 1% or less.

6.4 Results

The EGC ran over a period of five months in 2021. A total of 57 patients were reviewed in this clinic during this period. Of the 57 patients, 33 were ‘new’ to the clinic and 24 were ‘follow ups’. The ‘new’ patient base consisted of treatment-naïve patients, and the ‘follow ups’ were based on a combination of treatment-naïve and treated patients who were being monitored in the glaucoma clinics. Few patients, who were ‘new’ to the clinic initially, were reviewed in this clinic as ‘follow ups’ at their next appointment. All of the 57 patients were included in this retrospective study.

For analysis of the data obtained in these clinics, patients were divided into subgroups. Under the ‘follow up’ cohort, 16 patients presented to the EGC having already been treated with hypotensive eye drops. The other eight ‘follow up’ patients were being monitored as suspect glaucoma or OHT patients only, and so were not on any treatment.

Data analysis from here on in will therefore include three groups of patients:

1. ‘New patients’ (New): first visit into the eye clinic at RHH and not on any hypotensive treatment, n=33
2. ‘Treated patients’ (Tx): follow up patients presenting to the EGC, already on treatment for glaucoma or OHT, n=16

3. ‘Follow up patients’ (FU): treatment-naïve, suspect glaucoma or OHT patients, n=8

6.4.1 Demographics

Of all the patients reviewed in the EGC, 30 were females and 27 were males. The average age of the patients presenting in this clinic was 66.1±13.9 years (range 37-88 years). The bulk of patients presenting to the clinic were Caucasian (89%), with a smaller minority made up of Asian ethnicities (9%) and Afro-Caribbean (2%).

6.4.2 Tear film

6.4.2.1 Tear break-up time

TBUT was measured using two different methods in the clinics. For the first 25 patients presenting to the clinic, TBUT was measured using fluorescein instillation (FBUT). A change in protocol at the hospital during the course of the EGC resulted in the implementation of the EasyTear® VIEW tearscope for non-invasive measurements of TBUT and lipid layer viability. Thus, for the remainder of the clinic, NIBUT was measured using the EasyTear® VIEW tearscope. Regardless of technique, the measure was repeated three times per eye, for each patient.

New

Twenty-three patients in this newly-referred group had FBUT performed and the remaining ten had NIBUT performed using the EasyTear® VIEW tearscope. The average FBUT was 4.5±2.2 seconds for the right eye (RE) and 4.6±2.3 seconds for the left eye (LE). NIBUT readings were slightly higher averaging at 6.0±2.2 seconds for the RE and 7.2±3.6 seconds for the LE.

Follow up

For the eight patients being followed up as suspect cases of glaucoma or OHT, two had this piece of data missing. The NIBUT for the remaining six patients averaged at 5.7±2.1 seconds for the RE and 5.7±3.1 seconds for the LE.

On Treatment

Sixteen patients were commenced on treatment earlier in the pathway and attended the EGC as follow up patients. Of these, two had their FBUT taken, which was 4 seconds for both the

RE and LE, for both patients. The remainder had their NIBUT taken, which averaged at 6.5±1.7 seconds for the RE and 5.8±1.4 seconds for the LE.

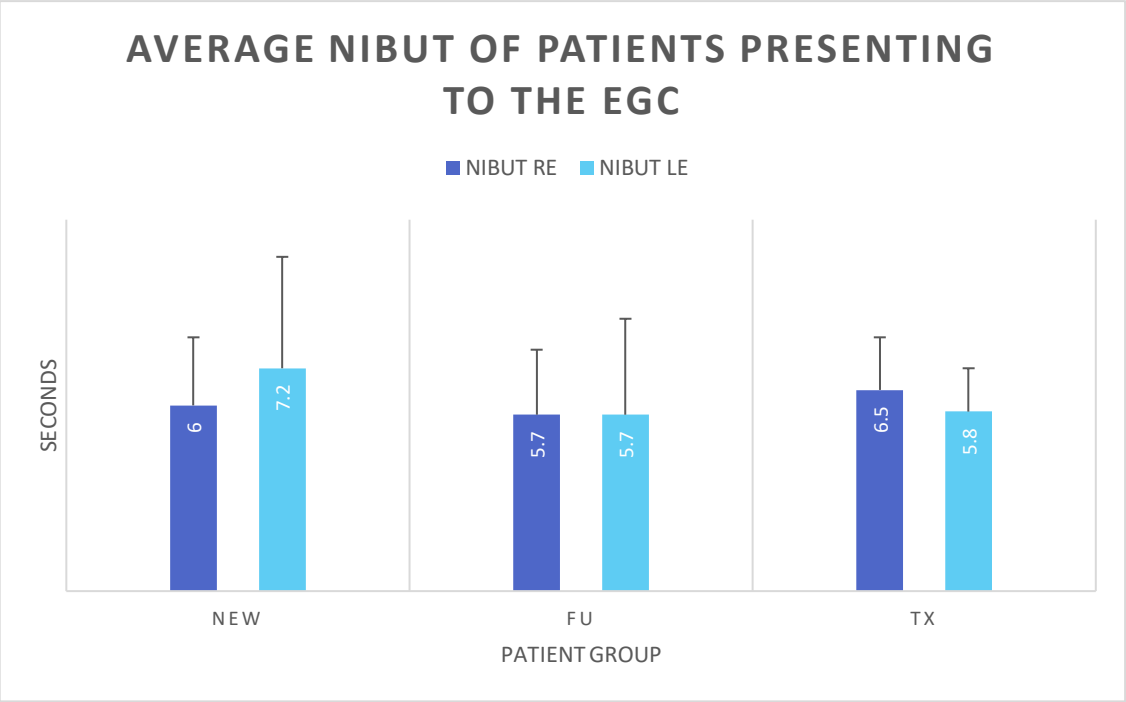


Figure 6.6: The average NIBUT for each eye, for all three patient groups.

6.4.2.2 Interferometry

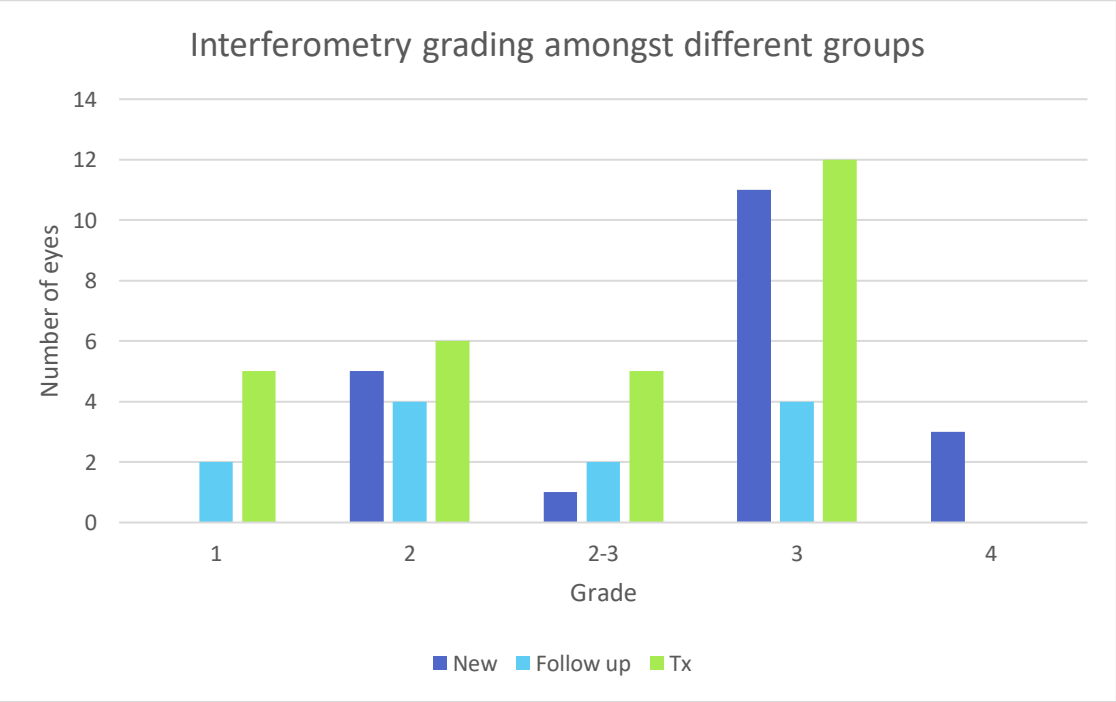


Figure 6.7: Fringe pattern grading for each group of patients presenting to the EGC.

Interferometry patterns were observed using the EasyTear® VIEW tearscope. Classification was based on the Guillon categories: Grade 1 Open Meshwork, Grade 2 Closed Meshwork, Grade 3 Wave and Grade 4 Coloured fringes (Bolón-Canedo et al., 2012, Guillon, 1998).

The EasyTear® VIEW device was implemented into the EGC after a change in the hospital protocol long after the clinic started. Interferometry readings are therefore unavailable for the first 25 patients. The fringe patterns were observed and graded for the remaining 32 patients attending the EGC.

Wave fringing at grade 3 was the most commonly observed pattern in both new and treated patients. Only a small proportion of new patients displayed coloured fringes at grade 4; no follow up patients or treated patients had lipid layer fringing at grade 4. Follow up patients showed the most prevalent fringing at grades 2 and 3. The majority of fringing appears to occur at grades 2, 2-3 and 3.

Grade	New	Follow up	Treatment
1	0%	17%	18%
2	25%	33%	21%
2-3	50%	17%	18%
3	55%	33%	43%
4	15%	0%	0%

Table 6.2: Percentage distribution of eyes in each group of interferometry fringe pattern category.

6.4.2.3 Tear Osmolarity

New

The average tear osmolarity reading for the thirty-three new patients presenting to the EGC was 302±12.1mOsm/L for the RE and 301±12.5mOsm/L for the LE. Of these results, 16 were >300mOsm/L for the RE and 17 were >300mOsm/L for the LE.

Follow up

Of the eight patients who were followed up with no prior treatment in the EGC, four had their tear osmolarity taken. The average tear osmolarity for the RE was 298±12.2mOsm/L and for the LE it was 305±20.9mOsm/L.

On Treatment

All sixteen patients presenting to the EGC who were previously prescribed hypotensive drops, had their tear osmolarity assessed. The average osmolarity for the RE was 300±10.6mOsm/L and 301±9.7mOsm/L for the LE.

>307mmHg	New	Follow up	Treatment
RE	30%	25%	25%
LE	27%	25%	25%

Table 6.3: Percentage of tear osmolarity readings of ≥ 308 mOsm/L for each eye, in each group of patients.

6.4.2.4 Tear Meniscus Height

New

TMH was taken for all new patients presenting to the EGC. The average TMH for the RE was 0.27±0.10mm and 0.26±0.11mm for the LE.

Follow up

The TMH was available for five out of the eight patients who were being monitored for glaucoma or OHT without treatment. The average TMH for this group was 0.32±0.04mm for the RE and 0.34±0.09mm for the LE.

On Treatment

All sixteen treated patients had their TMH taken at their visit to the EGC. The average TMH was 0.29±0.10mm for both the RE and the LE.

6.4.3 Lid margin analysis

Lid margin analysis was made with the aid of the Efron grading scale, defining MGD and blepharitis on a five point scale, with grade 0 representing ‘normal’ and ascending to grade 4 which is classed as ‘severe’.

6.4.3.1 Blepharitis

New

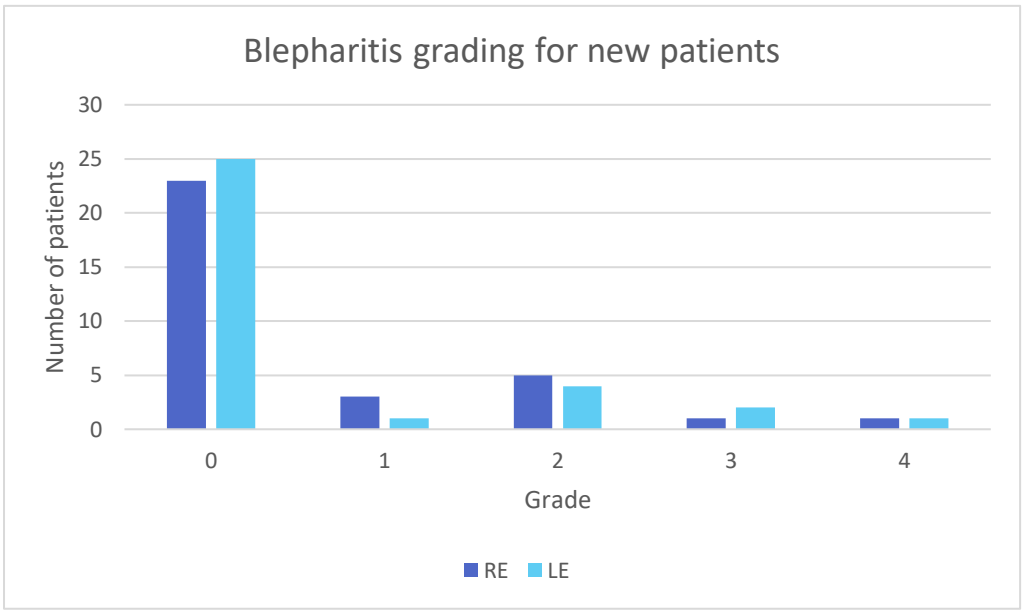


Figure 6.8: The distribution of blepharitis grading of new patients attending the EGC.

Though there were patients presenting with blepharitis of every grading, the most common grading of blepharitis was at 0 for new patients.

Follow up

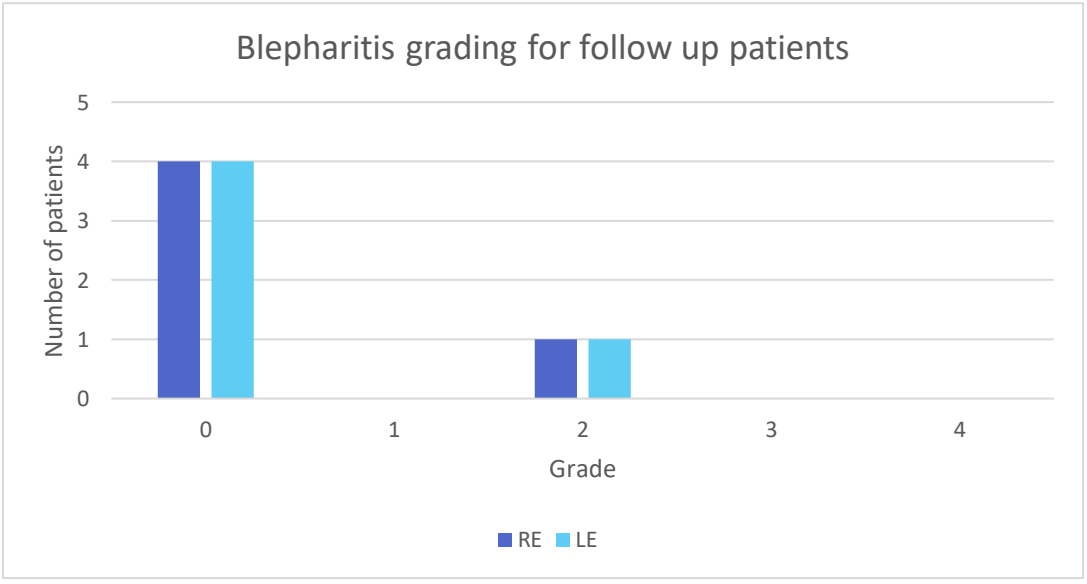


Figure 6.9: The distribution of blepharitis grading of follow up patients attending the EGC.

Follow up, treatment-naïve patients appeared to display blepharitis at grade 0 most commonly, with a smaller proportion showing signs of grade 2 blepharitis.

On Treatment

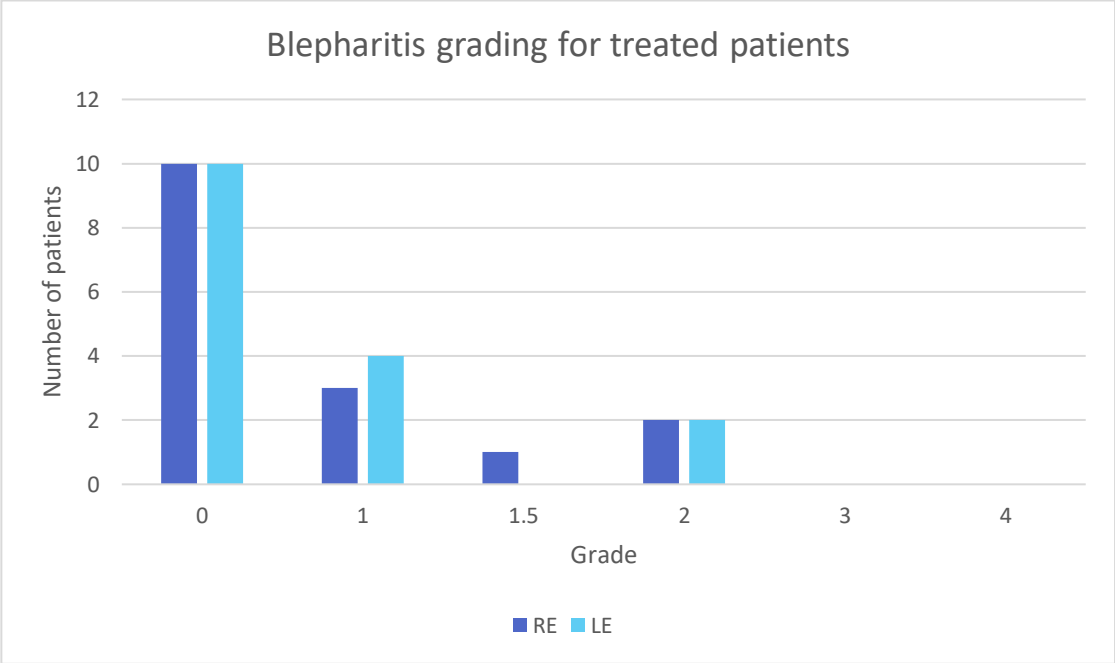


Figure 6.10: The distribution of blepharitis grading of treated patients attending the EGC.

As with the new and follow up groups, for treated patients, grade 0 blepharitis was also the most commonly noted score of severity. Few patients were recorded as having blepharitis of grades 1, 1.5 and 2. No patient was recorded of having blepharitis of grade 3 or more.

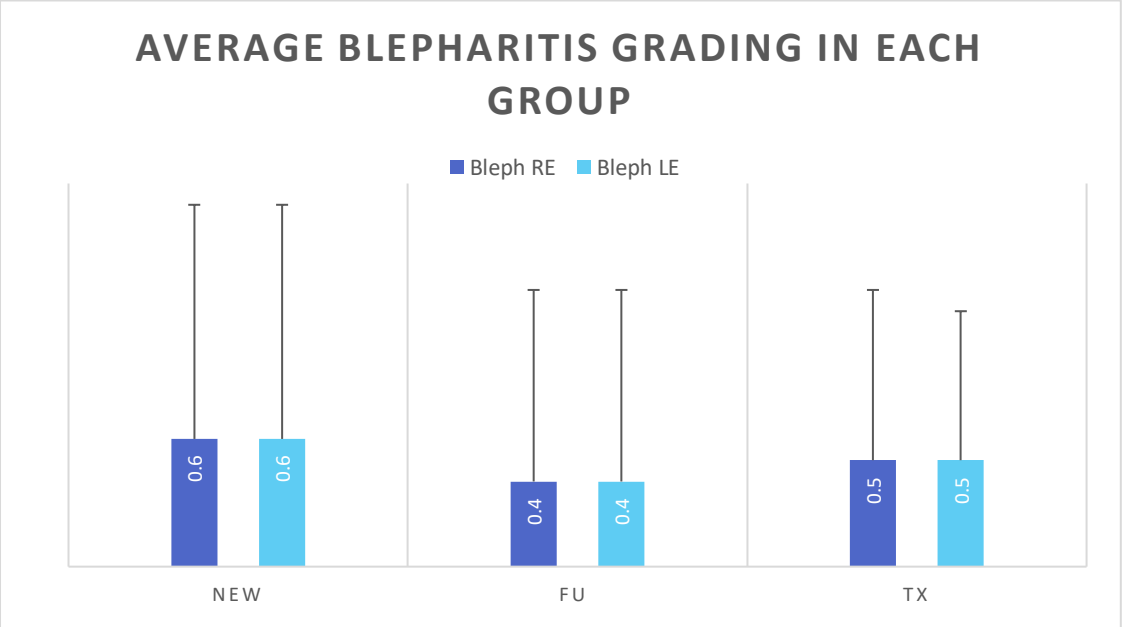


Figure 6.11: The average grade of blepharitis for each group of patients attending the EGC.

Overall, blepharitis grading appeared to be low for all patients attending the EGC, with each group showing an average grading of less than one. New patients appear to have slightly higher levels of blepharitis; however, this difference is small. Between the new and the treated group, and between the treated and the follow up group, the difference amasses to only 0.1 arbitrary units.

6.4.3.2 MGD

New

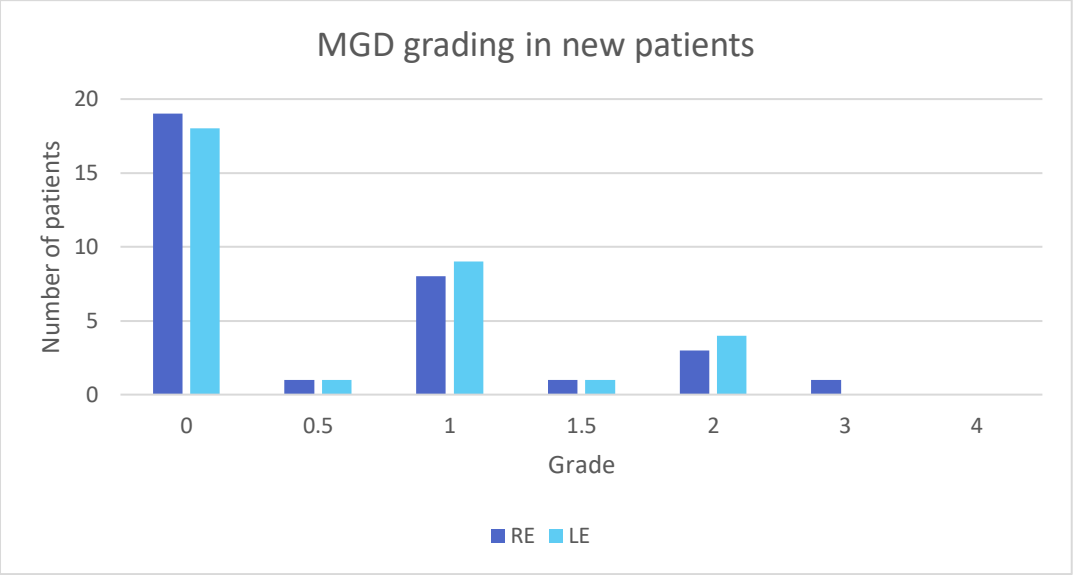


Figure 6.12: The distribution of MGD grading of new patients attending the EGC.

In new patients, grade 0 MGD was the most commonly recorded score of severity. This was followed by grade 1 and then grade 2. Grades 0.5, 1.5 and 3 made up a minute proportion of patients suffering with MGD at these levels of severity.

Follow up

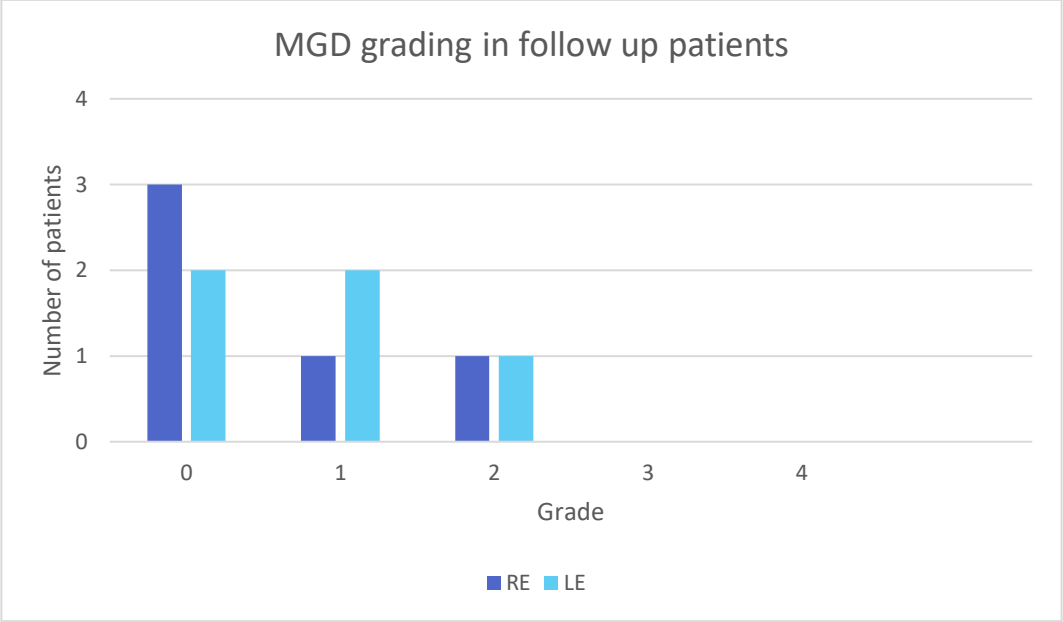


Figure 6.13: The distribution of MGD grading of follow up patients attending the EGC.

Follow up patients showed a distribution of MGD grading across grades 0 to 2. The largest proportion of patients showed signs of MGD at grade 0, descending in number across the grading scale.

On Treatment

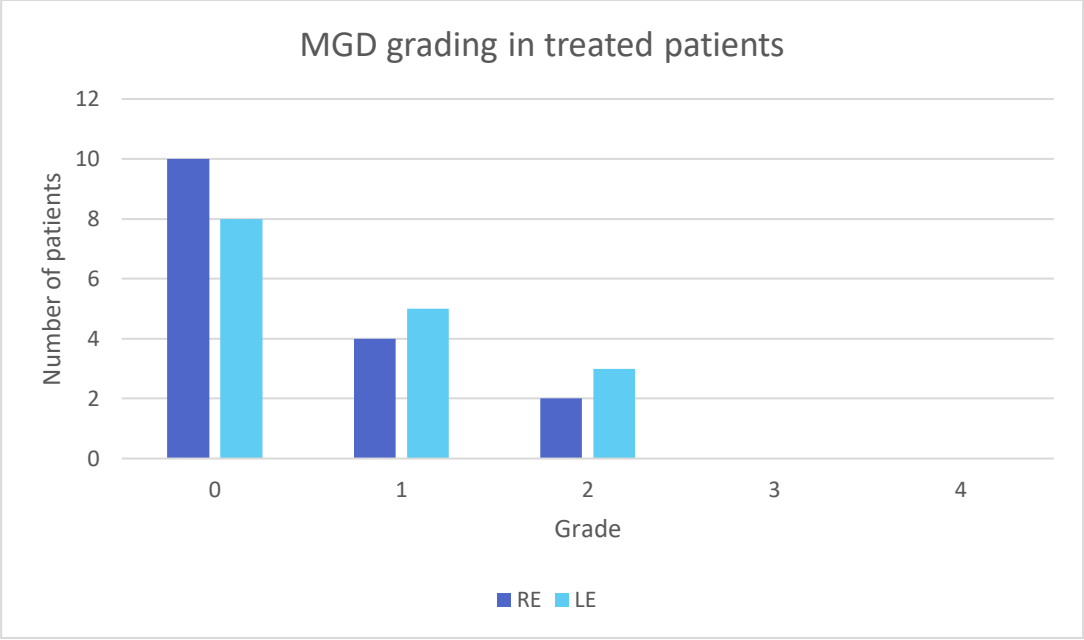


Figure 6.14: The distribution of MGD grading of treated patients attending the EGC.

As with the follow up group, treated patients displayed MGD for the grades 0, 1 and 2 only, with grade 0 being the most commonly noted grade. The number of patients decreases with increasing grades of MGD for this group.

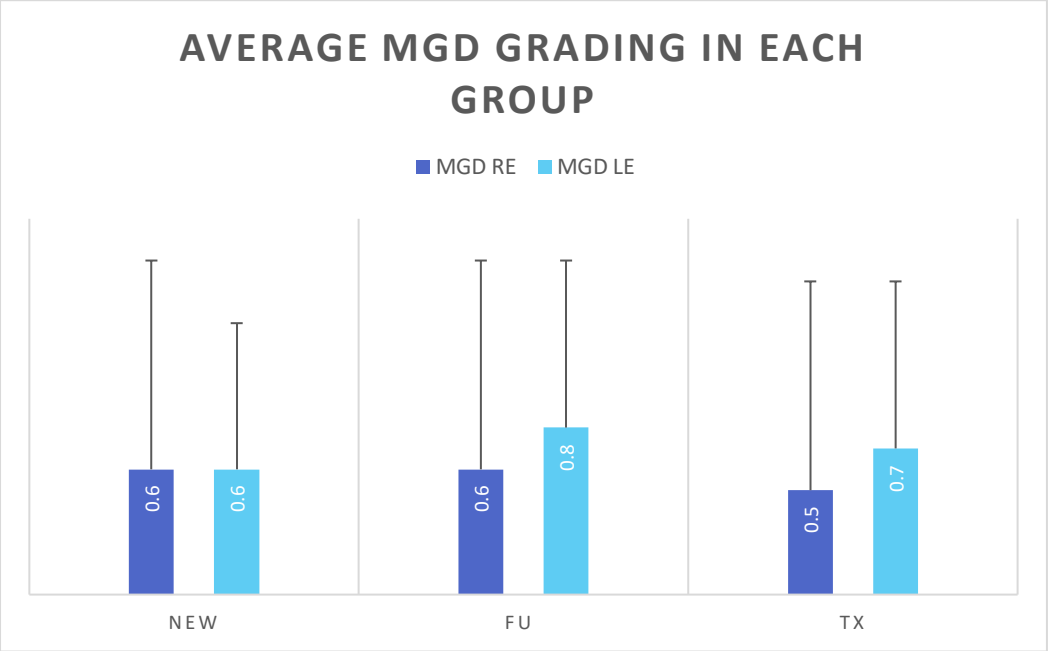


Figure 6.15: The average MGD grade for each group of patients attending the EGC, for each eye.

On the whole, MGD grading was low for each group, with the score being less than 1. Intergroup differences were very small, with the average of the eyes resulting in a grading of 0.6 for new patients, 0.7 for the follow up patients and 0.6 for the treated patients.

6.4.4 Ocular surface assessment

6.4.4.1 Corneal staining

Grade	New %/n (N=66)	Follow up %/n (N=8)	Treatment %/n (N=32)
0	59% / 39	75% / 6	63% / 20
0.5	2% / 1	0% / 0	0% / 0
1	20% / 13	0% / 0	19% / 6
1.5	2% / 1	0% / 0	0% / 0
2	11% / 7	25% / 2	6% / 2
3	6% / 4	0% / 0	13% / 4
4	2%/ 1	0% / 0	0% / 0

Table 6.4: Percentage distribution of eyes within each grade of corneal staining, for each group.

Table 6.4 highlights the grading of corneal staining amongst patients presenting to the EGC. The vast majority of patients in each group had corneal staining of grade 0. New patients had the highest spread of grading, with patients in each grade bracket. Grades 1 and 2 were the next most common grades for new patients, after grade 0. Follow up patients only showed the presence of grades 0 or 2, though the latter was a small percentage. With treated patients, though there was some spread of grading, it was small and covered grades 1, 3 and 2 in descending order of frequency.

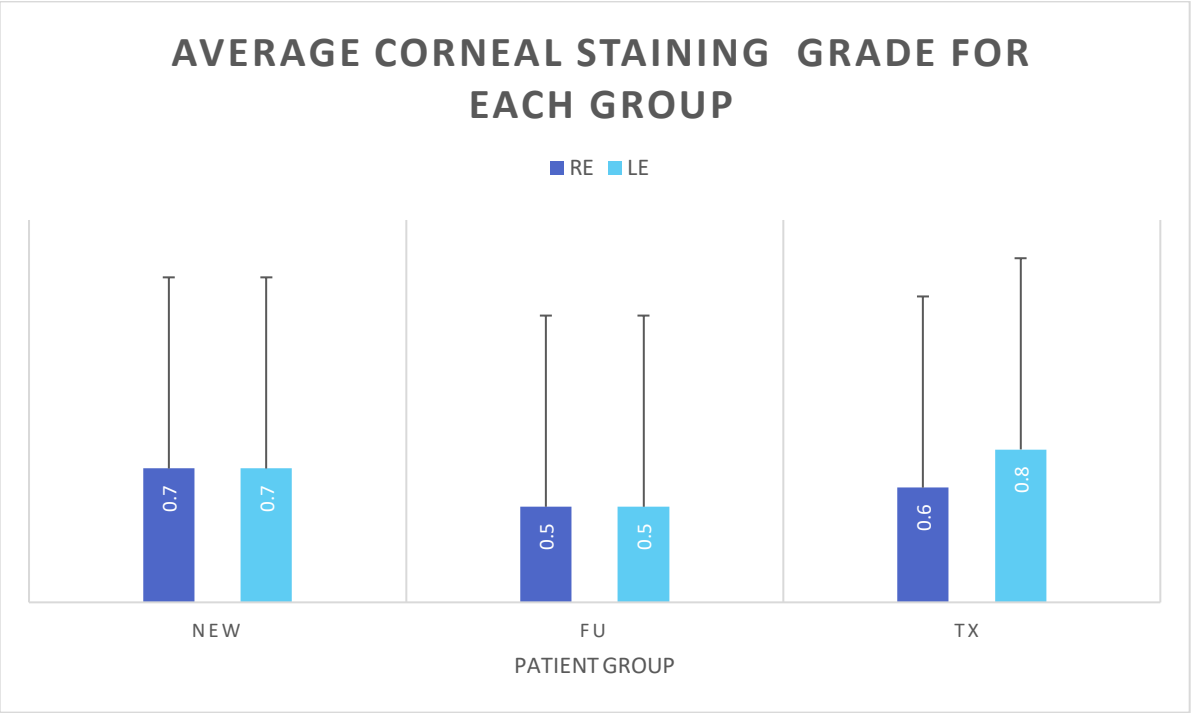


Figure 6.16: Average corneal staining grades for each group of patients and for each eye.

Figure 6.16 demonstrates the average corneal staining grades for each group, for each eye. New and treated patients appeared to have slightly higher scores than follow up patients on average, but on the whole, the average grading was between 'absent' and 'minimal' for all groups.

6.4.4.2 Conjunctival staining

Grade	New %/n (N=66)	Follow up %/n (N=8)	Treatment %/n (N=32)
0	32% / 21	13% / 1	19% / 6
1	39% / 26	38% / 3	44% / 14
2	21% / 14	25% / 2	25% / 8
3	8% / 5	25% / 2	13% / 4
4	0% / 0	0% / 0	0% / 0

Table 6.5: Percentage distribution of eyes within each grade of conjunctival staining for each group.

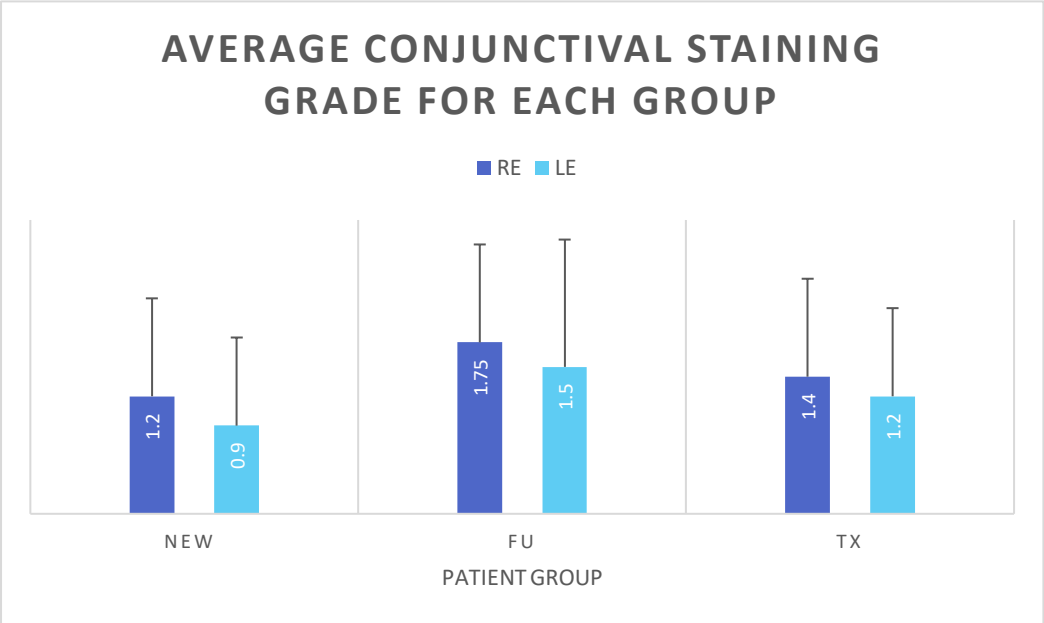


Figure 6.17: Average grade of conjunctival staining for each group of patients, for each eye.

As illustrated by Table 6.5, grade 1 was the most common score for conjunctival staining for all three groups of patients. For new patients, the next most common grades of staining were grade 0 and grade 2, in that order. Few new patients had conjunctival staining of grade 3 or more. Treated patients had a slightly lower average grade than follow up patients but slightly higher average grade than new patients, with grade 1, 2 and 0 being the most common, in that order.

6.4.4.3 Conjunctival hyperaemia

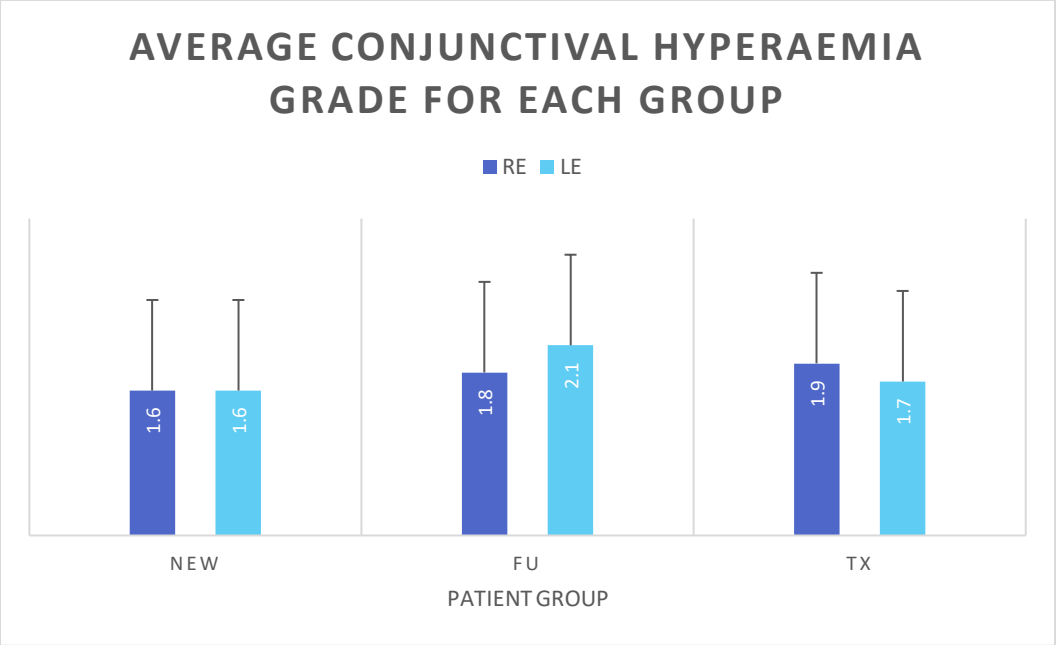


Figure 6.18: Average conjunctival hyperaemia grades for each group of patients and for each eye.

Grade	New %/n (N=66)	FU %/n (N=8)	Treatment %/n (N=32)
0	6% / 4	0% / 0	16% / 5
1	35% / 23	13% / 1	16% / 5
1.5	11% / 7	0% / 0	3% / 1
2	30% / 20	75% / 6	25% / 8
2.5	11% / 7	13% / 1	22% / 7
3	8% / 5	0% / 0	19% / 6
4	0% / 0	0% / 0	0% / 0

Table 6.6: Percentage distribution of patients within each grade of conjunctival hyperaemia, for each group.

For follow up and treated patients, conjunctival hyperaemia of grade 2 was the leading finding (Table 6.6). Treated patients appeared to have the most spread of conjunctival hyperaemia across grades 2, 2.5 and 3 (66%). Most new patients attending the EGC had conjunctival hyperaemia scores of grades 1 and 2. The average conjunctival hyperaemia grade was highest for the LE of untreated, follow up patients at 2.1. New patients showed the lowest average

grade at 1.6 for both eyes. The average grade for the RE of follow up patients was comparable to the RE and LE of treated patients (1,8, 1.9 and 1.7, respectively).

6.4.5 OSDI

New

For 45% of new patients attending the EGC, the OSDI severity score exceeded 13.

Follow up

None of the follow up patients presenting to the EGC had OSDI scores of more than 13.

On Treatment

In treated patients, 36% had OSDI scores of more than 13.

6.4.6 Prevalence of DED

To calculate the prevalence of DED amongst the patient groups used in this study, the TFOS DEWS II protocol for dry eye diagnosis was used. An OSDI score of ≥13 and any one of the following were deemed as a positive diagnosis of DED:

-TBUT <10 seconds (for NIBUT, the lower median of the two eyes was considered for the diagnosis, for FBUT, either eye showing a break-up of less than 10 seconds was considered)

-Osmolarity ≥308mOsm/L or an inter-eye difference of >8mOsm/L

-Grade 1 or more for corneal or conjunctival staining according to the Oxford grading scale

New

The prevalence of DED amongst new patients was 42%, with 13 patients out of 31 showing positive signs of DED as well as symptoms. The OSDI scores were missing for two of the new patients out of 33, so these patients were not used in this analysis.

In terms of the tear osmolarity, 42% of new patients had a reading of 308mOsm/L or more in either eye, with 55% of patients showing evidence of a difference of more than 8mOsm/L between right and left eyes.

Of the 13 new patients with DED, 97% had TBUT of less than 10 seconds in at least one eye.

For ocular surface staining measures, 55% of new patients had corneal staining of Grade 1 or more in at least one eye, and 81% of patients had conjunctival staining of Grade 1 or more in at least one eye.

Follow up

Of the eight patients followed up and reviewed in the EGC without treatment intervention, six patients completed the OSDI questionnaire. The other two patients were not included in this analysis due to this missing data. No patient had a score of 13 or more on the OSDI in this group, thus, the prevalence of DED for the follow up patients was 0% in this study. There were some positive signs in this group, which are discussed under Section '6.4.9 Prevalence of OSD'.

On Treatment

Of the sixteen patients in the treated group, fourteen completed the OSDI questionnaires on arrival into the clinic. Again, the two who did not have OSDI scores available, were not used in this analysis. Subsequently, 36% of patients in the treated group showed a positive diagnosis of DED.

Of this subgroup of DED diagnosed, treated patients, all had a TBUT of less than 10 seconds in either eye.

In terms of tear osmolarity, 36% of patients had a reading of ≥308mOsm/L and 29% had a difference of more than 8mOsm/L between the right and left eyes.

Ocular surface staining of Grade 1 or more was apparent in either eye for 57% of patients in terms of corneal staining, and 93% of patients in terms of conjunctival staining.

6.4.7 Prevalence of OSD

OSD in this study has been defined as a positive sign (TBUT <10 seconds or osmolarity ≥308mOsm/L or an inter-eye difference of >8mOsm/L or Grade 1 conjunctival or corneal staining), irrespective of the presence of symptoms.

New

Thirty-two out of thirty-three new patients displayed one of the aforementioned signs of OSD. The prevalence of OSD amongst new patients was therefore 97%.

Of the thirty-two patients with OSD, 97% had a TBUT of less than 10seconds in at least one eye.

For tear osmolarity, readings of ≥308mOsm/L and inter-eye differences of >8mOsm/L, were recorded in 44% and 53% of OSD patients, respectively.

Ocular surface staining was highly prevalent amongst new patients with a positive OSD diagnosis, with 56% showing corneal staining of Grade 1 or more in either eye, and 81% showing conjunctival staining of Grade 1 or more in either eye.

Follow up

Six patients out of the eight who were followed up without any treatment, had their anterior eye data available for analysis. For these six patients, prevalence of OSD was 100%.

Of the six patients, all had a TBUT of less than 10 seconds.

Osmolarity data was available for four patients. Of these, 25% had a tear osmolarity reading of ≥308mOsm/L, and 25% had an inter-eye difference of more than 8mOsm/L.

Ocular surface staining was available for four patients in this group. All of them had a conjunctival staining grade of 1 or more, while 25% had a corneal staining score of grade 1 or more.

On Treatment

All sixteen patients in this treated group showed signs of OSD, equating to a prevalence of 100%.

For TBUT, 100% of patients in this group had a measure of less than 10 seconds.

Tear osmolarity amongst OSD diagnosed, treated group was ≥308mOsm/L for 38% of patients, and a difference of >8mOsm/L was observed in 31% of patients between the right and left eyes. Corneal staining was present in 56% of OSD diagnosed, treated patients, and conjunctival staining was present in 88% of this patient group.

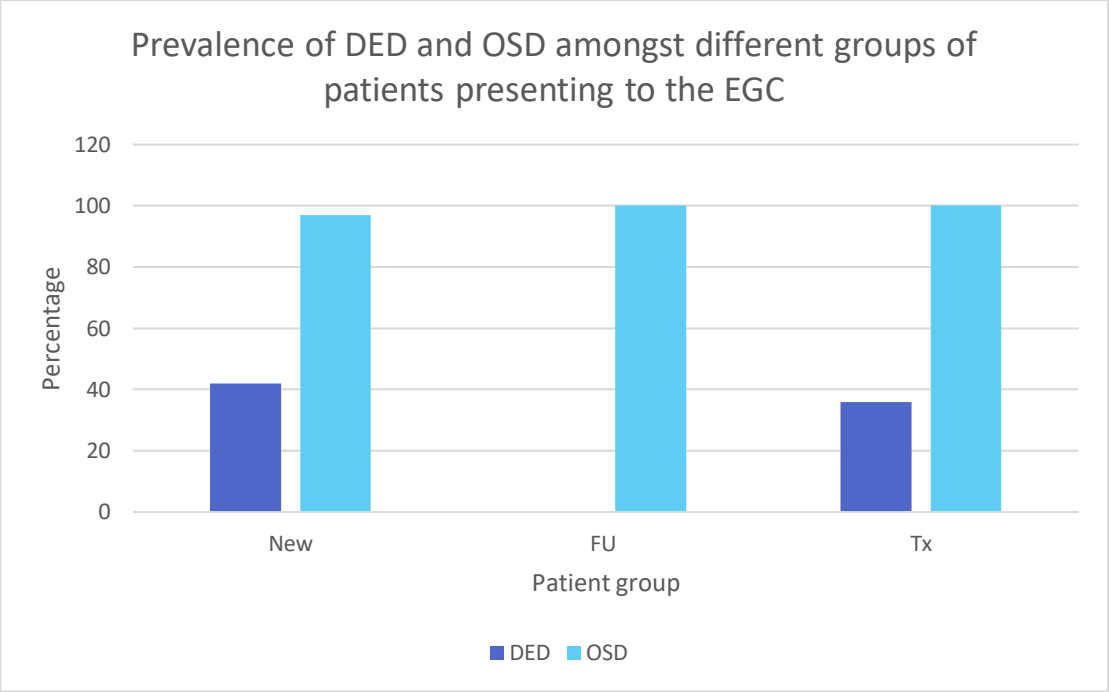


Figure 6.19: The prevalence of DED and OSD for each group of patients attending the EGC.

6.5 Discussion

6.5.1 Prevalence

The aim of this chapter was to highlight the prevalence of OSD within a UK glaucoma clinic. It has been widely reported in the literature that DED is highly prevalent amongst treated glaucoma patients, and such findings are echoed around within the literature (Orozco Garcia et al., 2020, Kobia-Acquah et al., 2019, Leung et al., 2008, Ramli et al., 2015, Garcia-Feijoo and Sampaolesi, 2012). However, there is less knowledge and discussion about the prevalence of OSD in glaucoma clinics, prior to the commencement of hypotensive drops. This is the first study of its kind, which aimed to look at glaucoma and OHT suspect patients, and to investigate the prevalence of OSD in such treatment-naïve patients.

The retrospective audit carried out in Chapter 5 highlighted some interesting findings. Though OSD was prevalent in glaucoma clinics, assessment of the ocular surface was lacking. The EGC was therefore formed, alongside the usual glaucoma clinics at Russells Hall Hospital

(Dudley NHS Trust, UK) in the West Midlands, to bridge this gap and allow for a simultaneous assessment of the ocular surface and investigate the routine glaucoma and OHT markers.

The results of this study indicate that OSD and DED are prevalent amongst all patient groups presenting to a UK glaucoma clinic, with OSD showing the highest prevalence levels of the two diseases. As mentioned earlier, DED is a subset of OSD; whilst OSD describes ocular surface signs, DED ties such signs in with symptoms. New, follow up and treated patients presenting to the EGC showed similar OSD prevalence levels (97% vs 100% vs 100%). DED prevalence levels were lower, with new, follow up and treated patients having rates of 42%, 0% and 36% respectively.

There is much variability in the prevalence rates of OSD and DED in current literature, which is mostly influenced by the tests and definitions used to meet such criteria, as well as the population characteristics of the samples used in such investigations (Savini et al., 2008, Nichols et al., 2004a, Stapleton et al., 2017). In the current study, DED diagnosis was made following the well-established TFOS DEWS II diagnostic test battery, with symptoms based on a score of 13 or more on the OSDI, and one positive homeostasis marker (either TBUT<10 seconds, osmolarity ≥308mOsm/L, difference between the eyes of >8mOsm/L or ≥grade 1 ocular staining). The presence of any of the aforementioned markers, irrespective of the presence of symptoms was deemed to be a positive diagnosis of OSD.

OSD prevalence rates in this study, based on the presence of a singular sign, show high levels as in other OSD studies (Ghosh et al., 2012, Leung et al., 2008, Ruangvaravate et al., 2018). An explanation of this could be that, unlike some studies where diagnosis is made using a combination of signs and symptoms, such as the prevalence study by Shanti and colleagues (2020), or where signs and symptoms have a minimum threshold in order to be classed as clinically significant, as in the study by Ghosh and colleagues (2012), the current study allowed the presence of a sole sign to be a positive diagnostic marker (Shanti et al., 2020, Ghosh et al., 2012). This may have led to a surplus of patients being classified as having OSD, though in reality, this may not translate to symptoms or be deemed clinically significant. However, patients classified as having OSD in the absence of symptoms, may go on to develop clinically significant OSD or indeed develop DED in the future, though the probability of such translation is one yet to be fully elucidated.

It has been reported that signs alone do generally show higher prevalence rates of OSD, and such clinical tests can be prone to variability (Nichols et al., 2004b, Stapleton et al., 2017,

Leung et al., 2008, Han et al., 2011). Signs and symptoms also show poor correlation (Nichols et al., 2004b, Hua et al., 2014). Moreover, clinical tests have been shown to suffer from repeatability issues (Nichols et al., 2004a). The combination of these factors can influence the prevalence rates obtained and explain the variance between studies. Once the symptoms are accounted for in the current study, DED prevalence of new and treated patients are on par with other studies in treated and untreated patients (Han et al., 2011, Rossi et al., 2009, Leung et al., 2008). Since only six follow up patients had completed the OSDI, and all had scores of less than 13, the prevalence of DED of 0% for this group appears to be an anomaly and not fully representative of this group.

The present study does highlight the prevalence of ocular surface problems amongst suspect glaucoma and OHT patients. This could provide a potential opportunity for further, long-term investigation of such patients. If there is already a compromised ocular surface, without the presence of accompanying symptoms, then such individuals may go on to develop DED once treatment is commenced for glaucoma or OHT. Future research should examine the treatment journey of such patients, and retrospectively investigate which factors influence conversion to DED in treated patients. Early indicators of OSD could be markers for developing DED once treated for glaucoma or OHT. Such markers when combined with other risk factors, could be cumulative components for increasing the likelihood of developing DED in treated patients.

Furthermore, it is interesting that 42% of new, treatment-naïve patients showed both signs and reported symptoms of dry eye. Currently, there is no standard practice of investigating the ocular surface during an assessment for glaucoma or OHT, though the NICE guidelines do recommend the assessment of the anterior segment using a slit lamp biomicroscope (National Institute for Health and Care Excellence, 2017). Therefore, unless patients report symptoms and so prompt a more in-depth ocular surface assessment, the true number of patients pre-DED or at risk of developing problems on preserved hypotensive drop treatment is underestimated. Such patients may benefit from preservative-free (PF) treatment at diagnosis. However, due to the lack of standardised testing, patients with OSD may easily be overlooked and undercounted in these clinics.

6.5.2 Clinical tests

Osmolarity

Hyperosmolarity has been specifically included as a requisite element in the revised definition of DED (Craig et al., 2017). Tear osmolarity has been shown to be the single most favourable diagnostic test for DED, showing high sensitivity and specificity (Lemp et al., 2011, Jacobi et al., 2011). It shows little variation amongst healthy individuals with low osmolarity readings, but more variability amongst dry eye sufferers (Keech et al., 2013).

There is some variance as to what constitutes a normal or abnormal osmolarity result. According to Lemp and colleagues (2011), sensitivity was greatest at 308mOsms/L in differentiating between normal and mild dry eye versus moderate dry eye. Specificity between these groups was greatest at 315mOsms/L. It was subsequently suggested that values over 308mOsms/L be regarded as indicators of dry eye, as reflected in the diagnostic battery recommended by the DEWS II report (figure 6.3)(Lemp et al., 2011, Wolffsohn et al., 2017). The TearLab® Osmolarity system states that a reading of >300mOsm/L indicates a loss of homeostasis, presumably due to the findings of Lemp and colleagues (2011), who state the mean osmolarity scores for normal and mild DED to be 300.8 ± 7.8mOsms/L and 315.5 ± 10.4mOsms/L, respectively (Lemp et al., 2011, TearLab, 2022).

With the latter cut off as described by TearLab® Osmolarity system, a loss of homeostasis is suggested in 48% of REs and 52% of LEs of new patients, in 50% of REs and 25% of LEs in follow up patients and in 50% of REs and 56% of LEs of treated patients. The average values for all three groups, however, was well below the proposed indicator of dry eye of over 308mOsm/L. Though patients appear to be within the scope of normal osmolarity on average, many who were diagnosed with DED or OSD in this study, were well associated with either elevated osmolarity readings or inter-eye differences of more than 8mOsm/L. At least 25% of patients in each group, for each eye, displayed tear osmolarities of >307mOsms/L, suggestive of dry eye. Such findings suggest that many patients are in the critical phase between normal and dry eye, and at least a quarter already show signs of clinical dry eye. The former are susceptible to transitioning up the scale of severity, whilst the latter are prone to developing symptomatic dry eye if the bio-system is disrupted further, as with the addition of preserved hypotensive drops.

Tear film

The average TBUT was less than 10 seconds for all three groups of patients, regardless of the method employed for its measurement. A change in the clinic protocol meant that the EasyTear® VIEW was implemented into the EGC, with its use favoured over the invasive FBUT in accordance with the TFOS DEWS II diagnostic protocol (Wolffsohn et al., 2017). Whilst fluorescein instillation has been argued to affect tear film stability, and potentially impact TBUT measures, the difference in FBUT and NIBUT has been demonstrated to be minimal at shorter readings (Cho and Douthwaite, 1995, Mengher et al., 1985a).

These findings are in line with previously prevalence studies which report a TBUT of less than 10 seconds as a common observation (Shanti et al., 2020, Titiyal et al., 2018). In terms of prevalence of OSD and DED, for TBUT the lower median value of repeated measurements of the two eyes was considered as a positive diagnostic marker (Wolffsohn et al., 2017). Though a reduced TBUT does not necessarily reflect immediate symptoms, such patients may require extra monitoring, especially when this is accompanied by other ocular signs suggestive of dry eye.

According to Mainstone and colleagues (1996), TMH is a 'powerful predictor' of an insufficient tear film (Mainstone et al., 1996). The DEWS II report states 0.29 ± 0.13mm to be the expected mean of a healthy population, when assessment is carried out using a slit lamp (Wolffsohn et al., 2017, Nichols et al., 2004a). In the present study, the average TMHs of each group fall within this range, suggesting normal, healthy tear volumes. The issue with TMH is the susceptibility of observer variability (Wolffsohn et al., 2017). Since the height of the tear lake is measured according to slit beam height, there is an assumption that the slit lamp is calibrated. There may also be slight discrepancies between slit lamps, especially in NHS settings where clinics may take place across different rooms. Future studies should therefore take such measurements with OCT or digital meniscometers, which have been shown to be more accurate (Canan et al., 2014, Bandlitz et al., 2014a, Bandlitz et al., 2014b).

Ocular surface staining

Corneal staining appears to be a latent marker of DED (Wolffsohn et al., 2017). This can be seen in the results of this study, since most of the staining was grade 1 or less for all 3 groups. Conjunctival staining appears to be dispersed more around grades 1 and 2, giving rise to increased cumulative grading scores of the two eyes combined, than for the corneal staining. It

has been suggested that corneal staining is helpful in monitoring progression, since severe symptoms of OSD have been associated with corneal staining (Lienert et al., 2016).

The Oxford grading scale was used for the scoring of staining severity, both for the conjunctiva and the cornea. The interpretation of ocular surface can be complicated due to the variability in presentation, poor repeatability and the lack of comparability between scales (Nichols et al., 2004a, Wolffsohn, 2004).

More recently however, conjunctival staining scores have been positively associated with inflammatory markers (Yang et al., 2019). In turn, early conjunctival staining may be indicative of ocular surface inflammation, an element specified in the revised DED definition (Craig et al., 2017). As a result, patients showing signs of conjunctival staining at baseline may be more prone to developing DED once commenced on preserved treatment, although this is to be elucidated.

6.5.3 Differences between groups

The primary aim of this research was to elicit the prevalence rates of OSD amongst treated and untreated patients presenting to the glaucoma clinic at Russells Hall Hospital (Dudley NHS Trust, UK) in the West Midlands, and to compare such rates between the groups. The literature review in Chapter 1 demonstrated that patients treated for glaucoma and OHT show higher prevalence rates of DED than untreated patients, particularly those treated with preserved hypotensive eye drops (Rossi et al., 2009, Pisella et al., 2002). There was also emphasis on the destructive effects of topical glaucoma and OHT treatment on ocular structures mainly due to the preservative constituents (Baudouin et al., 2010, Jaenen et al., 2007, Heijl et al., 2002, Miyake and Ibaraki, 2002, Chang et al., 2015).

One would expect then untreated patients to show lower rates of OSD and DED than those who are on topical medication for glaucoma or OHT. The results of the current study are therefore unexpected, since the rates of OSD were similar between treated and untreated patients, with new patients showing slightly lower rates than follow-up and treated patients (97%, 100% and 100%, respectively). This would suggest that commencing topical treatment bears little weight on the development of OSD.

Furthermore, when looking at symptomatic OSD, namely DED, the prevalence rates were lower across all three groups, and the difference between treated and new, untreated patients

was small (36% and 42%, respectively). Surprisingly, there was no apparent presence of DED in follow up patients presenting to the glaucoma clinic.

The results of this study must be interpreted with caution. The sample of treated patients utilised in this study was small and disproportional to untreated patients. The treated patients seen in the EGC were mostly new to topical treatment, having been started on treatment previously and their first follow up assessment subsequently made in the EGC. From the results of Chapter 5, the retrospective audit, it seems that most patients will develop OSD within the first 12 months of starting treatment for glaucoma and OHT. Since the treated patients in the EGC were so early on in their treatment journey, there is a chance that the effects of medication on the ocular surface may not have been apparent yet, and likely not produced any symptoms. The sample of treated patients in the EGC therefore, may be a poor representation of the wider treated glaucoma/OHT population, skewing results and making comparisons unreliable.

In terms of DED in the group of follow-up patients, it may be true that this group did not suffer from this and hence it was not picked up during the investigation. However, it would be expected that the prevalence of DED would be the same or similar for both the new and follow-up groups since both groups were untreated, which was not true in the findings of the current study. Again, the sample of follow-up patients may have been a poor overall representation since only eight patients were used in this group for analysis. This was the smallest sample size of all the groups.

Overall, there appeared to be little differences in the prevalence rates of OSD and DED between treated and untreated patients presenting to the EGC. Despite this finding, it is also clear that there were two major confounding variables which could have impacted the current study and a revision of the study design may be required for future investigations to allow for better comparisons.

One of these variables would be the duration of treatment. Since previous research (Chapter 5) suggests treated patients are likely to develop OSD within the first 12 months of treatment, perhaps comparisons would be better made to treated patients with a minimum treatment period of 12 months. Alternatively, the treated patient base should be a mixture of patients of varying lengths of treatment durations to be the best representation of this group.

Additionally, another confounding variable requiring re-assessment would be the number of patients within each group. With the restrictions imposed on the ECG, there was difficulty ensuring proportionate sample sizes for each group. Future revisions to this should ensure equal representations of patients within each group to allow for more accurate comparisons to be made.

6.5.4 Limitations and future research

The present study was severely impacted by the COVID-19 pandemic. In the midst of the pandemic, hospitals all over the UK had to cancel clinics, with minimal face-to-face consultations being undertaken. As a result, the inflow into the EGC was limited in number. The current study is promising; however, it is restricted in demonstrating statistically significant patterns due to the small sample size in general, and the even smaller and unevenly distributed patients in each of the three groups.

Since the ratio of patients in each group was 33:8:16 for new, follow up and treated patients, like-for-like comparisons cannot be made. Each patient represents a large percentage, particularly for the follow up group, which makes inter-group differences difficult to examine with certainty. With that being said, prevalence determination was possible even with such small numbers, and it is evident that OSD and DED are a prominent issue in glaucoma clinics.

The current study has paved the way for future research. Alterations to its original design, with appropriate sample size calculation, equal and increased numbers of included patients in each group, and redefining the diagnostic criteria to be more selective, could allow for intergroup differences to come to light. A pattern one may expect to see is the prevalence of OSD and DED to be higher in treated patients, when compared to new or follow up patients (Ghosh et al., 2012, Rossi et al., 2009, Baffa Ldo et al., 2008).

The retrospective audit carried out in Chapter 5 demonstrated that the majority of patients are diagnosed with OSD in the first twelve months of their glaucoma or OHT journey. Since the current study included patients who had only recently commenced treatment, such trends may not have come to light in the EGC. An interesting branch of this study would be to follow patients from the moment of starting their hypotensive drops and following the long-term treatment with regular dry eye reviews, to establish the most common point of conversion to DED. Based on the current literature review, no study so far has looked at the time to conversion to DED, when treated for glaucoma or OHT.

Furthermore, the present study has highlighted that OSD, and to a somewhat slightly lesser extent, DED, are prevalent comorbidities found in glaucoma clinics. Though the prevalence of OSD has been widely discussed in literature amongst treated glaucoma patients, no study to date has looked into the prevalence of OSD in glaucoma clinics prior to treatment. The data analysed from the EGC delves into this oversight and provides a novel element to the research surrounding OSD and glaucoma.

The sample of untreated glaucoma and OHT patients in this study provide a basis for comparison once treatment begins, and future studies could utilise this arm of untreated patients as a means for investigating the likelihood of conversion from OSD to DED during the course of glaucoma treatment.

In addition, the involvement of clinics such as the VGC and EGC has been a successful attribute to RHH in the glaucoma clinics. The COVID-19 pandemic has resulted in a huge backlog of patient appointments in the NHS. A proposal to run virtual clinics, where diagnostic tests are performed by ophthalmic technicians, and the findings reviewed remotely by consultants, has had its success shared in the media.

The newer EGC, has also relieved some pressure from glaucoma consultants, since simple cases of glaucoma, OHT and suspect cases are reviewed and managed by an Optometrist. The efficiency of such clinics shows that proper delegation of glaucoma screening could help to save time, money and reduce stress both for the NHS and the patient alike.

Such virtual clinics and referral refinement schemes have successfully established their place in the ophthalmic world and provided much cost-saving benefit to the NHS. By allowing eye clinic appointment slots to be freed up, one trust alone saw a benefit of a £244,200 saving per year (Trikha et al., 2012).

6.6 Conclusion

Though the current study does not highlight differences in the prevalence rates of OSD and DED between treated and untreated patients attending the EGC at Russells Hall Hospital (Dudley NHS Trust, UK) in the West Midlands, it is proposed that a revision of the current study design using larger and equally proportioned samples of the groups, with inclusion of treated

patients of varying treatment durations, would allow for more accurate and unbiased comparisons to be made.

This study has found OSD to be prominent issue in glaucoma clinics, regardless of the stage of visit, be that at baseline or after commencing treatment. The occurrence of OSD may well be overlooked, underestimated and perhaps mismanaged, due to the lack of routine ocular surface assessments in ordinary glaucoma clinics. An ideal scenario would be one where it would be the norm to conduct a battery of dry eye tests and present patients with a symptomology questionnaire. Tests such as TBUT and tear osmolarity have been shown to be quick and good indicators of compromised ocular surfaces. Questionnaires such as the OSDI, which can be easily completed by patients in the waiting area as demonstrated by the current study, are an effective way to assess visual function and the impact of OSD on daily tasks. With this extra information, it would put clinicians in better stead in treating their patients.

Much is yet to be explored in this area, to determine which combination of tests would provide the best overall ocular surface assessment in glaucoma clinics, as well as to allow for a comprehensive understanding of which clinical markers are most suggestive of individuals developing DED in the long term. Future research investigating these scenarios could enable an algorithm to be formed, which would classify risk of OSD amongst glaucoma, OHT and suspect patients presenting to such clinics.

Chapter 7

Pilot study investigating the predisposing factors to developing OSD in a glaucoma clinic

7.1 Introduction

Chapter 6 outlined the introduction of Enhanced Glaucoma Clinic (EGC) at Russells Hall Hospital (Dudley NHS Trust, UK) in the West Midlands. A clinic formed specifically to assess the ocular surface alongside managing glaucoma and ocular hypertension (OHT), the EGC revealed some interesting findings. Chapter 6 and other studies alike, demonstrate that ocular surface disease (OSD) is a prevalent issue in glaucoma clinics (Leung et al., 2008, Garcia-Feijoo and Sampaolesi, 2012). Sometimes coined the 'dual dilemma', glaucoma and OSD are well known to occur simultaneously (Nijm et al., 2020). Unlike previous studies, which investigated such links in treated patients, the EGC helped to reveal the hidden number of patients who show OSD signs, symptoms or both, prior to starting ocular hypotensive treatment.

Much of the topical treatment available for glaucoma and OHT contains preservatives (Steven et al., 2018, Joint Formulary Committee, 2022). Preservatives are an important constituent of eye drops to provide sterility, particularly in multi-dose containers (Baudouin et al., 2010). In a review by Baudouin and colleagues (2010), the consequences of preservatives in eye drops are discussed at great lengths (Baudouin et al., 2010). Exposure to preservatives such as benzalkonium chloride (BAK) has been shown to compromise the ocular surface in various ways. Notably, preservative containing glaucoma drops, as well as the preservatives alone, reduce goblet cell density, consequently affecting the stability of the tear film (Herreras et al., 1992, Rolando et al., 1991, Pisella et al., 2004).

Furthermore, an in-vitro study by De Saint Jean and colleagues (1999) found that exposure to BAK severely affected cell viability. Concentrations of 0.1% and 0.5% caused immediate cell lysis of human conjunctival cells. Concentrations of BAK at lower levels resulted in delayed deaths of such cells, following the hindrance of cell growth (De Saint Jean et al., 1999).

Similarly, BAK exposure can have apoptotic effects on corneal epithelial cells too. In an *in-vitro* animal study using cultures of rabbit corneal epithelial cells, Cha and colleagues (2004) incubated such cells in mediums containing different concentrations of BAK. Using ^{51}Cr as an indicator for cell lysis, Cha and colleagues found that its release was relative to both BAK concentration and exposure time. Structurally, profound changes were observed through electron microscopy examination in terms of disruptions to the cytoplasm membrane, enlargement of the mitochondria and nuclear impairment, with increased concentrations and longer exposure times of BAK (Cha et al., 2004).

BAK concentrations as low as 0.005% have been shown to cause cellular damage, with rising damage detected by scanning electron microscopy (SEM) between concentrations of 0.001% and 0.01% (Ichijima et al., 1992, Burstein, 1980). Perhaps it is surprising then, that most commercially available glaucoma eye drops contain concentrations of BAK of at least 0.01% or 0.02% (Steven et al., 2018, Joint Formulary Committee, 2022).

It has been argued that the active ingredients in prostaglandin analogue (PGA) glaucoma drops have some protective properties. Due to their antioxidant properties, PGAs appear to counteract BAK toxicity. Guenoun and colleagues (2005) investigated such phenomenon by exposing human epithelial cells to three commercially available PGAs and to BAK alone in concentrations respective to what is included in the aforementioned PGAs. It was found that preserved latanoprost and preserved travoprost were significantly less toxic than their BAK constituents of the same concentration (Guenoun et al., 2005).

Similarly, Pisella and associates (2004) looked at inflammatory markers on exposure to preserved latanoprost, preserved timolol and unpreserved timolol. Examinations were made both *in vitro* and *ex vivo*, using cell lines and impression cytology to look at microscopic changes. It was found that unpreserved timolol did not induce a significant inflammatory response. Preserved timolol and preserved latanoprost did trigger significant inflammatory response, but this was significantly more marked for preserved timolol than preserved latanoprost. Cell apoptosis was activated with both preserved formulations, but as with Guenoun and colleagues (2005), such toxicity was more pronounced with BAK alone (Pisella et al., 2004, Guenoun et al., 2005).

Though *in vivo* studies involving cell lines are exposed to glaucoma formulations and preservatives for longer periods at a time than eyes treated for glaucoma or OHT would be at a given time, one must consider the cumulative harmful effects of such preservatives in glaucoma and OHT patients who are chronically treated. Dosing is usually daily, for some a few times a day, and in more advanced cases, involves the use of polypharmacy. The additive effects may therefore play an important contributing role in the development of OSD in glaucomatous and ocular hypertensive patients.

Furthermore, glaucomatous patients have been shown to have lower basal turnover rates than healthy individuals and OHT patients. This, coupled with toxic preservatives in glaucoma medication, can act as cumulative factors to developing OSD in such individuals being treated for their glaucoma (Kuppens et al., 1995).

Attempts have been made to address BAK toxicity by substituting with less toxic preservative preparations such as SofZia® and Polyquad® (Polyquanternium, Alcon Inc., Fort Worth, TX). SofZia® is classed as an oxidising preservative, breaking down to less cytotoxic materials. Clinically, SofZia preserved glaucoma drops appear to be less harmful to the ocular surface than BAK preserved drops, with significantly less corneal and conjunctival damage (Kahook and Noecker, 2008, Aihara et al., 2013). Such improved clinical effects appear to translate to better tolerance amongst patients too, with lower OSDI scores in those on SofZia preserved travoprost than BAK preserved travoprost (C. R. et al., 2017).

Likewise, Polyquad (PQ) has also been a popular substitute to BAK in ocular hypotensive formulations. A derivative of BAK, its structural properties make it suitable as a preservative since it discriminates between bacterial and epithelial cells and its large size makes it difficult to penetrate epithelial cells (Coroi et al., 2015, Rolando et al., 2011, Brignole-Baudouin et al., 2011, Muz et al., 2021). Comparing the toxicity of PQ against BAK on cultures of human ocular surface cell lines reveals significantly greater surviving conjunctival and corneal cells following exposure with PQ than with BAK (Ammar et al., 2011). Similarly, Brignole-Baudouin and colleagues (2011) also looked at the differences in exposure of human cell lines of PQ, BAK and glaucoma medications containing the former as preservatives. It was found that PQ preserved travoprost had insignificant differences with phosphate-buffered saline (PBS) in terms of cell viability. PQ preserved travoprost was significantly less toxic than BAK preserved latanoprost and BAK preserved travoprost in terms of cell apoptosis and cell viability (Brignole-Baudouin et al., 2011).

In terms of clinical benefits of alternatively preserved glaucoma eye drops, switching from BAK preserved latanoprost to PQ preserved travoprost significantly improved TBUT and reduced the occurrence of punctate keratitis (Rolle et al., 2013).

In a comparative study by Muz and colleagues (2021), newly diagnosed glaucoma and OHT patients were randomised to receive treatment either with BAK preserved latanoprost or PQ preserved travoprost. Both treatments resulted in worsening of ocular surface measures such as TBUT, Schirmer test scores, ocular surface staining and OSDI from baseline to month 1. Although following this time-point, the clinical results stabilised for both groups, the findings were significantly different from baseline to year 1 at each follow up, for all subjects (Muz et al., 2021).

Such cellular and clinical reactions to preserved hypotensive drops readily translate into symptoms of OSD. In an epidemiological study by Pisella and colleagues (2002), 4107 patients under treatment for glaucoma or OHT were enrolled to investigate the incidence of ocular toxicity from their hypotensive drops. Symptoms of OSD were much more prevalent in those treated with preserved drops than preservative-free (PF) drops. Such symptoms included discomfort on instillation, foreign body sensation and irritation between instillations. The frequency of such symptoms was significantly higher in the preserved group (Pisella et al., 2002).

In this study, 349 patients were switched from preserved drops to PF drops as a result of the clinical findings during the first visit. There was subsequently a significant drop in the occurrence of symptoms, with reductions of 2.7-5.7 fold. For 57 patients who were on preserved medication originally, the number of preserved drops used was reduced. Again, a significant reduction in symptoms of OSD was reported (Pisella et al., 2002).

The results of the Pisella and colleagues' (2002) study were encompassed in a large multicentre epidemiology survey by Jaenen and colleagues (2007), who also investigated the prevalence of the signs and symptoms of OSD in patients treated with preserved and PF glaucoma drops. A total of 9658 patients were included across Europe in this study. All symptoms were significantly more frequent in the preserved group than the PF group, as were ocular signs. Examples of such symptoms included discomfort on instillation, stinging or burning and foreign body sensation, all of which were more prevalent amongst those on preserved treatment (47.6% vs 18.5%, 47.5% vs 19.6 and 41.9% vs 14.8% for preserved vs PF, respectively). Again, on switching from preserved to PF, the prevalence of both signs and symptoms of OSD reduced significantly (Jaenen et al., 2007).

It is evident from the literature that OSD is highly prevalent in treated glaucoma and OHT patients, and more so amongst those treated with preserved hypotensive drops than PF hypotensive drops (Jaenen et al., 2007, Pisella et al., 2002, Leung et al., 2008). Ideally, PF hypotensive drops should be recommended to all glaucoma and OHT patients, seeing as a large proportion of patients attending such clinics already fall into risk factor groups for developing OSD, as discussed in a recent review by Thygesen (2018) (Thygesen, 2018).

However, cost implications restrict the prescribing of PF drops in glaucoma clinics. For example, the Derbyshire Joint Area Prescribing Committee (JAPC) explicitly states: "Preservative free formulations are usually considerably more expensive than multi-dose

equivalents and reserved for use in patients with genuine cases of hypersensitivity" (DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE, 2019). Furthermore, travoprost, the first line therapy at this trust, is priced at £2.79 for 2.5ml bottle, whereas PF latanoprost is priced at £8.49 for 30 day unit dose (UD) vials (DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE, 2019).

The guidelines used at the Oxford University Hospital NHS Trust mimic similar advice to clinicians. Stinging on instillation lasting no more than five minutes is classed as 'normal' and PF drops are not indicated in such instance, even though the guidelines also state that the detergent properties of BAK result in an unstable tear film and damage the corneal epithelium with prolonged use (B. O'Riordan, 2021). It is therefore implied that PF drops are only to be considered on the evolution of OSD with prolonged preserved treatment, rather than as a preventative measure as first line therapy.

Perhaps a more logical approach then would be to consider which patients are at risk of developing OSD in the course of their glaucoma or OHT treatment. Naturally, not all patients treated with preserved hypotensive drops will acquire OSD in their treatment journey. A risk factor analysis of glaucoma or OHT patients could provide information on the likelihood of an individual to develop OSD in their lifetime.

Currently, there is a gap in the literature exploring such risks in glaucoma and OHT patients. No study to date has evaluated patients retrospectively to see whether there are baseline predisposing clinical factors which make some individuals more susceptible to developing OSD in the course of the treatment. Moreover, there is a lack of evidence-based knowledge as to the time-point at which treated glaucoma and OHT patients may develop OSD. The retrospective audit conducted in Chapter 5 suggests such turning point to be within the first 12 months of treatment.

The aim of this chapter is to illuminate on this matter and investigate the clinical measures which act as predisposing factors for the development of OSD in newly treated glaucoma and OHT patients, as well as exploring the timeframe to such development. By highlighting these details, clinicians will be better informed as to who is at risk of OSD, prior to hypotensive treatment and would therefore benefit from PF treatment as first line therapy. By knowing the critical time point for developing OSD, patients can be monitored better in such clinics with more emphasis on the ocular surface. Together, these details could provide a new paradigm for the management of patients in glaucoma clinics.

7.2 Aims

The aims of this study are to investigate:

- the time point at which patients treated with preserved treatment will go on to develop DED
- factors predisposing individuals to developing DED when treated with preserved treatment
- the baseline characteristics of patients commenced on PF treatment at diagnosis

7.3 Methods

New patients were referred to the EGC at Russells Hall Hospital (Dudley NHS Trust, UK) in the West Midlands for evaluation. New patients are defined as those who are suspected of having glaucoma or OHT but have not been seen at the eye clinic before and are not on any treatment currently. Such patients were referred to this clinic using a few different pathways. These were as follow:

- Direct referral from primary care including optometrists and GPs who suspect glaucoma or OHT in patients.
- Via the Virtual Glaucoma Clinic (VGC); a clinic where ophthalmic technicians see new patients for diagnostic tests. Usually, patients would be reviewed remotely by consultants and managed accordingly. Those suspected of requiring treatment or intervention, however, would be referred straight to the EGC.
- From consultants in other eye clinics, where patients were referred for a different matter, but investigation led to the discovery of glaucoma or OHT signs.

This clinic commenced in June 2021, during the COVID-19 pandemic. Previously, patients would be seen by consultants in the ‘new’ and ‘follow up’ glaucoma clinics at the hospital. The COVID-19 pandemic resulted in a restructure of the clinics, with the creation of the VGC to allow for efficient monitoring and management of glaucoma and OHT patients, and the EGC for those patients requiring possible medical intervention or close face-to-face monitoring.

Patients referred to the EGC were booked for their visual fields assessment and optical coherence tomography (OCT) scans. This was either done prior to the EGC appointment, on

the day of the EGC appointment or omitted altogether in cases where the referral was made via the VGC, where such tests would already have been done.

On arrival to the eye clinic, patients had their visual acuities taken by an eye clinic nurse, who would discuss the OSDI questionnaire with them. Whilst waiting to be seen in the EGC, patients would complete the OSDI ready for review in the clinic.

In the EGC, patients underwent two main stages of assessment. The first was a battery of dry eye tests, and the second, the routine glaucoma tests as per the normal protocol in these eye clinics. The dry eye examinations were made before the glaucoma checks since some glaucoma checks are invasive and require the instillation of drops such as topical anaesthetics or mydriatics, which could interfere with the ocular surface.

7.3.1 Clinical tests

The patient journey was divided into 4 stages, as outlined in Figure 7.1. The first stage involved preliminary tests of visual acuities (VAs), visual fields (VFs) testing, OCT scans and the first phase of the TFOS DEWS II diagnostic protocol for DED (Wolffsohn et al., 2017). The second stage of the examination was dedicated to the ocular surface. The clinical tests used to assess the anterior eye are outlined in Section 6.3.5.

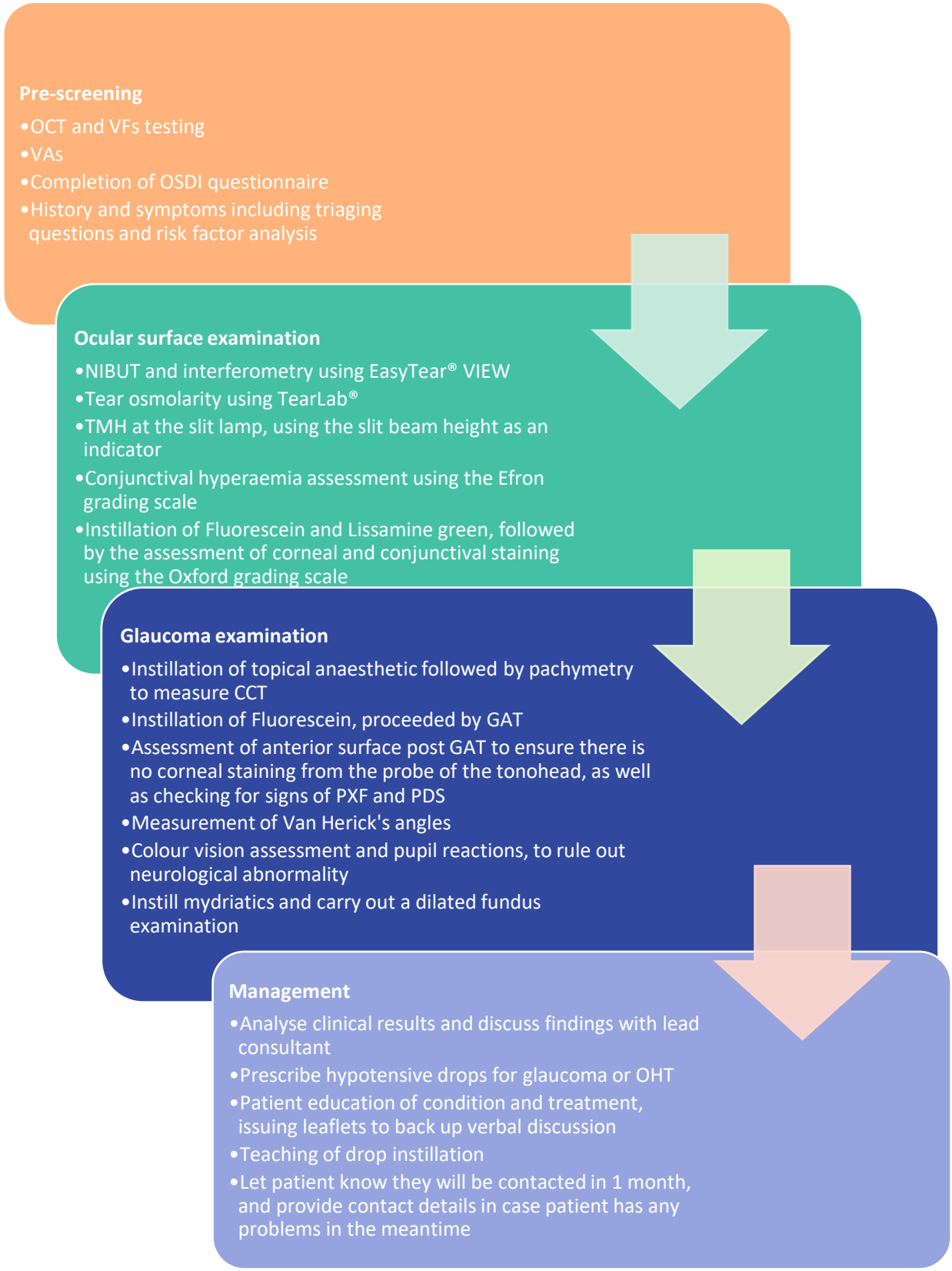


Figure 7.1: Patient journey through the EGC. The journey was divided into 4 main stages, 2 of which encompassed tests specific to glaucoma, OHT and dry eye.

The next stage of assessment involved routine clinical tests used in the glaucoma clinics at Russells Hall Hospital (Dudley NHS Trust, UK) in the West Midlands, as recommended by the NICE guidelines for glaucoma (National Institute for Health and Care Excellence, 2017). The tests were performed in the order as outlined below:

1. *Pachymetry*

A drop of Lidocaine 4% w/v and Fluorescein 0.25% w/v via a Minim® was instilled in each eye. At least sixty seconds were allowed for the topical anaesthetic to take effect. The DGH Pachmate2 was used as the pachymeter in this clinic. Patients were instructed to look slightly up and fix their attention on a clock in the room. The probe was then brought into contact with the centre of the cornea, and the slightest pressure was applied until the pachymeter finished its succession of beeps to confirm that the measurement had been taken of the central corneal thickness (CCT).

2. *Goldmann Applanation Tonometry (GAT)*

Straight after pachymetry, GAT measurements were made with the topical anaesthetic still in place. Patients were seated at the slit lamp, and the tonometer device with a new, clean tonohead was mounted on the slit lamp. A further drop of fluorescein was added if required. The light source was set to the highest illumination with blue light. Patients were instructed to look straight ahead and the tonohead was brought into contact with the central cornea. The mires were aligned, and the reading recorded. One reading was taken per eye.

3. *Anterior segment slit lamp examination*

A general anterior eye assessment was made post GAT and pachymetry. Ocular surface staining was assessed, with particular focus on the cornea, to ensure that the invasive methods of GAT and pachymetry had not caused any corneal damage or staining. The slit beam was adjusted and scanned the anterior segment to investigate the presence of any Pseudoexfoliation (PXF) and Pigment Dispersion Syndrome (PDS).

4. *Anterior chamber assessment using Van Herick's technique*

Anterior chamber assessment in the EGC was made using the Van Herick's technique. A narrow beam was directed at the temporal limbus of the eye, with the illumination system offset by 60 degrees on the slit lamp. The peripheral chamber depth was compared with the corneal section, and graded using the following categories: Grade 0 (closed angle), Grade 1 (extremely narrow, 1/4< of corneal thickness), Grade 2 (narrow, 1/4 of corneal thickness), Grade 3 (open,

>1/4 to 1/2 of corneal thickness) and Grade 4 (wide open, ≥1 of corneal thickness) (Källmark and Sakhi, 2013). In cases where the angle appeared narrow (Grade 2 or less), the consultant was called into the EGC to perform Gonioscopy.

5. *Neurological assessment*

A colour vision assessment was made using the Ishihara test. Patients were requested to read out the numbers seen on each of the presented tiles, consisting of coloured dots, and the results were recorded. Pupil reactions were also assessed, with direct and consensual reactions measured using a pen torch. Patients were assessed for the presence of a Relative Afferent Pupillary Defect (RAPD).

6. *Dilated fundus examination*

One drop of Tropicamide 1% was instilled into each eye and the patient was instructed to wait in the waiting area for around 20 minutes to allow for the mydriatic to take effect. Patients returned to the consulting room and a full, dilated VOLK fundus examination was performed, looking at both the disc and macula, as well as examination of the peripheral retina.

Once all the clinical tests were performed and the data analysed, the results were discussed with the lead glaucoma consultant to draw up an appropriate management plan. Patients were prescribed hypotensive eye drops for glaucoma or OHT. Patients were taught about their condition, shown the drop instillation technique, and informed about the importance of their drops and the reasons for needing to take them.

Information discussed during the consultation was issued in written form, which patients could take home. Patients were also told that they would be contacted via a telephone call in about a month's time to review how they were getting on with the drops. Advice was provided on what to do if there were any problems in the meantime, including the provision of contact details in cases of side effects or issues with the medication.

Four to six weeks after the first appointment at which the patient was issued a prescription for glaucoma drops, a telephone call was made to follow the patient up. At this telephone appointment, patients were asked how they had been getting on with the drops in general, as well as carrying out both the OSDI questionnaire and a 'drop specific' follow up questionnaire. The follow up questionnaire is attached in Appendix 14. For patients reporting problems at this stage, arrangements were made to see them in face-to-face clinics at an earlier date.

Otherwise, patients were reviewed at the routine follow appointment, which is usually around 3 months after the first appointment for patients 'new' to the glaucoma clinics.

7.3.2 Ethics

This study was an evaluation of the EGC at Russells Hall Hospital (Dudley NHS Trust, UK) in the West Midlands. The data obtained in these clinics during its course was reviewed retrospectively. This research followed the tenets of the Declaration of Helsinki. NHS Ethical approval was obtained under the IRAS PROJECT ID 173203.

7.3.3 Inclusion/Exclusion criteria

Inclusion criteria

- Newly referred patients suspected of having glaucoma or OHT but have not been commenced on topical hypotensive drops
- Newly referred patients who will require topical hypotensive treatment for glaucoma or OHT
- Patients aged 18-100 years, with a sound understanding to be able to complete the OSDI questionnaire
- Patients able to sit at the slit lamp for at least 1 hour

Exclusion criteria

- Follow up patients, both treated and treatment naïve, who have attended the glaucoma clinic before
- Patients who have previously had glaucoma surgery or laser interventions
- Patients who are not able to comprehend the OSDI or follow up questionnaire
- Patients who are unable to sit at the slit lamp for their assessments

7.4 Results

This was a single-site, 13-week, observational study. A total of 57 patients presented to the EGC as new and follow up patients. Fourteen patients who were new to the EGC at Russells Hall Hospital (Dudley NHS Trust, UK) in the West Midlands, subsequently started on ocular

hypotensive treatment after evaluation of their clinical results. These 14 patients met the inclusion criteria and so were used in the analysis of this study.

7.4.1 Demographics

The group was split equally, with 7 females and 7 males. The average age of the patients was 70.1±12.4 years (range 49-87). The majority of the patients were Caucasian (86%), and the remainder made up smaller proportions of Asian (7%) and Afro Caribbean (7%).

Of the 14 patients, 43% were diagnosed with POAG, 21% with OHT, 14% as OHT or glaucoma suspects, 14% with unspecified glaucoma and the remaining 7% had NTG.

7.4.2 Baseline measures of the group starting preserved treatment

After the first visit to the EGC, eleven patients were started on preserved hypotensive treatment. All of these patients were commenced on latanoprost as their first line therapy. Of the total 22 tear osmolarity readings for this group, 41% were readings of >300mOsm/L whilst 23% were readings of 308mOsm/L or more. In terms of blepharitis, only two patients had grades 2 for both the right eye (RE) and the left eye (LE), the remainder of patients were scored at grade 0 for both eyes. The CCT was ≥561µm for 14% of the total 22 eyes in this group, and ≤539µm for 50%. GAT showed elevated IOPs of ≥24mmHg for 27% of the 22 eyes in this group. The baseline measures of this group prior to preserved treatment are outlined in Table 7.1.

7.4.3 Baseline measures of the group starting PF treatment

Three patients were started on PF hypotensive drops following their first visit in the EGC. All of these were started on monopost as their first line therapy. Of the total six tear osmolarity readings for this group, 67% had readings of >300mOsm/L whilst 67% had readings of 308mOsm/L or more. In terms of corneal staining, one patient had grades of 3 and 4 for their RE and LE respectively. The other two patients were graded at 0 for both the RE and LE in terms of corneal staining. The CCT was ≥561µm for 67% of the total 6 eyes in this group, and no person had a CCT of ≤539µm for this group. GAT showed elevated IOPs of ≥24mmHg for 50% of the eyes in this group. The baseline measures for this group are outlined in Table 7.1.

Preserved group					PF group	
Average RE (SD)	**Average LE (SD)**	**N**	***Variable***	**N**	**Average RE (SD)**	**Average LE (SD)**
4.7 (2.9)	4.8 (2.7)	10	***FBUT (seconds)***	1	3.0	3.0
3.5	4.6	1	***NIBUT (seconds)***	2	5.3 (3.2)	5.6 (3.3)
3	3	1	***Interferometry***	2	3.5 (0.7)	3.5 (0.7)
302 (12.4)	297 (10.8)	11	***Tear osmolarity (mOsm/L)***	3	308 (19.9)	308 (13.0)
0.3 (0.1)	0.3 (0.1)	11	***TMH (mm)***	3	0.3 (0.1)	0.3 (0.1)
1.5 (0.7)	1.5 (0.7)	11	***Conjunctival hyperaemia***	3	1.5 (0.9)	1.5 (0.9)
0.4 (0.8)	0.4 (0.8)	11	***Blepharitis***	3	1.7 (2.1)	1.7 (2.1)
0.8 (0.9)	0.9 (0.8)	11	***MGD***	3	0.7 (0.6)	0.7 (0.6)
0.7 (0.6)	0.3 (0.6)	11	***Corneal staining***	3	1.0 (1.7)	1.3 (2.3)
0.9 (0.8)	0.8 (0.6)	11	***Conjunctival staining***	3	2.0 (1.0)	1.3 (1.2)
537 (24.4)	533 (22.8)	11	***Pachymetry (µm)***	3	580 (24.4)	577 (28.4)
21.0 (6.0)	19.8 (5.1)	11	***GAT (mmHg)***	3	22.7 (4.0)	26.7 (6.4)
3.4 (1.0)	3.5 (0.7)	11	***Van Herick's***	3	3.7 (0.6)	3.7 (0.6)
0.6 (0.2)	0.6 (0.2)	11	***CDR***	3	0.6 (0.2)	0.7 (0.2)
70%	70%	10	***VFI (ONL)***	3	100%	100%

N= number of patients who have had the measure taken
VFI=Visual field index
ONL= outside normal limits
Interferometry= Guillon categories (grades 1-4)
Conjunctival hyperaemia, Blepharitis, MGD=Efron grading scale (grades 0-4)
Corneal staining, conjunctival staining=Oxford grading scale (grades 0-5)
Van Herick's= Van Herick's Grading system (grades 1-4) *CDR*=Cup-to-disc ratio

Table 7.1: Baseline measures for patients presenting to the EGC and subsequently starting on ocular hypotensive drops. All values are given as an average for each eye with the exception of the VFI, which is calculated as the percentage of patients displaying results ONL.

Average IOPs were higher at baseline for the PF group (PFG) (22.7±4.0mmHg RE, 26.7±6.4mmHg LE) compared to the preserved group (PG) (21.0±6.0mmHg RE, 19.8±5.1mmHg LE). VFIs outside of the normal limits were also more common in patients in the PFG than the PG (100% vs 70%, respectively). Furthermore, CCT was thicker on average

amongst the PFG than the PG (580±24.4µm RE, 577±28.4µm LE vs 537±24.4µm RE, 533±22.8µm LE, respectively).

Ocular surface staining grades were higher on average in the PFG than the PG, both in terms of conjunctival and corneal staining. Corneal staining scores were averaging at 0.7±0.6 for the RE and 0.3±0.6 for the LE for the PG, and 1.0±1.7 for the RE and 1.3±2.3 for the LE for the PFG. In terms of conjunctival staining, average scores were 0.9±0.8 for the RE and 0.8±0.6 for the LE for the PG, and 2.0±1.0 for the RE and 1.3±1.2 for the LE for the PFG.

TMH and conjunctival hyperaemia were two measures which were indifferent between the two groups. The TMH was 0.3±0.1mm for both the RE and LE, for both groups. Conjunctival hyperaemia was graded at 1.5±0.7 for both the RE and LE for the PG, and 1.5±0.9 for the RE and LE for the PFG.

There was also little difference for CDR and Van Herick's angles between the groups. CDR averaged at 0.6±0.2 for both eyes for the PG and, 0.6±0.2 for the RE and 0.7±0.2 for the LE, for the PFG. Van Herick's angles averaged at 3.4±1.0 for the RE and 3.5±0.7 for the LE for the PG, and 3.7±0.6 for both eyes for the PFG.

FBUT was slightly higher in the PG than then PFG, but NIBUT was higher in the PFG than the PG. FBUT values averaged at 4.7±2.9seconds for the RE and 4.8±2.7seconds for the LE for the PG. For the PFG, the FBUT averaged at 3.0seconds for both eyes. For NIBUT, the PG averaged at 3.5seconds for the RE and 4.6seconds for the LE, and the PFG averaged at 5.3±3.2seconds for the RE and 5.6±3.3seconds for the LE.

In terms of lid margin analysis, the mean blepharitis was graded at 1.7±2.1 for both eyes in the PFG and at 0.4±0.8 for both eyes in the PG group. MGD showed minor differences between the groups, with the PG group having slightly higher average scores (0.8±0.9RE, 0.9±0.8LE vs 0.7±0.6 RE 0.7±0.6 LE, for the PG and PFG, respectively).

Tear osmolarity was higher for the PFG group than the PG group, with average readings of 302±12.4mOsm/L for the RE and 297±10.8mOsm/L for the LE for the PG, and average readings of 308±19.0mOsm/L for the RE and 308±13.0mOsm/L for the LE for the PFG.

In terms of symptoms, the mean OSDI score for the PG was 11.26±12.3, with 33% of patients

having a score of ≥13. For the PFG, the mean OSDI score was 22.54±10.2, with 67% of patients having an OSDI score of ≥13.

7.4.4 Preserved first line therapy

7.4.4.1 Follow up telephone appointments

Five patients who started preserved treatment were available for a follow up telephone consultation. All five patients completed both the OSDI and the clinical study follow up questionnaire at the follow up telephone consultation.

OSDI

	OSDI	
Patient	Before	After
Px 1	10.42	0.00
Px 2	0.00	0.00
Px 3	18.75	2.27
Px 4	2.08	0
Px 5	2.08	0

Px=Patient
Table 7.2: OSDI scores for patients at baseline, before treatment, and after, following 1 month of preserved ocular hypotensive treatment.

One patient had a score of 13 or over on the OSDI at baseline, prior to treatment. The remainder of the patients had scores less than 13, indicative of normal values. After 1 month of treatment, for 80% of patients, the OSDI scores improved (decreased), and the remainder had unchanged values from baseline to month 1. The greatest reduction was for the patient who had the highest baseline OSDI score (↓16.48).

Clinical study follow up questionnaire

All five patients were aware of their dosing regimen as prescribed in clinic. On questioning the patients about the reason for using their drops, all five explained it was to lower their eye pressure.

In terms of missed doses, one patient missed their drops on 2 occasions, two patients missed them on one occasion and two patients did not miss any doses since starting their treatment.

The reason for missing their drops was forgetfulness for all three patients who confessed to missed doses.

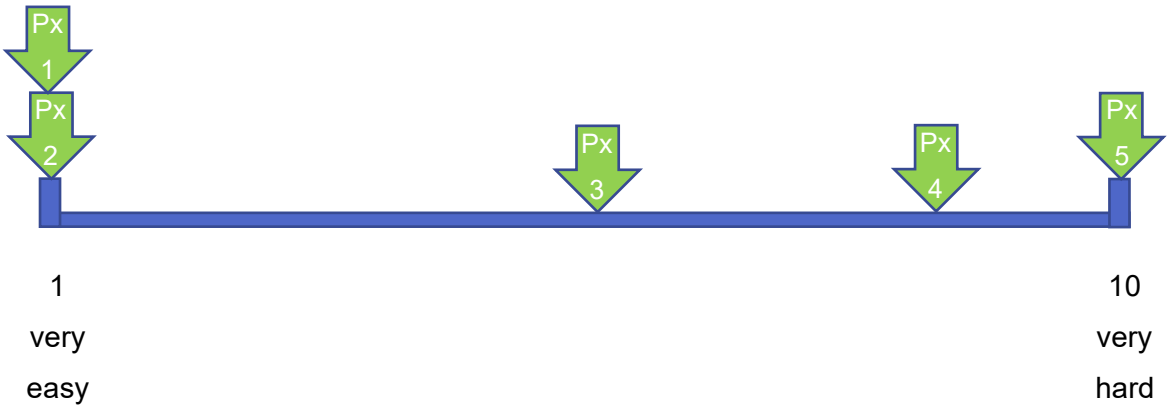


Figure 7.2: Ease of handling of the ocular hypotensive drops on a scale of 1 to 10, with 1 being very easy and 10 being very hard. Two patients felt it was very easy to handle the drops, one person felt it was neither easy or hard, and two patients found it hard or very hard.

No patient reported any side effects from the drops at their one-month telephone appointment. All patients reported that they were happy to continue with their treatment and no one had to be brought into the EGC clinic sooner for a review.

In terms of additional comments from the patients, one patient reported that they were 'very satisfied' with the drops as the 'pain at the back of the eyes' they were experiencing prior to the drops had disappeared since starting treatment. One patient reported that they had her IOPs checked at the Opticians since starting their treatment and was pleased to inform us that the IOPs had reduced from 27mmHg to 17mmHg. One patient needed advice regarding their status on driving, whilst another required some advice on their floaters.

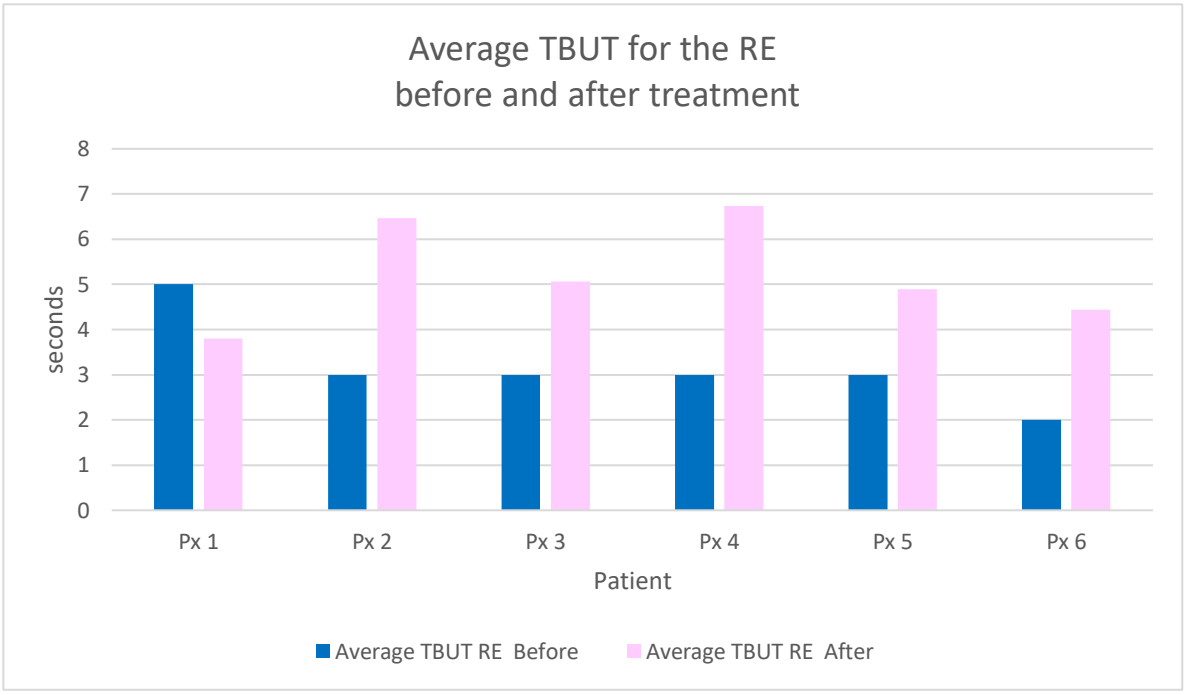
One patient did report some soreness in the corner of their LE at this appointment, however, this was a longstanding, infrequent issue and one they had experienced long before the start of the drops. They were advised to see their optometrist for examination of this and advised to use dry eye drops since this had helped them in the past.

7.4.4.2 Follow up clinic appointments

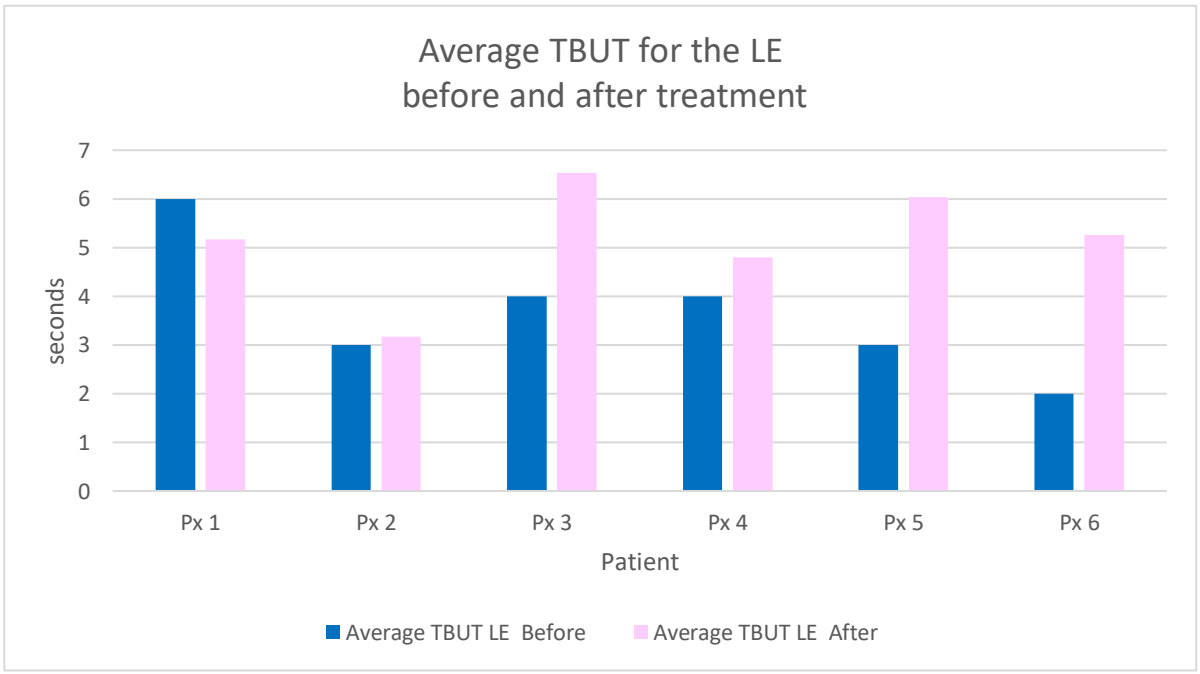
Seven patients were reviewed again in the EGC after having started their ocular hypotensive treatment at the last visit. Of these, six were on preserved medication.

TBUT

a)



b)

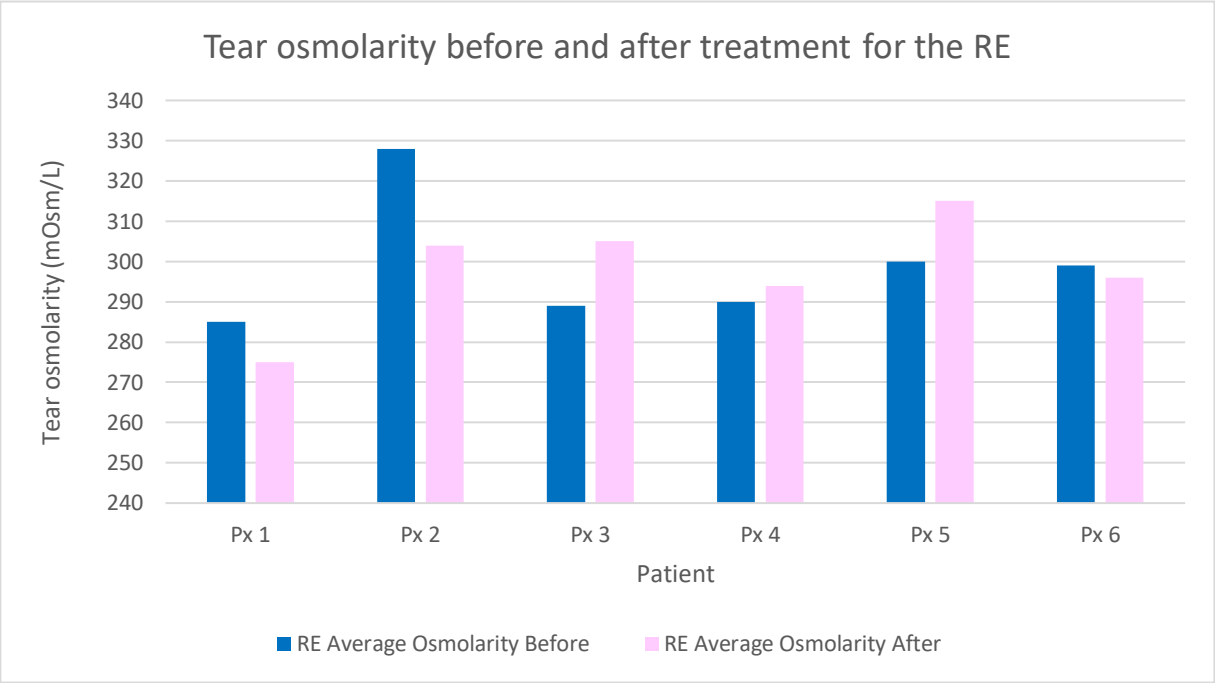


Figures 7.3: Average TBUT for patients before and after starting treatment for the RE (7.3a) and LE (7.3b)

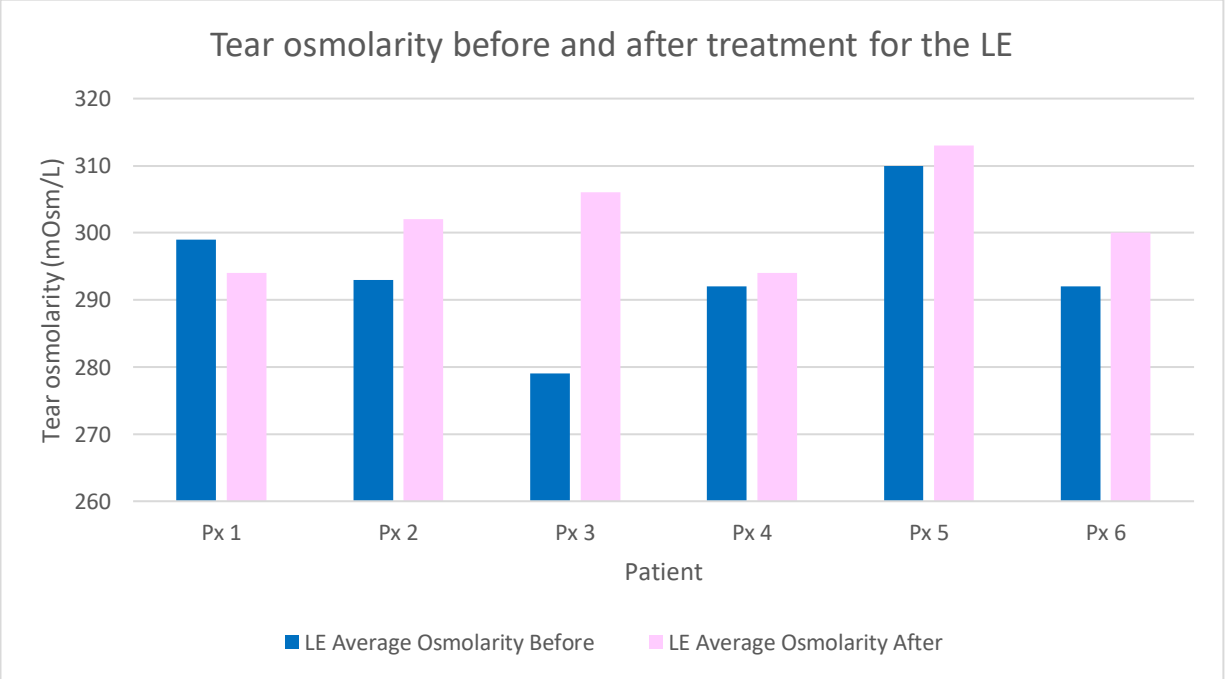
For average TBUT, five out of the six patients showed an increase in this at their first visit compared to baseline, for both the RE and LE. Only one patient showed a decrease in TBUT after starting treatment (Figure 7.3a and 7.3b, Px 1).

Tear osmolarity

a)



b)



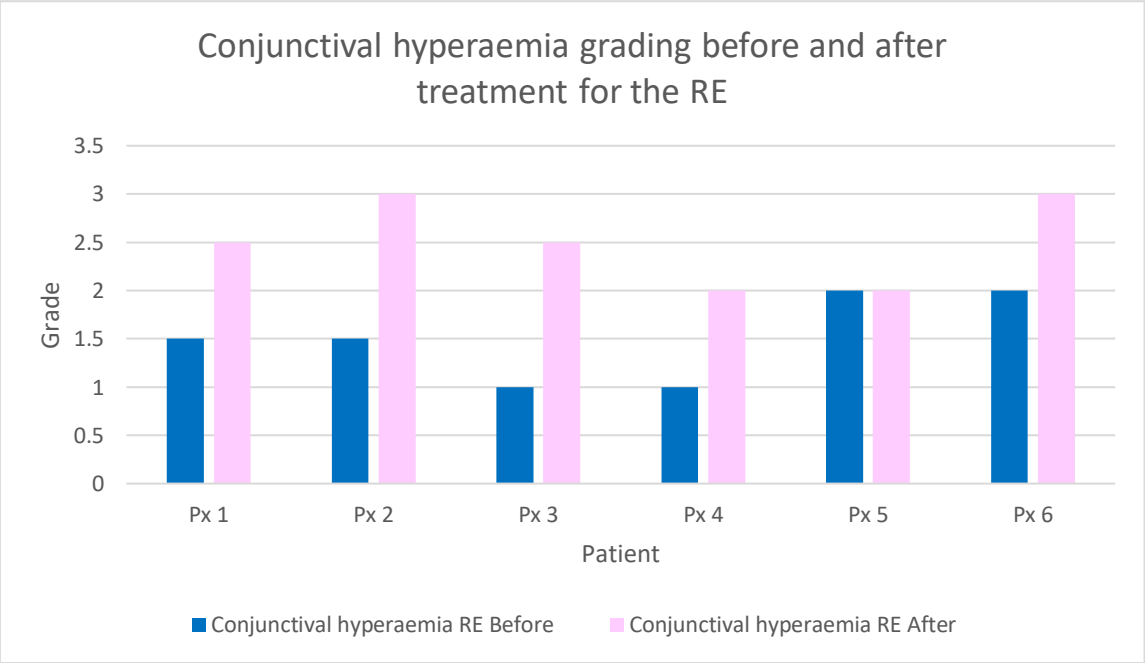
Figures 7.4: Tear osmolarity for patients before and after starting treatment for the RE (7.4a) and LE (7.4b)

Tear osmolarity showed an increase in 67% of the 12 eyes that were examined from baseline to visit one. In 33% of the eyes, there was a reduction in tear osmolarity. There was an inter-eye difference of >8mOsm/L in 67% of patients pre-treatment, and in 17% of patients post treatment.

Conjunctival hyperaemia

Conjunctival hyperaemia grading increased in five out of the six REs, and in four of the six LEs. For one patient the score remained unchanged for the RE, for one patient the score remained unchanged for the LE. A decrease in hyperaemia grading was observed for one patient only for the LE (Figure 7.5b, Px 5).

a)



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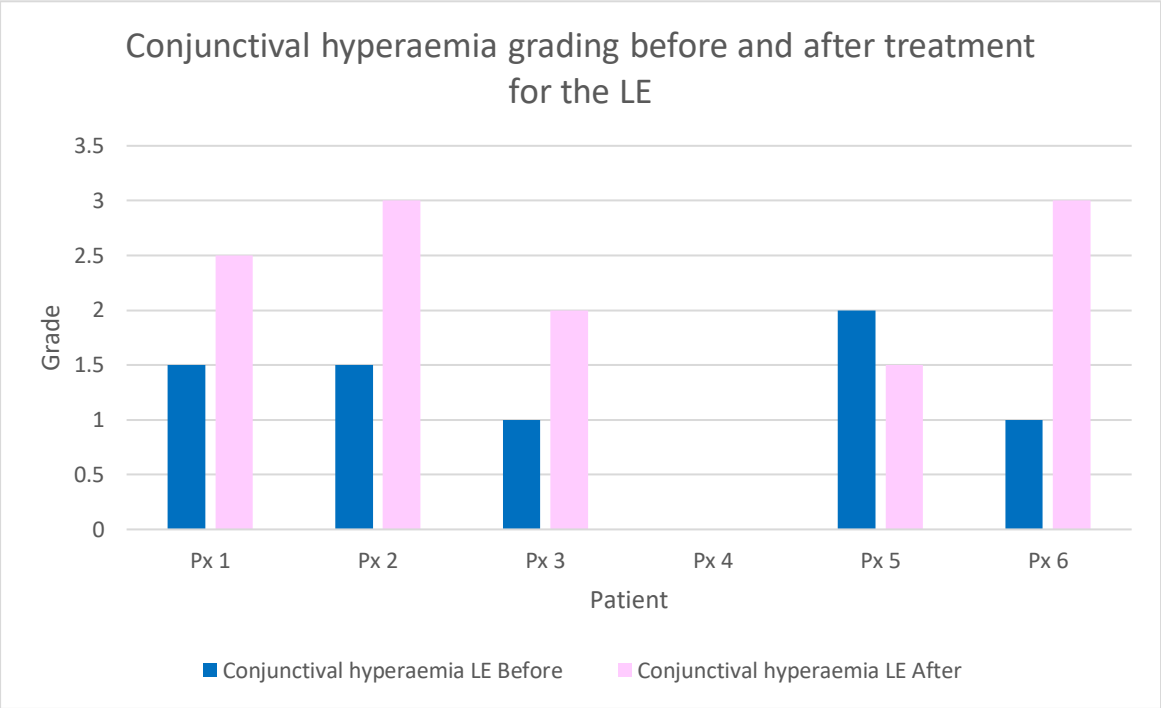


Figures 7.5: Conjunctival hyperaemia grading for patients before and after starting treatment for the RE (7.5a) and LE (7.5b)

Blepharitis

Blepharitis RE			Blepharitis LE	
Before	**After**		**Before**	**After**
0	0	**Px 1**	0	0
2	0	**Px 2**	2	0
0	0	**Px 3**	0	0
0	0	**Px 4**	0	0
0	0	**Px 5**	0	0
2	2	**Px 6**	2	2

Table 7.3: Blepharitis grading before and after starting preserved hypotensive drops

MGD

MGD RE			MGD LE	
Before	**After**		**Before**	**After**
1	1	**Px 1**	1	1
1.5	0	**Px 2**	1.5	0
0	0	**Px 3**	0	0
1	2	**Px 4**	2	2
0	0	**Px 5**	1	1
1	0	**Px 6**	1	1

Table 7.4: MGD grading before and after starting preserved hypotensive drops

In terms of lid margin analysis, overall, little difference was observed between baseline and visit 1 measures. Blepharitis was unchanged in 10 out of the 12 eyes that were examined in the EGC. Only one patient displayed a drop in blepharitis grading between the two visits, reducing from grade 2 at baseline to grade 0 at follow up for both eyes (Table 7.3, Px 2). Similarly, with MGD, there was little change in MGD grading between visits. For three out of the twelve eyes, the MGD score decreased (Table 7.4). For one patient, the MGD score increased by 1 for the RE only, at follow up. The remainder were unchanged between visits.

Ocular surface staining

Corneal staining RE			Corneal staining LE	
Before	**After**		**Before**	**After**
1	0	**Px 1**	0	0
1	0	**Px 2**	2	2
0	0	**Px 3**	1	1
1	1	**Px 4**	0	0
1	1	**Px 5**	0	3
0	1	**Px 6**	0	0

Table 7.5: Corneal stain grading before and after starting preserved hypotensive drops

Conjunctival staining RE			Conjunctival staining LE	
Before	**After**		**Before**	**After**
0	2	**Px 1**	1	2
1	3	**Px 2**	1	2
0	2	**Px 3**	1	2
0	1	**Px 4**	0	1
1	1	**Px 5**	1	1
1	1	**Px 6**	1	0

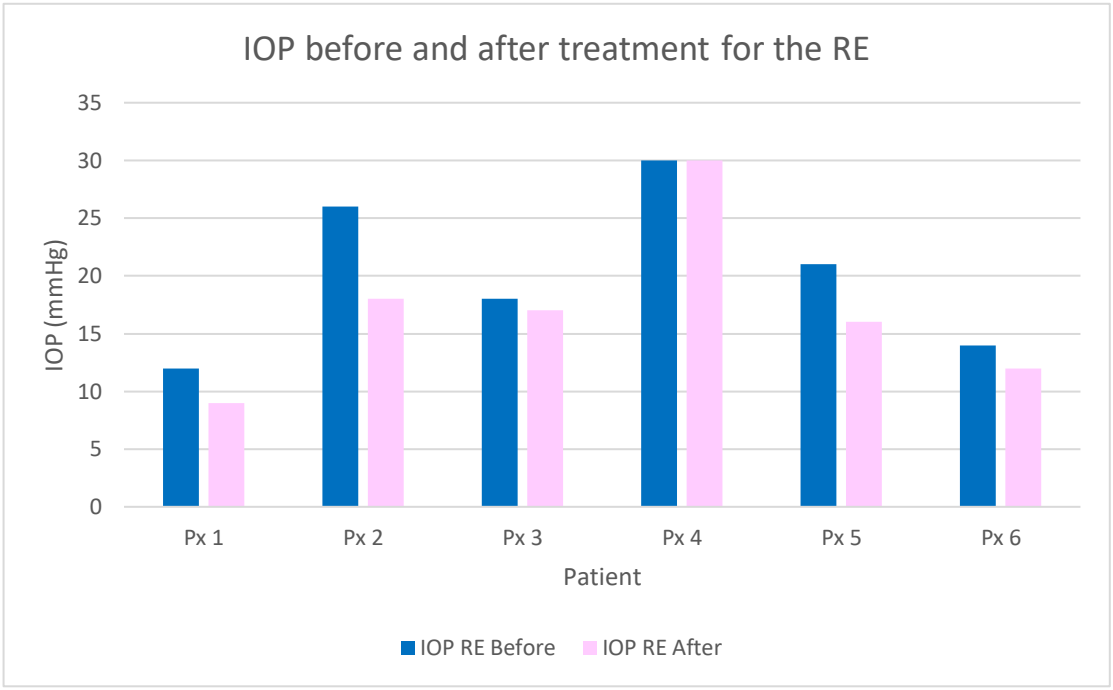
Table 7.6: Conjunctival stain grading before and after starting preserved hypotensive drops

In terms of baseline corneal staining, four patients had some staining in the RE and two patients had some staining in the LE. Following the treatment period, for three patients, the RE staining remained unchanged, for two patients it decreased, and for one patient it increased. For the LE, the corneal staining grade remained unchanged for five out of the six patients; it increased from grade 0 to grade 3 for one patient only (Table 7.5).

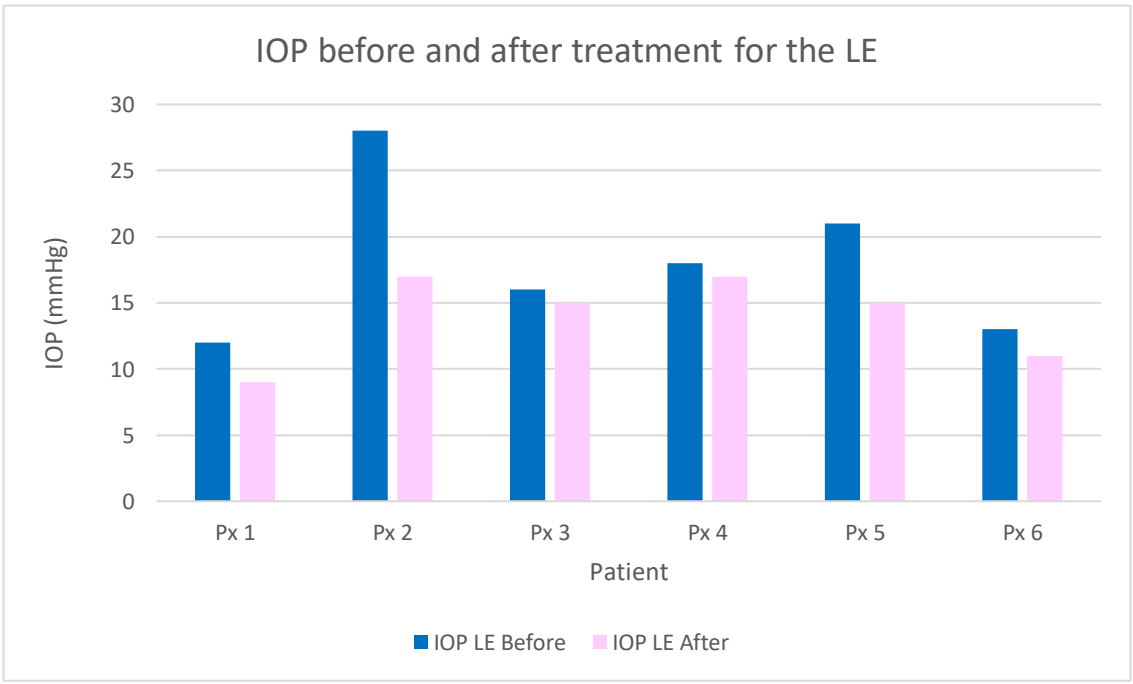
Conjunctival staining showed greater changes from baseline to follow up. For eight out of the twelve eyes, there was an increase in staining scores between visits. Out of these eight patients, three showed increases of two grades, with the other five showing increases of one grade. For three eyes, the staining score remained unchanged between visits, and only one patient showed a reduction in conjunctival staining from baseline to follow up (Table 7.6).

IOP

a)



b)



Figures 7.6: IOPs before and after starting treatment for the RE (7.6a) and LE (7.6b)

Figures 7.6a and 7.6b demonstrate the IOP changes for the RE and LE between the first and second visit. Two patients showed elevated IOPs of 24mmHg or more at baseline (Px 2 and Px 4). A reduction in IOP was observed in all six LEs, and in five out of six REs. For Px 4, the IOP of the RE remained unchanged at 30mmHg at the follow up visit. The drop was most pronounced for Px 2 followed by Px 5; for all other patients the reduction was less marked.

In terms of OSDI, for 50% of the patients in this preserved group who were reviewed in clinic, there was a decrease in scores. For one patient the score remained unchanged at 0.00, for one it increased slightly but stayed well below 13. For one patient, the baseline data was unavailable for their OSDI score, but it was elevated at 25.00 at follow up, and as such, this person was changed from latanoprost to monopost therapy.

7.4.5 Change of therapy

	Baseline		Latanoprost		Timolol	
Variable	**RE**	**LE**	**RE**	**LE**	**RE**	**LE**
TBUT (seconds)	3	4	6.7	4.8	8.6	7.8
Interferometry	X	X	1	1	1	2
Tear osmolarity (mOsm/L)	290	292	294	294	288	281
TMH (mm)	0.2	0.2	0.4	0.4	0.2	0.2
Conjunctival hyperaemia	1	0	2	0	0	0
Blepharitis	0	0	0	0	0	0
MGD	1	2	2	2	1	2
Corneal staining	1	0	1	0	1	0
Conjunctival staining	0	0	1	1	1	1
GAT (mmHg)	30	18	30	17	22	19

X=missing data

Table 7.7: Characteristics of the patient who changed to timolol drops twice a day, from latanoprost once a day, following the second visit to the EGC. The measures are given for each visit; baseline, follow up after latanoprost treatment (second visit) and follow up after being swapped timolol treatment (third visit).

One patient who was initially prescribed latanoprost following the baseline visit, was reviewed in clinic. The latanoprost was deemed ineffective since the RE IOP had not decreased from its

baseline value. This patient was then changed to timolol to be used twice a day. The clinical measures are compared for each visit in Table 7.7.

The TBUT appeared to have increased between the baseline and second visit, and then from the second visit to the third visit (3seconds RE, 4seconds LE at baseline, 6.7seconds RE, 4.8seconds LE at second visit, 8.6seconds RE, 7.8seconds LE at third visit). FBUT was used for the baseline visit, and NIBUT was used for subsequent visits.

Tear osmolarity increased minimally from baseline to visit two, following preserved latanoprost treatment (from 290mOsm/L RE, 292mOsm/L LE at baseline to 294mOsm/L for both eyes at visit two). By visit three, the tear osmolarity appeared to drop in both eyes, although the inter-eye difference increased (288mOsm/L RE, 281mOsm/L LE on visit three). Overall, the tear osmolarity values fluctuated around similar figures.

Conjunctival hyperaemia increased for the RE only following preserved latanoprost treatment from grade 1 to grade 2, but by the third visit after timolol use, dropped to 0 for both the RE and the LE. The conjunctival hyperaemia grade for the LE was unchanged across the three visits, at grade 0.

Blepharitis grading was at 0 and unchanged across all visits, whilst corneal staining was graded at 1 for the RE and 0 for the LE, but also remained unchanged across all visits. MGD increased by a grade in the RE from baseline to visit two (from grade 1 to grade 2), but by visit three, the values matched those at baseline (grade 1 RE, grade 2 LE).

Conjunctival staining increased from baseline to visit two, from grade 0 to grade 1 for both eyes, and then remained at this level by visit three. Corneal staining was graded at grade 1 for the RE and grade 0 for the LE, and these scores remained the same throughout the visits.

Another patient was initially prescribed latanoprost drops at baseline. When they were reviewed in the follow up clinic, it was decided to change their treatment to PF monopost. The details of this patient at baseline and visit two are outlined in Table 7.8 below.

	Baseline		Visit 2	
Variable	**RE**	**LE**	**RE**	**LE**
TBUT (seconds)	2	2	4.4±0.8	5.3±1.8
Interferometry	X	X	3	2
Tear osmolarity (mOsm/L)	299	292	296	300
TMH (mm)	0.5	0.5	0.2	0.2
Conjunctival hyperaemia	2	1	3	3
Blepharitis	2	2	2	2
MGD	1	1	0	1
Corneal staining	0	0	1	0
Conjunctival staining	1	1	1	0
GAT (mmHg)	14	13	12	11
OSDI	X		25	

X=missing data
Table 7.8: Baseline and follow up characteristics of patient who was originally prescribed latanoprost, but following the second visit, was subsequently changed to monopost treatment

The TBUT appeared to increase slightly between baseline and follow up for this patient, albeit still being below 10 seconds for both eyes. FBUT was employed at baseline, with results of a break-up time of 2 seconds for each eye, and NIBUT for visit two, with results of 4.4±0.8seconds for the RE and 5.3±1.8seconds for the LE.

The tear osmolarity was within the normal range at baseline and follow up, and showed little change between visits. At baseline, the tear osmolarity was 299mOsm/L for the RE which changed to 296mOsm/L by visit two, and for the LE it was 292mOsm/L at baseline, changing to 300mOsm/L by visit two.

The TMH decreased following treatment with latanoprost in both eyes by 0.3mm. Conjunctival hyperaemia did increase for both eyes for this patient, from grade 2 to grade 3 in the RE and from grade 1 to grade 3 in the LE. Blepharitis was unchanged, but present at grade 2 at both visits. Corneal staining increased by one grade for the RE only, and conjunctival staining decreased by one grade in the LE only, by the second visit. Unfortunately, the OSDI questionnaire was not completed at baseline, but at the second visit, it showed moderate to severe dry eye.

7.4.6 Preservative-free first line therapy-Follow up clinic appointments

One patient was started on PF treatment (monopost) at their first visit was reviewed in the EGC. They were subsequently changed to PF combination therapy (fixapost) since the IOP had not reduced adequately. The characteristics of the two visits are compared in Table 7.9 below.

	Baseline		Visit 2	
Variable	RE	LE	RE	LE
TBUT (seconds)	3	3	7.2±2.3	5.0±1.0
Interferometry	X	X	3	3
Tear osmolarity (mOsm/L)	320	309	301	308
TMH (mm)	0.3	0.3	0.3	0.3
Conjunctival hyperaemia	2.5	2.5	3	3
Blepharitis	0	0	0	0
MGD	0	0	0	0
Corneal staining	0	0	0	0
Conjunctival staining	1	0	1	1
GAT (mmHg)	19	34	20	25
OSDI	25.00		22.73	

X=missing data
Table 7.9: Characteristics of the patient who was commenced on PF monopost treatment and then changed to PF fixapost on the second visit after assessment in the EGC.

TBUT increased from baseline to visit 2 after use of monopost. The change was more pronounced for the RE than the LE. FBUT was used at baseline and NIBUT at visit two, resulting in values of a break-up time of 3seconds at baseline for both eyes, and 7.2±2.3seconds for the RE and 5.0±1.0seconds for the LE at follow up.

Tear osmolarity decreased for the RE by 19mOsm/L from baseline to visit two but changed only by 1 unit for the LE by the second visit. The inter-eye difference improved by visit 2 in terms of osmolarity.

TMH remained unchanged across visits for both eyes at 0.3mm, and conjunctival hyperaemia increased by 0.5 units for both eyes. Blepharitis, MGD and corneal staining were graded at 0

for both eyes and remained so across visits. Conjunctival staining worsened by 1 grade for the LE from baseline to visit 2 but remained unchanged at grade 1 for the RE. OSDI scores for this patient remained in the early twenties at both visits.

7.4.7 Statistical analysis

Due to the small numbers in the current study, statistical tests were not possible. In this instance, the mean± standard deviation has been evaluated. However, if this pilot study was converted to a full, prospective, longitudinal study, the following statistical tests are recommended to establish associations.

7.4.7.1 Receiver Operating Characteristic (ROC)

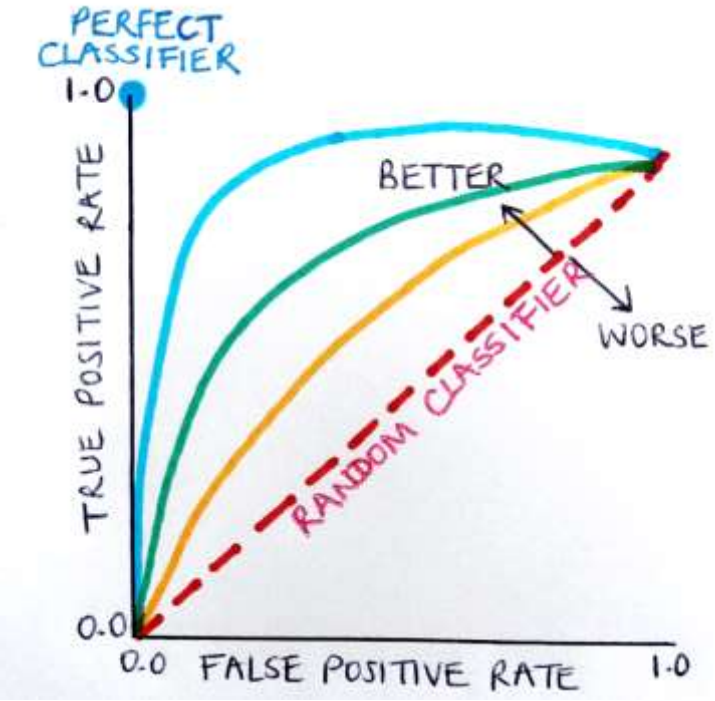


Figure 7.7: Generic ROC curve

With the dataset obtained from this study, ideally a Receiver Operating Characteristic (ROC) curve would provide the best insight as to which clinical tests, with a minimum threshold score in place, would act as best indicators of DED.

Since the dataset would be of binary nature, that is, the presence or absence of DED, the ROC curve could help to establish a prediction model. By setting the minimum threshold for each clinical metric, the results can be plotted on the graph to establish the sensitivity (how many

people were predicted to develop DED and truly did) versus the false positive rate, otherwise known as (1-specificty) (how many people were predicted to develop DED but did not). The Area Under the Curve (AUC) can then be calculated. A value of AUC over half is indicative of a good prediction, whereas a value under a half is indicative of poor prediction. The random classifier line, as illustrated in Figure 7.7, suggests no predictive pattern, with the result occurring at random.

Several ROC curves can be plotted for the same variable with different threshold criteria, to establish which criteria acts as the best predictive model. Furthermore, ROC curves can be plotted for different clinical metrics to make independent analysis for each diagnostic test.

Since the results of Chapter 6 illustrated that the majority of patients attending glaucoma clinics have some form of OSD, even prior to starting treatment, it would be more beneficial and plausible to target DED as the dependent variable and determine which independent variables would lead to a positive DED diagnosis. Based on the indications of the current study and the previous chapters, as well as input from the TFOS DEWS II report, the independent variables which would be tested for their predictive abilities would be as follows:

- TBUT (Wolffsohn et al., 2017)
- Tear osmolarity (Wolffsohn et al., 2017)
- Conjunctival staining (Wolffsohn et al., 2017)
- Corneal staining (Wolffsohn et al., 2017)
- Lid margin staining (Wolffsohn et al., 2017)
- CCT (Chapter 5 and Chapter 7)

7.4.7.2 Decision Tree Analysis

Alternatively, Decision Tree Analysis (DTA) could be used to decide which variables, or combination of variables, best predict DED in the treatment of glaucoma and OHT. A form of multivariate analysis, DTA could identify the hierarchy of independent variables in terms of their importance as predictive factors, whilst overcoming confounding between variables. As it is possible to use DTA with both discrete and continuous data, its use would be ideal in terms of the proposed variables to be tested since they are a mix of the two (Song and Lu, 2015). A schematic of a possible DTA for this study is demonstrated in Figure 7.8 below.

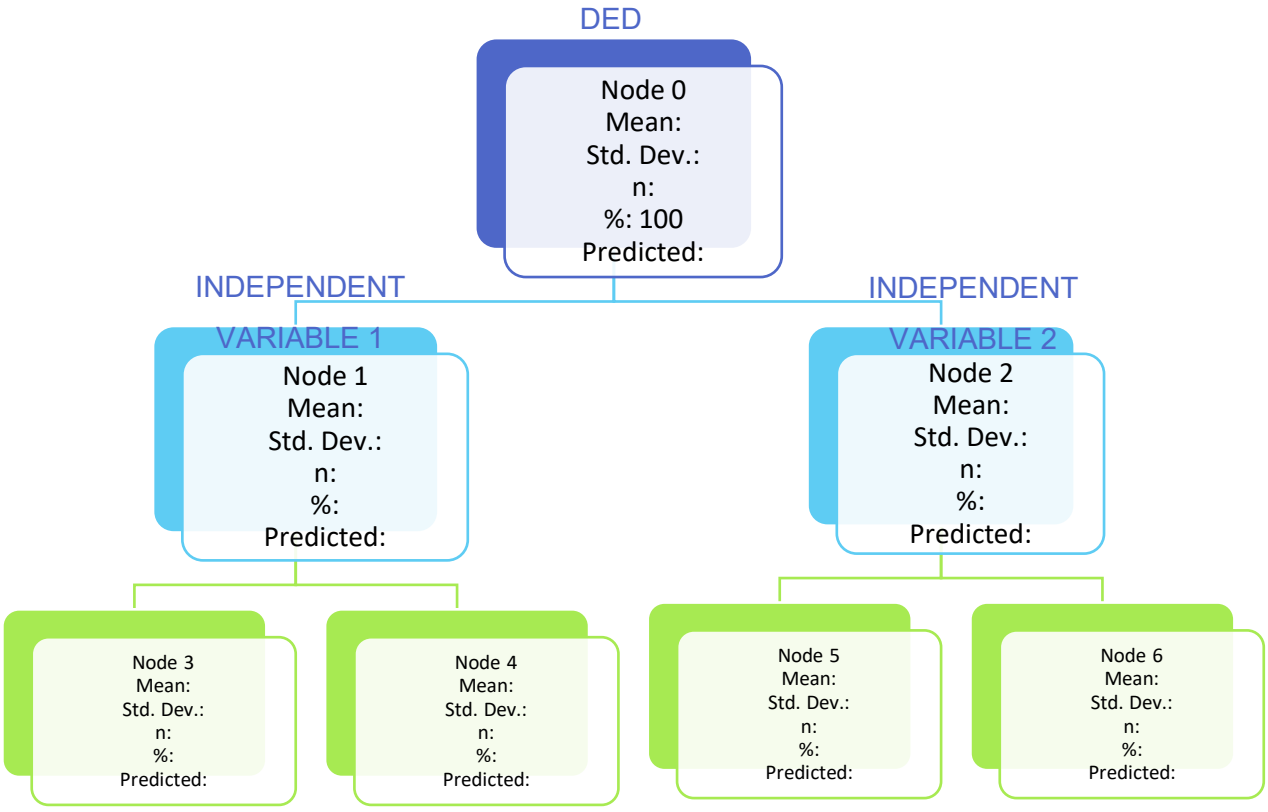


Figure 7.8: Schematic representation of a possible DTA for determining which predictive variables are the best indicators for development of DED during glaucoma or OHT treatment.

7.4.7.3 Sample size determination

Power calculations, made using G*Power (version 3.1.9.7), show that 349 participants are required to detect statistically significant effects at the 5% significance level (α = 0.05) with 80% power, with an effect size of 0.15 using the results of the systematic review of Chapter 2, judged by the current literature.

7.5 Discussion

There were two main aims of this study. Firstly, to determine the predisposing factors making individuals susceptible to developing OSD on preserved ocular hypotensive treatment, and secondly, establishing the time-point at which OSD develops following such treatment. The EGC was formed during the later stages of the COVID-19 pandemic. A clinic formed to address ocular surface diseases and glaucoma and OHT concurrently, the EGC was developed following the findings that were uncovered from the retrospective audit (Chapter 5). The

retrospective audit highlighted the lack of anterior eye assessments made in the glaucoma clinics. Currently, there is no standardised method for testing the ocular surface within glaucoma clinics. NICE guidelines recommend anterior segment assessment using slit lamp biomicroscopy in the diagnosis and monitoring of glaucoma and OHT, but fail to address the methods advisable for this (National Institute for Health and Care Excellence, 2017). This absence of conformity in assessing the ocular surface may lead to an underestimation of the true prevalence of OSD in glaucoma clinics.

Based on the current literature review, no previous study has looked at ocular surface measures before and after commencing hypotensive ocular medication, with the aims of establishing predictive baseline clinical factors for developing DED. Several studies have looked at the effects of preserved versus PF topical drops in the treatment of glaucoma and OHT (Pisella et al., 2002, Kim et al., 2021, Jaenen et al., 2007). It is well publicised that PF treatment is as effective as preserved treatment in lowering IOP, with similar tolerability and safety profiles (Aptel et al., 2016, Lemmens et al., 2021, Hamacher et al., 2008). There are, however, still barriers to prescribing PF drops in the management of glaucoma and OHT, with particular emphasis on the cost burden upon the NHS. Hypothetically, £13million could have been saved if all PF prescriptions were switched with their BAK preserved counterparts in 2018 (Hogg and Connor, 2020).

Clearly, there is a need to be selective as to who should be prescribed PF treatment. This is particularly important, since there is a tendency for some patients to develop DED with preserved glaucoma medication (Su et al., 2021). This has the potential to lead to subsequent cost implications through more frequent hospital visits, changes to medication, poor adherence, poor quality of life and unsuccessful glaucoma surgery (Chawla et al., 2007, Nordmann et al., 2003, Broadway et al., 1994). These cost repercussions have to be weighed up against the cost of prescribing PF treatment in the first place. Such long-term cost comparisons in the treatment of glaucoma and OHT are yet to be elucidated.

The aim of this study was to address this by evaluating newly diagnosed and treated patients retrospectively, to establish which underlying factors make some patients more susceptible to developing ocular surface problems with preserved glaucoma drops. These factors can then be considered when prescribing treatment naïve patients in glaucoma clinics, so that PF options are readily prescribed to those at most risk to developing DED in the course of the glaucoma or OHT treatment.

A recent study by Su and colleagues (2021) set out to explore similar aims by following a group of newly diagnosed glaucoma and OHT patients for a four-month period. Unlike the present study which was inclusive of all hypotensive eye drops, Su and colleagues (2021) set out to investigate specifically, the effects of BAK preserved latanoprost on treatment naïve patients. Furthermore, lubricants were prescribed to symptomatic patients with Schirmer's result of ≤5mm at baseline and the consequences of this were evaluated at follow up (Su et al., 2021).

Su and colleagues (2021) found that OSDI scores improved significantly by month 1 and continued to improve by month 4. This is also true in the present study. The individuals who were followed up with telephone appointments 1 month after starting treatment, all showed a decrease in OSDI scores at the follow up telephone consultation, apart from one individual who was unchanged at 0.00 from baseline to follow up. Moreover, clinic follow up consultations revealed that 50% of patients on preserved medication showed an improvement in OSDI scores at the second visit. For one person it remained unchanged at 0.00, for another it did increase slightly but remained well below 13. For the patient who started PF medication, the OSDI score remained in the early twenties between visits.

This finding may be explained by the demonstrated discordance of OSD symptoms and signs (Sullivan et al., 2014, Fuentes-Páez et al., 2011, Nichols et al., 2004b). Despite the fact that the OSDI has been shown to have good re-test reliability, excellent validity and good sensitivity and specificity, its use can be limited in DED monitoring since such robust metric may not capture the fluctuating condition that is DED (Schiffman et al., 2000). Furthermore, OSDI relies on recall of symptoms over the past week. This poses two limitations; firstly, it relies on patients' memory, which can be poorer amongst older patients, of which make up the vast majority of patients presenting to glaucoma clinics, and secondly, DED symptoms are fluid and can vary weekly (Yochim et al., 2012, Jonas et al., 2017, Kanellopoulos and Asimellis, 2016). Perhaps future studies could administer OSDI questionnaires to patients to be completed on a weekly basis, between visits, to fully appreciate changes in dry eye symptoms over the course of the treatment.

In the present study, TBUT appears to increase following the start of ocular hypotensive drops. In the preserved group, only one patient showed a decrease in TBUT at follow up. The remainder of patients showed an improvement in TBUT by the second visit. Similarly, for the PF group, the TBUT also appeared to have increased by the second visit. Regardless of this, the average TBUT was less than 10 seconds for both groups of patients at all visits.

With an 82% sensitivity and 86% specificity, 10 seconds has been a favourable critical value for diagnostic purposes (Mengher et al., 1986). In the TFOS DEWS II report for the diagnostic battery of tests in assessing patients, a NIBUT of less than 10 seconds is regarded as one of the homeostatic markers, and this combined with a positive symptomology score, would class an individual as having DED (Wolffsohn et al., 2017). According to the baseline measures, all 14 patients displayed signs of OSD, though it only translated into symptoms for 42% of patients.

There was a change in protocol for measuring TBUT in the EGC during the course of the study. Originally, only fluorescein strips were available to measure FBUT. Weeks into the EGC, there was an introduction of the EasyTear® VIEW device; a slit lamp mountable tearscope capable of taking NIBUT measures as recommended by the TFOS DEWS II report (Wolffsohn et al., 2017). As NIBUT is endorsed as the preferential method by the TFOS DEWS II report, the protocol was changed to be implement this device in the EGC (Wolffsohn et al., 2017).

Although NIBUT measures have been reported to be slightly longer than invasive methods by an average 3.7seconds, such differences are less pronounced when shorter average tear break up values are considered (Cho and Douthwaite, 1995, Nichols et al., 2002). Therefore, TBUT and NIBUT have been compared between visits in this study, with the assumption that the two measures are comparable as demonstrated previously (Amaechi and Osunwoke, 2011). This change in methodology, however, may account for the increases in TBUT for most patients presenting to the EGC, rather than indicating improved tear film stability post treatment.

The third aim of this study was to determine the baseline characteristics of patients commenced on PF treatment at diagnosis. It appears that those individuals with more advanced glaucoma or OHT, driven by higher IOPs and worse visual fields, were more likely to be in the group prescribed PF treatment as first line therapy. Moreover, those with thicker than average CCTs, appeared to be in the group prescribed PF at diagnosis. Average ocular staining grades, blepharitis scores and tear osmolarities were elevated in the PFG than the PG at baseline. These clinical characteristics were coupled with higher OSDI scores for those prescribed PF at diagnosis than those prescribed preserved drops.

In a typical glaucoma clinic, there are no set anterior eye checks which are required as part of the routine appointment (National Institute for Health and Care Excellence, 2022). The EGC was developed for enhanced ocular surface assessments to be made alongside the typical

glaucoma checks. Again, due to the sparsity of the data available, it is difficult to associate the aforementioned clinical results as being the factors driving PF prescribing as first line therapy. However, it could be assumed that those patients presenting to glaucoma clinics and complaining of dry eye symptoms, would have had more thorough ocular surface checks and thus, likely to be diagnosed with DED and subsequently prescribed PF treatment.

7.5.1 Predictive factors

Since the formation of the EGC came about during the COVID-19 pandemic, its success in terms of patient numbers was confined by external factors. In the later stages of the pandemic, non-urgent clinics such as the EGC were reintroduced; however, patient numbers were limited to control the spread of the coronavirus. Although the clinic spanned a 13-week period, due to a single EGC a week and patients missing appointments with fear of the virus, only 14 patients were suitable to be included in the analysis of this study. Out of this group, eleven were prescribed preserved glaucoma eye drops at baseline. Although the majority did not display any particular concerns of symptomatic OSD, one patient did require a change to PF monopost at the follow up visit from preserved latanoprost.

The baseline characteristics of this patient revealed the lowest TBUT readings in this cohort of treatment-naïve patients presenting to the EGC, with values of 2 seconds for both eyes. Though these values were slightly higher at the second visit, they were still below 10 seconds, with a reading of 4.4±0.8 seconds for the RE, and 5.3±1.8 seconds for the LE. This could therefore be an indicator of predisposition to developing OSD in treatment-naïve patients in glaucoma clinics. Unfortunately, the clinic numbers are too low to deduce conclusions of significance, but it is a credible finding to explore further.

It has been suggested that lower cut off values for TBUT should be employed in the diagnosis of DED. Hong and colleagues (2013) proposed a cut of value of 2.65seconds in cases of NIBUT, with a sensitivity of 84.1% and a specificity of 75.6% at this value (Hong et al., 2013). Bhandari and colleagues (2016), determined a cut off value of 6.2seconds for NIBUT, with a sensitivity of 86.1% and specificity of 81.1% at this value (Bhandari et al., 2016). Based on the findings of the present study and the recommendations of the aforementioned studies, it might be more useful for OSD diagnosis to be made for NIBUT of less than 5 seconds, and prescribing PF glaucoma drops to patients with baseline values of less than 3 seconds.

Other characteristics of the patient requiring a change from preserved to PF ocular hypotensive treatment included an age of 66 and classification as a male. This does not conform to the typical risk factors for both dry eye and glaucoma, which both list older age and females as increased risk factors (Jonas et al., 2017, Quigley and Broman, 2006, Stapleton et al., 2017). Although this gentleman was over 40 years of age, 57% of patients were older than him. Age alone therefore, does not seem to be a predictive factor, and perhaps other factors combined with older age result in a cumulative risk. Again, the numbers are too low to draw conclusions, but such assumptions are an area of interest to be explored further.

Another variable which was of interest in this individual was the thinner than average CCT. The CCT was 515μm for the RE and 506μm for the LE. Only one other individual had a CCT lower than this. Although it is speculative, the CCT may be influential in determining who is at risk of OSD in such clinics. Interestingly, the retrospective audit of Chapter 5 found that those with thicker than average corneas were more likely to be switched to PF treatment, while those with thinner than average corneas were less likely to be switched to PF treatment. Perhaps patients within the extremities of CCT need to be carefully considered before prescribing preserved treatment. Though studies have looked at the link between glaucoma medication and the effect on CCT, future investigations looking at the association between glaucoma medication, CCT and OSD are welcomed (Bafa et al., 2011, Wilkerson et al., 1993).

As expected with prostaglandin analogues (PGAs), conjunctival hyperaemia increased for most patients by the second visit for at least one eye in the current study (Holló, 2007). In the study by Su and colleagues (2021), significant increases in ocular redness were also found by one month. An interesting accompanying finding was the predisposition for younger patients and males towards bulbar redness at month one (Su et al., 2021). Perhaps due to the small numbers in the present study, such relationship was not observed.

Tear osmolarity has often been cited as the best diagnostic tool in the classification of DED, with superiority over other clinical tests (Sullivan et al., 2010, Tomlinson et al., 2006, Lemp et al., 2011). For the group who started on preserved drops at their first visit, 67% of eyes showed an increase in tear osmolarity post treatment. There was an inter-eye difference of >8mOsm/L in four out of the six patients pre-treatment and in one of six patients post treatment. For the patient commenced on PF treatment at baseline, the review in clinic showed a drastic reduction in tear osmolarity for one eye only.

Although the current study fails to detect a predictive element in tear osmolarity, it provides a useful tool in the monitoring of DED and with longer study durations, trends may be picked up. Perhaps patients with certain baseline osmolarities, or those whose tear osmolarity increases more rapidly in the first few visits, may indicate a predisposing path to OSD. These are assumptions which are yet to be studied. Interestingly, the patient who was on latanoprost and then changed to monopost at the second visit, had tear osmolarity readings well within normal limits for both eyes, at each visit, with no major fluctuation from baseline to follow up. Though a helpful aid, tear osmolarity appears to be a measure that must be evaluated as part of a battery of tests, and not be relied upon solely.

Conjunctival staining was another measure which increased for most patients following preserved treatment. The patient who was on PF treatment showed no change to their conjunctival staining at visit two, remaining at grade 0 for both eyes. Previous studies have demonstrated similar findings, with increased conjunctival staining following application of preserved glaucoma drops (Thygesen et al., 2000). Leung and colleagues (2008), found that each addition of BAK preserved drop increases the likelihood of developing abnormal lissamine green staining by around two-fold (Leung et al., 2008). Switching studies have also demonstrated significant reductions in conjunctival and corneal staining when switched from a preserved PGA to a PF PGA (Uusitalo et al., 2010).

Mohammed and colleagues (2020) set out to explore the inflammatory effects of preserved and PF glaucoma medication on treatment-naïve patients over a 24-month period. Impression cytology was used to assess inflammatory markers at each visit, which was accompanied with completion of the OSDI to assess symptoms. It was found that BAK preserved drops induced inflammatory responses which were noticeable at month 3 and sustained thereafter. For PQ preserved drops, there was increased expression of some inflammatory cytokines from month 12 onwards. OSDI was positively attributed to increasing levels of cytokines (Mohammed et al., 2020).

Although this study looked at cytokines and OSDI, it is similar to the current study in comparing the effects of preserved and preservative medication on the ocular surface prior to treatment, and then for some time after treatment. It is evident that inflammatory effects are delayed and are perhaps sub-clinical in the early stages. This could explain why our short study did not show intolerance to preserved glaucoma drops within the first 4-6 weeks of treatment. As demonstrated by the retrospective audit in Chapter 5, OSD is typically diagnosed within the first twelve months of treatment. The study by Mohammed and colleagues (2020) demonstrates

such effects to be detectable after month 3 for BAK preserved drops and after month 12 for PQ preserved drops, with abnormal OSDI scores in most patients from 6 months onwards (Mohammed et al., 2020). We suspect then, that that the window between month 3 and month 12 as being critical for patients developing symptoms of OSD.

7.5.2 Limitations and future work

The current study does have its limitations. Unfortunately, the COVID-19 pandemic severely affected the success of the EGC. With the ever-changing restrictions and regulations regarding both primary and secondary care in the NHS, it was difficult to implement this clinic at Russells Hall Hospital initially. At the latter end of 2021, the EGC went live but the inflow of patients was still limited. Restrictions as to the number of patients allowed per clinic, the number of patients allowed to be in the waiting area at a given time and the number of clinics allowed per week, meant that patient count into the EGC was low. Thus, the current study lacks the necessary numbers needed to form concrete conclusions with data of statistical significance.

However, the EGC has demonstrated a useful place alongside the regular glaucoma clinics. Once it was established at Russells Hall Hospital, the EGC provided extra support with the backlog of glaucoma patients following the COVID-19 pandemic. Ran by an optometrist, the EGC demonstrated that straightforward cases of glaucoma and OHT can be monitored by optometrists, allowing glaucoma consultants to focus on more complex cases.

Furthermore, the EGC provided additional support for patients both during the initial consultation and with follow up appointments. The patient survey carried out at Corbett Hospital and online at a national scale (Chapter 4) highlighted that many patients did not feel that they received sufficient information prior to starting treatment. In addition, many patients did not receive written information regarding their condition or drops and felt that they were not informed about drop instillation. The EGC set out to explain the diagnosis to the patient at the first visit, and each patient was given a leaflet on glaucoma or OHT, and if warranted, leaflets on other ocular comorbidities such as cataracts and age-related macular degeneration (AMD). Patients were shown drop instillation techniques at diagnosis. Since the clinic time was one hour per patient for the EGC, it allowed time for a discussion with the patient, which perhaps is more difficult due to time restrictions in the normal glaucoma clinics. Moreover, patients were followed up a month later with telephone consultations and asked about the diagnosis, reasons for using the drops, drop handling and potential side effects. Such open conversation with the

patient may help with adherence, reiterating the importance of glaucoma drops and addressing any patient issues early on in the treatment journey.

Future studies could compare conventional glaucoma clinics to the EGC, in terms of patient satisfaction and its impact on adherence. If the EGC is shown to be appreciated by patients and reflected by better compliance, future clinics could implement a short telephone appointment to review patients 6-8 weeks after starting medication. This would mean better management of the patient and help to highlight and resolve problems early on.

Lastly, the current study was purely observational, analysing data retrospectively in the EGC as an evaluation of the clinic. There was no constraint on patients with previous DED or patients using ocular lubricants from being involved in the study. It might be more insightful for future studies to exclude such patients since this could skew the findings. This pilot study has potential to convert to a prospective, cohort, longitudinal study, and should ideally follow patients over a period of 12 to 24 months from pre-treatment to post treatment.

7.6 Conclusion

The current study set out to test two main aims: baseline risk factors predisposing patients to DED when treated for glaucoma and OHT using preserved hypotensive eye drops, and the time-point to conversion to DED. However, due to the Covid-19 pandemic, the resultant data is too sparse to draw viable conclusions. A revision of the current study is encouraged to bridge these gaps, monitoring more patients within both treatment groups (preserved and PF), and following their journey for a minimum of twelve months from the point of diagnosis, to establish the clinical factors which increase the likelihood of developing DED. By uncovering such information, a predictive algorithm could be formed as to who is likely to develop DED when treated for glaucoma or OHT, and in turn, who would benefit from PF treatment as first line therapy. By knowing the critical period during which DED conversion is likely to occur, patients can be monitored more closely during this time and clinical features suggesting conversion could be acted upon early on. PF treatment is costly to the NHS, and so it is important to select patients appropriately for this therapy.

Chapter 8

Conclusions and future work

8.1 Summary of research findings

The main aim of this thesis was to explore the effects of glaucoma medication on the ocular surface. Ultimately, this research was conducted to investigate the role glaucoma medication plays in the development of ocular surface disease (OSD) and the consequences this has on patients and their treatment journeys. Chapter 1 provided the narrative behind the intricate relationship between glaucoma and OSD. The prevalence of symptomatic OSD amongst glaucomatous and ocular hypotensive patients is high, estimated to be around 59% (Leung et al., 2008). From a slightly different perspective, when investigating patients with severe OSD and looking at the prevalence of glaucoma within such a population, levels reach 65.7% (Tsai et al., 2006).

The primary method for managing glaucoma and ocular hypertension (OHT) is by means of lowering the intraocular pressure (IOP) (National Institute for Health and Care Excellence, 2017). To date, this appears to be the only modifiable risk factor (Gordon et al., 2002). In cases of OHT, medical management of raised IOP has been shown to prevent or delay conversion to Primary Open Angle Glaucoma (POAG) (Kass et al., 2002).

Since the start of the current research, the National Institute for Health and Care Excellence (NICE) has had a shift in paradigm in the management of glaucoma and OHT. Changes were made to the guidelines so that from the beginning of 2022, 360° selective laser trabeculoplasty (SLT) is to be offered to newly diagnosed patients of OHT and POAG. Where such treatment is unsuitable (as in pigment dispersion syndrome (PDS)), the patient declines SLT, there has been an insufficient IOP drop with SLT, or in the interim periods prior to laser or surgical treatment, NICE recommends the use of pharmacological intervention using ocular hypotensive drops. The preferred first line therapy in such cases is generic prostaglandin analogues (PGAs) (National Institute for Health and Care Excellence, 2017). Though SLT has been shown to be as effective as hypotensive eye drops in the control of IOPs (Li et al., 2015), pharmacological intervention will still form a mainstay, long-term treatment option for patients suffering from glaucoma and OHT, particularly since SLT degrades in efficacy with repeat sessions (Khouri et al., 2014).

Chapter 1 outlined the medical management of glaucoma and OHT, describing the current literature and highlighting commonly used hypotensive eye drops. Though such eye drops are effective in controlling IOP, they often contain preservatives as a constituent (Lee et al., 2017, Steven et al., 2018, Joint Formulary Committee, 2022). The literature review discussed the

toxic effects of such preservatives on the ocular surface, leading to OSD and subsequent problems (Rossi et al., 2013b, Pisella et al., 2002, Rossi et al., 2009). This is of particular issue in glaucoma and OHT, where these chronic conditions require regular, long-term treatment, and so the cumulative effects of preservatives could inflict damage to the ocular surface.

Several studies have shown preservative-free (PF) drops to be better tolerated than preserved drops (Pisella et al., 2002, Jaenen et al., 2007, Harasymowycz et al., 2021). Such differences have been evaluated through comparison studies and switching studies (Uusitalo et al., 2010, Jaenen et al., 2007, Pisella et al., 2002). Even so, preserved drops still fall under the recommended first line medical therapy for glaucoma and OHT, with PF drops only to be offered to those with allergies to the preservatives or 'clinically significant and symptomatic OSD' (National Institute for Health and Care Excellence, 2017).

Though the studies discussed in the literature review of Chapter 1 favoured PF drugs on the whole, many were conducted in uncontrolled environments with confounding factors. As such, there was a need to compare the efficacy of preserved and unpreserved glaucoma eye drops using randomised controlled trials (RCTs), where such factors could be accounted for and controlled, to allow for a thorough and more conclusive comparison of the two treatment arms.

This led to the development of the systematic review of Chapter 2. The systematic review sought to compare the efficacy of preserved versus PF treatment in the management of glaucoma and OHT, in terms of IOP control, signs and symptoms of OSD, as well as exploration into cellular changes with treatment. This was the first systematic review of its kind exploring all four categories. More recently published reviews have looked at the efficacy of benzalkonium chloride (BAK) preserved eye drops versus PF or alternatively preserved eye drops in glaucoma, or concentrated on preserved and unpreserved beta-blockers, when comparing the safety and efficacy of both treatment arms (Hedengran et al., 2020, Skov et al., 2022). The current systematic review was broader and encompassed more domains to base such comparisons upon, as well as being specific to preserved and PF medication.

The main outcomes of the systematic review revealed preserved and PF hypotensive drops to be equally effective at lowering the IOP. Four studies revealed a greater percentage drop with preserved drops versus PF drops (>3%), however, such differences were not clinically significant and overall, the difference between the weighted percentage drop in IOP from baseline to endpoint for preserved and PF drops stood at 0.48%, which was non-significant (t-test, $p=0.253$).

In terms of safety and tolerability, the methodologies of the included studies varied greatly. It was therefore difficult to collate the information and provide a pooled analysis for most clinical outcomes. Attempts were made for a meta-analytic approach to investigate the symptoms reported in the studies, and signs of conjunctival hyperaemia. The findings of the meta-analysis revealed that preserved ocular hypotensive therapy increases the odds of developing symptomatic ocular problems (OR 1.265, 95% CI 1.005-1.593).

For conjunctival hyperaemia, the confidence intervals of all the studies included in the meta-analysis crossed the midline at one, indicating non-significance of the findings. There was no clear direction of preferred treatment, and the overall odds revealed the lack of substantial evidence to suggest preference of one treatment over the other (OR 1.072, 95% CI 0.871-1.319).

The cellular studies used in the descriptive analysis suggest pre-clinical inflammatory effects of both types of ocular hypotensive treatment, albeit more so for the preserved option overall. Methods looking at sub-clinical measures could therefore provide an early indication of patients who are likely to develop OSD with chronic treatment.

The vastly different methods of executing, recording, study design and treatment follow up in the included studies presented obstacles in the comparison of preserved and PF ocular hypotensive drops. On the whole, PF ocular hypotensive drops are a viable option in the treatment of glaucoma and OHT, which is of particular significance in patients with a compromised ocular surface, or those at a predisposition to developing OSD. With both formulations providing equal efficacy for IOP control, with better tolerance with PF eye drops and arguably, slightly better safety with PF drops, unpreserved hypotensive drops provide the best benefit-to-risk ratio to medically managed patients.

With the knowledge of Chapter 2 carried forward, it was important to investigate the current prescribing habits of clinicians in UK glaucoma clinics. The clinician survey was developed to understand the rationale behind prescribing preserved drops in glaucoma clinics, as well as to determine clinicians' views towards OSD in glaucoma clinics.

Results of the survey revealed that on the whole, clinicians understand that OSD is a prevalent issue in their glaucoma clinics, with 93% regarding OSD an important factor when prescribing and managing glaucoma in a new patient. However, certain constraints such as cost, affect the

clinical prescribing habits of clinicians, and so preserved latanoprost is still the leading choice for first line therapy amongst a large proportion of clinicians (78%).

The survey did highlight that prescribing and management in glaucoma clinics is disproportionate amongst clinicians, and appears to be influenced by the age of the clinicians, the role of the individual as well as the number of years the clinician has been qualified. Such differences in management can translate into disparity within care and affect adherence in patients attending glaucoma clinics, depending on which clinician they see.

In addition, the survey revealed that patient education is lacking in glaucoma clinics. In the present survey, 22% of clinicians admitted that they do not teach their patients the drop instillation technique, with 29% not issuing written information about the drops on diagnosis, with a further 32% only issuing leaflets if they are available.

It is clear from the survey that OSD is a known concurrent problem in the management of glaucoma, and though clinicians would likely consider PF drops in those even without OSD, cost appears to be the biggest barrier to this. It is also evident that patient education is an area which needs to be improved and become more consistent amongst different clinicians. This survey provided a clinician's perspective on the matter; however, in order to form the whole picture, it was necessary to investigate how such clinical decisions are impacting patients in clinics.

The curiosity of this led to the development of the patient survey in Chapter 4. The aim of this survey was to investigate adherence to glaucoma and OHT medication. Unlike previous studies investigating factors contributing to non-adherence, the present survey focussed on two specific variables, which were topical issues highlighted in the clinician survey; patient education and symptoms of OSD. The objective of the patient survey was to assess the impact of these variables on adherence rates in the UK.

The survey was split into two cohorts; the first being a national cohort of glaucoma and OHT patients, and the second, a cohort based at Corbett Hospital (Dudley NHS Trust, UK) in the West Midlands. For the national cohort, 12 participants skipped the question about missed doses, which could potentially disguise the real adherence rates if those 12 participants were in fact non-adherent. Taking this into account, a range of adherence rates was calculated for the national cohort, which was 63%-76%, with the lower percentage assuming that those who skipped the question did so due to non-adherence. For the hospital cohort, all participants

answered the question regarding missed doses, and the adherence rate for this group was slightly higher at 79%.

Though the adherence rates for both cohorts were slightly higher for those who felt they had sufficient information at diagnosis, this association was not significant for the hospital cohort [X2 (1, N = 63)=0.211 (p=0.646)] or for the national cohort [X2 (1, N = 54)=0.120 (p=0.730)]. Similarly, though percentage differences indicate that those with symptoms on instillation of drops are less adherent, this relationship was not significant for the national cohort [X^2 (1, N = 55)=0.720 (p=0.396)] or the hospital cohort [X^2 (1, N = 63)=1.078 (p=0.300)].

Unfortunately, due to the low number of participants within each subgroup of each cohort, the survey lacks the power to draw out conclusive results. Future studies in this area should aim to drive participant responses, and study adherence using a combination of objective and subjective measures. Adherence is difficult to accurately quantify, but it remains a pivotal topic in the treatment for glaucoma and OHT.

There appears to be much room for improvement in terms of patient education. A high proportion of patients are not taught drop instillation techniques, they feel they did not receive adequate information prior to starting treatment and many do not have a system in place to remind them to take their drops. Although the survey did not reflect better adherence in those better educated, in the long run, patient satisfaction could translate to better adherence. Further research is needed in this area.

Having identified the issue of OSD in glaucoma clinics, Chapter 5 went on to examine if there are any predisposing factors making some individuals more susceptible to developing OSD. Since cost appears to be the major barrier in preventing the prescription of PF treatment, it was important to establish which individuals would benefit from PF treatment at diagnosis, to allow for the best cost-effective management of glaucoma and OHT.

The retrospective audit of Chapter 5 revealed that 40% of patients were diagnosed with OSD at some point during their glaucoma or OHT journey, and most patients were diagnosed with OSD within the first 12 months of their medical management. The prescribing of PF drops appeared to be mismatched; only 25% changed to PF treatment in the course of the treatment.

Surprisingly, 84% of patients had no anterior eye signs recorded at the first visit, and 90% had no anterior eye signs recorded at their second/diagnosis visit. It is difficult to ascertain whether this omission was due to the true lack of OSD signs, or whether it was simply not checked. This

suggests that there needs to be a better system in place for monitoring and checking the ocular surface at each appointment in these clinics.

As for known risk factors, smoking, alcohol consumption and allergies appeared to be more prevalent amongst patients in the group that were changed to PF treatment

Female sex and aging appeared to be highly prevalent in glaucoma clinics. At least 50% of the patients in each group were females and over 65. A high proportion of patients over 65 years old were in the group that were prescribed PF drops from day 1 (76.5%).

In terms of predictive factors, a higher proportion of patients on polypharmacy were prescribed PF drops on day 1. Those with hypertension or 'other' anterior eye signs were more likely to be placed in the group that were changed to PF treatment or those that were placed on PF from day 1. Interestingly, the average baseline IOPs were higher in the group that needed changing to PF treatment. Cup-to-disc ration (CDR) of >0.5 was also more common in this group (76%). Patients with thicker than average central corneal thickness (CCT) were more common in the 'changed to PF' group, while patients with thinner than average CCT were more common in the 'not changed to PF' group.

All of these elements could be of predictive value, however, there is a need to have larger sample sizes, equally distributed within the groups, to make fair and more accurate comparisons. This study showed that there are predictive indicators, but further investigation is needed, ideally by means of a prospective, longitudinal study following treated glaucoma and OHT patients from diagnosis.

This study also highlighted the lack of anterior eye checks both before and during treatment. The need for OSD to be investigated prior to treatment is essential, since the prevalence of OSD within glaucoma clinics may be underestimated unless patients are symptomatic and report this. Furthermore, to date, there are no published prevalence rates of OSD within glaucoma clinics, prior to treatment. Discovery of these rates would provide for better long-term management, by ensuring patients are prescribed the most suitable therapy at diagnosis based on the status of their ocular surface.

With the findings of Chapter 5 highlighting such gaps, Chapters 6 and 7 were synthesised to address these shortcomings. The development of the Enhanced Glaucoma Clinic (EGC) at Russells Hall Hospital (Dudley NHS Trust, UK) in the West Midlands, was brought about to a) provide enhanced ocular surface assessments at baseline and follow up to glaucoma and OHT

patients and b) to take some pressure off the usual glaucoma clinics, particularly in the midst of the global COVID-19 pandemic.

The EGC was easily implemented at a UK hospital and provides confirmation that simpler cases of OHT and glaucoma can be managed by specialised optometrists under the supervision of lead consultants, which provides some relief to the busy ophthalmology clinics which have huge backlogs of patients due to the pandemic.

In addition, the data in these clinics was analysed in retrospect to investigate two pressing issues as underlined by the previous chapters: what is the prevalence of OSD prior to ocular hypotensive treatment, and are there predictive factors at baseline, which put some individuals in a predisposition to developing OSD?

Results of the Chapter 6 study confirm that the levels of OSD and dry eye disease (DED) are high in glaucoma clinics. The prevalence of OSD was found to be 97% vs 100% vs 100% amongst new, follow up and treated patients presenting to the EGC, respectively. This translated to symptoms in 42% of new patients and 36% of treated patients. Since no patient in the follow up group presented symptoms, the prevalence of DED was classed at 0% for this group. The rates vary in the literature and depend on which diagnostic tests are used and how symptom assessment is made. In the present study, the diagnostic tool from the TFOS DEWS II Diagnostic Methodology report was used to make such judgement (Wolffsohn et al., 2017).

Overall, average tear osmolarity was within normal limits (<308mOsm/L) for treated, treatment naïve and suspect patients. However, at least 25% per group, for each eye, had an osmolarity readings of >307mOsms/L, suggesting that patients may be in the critical phase between asymptomatic and symptomatic OSD. The EGC also highlighted that the tear break-up-time (TBUT) reduced is for most patients presenting to the EGC, and this could be of clinical importance in the long-term management of such patients.

The pilot study of Chapter 7 followed on from this by investigating when and which patients convert to DED when treated for glaucoma or OHT. Unfortunately, the COVID-19 pandemic affected this study massively, resulting in a short study period, with low numbers of patients. Originally, these objectives were going to be met using a prospective, longitudinal study. With restrictions of the pandemic, the EGC data was analysed retrospectively to provide some scope on the topic.

Interestingly, for majority of the patients commenced on preserved treatment had a reduction is Ocular Surface Disease Index (OSDI) scores from baseline to month one. However, with such a short follow up, this is not representative of the typical glaucoma or OHT patient. The retrospective audit of Chapter 5 suggested that OSD is typically diagnosed within the first 12 months of treatment. Future studies should look at a minimum period of twelve months to allow for any changes to become apparent.

Clinically, baseline TBUT could be an indicator to conversion to OSD. The TBUT was less than 10 seconds for all but one of the patients included in the pilot study. Ten seconds was taken as the cut off according to the TFOS DEWS II Diagnostic Methodology report (Wolffsohn et al., 2017). The only patient who required changes to PF medication following preserved therapy had TBUT values of 2seconds for each eye. Perhaps lower TBUT values at baseline are a clinical indicator for the development of OSD in the course of preserved treatment for glaucoma or OHT. Of course, further research is needed, as one cannot make such assumptions based on the results of one individual. Also, a cut off criteria <5seconds may provide better diagnostic value for OSD, as illustrated in this current pilot study, and corroborated by previous studies (Bhandari et al., 2016, Hong et al., 2013). A TBUT lower than this value still, might be of clinical significance.

The tear osmolarity increased for 67% of patients who started on preserved medication. Though in this short study such findings did not convert into clinical outcomes, there is a need to observe this metric for longer treatment periods to analyse changes in trends in tear stability in the course of preserved therapy. An area of interest may be to evaluate the rate of change in tear osmolarity in the treatment journey, and perhaps higher rates may be an indicator in the likeliness of conversion to OSD.

There were two patients who were put on PF treatment at diagnosis. The OSDI for these individuals exceeded 20. This indicates that perhaps PF treatment in glaucoma clinics is symptoms led. One of the patients in this PF group was followed up and subsequently changed to PF combination therapy since IOPs had not sufficiently reduced. The OSDI did not improve after commencement of PF drops. There needs to be concurrent management of OSD and glaucoma, and in cases where baseline DED is evident and problematic, the introduction of any topical therapy is likely to aggravate the ocular surface further rather than heal it. Thus, there is a need to manage OSD at baseline in such individuals.

The current pilot study has provided a scope on the issue of OSD in newly treated glaucoma and OHT patients. Extrapolation of such a study into a prospective, long-term investigation has the ability to uncover predisposing clinical risk factors of OSD, as well as providing an insight to the point at which OSD becomes evident in treated glaucoma and OHT patients. Such discoveries have the potential to change the paradigm of the concurrent management of glaucoma/OHT and OSD.

8.2 Limitations and future work

Much of the clinical research in this current thesis has been impeded by the COVID-19 pandemic. The restrictions which came with the pandemic made a hospital-based investigation near impossible to achieve. Clinics were cancelled, patients were reluctant to attend appointments, staff were redeployed, and the hospital Research and Development department were inundated with COVID-19 related work, all of which hindered data collection.

Attempts have been made to investigate the aims of the thesis using the resources which were available, with surveys and smaller clinics towards the end of the pandemic, but this has resulted in data which is too low in numbers, and of short durations. It is therefore difficult to apply the findings of this work to the general glaucoma and OHT population with much confidence.

Though there was paucity in the data collected in Chapter 6, which looked at the prevalence of OSD and DED in treated and untreated glaucoma and OHT patients, the outcomes of this study warrant further investigation. The data suggests that starting topical treatment for glaucoma or OHT does not influence the prevalence of OSD or DED. However, given the small sample size and short study period, it is possible that the data has been skewed by confounding variables. As one of the main hypotheses of this thesis was to test the notion that topical treatment precipitates DED, it is vital that this idea is re-assessed and a repeat of the study in Chapter 6 is conducted using a larger sample size, which would be powered enough to allow accurate conclusions to be drawn. Depending on the outcomes of this repeat investigation, a redesign and repetition of the study in Chapter 7 may be necessary to determine which factors are predictive to developing DED in the course of treatment.

Nonetheless, the current research has highlighted some potential patterns and trends that do require further investigation. Future work should look at large-scale, prospective studies following the treatment journeys from the beginning of patients on preserved and PF treatment.

Baseline characteristics such as demographics, comorbidities, medication and clinical metrics should all be evaluated in those who go on to develop DED and compared with those who do not. Such comparisons and evaluations could help to highlight cumulative risk factors for DED in medically treated glaucoma patients.

These risk factors could help to form an algorithm for the diagnosis and treatment of glaucomatous patients in relation to the ocular surface. The ultimate goal of this research would be to design a risk calculator much like the predictive models used in 'OHT to POAG' conversion calculators (Ocular Hypertension Treatment Study and the European Glaucoma Prevention Study, 2008, Miglior et al., 2005, Kass et al., 2002). Attempts have been made to form 'decision algorithms', to help establish who is most likely to benefit from PF ocular hypotensive therapy, with an assumption that around 20% of patients fall into this group (Stalmans et al., 2013). However, such predictive models require power from large scale, long-term studies in order to establish themselves in the clinical world. Future research in this area is welcomed.

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Appendices

1. Methodology table of systematic review

Author & Year	Device used to measure IOP	Consistency of measurement time	Symptoms assessed	Method of recording symptoms	Ocular Signs assessed	Instrumentation used to assess ocular surface	Randomisa-tion	Masked	Sample size determina-tion
(Aptel et al., 2016)	GAT	Set times stated: a 08:00, 12:00, 16:00, and 20:00 (±30 minutes). On days 0, 42 and 84.	●pruritus ●burning/ stinging ●blurred vision ●sticky eye sensation ●foreign body sensation ●eye dryness sensation ●irritation ●itching ●tearing ●photophobia	Number of patients reporting symptoms. Subgroups of severity and frequency of symptoms recorded too.	●conjunctival hyperaemia ●folliculo-papillary conjunctivitis ●palpebral abnormality ●punctate corneal staining ●anterior chamber flare	●Slit lamp with Fluorescein ●Conjunctival Hyperaemia graded using a descriptive scale	Patients	●Investigator ●Patients	No sample size calculation performed

(Baudouin and de Lunardo, 1998)	AT	Set times stated: 30, 60, 180 minutes after 1st instillation and 8 hours after very last instillation	●Immediate tolerance/irritation ●Subjective sensations of itching, burning, foreign body sensation, and photophobia	●Tolerance/Irritation recorded using a visual analogue scale score ●Subjective symptoms recorded using scoring system of intensity ranging from 0 to 3	●TBUT ●Fluorescein staining ●Schirmer's test	●Slit lamp with Fluorescein ●No other instruments specified	Subjects	●Investigator ●Patients	No sample size calculation performed
(Ciancaglini et al., 2008)	N/A	N/A	N/A	N/A	N/A	N/A	Patients	●Patients	Sample size calculated
(Day et al., 2013)	GAT	Set times stated: 8:00, 10:00 and 16:00	●Dry Eye ●Pruritus ●FB sensation	Number of patients reporting symptoms.	●Conjunctival hyperaemia ●Punctate Keratitis	●Slit Lamp ●Conjunctival hyperaemia graded using standard photographs ●Punctate Keratitis	Patients	●Investigator ●Patients	Sample size calculated

						grading scale not specified			
(Easty et al., 2006)	GAT	Not specified. Taken at H0 (before instillation) and H2 (2 hours after instillation).	●Irritation/burning/ stinging ●Eye dryness ●Foreign body sensation ●Blurred vision	Number of patients reporting symptoms.	●Palpebral abnormality ●conjunctival hyperaemia ●folliculo-papillary conjunctivitis ●corneal staining punctuations ●anterior chamber flare	●Slit lamp ●Grading of conjunctival hyperaemia not specified	Patients	Open design/masking not possible	Sample size calculated

(Goldberg et al., 2014)	GAT	Set times stated: 08.00, 10.00, 16.00, measured at each visit (baseline, week 2, week 6, week 12).	●Pruritus ●Dry eye ●Eye pain ●Eye irritation ●Foreign body sensation ●Erythema of eyelid	Number of patients reporting symptoms.	●Conjunctival hyperaemia ●Punctate Keratitis	●Slit lamp ●Conjunctival hyperaemia graded using standard photographs and gross inspection ●Punctate keratitis grading not specified	Patients	●Investigator ●Patients	Sample size calculated
(Gómez-Aguayo et al., 2018)	GAT	Set times stated: Hour 0 and Hour 2	●Itching ●Burning ●Pain ●Dryness ●FB sensation ●Tearing	●Number of patients reporting symptoms (Tearning, FB sensation, Burning) ●Ocular comfort questionnaire (Burning,	●Conjunctival hyperaemia ●TBUT	●Slit lamp with Fluorescein ●Abnormal findings of ocular surface graded as mild, moderate or severe ●TBUT method not specified	Patients	●Investigator ●Patients	Sample size calculated

				itching, dryness, pain)					
(Hamacher et al., 2008)	AT	Set times stated: 08.00,12.00, 16.00 and 20.00	●Pruritus ●FB sensation ●Eye pain ●Increased Lacrimation ●Blurred vision	Number of patients reporting symptoms	●Conjunctival hyperaemia ●Ocular hyperaemia ●Erythema of eyelid ●Anterior chamber cells ●Blepharitis ●Punctate Keratitis	●Slit Lamp ●Grading not specified	Patients	●Investigator ●Patients	Sample size calculated
(Konstas et al., 2013)	●GAT ●Perkins	Set times stated: 10:00, 14:00, 18:00 and 22:00 (GAT) 02:00 and 06:00	●Stinging ●FB sensation ●Itching ●Watering ●Blurred vision	Number of patients reporting symptoms	●Ocular hyperaemia	Not specified	Patients	●Investigator ●Patients	No sample size calculation performed

		(Perkins) (±1 h)	●Ocular ache ●Burning						
(Kumar et al., 2018)	GAT	11am±30 minutes at each visit	N/A	N/A	●TBUT ●Hyperaemia	●Slit Lamp ●TBUT- Fluorescein used and break up measured between blinks ●Hyperaemia graded using photographic standards and recorded as scores	Patients	Not specified	Sample size calculated

(Lee et al., 2017)	GAT	Set times stated: 9:00 am to 12:00 pm	●Stinging ●Itching ●Dryness ●FB sensation	Modified OSDI	●TBUT ●Corneal erosion ●Schirmer	●TBUT-Fluorescein used and break up measured between blinks ●Corneal erosion-scale used according to area of erosion ●Schirmer-tear secretion checked after 5 minutes using Schirmer test paper	Patients	●Investigator ●Patients	Sample size calculated

(Manni et al., 2005)	GAT	9am ±1 hour at each visit	N/A	N/A	●Conjunctival hyperaemia ●TBUT ●Corneal staining	●Slit lamp ● Conjunctival hyperaemia-graded using standard photographic chart ●TBUT-Fluorescein used and break up measured between blinks ●Corneal staining-using fluorescein, noting down presence or absence. Grading scale not used.	Patients	Single masked	Not mentioned
(Mastropasqua et al., 2013)	GAT	Not specified	Not specified	OSDI questionnaire	●TBUT ●Schirmer test	●Slit Lamp	Patients	●Observer	Not mentioned

(Mastropasqua et al., 2014)	GAT	Not specified	N/A	N/A	N/A	N/A	Patients	●Observer	Not mentioned
(Rouland et al., 2013)	GAT	09:00 am±1h at each visit	●Pruritus ●Burning/ stinging ●Blurred vision ●Sticky eye sensation ●Eye dryness sensation ●FB sensation	Ocular symptom score	●Conjunctival hyperaemia ●Corneal staining	●Slit lamp ●Conjunctival hyperaemia- graded using photographic scale (McMonnies grading) ●Biomicroscopic findings graded on a 4 point scale: none, mild, moderate, severe	Patients	●Investigator	Not mentioned

(Shedden et al., 2010)	GAT	Set times stated: ~ 8:30 a.m., prior to the morning dose (hour 0; trough drug level) and 11:00 a.m. (hour 2; peak drug level)	●Irritation/ Burning	Number of patients reporting symptoms	●Conjunctival hyperaemia ●Corneal staining ●Punctate keratitis	Not specified	Patients	Double masked	Sample size calculated
(Stevens et al., 2012)	Not specified	N/A	N/A	N/A	N/A	N/A	Patients	Single masked-operator	Sample size calculated
(Uusitalo et al., 2008)	AT	Not specified	●Eye pain ●Pruritis ●Irritation ●FB sensation ●Erythema of eyelid ●Eyelid sensory disorder ●Eyelid	Number of patients reporting symptoms	●Conjunctival hyperaemia	●Slit lamp ●Conjunctival hyperaemia grading method not specified	Subjects	●Investigator	Not mentioned

			oedema ●Increased lacrimation ●Photophobia						
(Duru and Ozsaygili, 2020)	GAT	9.00-10.00am at each visit, ~30 minutes after drop instillation	●Pain ●Blurred Vision ●Stinging ●Burning ●Itching ●Tearing ●Photophobia	Mean symptom score on a scale of 0 to 4 (0=no discomfort, 4=severe discomfort)	●TBUT ●Schirmer test	Not specified	Eyes	Not specified	Not mentioned
(Mohammed et al., 2020)	Not specified	Not specified	Not specified	OSDI questionnaire	N/A	N/A	Patients	Not possible of patients and clinicians. Masking of tear and IC samples though.	Estimated using previous studies

(Denis et al., 1993)	GAT	Measured between 7-10am	N/A	N/A	Unable to establish	Unable to establish	Patients	Double blind	
(Denis, 2016)	GAT	Three IOP measurements were made at each visit at the same time and using the same technique'	●dryness ●irritation/ stinging/ burning ●itching ●watery eyes ●sensation of foreign body ●sensitivity to light	Subjective grading by patient on the following scale: 0= None 1= Present but not disturbing 2= Disturbing 3= Very disturbing	Modification of iris pigmentation -Normal aspect of lashes (hypertrichosis) -Abnormal coloration of eyelids -Eyelids abnormalities -Follicular Papillary Conjunctivitis -Anterior chamber inflammation	●Slit lamp ●Efron Scale (Grad 0-4)		Not possible due to vials of single dose vs multidose	

					-Positive cornea fluorescein staining -Conjunctival hyperaemia				

2. Characteristics table of systematic review

Author & Year	Country	Sample Size	Participant Demographics	Intervention	Methods	Main Outcomes	Additional comments/ Limitations
(Ciancaglini et al., 2008)	Italy	Twenty-seven white patients	**Group 1** -8 Male, 6 Female -Age range: 54±8.34 -POAG 9, OHT 5 **Group 2** -6 Male, 7 Female -Age range: 52±7.23 -POAG 6, OHT 7	**Group 1** preserved levobunolol hydrochloride 0.5% (Vistagan®) **Group 2** preservative-free levobunolol hydrochloride 0.5% (Vistagan®) -Drops administrated	-*In vivo* confocal microscopy (IVCM) -Impression cytology	**a)IVCM** **Group 1** Index of epithelial regularity*: 3 at baseline, 34 at 6 months ($p<0.001$) Goblet cell density: 88.1±45.2 at baseline, 25.2±4.5 (39%) at 6 months ($p<0.001$) Goblet cell density decrease from baseline: 61% **Group 2:** Index of epithelial regularity*: 4 at baseline, 8 at 6 months ($p<0.001$)	-Study was single masked -no controls -The microscopic changes induced from treatment, suggest toxicity from preserved levobunolol -There are significant changes in the unpreserved group too,

				once daily (between 7:00 and 9:00 am).		Goblet cell density: 90.0±45.8 at baseline, 75.4±48.7 (83%) at 6 months (p<0.001) Goblet cell density decrease from baseline: 17% **b)Impression Cytology** **Group 1** 7 at baseline, 39 at 6 months* (p<0.001) **Group 2:** 9 at baseline, 6 t 6 months* (p<0.001) (*cumulative scores)	suggesting toxicity -Changes are significantly worse in Group 1 compared to Group 2 (p<0.001), and the changes are significant in both groups from baseline (p<0.001)
(Hamacher et al., 2008)	Germany and Finland	43 patients with Intention to treat (ITT). The per	-16 male, 27 female -Mean age of patients:	-Crossover study 1. Screening 2. Washout period 3. Baseline visit 1	-IOP -Adverse events	**a)IOP** **Treatment differences (PF vs P) post baseline at weeks 1 and 4**	-Randomisation by permutation blocks -Limitations=Small scale study

		protocol (PP) included 41 patients.	65.3 years (range 35–85 years) -all participants white No of eyes with: -POAG 26 RE 28 LE -OHT 14 RE 13 LE -Capsular glaucoma 3 RE 1 LE -Normal 0 RE 1 LE	-**Group 1**- Tafluprost 0.0015% (preserved) to be instilled once a day for 4 weeks -**Group 2**- Tafluprost 0.0015% PF (unpreserved) to be instilled once a day for 4 weeks 4.Washout 5. Baseline visit 2 6. Crossover in treatment between groups 1 and 2		**Week 1** 08.00 hours -0.32 12.00 hours -0.25 16.00 hours -0.39 20.00 hours -0.13 **Week 4** 08.00 hours 0.24 12.00 hours 0.11 16.00 hours 0.00 20.00 hours -0.30 **b)Adverse effects**	- Pharmacodynamic study -Preserved Tafluprost and PF tafluprost are equally effective in lowering IOP and maintaining the reduced IOP levels over a 4-week period. -The incidence of adverse events similar in both groups (though it was slightly higher in the PF group), and reactions

				Visits at the end of week 1 and week 4 as well		11 (25.6%) on PF treatment, and 7 (16.7%) on preserved treatment experienced adverse events. Of the total 31 adverse events reported, 27 (87.1%) were ocular and 4 (12.9%) non-ocular. Most common adverse event was conjunctival hyperaemia.	were mild, and mostly ocular.
(Lee et al., 2017)	Seoul, South Korea	20 patients (20 eyes)	-10 males, 10 females, 5 of each sex in each group -Mean age of 55.26 ± 14.22 years	**Group 1 NPT to PT** (n=10) 1st 6 months using non- preserved treatment of 0.0015% tafluprost	-IOP -Subjective discomfort -Corneal erosion (staining) grade -Schirmer test	**a)IOP** Mean IOP at baseline: 16.84 ± 2.75 mmHg Mean IOP at 12 months: 14.85 ± 3.05 mmHg After commencing Tafluprost treatment, IOP well maintained for 12 months	-Simple randomisation by sequential enrolment through flipping a coin. -No washout period between treatments.

				(Taflotan-S® unit dose) then changed to preserved treatment of 0.0015% tafluprost (Taflotan®) containing 0.001% Benzalkonium chloride (BAK) for 6 months. **Group 2 PT to NPT** (n=10) 1st 6 months using preserved treatment of	-TBUT	**b)Subjective discomfort (points 0 to 3)** **Group 1 NPT to PT** At start: 0.70 ± 0.67 At 1 month: 1.87 ± 1.24 p = 0.02* At 6 months: 0.80 ± 1.39 p = 0.91* At 7 months: 0.50 ± 0.83 p > 0.99* p = 0.31† At 12 months: 0.60 ± 0.89 p = 0.78* p > 0.99† **Group 2 PT to NPT** At start: 1.33 ± 1.00 At 1 month: 1.55 ± 1.66 p = 0.34* At 6 months: 1.14 ± 0.69 p = 0.24* At 7 months: 1.60 ± 2.07 p = 0.10* p = 0.56†	-Double blind -It is possible that conjunctival hyperaemia may be the cause of subjective discomfort as even starting NPT increased the scores. -Conjunctival injection appears to be the most common adverse reaction to prostaglandin analogues, and is most severe in the first 2

				Taflotan® and then changed to non-preserved treatment of Taflotan-S® for 6 months. All tafluprost treatments were to be instilled one a day. Follow up tests and questionnaires at 1, 3 and 6 months for each treatment path and after the changeover too.		At 12 months: 0.87 ± 1.72 p = 0.08* p = 0.03† **c)Corneal erosion (staining) grade** **Group 1 NPT to PT** At start: 0.30 ± 0.48 At 1 month: 0.25 ± 0.46 p = 0.56* At 6 months: 0.40 ± 0.51 p = 0.56* At 7 months: 0.50 ± 0.54 p = 0.56* p > 0.99† At 12 months: 0.60 ± 0.54 p = 0.31* p = 0.56 **Group 2 PT to NPT** At start: 0.55 ± 0.52 At 1 month: 0.33 ± 0.50 p = 0.15* At 6 months: 0.14 ± 0.37 p = 0.15*	weeks of treatment, which would explain relief of symptoms after 3 months. -Short term study and small sample size -Crossover study so covariates controlled. -No controls needed as each participant acted as their own control -However, results could have been

						At 7 months: 0.80 ± 0.83 p > 0.99* p = 0.15† At 12 months: 0.25 ± 0.46 p = 0.18* p > 0.99† **d)Schirmer test** **Group 1 NPT to PT** At start: 5.80 ± 3.88 At 1 month: 2.62 ± 2.87 p = 0.20* At 6 months: 4.60 ± 3.97 p = 0.40* At 7 months: 4.83 ± 6.27 p = 0.34* p = 0.58† At 12 months: 4.60 ± 4.56 p = 0.34* p = 0.78† **Group 2 PT to NPT** At start: 3.33 ± 3.04 At 1 month: 5.66 ± 7.01 p = 0.88* At 6 months: 5.14 ± 3.67 p = 0.40*	impacted by treatment order, and over time, patients will have become better at drop instillation. -Tafluprost 0.015% is effective at reducing IOP, irrespective of containing preservative or not.

						At 7 months: 4.40 ± 1.34 p = 0.46* p = 0.70† At 12 months: 5.00 ± 3.02 p = 0.23* p = 0.73† **e)TBUT (secs)** **Group 1 NPT to PT** At start: 5.80 ± 2.39 At 1 month: 3.25 ± 1.28 p = 0.03* At 6 months: 5.00 ± 1.88 p = 0.32* At 7 months: 4.83 ± 1.16 p = 0.28* p = 0.71† At 12 months: 3.60 ± 2.07 p = 0.06* p = 0.85† **Group 2 PT to NPT** At start: 4.55 ± 2.18 At 1 month: 5.44 ± 2.29 p = 0.16* At 6 months: 4.42 ± 1.71 p = 0.71*	

						At 7 months: 4.14 ± 1.06 p = 0.67* p = 0.48† At 12 months: 4.75 ± 1.83 p = 0.60* p = 0.52† *compared with baseline prior to start of therapy †compared with 6 months, prior to changing therapy	
(Uusitalo et al., 2008)	Finland	-16 healthy volun-teers	-9 women, 7 men -All volunteers were white -all volunteers Caucasian -Mean age of 29.2 years	-Crossover study 1. Screening and baseline visit Randomised into the 2 sequential groups: **Group 1** Preserved Tafluprost 0.015% instilled in both eyes once a day	-Tafluprost acid concentrations determined by high-performance liquid chromatography with tandem mass	**Adverse events** **Preserved therapy (n=16):** 36 total adverse events, 29 of those ocular, 7 non-ocular. **Preservative-free therapy (n=16):** 27 total adverse events, 24 of those ocular, 3 non-ocular. Most common adverse event for both groups was ocular hyperaemia.	-Randomisation by permuted blocks -Tafluprost 0.015%, both with and without BAK preservative, show similar safety, efficacy and pharmacokinetic profiles.

				(at 8pm), for 8 days **Group 2** Preservative-free Tafluprost 0.015% instilled once a day in both eyes(at 8pm), for 8 days 2. Washout period of 4 weeks 3.Crossover-> Group 1 to commence PF treatment for 8 days, and Group 2 to commence preserved treatment for 8 days	spectrometric (MS/MS) detection -Adverse events	**Pharmacokinetic Outcomes** AUC0–last = area under curve (time 0 to last measurable value); Cmax = maximum concentration; SD = standard deviation; tmax = time to maximum concentration. **Day 1** **Preserved therapy** AUC0–last *(pg/ml/min)*: 405.9 ± 395.2 Mean ± SD Cmax *(pg/ml)* Mean ± SD: 24.4 ± 15.8 tmax *(mins)* Mean *(range)*: 10 (10–15) **Preservative-free therapy** AUC0–last *(pg/ml/min)*: 394.3 ± 286.4 Mean ± SD	-IOP reductions from both therapies were similar over the course of the study. -Plasma concentrations of tafluprost acid were low across all time points, peaking at 10 minutes and falling to below quantifiable levels within an hour of instillation, for both groups. -No statistical differences

				4. Post study visit 1-3 weeks after completion of second phase treatment.		Cmax *(pg/ml)* Mean ± SD: 26.2 ± 10.4 tmax *(mins*) Mean *(range)*: 10 (5–15) **Day 8** **Preserved therapy** AUC0–last *(pg/ml/min)*: 581.1 ± 529.9 Mean ± SD Cmax *(pg/ml)* Mean ± SD: 31.4 ± 19.5 tmax *(mins)* Mean *(range)*: 10 (5–15) **Preservative-free therapy** AUC0–last *(pg/ml/min)*: 431.9 ± 457.8 Mean ± SD Cmax *(pg/ml)* Mean ± SD: 26.6 ± 18.0 tmax *(mins)* Mean *(range)*: 10 (5–15)	were found between the two groups of therapy, in terms of AUC0–last, Cmax and tmax at days 1 and 8.

<table>
<tr>
<td>(Mastropasqua et al., 2013)</td>
<td>Italy</td>
<td>-30 eyes of 30 patients with newly diagno-sed POAG, and naïve to hypoten-sive treat-ment

-30 healthy partici-pants served as controls</td>
<td>-All Caucasian

Group 1

-Mean age 51.06 ± 6.94 years

-8 male, 7 female

Group 2

-Mean age 49.25 ± 9.68 years

-9 male, 6 female

Group 3

-Mean age 53.5 ± 7.43 years

-5 male, 10 female

Group 4</td>
<td>Treatment groups

Group 1 (n=15)

PF tafluprost 0.0015% (Taflotan), instilled once a day at 9pm

Group 2 (n=15)

Latanoprost 0.005% (Xalatan), instilled once a day at 9pm

Control groups

Group 3 (n=15)</td>
<td>-Laser scanning confocal microscopy (LSCM)

-Impression cytology (IC)

-OSDI questionnaire

-TBUT

-Schirmer I

-IOP</td>
<td>LSCM (cells⁄mm2)

<table><tr><th>Group</th><th>Baseline</th><th>1 month</th><th>6 month</th></tr><tr><td>1</td><td>240.69 ± 25.44</td><td>284.16 ± 43.88</td><td>282.8 ± 47.69</td></tr><tr><td>2</td><td>232.65 ± 23.50</td><td>297.86 ± 26.87</td><td>227.55 ± 26.13</td></tr><tr><td>3</td><td>237.71 ± 27.98</td><td>205.88 ± 25.04</td><td>166.32 ± 22.31</td></tr><tr><td>4</td><td>240.98 ± 24.36</td><td>238.68 ± 25.33</td><td>235 ± 28.44</td></tr></table>
IC (cells⁄mm2)

<table><tr><th>Group</th><th>Baseline</th><th>1 month</th><th>6 month</th></tr><tr><td>1</td><td>162.10 ± 23.44</td><td>230.62 ± 48.32</td><td>237.96 ± 52.12</td></tr><tr><td>2</td><td>164.71 ± 21.03</td><td>221.78 ± 43.02</td><td>156.06 ± 16.68</td></tr><tr><td>3</td><td>155.44 ± 15.14</td><td>139.54 ± 17.37</td><td>120.76 ± 11.66</td></tr></table></td>
<td>-Computer generated randomisation

-Limitations as small sample size, and pilot study.

-Goblet cell density (GBD) appears to increase initially for groups 1 and 2 (at 1 month), which may be linked to PG derivatives' ability to trigger mucin secretion and cell proliferation.</td>
</tr>
</table>

			-Mean age 51.45 ± 9.65 years -9 male, 6 female	Vehicle of latanoprost including BAK 0.02%, instilled once a day at 9pm **Group 4 (n=15)** Physiological buffered saline (PBS) solution, instilled once a day at 9pm						-PF Tafluprost sustains this increased GCD, whereas preserved Latanoprost shows a decrease by month 6, which may be linked to the negative effects of BAK, as can be illustrated by the decrease in GCD in Group 3 across the whole study. -The study may have provided better comparisons had it included

4	155.31 ± 16.8	159.06 ± 19.95	157.06 ± 15.28

TBUT (secs)

Group	**Baseline**	**1 month**	**6 month**
1	11.5 ± 1.93	12.06 ± 1.98	12.12 ± 2.41
2	12.06 ± 1.80	12.62 ± 1.92	10.18 ± 1.47
3	12.62 ± 1.54	8.43 ± 1.03	6.43 ± 1.26
4	12.06 ± 1.80	12.87 ± 1.2	13.5 ± 1.75

Schirmer I (mm)

Group	**Baseline**	**1 month**	**6 month**
1	16.68 ± 2.86	16.75 ± 2.35	15.87 ± 1.66
2	17.06 ± 2.11	17.56 ± 2.44	14 ± 2.19

3	17.96 ± 3.2	12.12 ± 1.78	9.06 ± 1.52
4	17.06 ± 2.11	17.56 ± 1.34	17.5 ± 1.86

OSDI scores

Group	**Baseline**	**1 month**	**6 month**
1	4.55 ± 2.54	4.68 ± 2.99	5.85 ± 4.18
2	5.46 ± 2.93	8.58 ± 4.15	12.75 ± 4.8
3	4.42 ± 2.26	13.51 ± 7.69	36.32 ± 13.22
4	4.55 ± 2.3	6.99 ± 5.85	5.59 ± 3.28

IOP

For Group 1, IOP changed from 24.68 ± 2.02mmHg at baseline, to 17.0 ± 0.89mmHg at 6 months. For Group 2, the IOP changed from 24.75 ± 1.94mmHg at baseline, to 16.68 ± 1.4 mmHg at 6 months.

preserved Tafluprost than preserved Latanoprost.

<table>
<tr>
<td>(Mastropasqua et al., 2014b)</td>
<td>Italy</td>
<td>-80 eyes of 80 patients, newly diagnosed with POAG and naïve to hypotensive treatment

-30 eyes of 30 healthy subjects, acting as controls.</td>
<td>Group 1

-Mean age 57.80±4.52 years

-12 male, 8 female

Group 2

-Mean age 59±3.65 years

-10 male, 10 female

Group 3

-Mean age 54±5.50 years</td>
<td>POAG subjects

Group 1 (n=20): PF-Latanoprost 0.005 % (Optigen) instilled once a day at 9 PM

Group 2 (n=20):

Latanoprost 0.005 % (Xalatan) instilled once a day at 9 PM

Group 3 (n=20):

PF-timolol 0.5 % (Timolol Novartis) instilled twice a day at 8am and 8pm

Group 4 (n=20):</td>
<td>-LSCM looking at the following parameters:

a) mean microcyst density (MMD, cysts/mm2)

b) mean microcyst area (MMA, µm2)

-IOP</td>
<td>IOP (mmHg ±SD)

<table>
<tr><th>Group</th><th>Baseline</th><th>1 month</th><th>3 month</th></tr>
<tr><td>1</td><td>25.96±2.16</td><td>16.54±

1.58*§</td><td>16.34±

2.03*§</td></tr>
<tr><td>2</td><td>25.98±1.39</td><td>16.16±
1.5*§</td><td>16.45±
1.7*§</td></tr>
<tr><td>3</td><td>25.52±1.65</td><td>17.98±
0.96*</td><td>17.85±
1.34*</td></tr>
<tr><td>4</td><td>25.95±1.52</td><td>18.25±
1.01*</td><td>18.84±
1.23*</td></tr>
<tr><td>5</td><td>16.53±
2.89†</td><td>16.82±
1.94</td><td>16.65±2.53</td></tr>
<tr><td>6</td><td>17.02±
1.78†</td><td>16.87±
2.18</td><td>16.9±1.85</td></tr>
</table>

*p<0.05 vs. baseline

†p<0.05 vs. groups 1–4

§p<0.001 vs. groups 3–4</td>
<td>-Computer generated randomisation

-PGAs have significantly higher IOP reductions than beta-blockers

-Microcysts are indicators of aqueous humour outflow and generally appear unchanged unless exposed to medical and surgical stimuli.

-Exposure to PGA shows microcyst</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>-8 males, 12 females

Group 4

-Mean age 56.43±6.80 years
-9male, 11 female

Group 5

-Mean age 53.5±7.43 years
-5 male, 10 female

Group 6</td>
<td>Timolol 0.5 %, (Timoptol) instilled twice a day at 8am and 8pm

Healthy subjects

Group 5 (n=15):

Vehicle of Latanoprost including BAK 0.02 % instilled once a day at 9pm

Group 6 (n=15):

Physiological buffered saline</td>
<td></td>
<td>MMD (cysts/mm^2 ±SD)

<table><tr><th>Group</th><th>Baseline</th><th>3 month</th></tr><tr><td>1</td><td>20.81±3.92</td><td>21.9±3.22</td></tr><tr><td>2</td><td>21.2±5.39</td><td>23.94±4.91</td></tr><tr><td>3</td><td>21.22±5.36</td><td>21.075.21</td></tr><tr><td>4</td><td>21.25±6.09</td><td>21.56±5.53</td></tr><tr><td>5</td><td>14.82±3.32 †</td><td>14.53±4.12 †</td></tr><tr><td>6</td><td>15.53±3.4†</td><td>13.76±3.56 †</td></tr></table>
MMA (µm^2 ±SD)

<table><tr><th>Group</th><th>Baseline</th><th>3 month</th></tr><tr><td>1</td><td>2,158.81±524.03</td><td>3,877.77±867.31*</td></tr><tr><td>2</td><td>2,019.71±541.03</td><td>5,560.39±1,176.14*‡</td></tr></table></td>
<td>changes by 0.5-2 fold in terms of the cysts/mma^2, but not with beta blockers.

-Baseline MMD and MMA results are higher for glaucomatous patients, perhaps, due an adaptive mechanism.

-Limitation as we cannot be sure what the PGA related changes to CEM indicate exactly. It could</td>
</tr>
</table>

			-Mean age 51.45±9.65 years -9 male, 6 female	(PBS) solution instilled once a day at 9pm		<table><tr><td>3</td><td>2,093.07± 654.77</td><td>2,063.21± 451.44</td></tr><tr><td>4</td><td>2,150.08± 453.17</td><td>2,214.56± 507.50</td></tr><tr><td>5</td><td>1,582.19± 314.21†</td><td>1,660.63±2 81.42</td></tr><tr><td>6</td><td>1,499.65± 299.35†</td><td>1,530.03±2 95.47</td></tr></table> *p<0.001 vs. baseline, and vs. groups 3–6 †p<0.05 vs. groups 1–4 ‡p<0.001 vs. group 1		be an inflammatory response, or suggest alterations to pre-existing pathways, enhancing AH outflow. -MMA is a fixed unit measure, and so it is difficult to use it as a measurement of the dynamic aqueous outflow.

(Shedden et al., 2010)	USA	-261 patients in total -254 completed the full study (127 in each group)	**Preservative-free (PF) fixed combination (n=131)** -Mean age 56.0±15 years -67 female, 64 male -Mean trough IOP (0 hour) 23.7±1.5mmHg -Mean peak IOP (2 hour) 21.2±2.5mmHg **Preservative containing (PC) fixed**	1. Run in period: Stop all prior hypotensive treatment 3 weeks before trial and commence 0.5%timolol, to be administered twice a day (9am/bedtime). 2. Randomisation to the 2 treatment groups: **a) PF fixed combination (n=131)** dorzolamide 2%/timolol 0.5% combination (COSOPT™) to be instilled twice a	-IOP -Adverse events	**IOP** **PF Fixed combination Mean IOP (mmHg)** **Trough (Hour 0)** Week 2 : 21.3 Week 6 : 21.0 Week 12 : 20.8 **Peak (Hour 2)** Week 2 : 18.6 Week 6 : 18.4 Week 12 : 18.1 **PC Fixed combination Mean IOP (mmHg)** **Trough (Hour 0)**	-Computer generated randomisation -PF formulation seemed to cause fewer adverse reactions, so may be better tolerated. However, there is limitation in this statement, as Dorzolamide itself can cause stinging. -PF and PC fixed combination dorzolamide/timolol are equally as effective at

<table>
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<td>combination (n=130)

- Mean age 54.8±15.4 years

-87 female, 43 male

-Mean trough IOP (0 hour) 23.7±1.5mmHg

-Mean peak IOP (2 hour) 21.4±2.7mmHg</td>
<td>day at 9am and bedtime.

b) PC fixed combination (n=130)

dorzolamide 2%/timolol 0.5% combination (COSOPT™) to be instilled twice a day at 9am and bedtime.</td>
<td></td>
<td>Week 2 : 21.1

Week 6 : 21.2

Week 12 : 21.1

Peak (Hour 2)

Week 2 : 18.6

Week 6 : 18.4

Week 12 : 18.2

Adverse events (AE)

<table>
<tr><th>Type</th><th>PF FC</th><th>PC FC</th></tr>
<tr><td>Drug related AE</td><td>27</td><td>35</td></tr>
<tr><td>Discontinuation due to AE</td><td>4</td><td>3</td></tr>
</table>
</td>
<td>controlling IOPs.

-Some previous research has suggested that the inclusion of BAK in the formulation allows better penetration and so improves efficacy but the results of this study do not support this, as both formulations were equally as effective.</td>
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<td>
<table>
<tr><td>Ocular Burning/Stinging</td><td>21</td><td>28</td></tr>
<tr><td>Taste Perversion</td><td>4</td><td>7</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>(Aptel et al., 2016)</td>
<td>India</td>
<td>-30 patients</td>
<td>-Mean age 50.7 ± 12.8

-70% males

-30% females</td>
<td>Crossover study

1. Baseline visit (Day 0). Patients randomly assigned to receive either:

a) Preserved Latanoprost 0.005% (Xalatan) or

b) Preservative-free Latanoprost 0.005% (Monoprost)</td>
<td>-IOP

-Global efficacy determined by investigator

-Adverse events

-Ocular symptoms

-Global tolerance

-Plasma analysis by liquid</td>
<td>
Mean IOP (mmHg) after 6 weeks of treatment
<table>
<tr><th>Time</th><th>Baseline</th><th>Preserved Latanoprost</th><th>Preservative-Free Latanoprost</th></tr>
<tr><td>8am</td><td>22.8 ± 2.9</td><td>16.2 ± 2.9</td><td>16.6 ± 2.2</td></tr>
<tr><td>12pm</td><td>23.6 ± 3.6</td><td>16.4 ± 2.9</td><td>16.5 ± 2.6</td></tr>
<tr><td>4pm</td><td>22.6 ± 3.7</td><td>16.4 ± 3.0</td><td>15.9 ± 3.0</td></tr>
<tr><td>8pm</td><td>21.9 ± 4.4</td><td>16.6 ± 3.2</td><td>16.3 ± 3.3</td></tr>
<tr><td>Diurnal</td><td>22.7 ± 3.0</td><td>16.4 ± 2.6</td><td>16.3 ± 2.4</td></tr>
</table>
</td>
<td>-Small sample size

-Short duration of study

-No washout period between treatments

-Both preserved and preservative-free Latanoprost show no significant difference in</td>
</tr>
</table>

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<td></td>
<td>To be instilled at 8pm, once a day, for 6 weeks.

2. Visit 2 (Day 42)

After 6 weeks, the patients crossed over to the fellow treatment arm for the second phase of the study.

3. Visit 3 (Day 84)

The last visit after the second phase of treatment.</td>
<td>chromatography–

mass spectrometry</td>
<td>Compared to baseline measures, the diurnal data shows a reduction of 6.3 mmHg (27.9%) for preserved Latanoprost and 6.4 mmHg (28.1%) for preservative-free Latanoprost.

Investigator assessed Global efficacy

<table>
<tr><th></th><th>Preserved Latanoprost</th><th>PF Latanoprost</th></tr>
<tr><td>Very satisfactory</td><td>38.5%</td><td>46.2%</td></tr>
<tr><td>Satisfactory</td><td>50.0%</td><td>34.6%</td></tr>
<tr><td>Not very satisfactory</td><td>11.5%</td><td>19.2%</td></tr>
</table>
No treatment was deemed unsatisfactory by any investigator.

Global Tolerance

Only one patient reported his tolerance as not very satisfactory (under PF Latanoprost). Everyone else</td>
<td>IOP reductions across all the investigated time points.

-No difference in tolerance to the two treatment types, but this may be down to the small sample size and short study duration.

-Safety and efficacy appear to be similar with preserved and preservative-free Latanoprost.</td>
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<td></td>
<td>was either satisfied or very satisfied with the treatments.

Signs and symptoms

<table>
<tr><th>Sign/Symptom</th><th>Preserved Latanoprost</th><th>PF Latanoprost</th></tr>
<tr><td>Burning/stinging on instillation</td><td>5</td><td>3</td></tr>
<tr><td>Burning/stinging not on instillation</td><td>2</td><td>3</td></tr>
<tr><td>Sticky eye on instillation</td><td>1</td><td>6</td></tr>
<tr><td>Itching not on instillation</td><td>9</td><td>8</td></tr>
<tr><td>Conjunctival hyperaemia</td><td>7</td><td>5</td></tr>
<tr><td>Corneal staining</td><td>3</td><td>2</td></tr>
</table>
</td>
<td>-Though there were some pharmacokinetic differences between the two treatments, this was not reflective in the overall efficacy or tolerability of the treatments.</td>
</tr>
</table>

Adverse events

Overall, incidence of AEs was very low and no participants discontinued their treatments due to an AE related to the study drug.

Pharmacokinetics (Arithmetic means)

Parameter	BLQ[a] (pg/mL)	Preserved Latano-prost	PF Latanoprost
AUC_{0-30} (mins*pg/mL)	0	1063.5	726.0
C_{max}(pg/mL)	0	70.8	47.9*
t_{max}(mins)	-	7.3	10.7

$AUC_{0–30}$ (Area under curve) and C_{max} (maximum concentration) *p < 0.05 compared to preserved latanoprost.

<table>
<tr>
<td>(Day et al., 2013)</td>
<td>USA</td>
<td>-597 partici-pants (98% comple-ted the study)</td>
<td>Group 1: Bimatoprost PF (n=302)

-Mean age and range: 64.6 (29–91)

-Male 132, female 170

-OHT 105

-Glaucoma 197

Group 2: Preserved Bimatoprost (n=295)

-Mean age and range: 65.0 (29–92)</td>
<td>Group 1: Bimatoprost PF (n=302)

- 0.03%

-without BAK

-unit dose

Group 2: Preserved Bimatoprost (n=295)

-0.03%

-with BAK

-unit dose

-Both identical formulations other than the presence</td>
<td>-IOP

-Adverse events</td>
<td>Mean diurnal IOP (mmHg) for worse eye

<table><tr><th>Visit</th><th>Bimatoprost PF</th><th>Bimatoprost</th></tr><tr><td>Baseline</td><td>23.83±2.43</td><td>23.80±2.33</td></tr><tr><td>Week 2</td><td>17.13±2.53</td><td>16.84±2.44</td></tr><tr><td>Week 6</td><td>16.97±2.69</td><td>16.81±2.61</td></tr><tr><td>Week 12</td><td>16.99±2.59</td><td>16.82±2.61</td></tr></table>
Adverse Events

<table><tr><th>Adverse event (n)</th><th>Bimatoprost PF</th><th>Bimatoprost</th></tr><tr><td>Conjunctival Hyperaemia</td><td>72</td><td>77</td></tr><tr><td>Eye pruritus</td><td>12</td><td>12</td></tr></table></td>
<td>-Randomisation by an automated voice/web response system.

-Bimatoprost PF was equivalent to preserved Bimatoprost in mean IOP (at all time points at follow up visits).

- Overall, both treatments were well tolerated by patients. - Adverse events were present in

40.5% of bimatoprost PF</td>
</tr>
</table>

			-Male 114, female 181 -OHT 98 -Glaucoma 195	or absence of BAK. -Patients to administer one drop in both eyes, once a day in the evening, between 7pm and 9pm. -Treatment commenced on evening of baseline visit, and follow ups scheduled at weeks 2, 6 and 12.		<table><tr><td>Punctate keratitis</td><td>9</td><td>9</td></tr><tr><td>FB sensation</td><td>7</td><td>2</td></tr><tr><td>Dry eyes</td><td>5</td><td>9</td></tr></table>	cases and 44.1% of Preserved bimatoprost cases. -Ocular adverse events were reported by 31.9% of the PF Bimatoprost patients, and by 34.9% of the preserved Bimatorpost patients.
(Denis et al., 1993)	France	-27 patients	-75% women and 25% men - >21 years old	A: Betaxolol 0.25% with BAK (5mL bottle) B: Betaxolol 0.25% unit dose	-Biomicroscopy -IOP	-14 patients first received solution B, 13 patients solution A. -3 patients excluded from efficacy assessment: 1 for non-compliance with the protocol, 1 for lack of IOP control, 1 as they did not meet the inclusion	-Both treatments significantly reduced baseline IOPs.

<table>
<tr>
<td></td>
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<td>-POAG=20

-OHT=7</td>
<td>Treatment sequence 1: A then B

Treatment sequence 2: B then A

7-10 day washout period between treatments.</td>
<td></td>
<td>criteria.

IOP (mmHg)

<table><tr><th></th><th>Baseline</th><th>Day 7</th></tr><tr><td>Preserved</td><td>26.1</td><td>21.6</td></tr><tr><td>PF</td><td>25.7</td><td>22.3</td></tr></table></td>
<td>-No significant difference in IOP reduction between treatments on Day 3 or Day 7.</td>
</tr>
<tr>
<td>(Denis, 2016)</td>
<td>France</td>
<td>-183 patients</td>
<td>-82 Males, 101 Females

-38,7% had an ocular hypertension and 61,4% a Primary open angle glaucoma</td>
<td>LSC Group
-130 patients in the group: “Latanoprost without preservative”

- Latanoprost 0.005 % preservative-free</td>
<td>-IOP
-Ocular signs
-Ocular symptoms
-Adverse events
-Quality of life questionnaire</td>
<td>IOP (mmHg) change in eye with highest IOP

<table><tr><th></th><th>Day 0</th><th>Day 84</th></tr><tr><td>LSC</td><td>16.0±2.5</td><td>15.6±2.8</td></tr><tr><td>LBAK</td><td>15.9±2.2</td><td>14.9±2.3</td></tr></table>
Ocular Signs</td>
<td>-Double blind not possible due to multi-dose and single dose vials.

-PF Latanoprost is just as effective as preserved</td>
</tr>
</table>

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<td>eye drops in single doses (Monoprost®, Théa laboratories)

LBAK Group
53 patients in the group: Latanoprost with preservative: LBAK Group

- Latanoprost 0.005% eyedrops with preservative in multidose vial (Xalatan®)

-Instillation once daily at 9 p.m. for 3 months for both groups.</td>
<td></td>
<td>Little to no variation of ocular signs over the 3 months period except a slight score reduction in hypertichiasis grading in the LSC group (-0.3+/- 0.7) in comparison with the LBAK group (0.0+/- 0.5 (p=0,0011)

Reduction in % of patients with hyperaemia of scores 2 and 3: more so in LSC group (absolute difference of −33%) than in the LBAK group (−6%).

Conjunctival Hyperaemia score in eye with highest IOP

<table>
<tr><th></th><th>Day 0</th><th>Day 84</th></tr>
<tr><td>LSC</td><td>1.4 ± 0.8</td><td>0.9 ± 0.7</td></tr>
<tr><td>LBAK</td><td>1.2 ± 0.9</td><td>1.1 ± 0.8</td></tr>
</table>

Difference between groups statistically significant (p = 0.0004). Similar results for contralateral eye (p = 0.0012).

Ocular Symptoms

On instillation</td>
<td>Latanoprost in terms of IOP control, whilst offering better tolerability.

-Current study used patients already on treatment to show PF Latanoprost can maintain efficacy of preserved Latanoprost.

-Short study duration and limited number of patients commenting on daily work/leisure</td>
</tr>
</table>

						<table><tr><th></th><th>Day 0</th><th>Day 84</th></tr><tr><td>LSC</td><td>2.9 ± 2.9</td><td>0.9 ± 1.3</td></tr><tr><td>LBAK</td><td>2.5 ± 3.0</td><td>1.6 ± 2.3</td></tr></table> Significantly greater decrease in symptom scores from baseline to endpoint for LSC compared to LBAK (p = 0. 0035). Decrease in frequency of bothersome (score 2) or very bothersome (score 3) symptoms on instillation in the LSC group compared to the LBAK group as follows: dryness (respectively, −11.2% vs. −4, 1% absolute change), irritation / stinging / burning (−22.8% vs. −8.2%), tearing (−9.6% vs. −4.3%), foreign body sensation (−12.0% vs. −8.3%), and glare / discomfort in light (−5.6% vs. −2.1%). Thus, there's a great decrease in the frequency of symptoms in the LSC group than the LBAK group. **Between instillations** <table><tr><th></th><th>Day 0</th><th>Day 84</th></tr><tr><td>LSC</td><td>2.7 ± 3.1</td><td>0.9 ± 1.5</td></tr><tr><td>LBAK</td><td>1.6 ± 2.3</td><td>1.3 ± 2.2</td></tr></table>	(<10%), to realistically conclude that unpreserved drops allow for a better quality of life.

						Significantly greater decrease in symptom scores from baseline to endpoint for LSC compared to LBAK (p = 0.0003) Decrease in frequency of bothersome or very bothersome symptoms between instillations in the LSC group compared to the LBAK group as follows: dryness (respectively −17.2% vs. −4.1% absolute variation), irritation / tingling / burning (−15.3% vs. 0.0%), itching (−8.8% vs. 0.0%), tearing (−5.6% vs. 0.0%), foreign body sensation (−7.2% vs. −2.1%), and glare / discomfort in the light (−5.6% vs. 0.0%). Thus, there's a great decrease in the frequency of symptoms in the LSC group than the LBAK group. **Adverse events** Both treatments well tolerated in the study. 2 patients in the LSC group (1.5%) and 2 patients in the LBAK group (3.8%) reported an ocular adverse event.	

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>Quality of life questionnaire

LSC Group demonstrated better satisfaction than LBAK in terms of handling products (59.4% vs 29.4% respectively, p = 0.0009), improvement in vision (7.8% vs 3.8%, p=0.3689), improvement on daily activities/work (6.9% vs 0.0%, p = 0.0204), an improvement on leisure activities (9.2% vs 0.0%, p = 0.0097) and an improvement in the patient's sleep (5.4% vs 1.9%, p = 0.1457).</td><td></td></tr>
<tr><td>(Easty et al., 2006)</td><td>France and Portugal</td><td>-Total of 175 patients were randomised among 53 centres

-29 patients either deviated</td><td>-Mean age of participants: 61.5 (SD 11.2) years

-56% females

-44% males

-No significant differences in age and sex between the two groups.

-Prior to the study, 81 patients</td><td>Group 1: T-Gel 0.1% MD (Preserved)

-Timolol-Gel 0.1%

-Multidose (MD)

- Timogel from

Laboratorios Thea</td><td>-IOP

-Adverse events</td><td>Mean IOP (mmHg)

<table><tr><th>Visit</th><th>T-gel Preserved</th><th>T-gel PF</th></tr><tr><td>Baseline H0</td><td>23.51</td><td>23.76</td></tr><tr><td>Baseline H2</td><td>17.97</td><td>18.07</td></tr><tr><td>Week 4 H0</td><td>17.63</td><td>17.61</td></tr><tr><td>Week 12 H0</td><td>17.88</td><td>18.13</td></tr><tr><td>Week 12 H2</td><td>16.09</td><td>16.28</td></tr><tr><td>Change from baseline H0</td><td>5.63</td><td>5.63</td></tr></table></td><td>-Open design study as vials and single dose units could not be masked. However, efficacy was measured using IOP readings, which is an objective measure so</td></tr>
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<tr>
<td></td>
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<td>from the protocol or ended the study early.

-The PP was therefore comprised of

146 patients: 72 in the T-Gel 0.1% MD group and

74 in the T-Gel 0.1%</td>
<td>were on β-blocker monotherapy, while 65 patients were untreated.</td>
<td>Group 2: T-Gel 0.1% SDU (PF) - Timolol -Gel 0.1%

-Single dose unit (SDU)

-Geltim/ Timogel from Laboratoires

Thea</td>
<td></td>
<td>H0= before instillation
H2= 2 hours after instillation

Ocular Signs upon instillation

a)Irritation/burning/stinging
<table>
<tr><th>Visit</th><th colspan="2">T-gel Preserved</th><th colspan="2">T-gel PF</th></tr>
<tr><th></th><th>Total no.</th><th>No. reporting symptoms</th><th>Tot-al no.</th><th>No. report-ing symp-toms</th></tr>
<tr><td>Base-line H0</td><td>87</td><td>5</td><td>88</td><td>4</td></tr>
<tr><td>Week 4</td><td>84</td><td>8</td><td>86</td><td>7</td></tr>
<tr><td>Week 12</td><td>86</td><td>10</td><td>86</td><td>5</td></tr>
</table>
b) Eye dryness
<table>
<tr><th>Visit</th><th>T-gel Preserved</th><th>T-gel PF</th></tr>
</table></td>
<td>would not have been impacted.

-Both treatment types reduced IOP by 24% from baseline.

-PF T-gel is non- inferior to Preserved T-gel.

-Global tolerance assessments similar for both groups, and differences in symptoms on instillation of drops were not significant</td>
</tr>
</table>

		SDU group.					**Total no.**	**No. reporting symptoms**	**Tot-al no.**	**No. report-ing symp-toms**	between the groups.
						Base-line H0	87	1	88	2	
						Week 4	84	0	86	6	
						Week 12	86	4	86	5	
						c) Foreign Body sensation					
						Visit	**T-gel Preserved**		**T-gel PF**		
							Total no.	**No. reporting symptoms**	**Tot-al no.**	**No. report-ing symp-toms**	
						Baseline H0	87	1	88	4	
						Week 4	84	4	86	6	

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<table>
<tr><td>Week 12</td><td>86</td><td>2</td><td>86</td><td>4</td></tr>
</table>
d) Blurred vision
<table>
<tr><th>Visit</th><th colspan="2">T-gel Preserved</th><th colspan="2">T-gel PF</th></tr>
<tr><th></th><th>Total no.</th><th>No. reporting symptoms</th><th>Tot-al no.</th><th>No. report-ing symp-toms</th></tr>
<tr><td>Baseline H0</td><td>87</td><td>0</td><td>88</td><td>1</td></tr>
<tr><td>Week 4</td><td>84</td><td>9</td><td>86</td><td>12</td></tr>
<tr><td>Week 12</td><td>86</td><td>11</td><td>86</td><td>9</td></tr>
</table>
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<td></td>
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<tr>
<td>(Goldberg et al., 2014)</td>
<td>Australia, Czech Republic, Germany, Hungary,</td>
<td>Total= 561 with 540 completing the study</td>
<td>Group 1: Bimatoprost/Timolol PF (n=278)

Mean age 63.6 (20–85)

Female 159, Male</td>
<td>Group 1: Bimatoprost/Timolol PF

Group 2: Bimatoprost/Timolol preserved</td>
<td>-IOP

-Adverse events</td>
<td>Worse Eye Analysis

Percentage of patients with at least a 20% reduction in worse eye IOP at week 12:

Group 1 B/T PF: from 86.3% to 90.6%
Group 2 B/T Preserved: from 85.5% to 89.8%</td>
<td>-Randomisation via an automated interactive voice/web response system</td>
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<td></td>
<td>Israel, Russia, Spain, UK and the USA</td>
<td></td>
<td>OHT 55

Glaucoma220

OHT+Glaucoma 3

Group 2: Bimatoprost/Timolol preserved (n=283)

Mean Age 63.5 (23–86)

Female 162, Male

OHT 56

Glaucoma220

OHT+Glaucoma 7</td>
<td>Both dispensed as single dose units, with patients requiring to instil them once in the morning, with 8am being classed as Hour 0 (H0).</td>
<td></td>
<td>(Ranging over the 3 times points of 08.00,10.00 and 16.00)

Average Eye analysis

There were no differences in the average eye IOP between Groups 1 and 2 for the ITT population at any time point.

Both treatments showed a significant drop in average IOP from baseline across all time points.

B/T PF showed equivalence to B/T preserved, with the between treatment difference in average IOP being within ±1.00mmHg.

Ocular Adverse Events (AEs)

<table>
<tr><th>AE</th><th>B/T PF (n=278)</th><th>B/T Preserved (n=282)</th></tr>
<tr><td>Overall occurrence of AE</td><td>92</td><td>95</td></tr>
</table>
</td>
<td>-Both formulations were issued as unit dose vials, masking both investigators and patients alike.

-Goldman used for IOP readings, with a two-person masked reading approach.

-Overall, both treatments were well tolerated.

-The number of ocular AEs reported were</td>
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</table>

						Conjunctival Hyperaemia	59	55	similar for the two groups. -B/T PF shows equivalence and non-inferiority to preserved B/T. -No significant difference in tolerability and safety between the Preserved and Non-preserved formulations, other than skin pigmentation which was more common in the PF Group.
						Eye Pruritus	12	5	
						Skin pigmentation	11	4	
						Eye irritation	6	5	

<table>
<tr>
<td>(Konstas et al., 2013)</td>
<td>Not specified</td>
<td>-40 patients enrolled, of whom 38 completed the study</td>
<td>-18 male, 20 female

-Mean age 66.7 years</td>
<td>1. Baseline visit: 24-hour IOP monitoring.

2. Randomisation to either:

Group 1:

Preserved Latanoprost

0.005% solution (Xalatan; Pfizer)
OR

Group 2:
PF Tafluprost 0.0015% solution

(Saflutan; MSD)

3. Both treatments to be instilled once at</td>
<td>1º Endpoint: Mean 24-hour IOP

2º Endpoint:

Peak, trough, fluctuations in 24-hour IOP</td>
<td>
<table>
<tr><th>Time-point</th><th>Baseline</th><th>Latano-prost</th><th>PF Taflu-prost</th></tr>
<tr><td>06.00</td><td>25.1</td><td>17.5</td><td>17.5</td></tr>
<tr><td>10.00</td><td>26.9</td><td>17.9</td><td>18.4</td></tr>
<tr><td>14.00</td><td>24.1</td><td>17.3</td><td>17.8</td></tr>
<tr><td>18.00</td><td>23.8</td><td>17.3</td><td>17.7</td></tr>
<tr><td>22.00</td><td>24.9</td><td>17.8</td><td>17.6</td></tr>
<tr><td>02.00</td><td>24.4</td><td>18.0</td><td>17.6</td></tr>
</table>
<table>
<tr><th>IOP measure-ments</th><th>Base-line</th><th>Latano-prost</th><th>PF Taflu-prost</th></tr>
<tr><td>Mean 24h IOP</td><td>24.9</td><td>17.7</td><td>17.8</td></tr>
<tr><td>Peak 24h IOP</td><td>27.7</td><td>19.7</td><td>19.5</td></tr>
<tr><td>Trough 24h IOP</td><td>18.3</td><td>15.9</td><td>16.3</td></tr>
<tr><td>24h fluctuation</td><td>3.7</td><td>3.8</td><td>3.2</td></tr>
</table>
^Mean IOP(mmHg) measurements
</td>
<td>-Mean 24 hour, peak, trough and fluctuations in IOP were all significantly lower with both treatments compared to baseline.

-PF Tafluprost is just as effective as preserved Latanoprost when comparing 24-hour efficacy.

-PF Tafluprost provided less 24-hour fluctuations in</td>
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</table>

				night (20.00hrs), in both eyes, for 3 months. 4. 24 hour IOP monitoring . 5. Crossover to alternate treatment for another 3 months. 6. Final 24 hours IOP monitoring at the end of the 3 months.		**^Mean IOP (mmHg)**	IOP compared to Latanoprost. -Latanoprost demonstrated lower trough IOP over 24 hours than PF Tafluprost. -No significant difference in incidence of adverse events between the two treatments. -Study duration is short, so unable to comment on long term safety and tolerability of these agents.

<table>
<tr>
<td>(Manni et al., 2005)</td>
<td>Not specified</td>
<td>-20 patients with either POAG or OHT
-These patients were treated

with timolol maleate 0.5% in both eyes</td>
<td>-9 male

-11 female

-mean age 53.15±12.9 years</td>
<td>1. Baseline Visit (After a 3 week washout period), patients randomised into 2 groups:

Group 1: preservative-free timolol 0.5% (Timolabak, Théa, Paris, France)

Group 2: preserved timolol 0.5% eyedrops (Timoptol, MSD Chibret, Paris, France)

2. 60 days of therapy in allocated groups.</td>
<td>-IOP

- IL-1β Tear Levels

-TBUT</td>
<td>IOP (mmHg)

<table><tr><th>Time</th><th>Group 1</th><th>Group 2</th></tr><tr><td>Baseline</td><td>19.3</td><td>18.6</td></tr><tr><td>30 days</td><td>17.1</td><td>16.9</td></tr><tr><td>60 days</td><td>17.0</td><td>16.7</td></tr><tr><td>Baseline 2</td><td>19.3</td><td>18.3</td></tr><tr><td>30 days</td><td>17.5</td><td>16.3</td></tr><tr><td>60 days</td><td>17.5</td><td>16.3</td></tr></table>
IL-1β Tear Levels (pg/ml)

<table><tr><th>Time</th><th>Group 1</th><th>Group 2</th></tr><tr><td>Baseline</td><td>49.9±20</td><td>32.4±10</td></tr><tr><td>30 days</td><td>46.9±5.3</td><td>53.2±5.8</td></tr><tr><td>60 days</td><td>57.1±7.8</td><td>88.5±9.8</td></tr><tr><td>Baseline 2</td><td>51.6±7.4</td><td>36.3±8.9</td></tr><tr><td>30 days</td><td>59.8±6.7</td><td>43.4±8.8</td></tr><tr><td>60 days</td><td>95.5±5.4</td><td>46.1±7.3</td></tr></table></td>
<td>-Small sample size

-Randomisation via computer generated list

-The incidence of hyperaemia and superficial punctate keratitis was low in the study, regardless of group. However, the levels of tear IL-1β concentrations definitely increased with treatment (Preserved>>PF), as well as a</td>
</tr>
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<tr>
<td></td>
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<td></td>
<td>3. 3 weeks of washout from initial therapy.

4. Switch over to alternative treatment: Group 1 switched to preserved timolol, and Group 2 switched to preservative-free timolol.

Visits were as follows: baseline, 30 and 60 days after the start of first therapy, after the second washout period, and 30 and 60 days after the</td>
<td></td>
<td>TBUT (seconds)

<table>
<tr><th>Time</th><th>Group 1</th><th>Group 2</th></tr>
<tr><td>Baseline</td><td>8.8±1.3</td><td>8.9±1.1</td></tr>
<tr><td>30 days</td><td>8.5±1.5</td><td>7.5±2.0</td></tr>
<tr><td>60 days</td><td>9.0±1.1</td><td>7.6±1.6</td></tr>
<tr><td>Baseline 2</td><td>9.0±1.1</td><td>9.2±0.9</td></tr>
<tr><td>30 days</td><td>7.2±0.9</td><td>9.0±1.1</td></tr>
<tr><td>60 days</td><td>7.2±0.8</td><td>8.9±1.4</td></tr>
</table>
</td>
<td>drop in TBUT, which suggests that inflammation is definitely underway and may require longer than 2 months to show clinical signs of such.

-Both treatments were equally efficient in reducing IOP.</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td>start of second therapy.</td><td></td><td></td><td></td></tr>
<tr><td>(Rouland et al., 2013)</td><td>France,

Belgium, Italy, Spain, Portugal and Tunisia</td><td>-463 patients screened

-404 randomised

-402 received the study treatment

-Modified ITT= 353 patients

-392 patients completed the study</td><td>Group 1: PF Latanoprost T2345

-Mean age: 63.9 years (range=24-90)

-114 female, 99 male

Group 2: Preserved Latanoprost BPL

-Mean age 65.7 (range=24-93)

-86 Female, 103 male</td><td>Group 1: PF Latanoprost T2345

-single dose units

-unpreserved

Group 2: Preserved Latanoprost BPL

-multidose bottles

-0.005% Latanoprost, 0.02% BAK</td><td>-IOP

-AEs

-Ocular signs

-Ocular Symptoms

-Global tolerance</td><td>Mean IOP (mmHg) (mITT)

<table><tr><th>Time</th><th>T2345</th><th>BPL</th></tr><tr><td>Baseline (D0)</td><td>24.1±1.8</td><td>24.0±1.7</td></tr><tr><td>D15</td><td>15.8±2.6</td><td>15.2±2.4</td></tr><tr><td>D42</td><td>15.3±2.3</td><td>15.0±2.0</td></tr><tr><td>D84</td><td>15.4±2.3</td><td>15.0±2.0</td></tr></table>
Adverse Events

Ocular Signs: Conjunctival Hyperaemia

Less frequent and less severe in T2345 Group compared with BPL group.

Statistically significant lower incidence at:</td><td>-The investigator classed tolerance as ‘very satisfactory’ or ‘satisfactory’ for more than 97% of participants in both groups.

-PF Latanoprost T2345 provided better local tolerance, than preserved Latanoprost, with less burning and stinging on instillation as well as less</td></tr>
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<td></td>
<td>D42: 20.2% T2345 vs 30.6% BPL (p=0.003)

D84: 21.4% T2345 vs 29.1% BPL (p=0.019)

Also, Grade of moderate to severe hyperaemia increased over time in the BPL group and decreased in the T2345 group.

Ocular Symptom score upon instillation

<table>
<tr><th>Time</th><th>T2345</th><th>BPL</th></tr>
<tr><td>D15</td><td>0.25±0.81</td><td>0.40±0.89</td></tr>
<tr><td>D42*</td><td>0.15±0.51</td><td>0.41±1.03</td></tr>
<tr><td>D84*</td><td>0.18±0.66</td><td>0.46±1.05</td></tr>
</table>
*p=0.001

Burning/Itching

T2345 and BPL, respectively:</td>
<td>conjunctival hyperaemia.

-T2345 non-inferior to BPL, and in fact shows a better safety profile than BPL.

-The majority of the IOP reduction for both groups was achieved by D15, and both were as effective as each other in reducing the IOP.</td>
</tr>
</table>

<table>
<tr>
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<td></td>
<td></td>
<td>5.2% versus 14.0% on D15 (p=0.004)
6.8% versus 15.1% on D42 (p=0.006)
7.3% versus 19.9% on D84 (p<0.001)

Global Tolerance

Rate of “very satisfactory” higher in

the T2345 group versus the BPL group on:
-D15 (65.1% vs 59.7%),
-D42 (74.0% vs 65.1%)
-D84 (71.4% vs 62.9%).

Global tolerance assessment favoured T2345 at

D42 (p=0.013) and D84 (p=0.047).</td>
<td></td>
</tr>
<tr>
<td>(Baudouin and de Lunardo, 1998)</td>
<td>France</td>
<td>-30 healthy volun-teers</td>
<td>-Mean age 26.7 years (range=19-40 years old)

-18 females

-12 males</td>
<td>-2% Carteolol prepared with and without benzalkonium chloride (0.005%, as in the</td>
<td>-
Tolerance/SEs

-TBUT

-IOP</td>
<td>TBUT (secs)

<table><tr><th>Visit</th><th>PF Carteolol</th><th>Preserved Cartolol</th></tr><tr><td>Baseline</td><td>9.1</td><td>10.4</td></tr><tr><td>After 3 days</td><td>8.4</td><td>7.7*</td></tr></table></td>
<td>-Randomisation through computer system.

-Good tolerance reported for</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>commercial solution: Cartéol)

-Subjects randomised to either Preserved or PF Carteolol drops and to RE or LE for study duration.

1. Ophthalmic checks performed at the following intervals:

Just before, 30, 60 and 180 minutes after instillation of one drop of the solution.</td>
<td></td>
<td>*Significant decrease from baseline

<table>
<tr><th>Time</th><th>PF Carteolol</th><th>Preserved Cartolol</th></tr>
<tr><td>Baseline</td><td>9.0</td><td>10.4</td></tr>
<tr><td>T0+ 30minutes</td><td>8.1</td><td>7.9</td></tr>
<tr><td>T0+ 1 hour</td><td>7.3</td><td>7.4</td></tr>
<tr><td>T0+ 3 hours</td><td>7.9~</td><td>6.1*</td></tr>
</table>

*Significant decrease from baseline

~Decrease significantly lower in PF Group than the Preserved Group.

IOP (mmHg)

<table>
<tr><th>Visit</th><th>PF Carteolol</th><th>Preserved Cartolol</th></tr>
<tr><td>Baseline</td><td>13.8</td><td>13.7</td></tr>
<tr><td>After 3 days</td><td>12.4</td><td>12.4</td></tr>
</table>
</td>
<td>both preserved and PF Carteolol.

-Study duration very short, and so unable to deduce long term effects.

-Significantly reduced TBUT after first drop and after 3 days of preserved treatment, in comparison with PF Carteolol which did not produce significant changes.</td>
</tr>
</table>

				2. Participants then instilled 1 drop twice a day for 2 days, and then 1 drop in the morning of the third day. 3. Ophthalmic checks performed 8 hours after last instillation. 4. 5 day washout period. 5. Crossover to other treatment, on the same eye begins (Steps 1 to 3).		**Subjective tolerance measured on Visual Analogue Scale (0-100mm)** [0=not irritating 100=extremely irritating] **PF Carteolol=2.83mm** **Preserved Carteolol=3.66mm**	-Healthy, young individuals were used for this study so it isn't very relatable to the typical Glaucoma population, who are elderly with comorbidities and who are on multiple drops.

<table>
<tr>
<td>(Gómez-Aguayo et al., 2018)</td>
<td>Mexico</td>
<td>-51 patients comple-ted the trial</td>
<td>Baseline characteristics of all 51 subjects:

-37 female, 14 male

-Mean age 65.6 years, ranging from 22-93 years</td>
<td>1. Randomisation to the following groups:

Group 1-Sequence A (n=24)

-received PRO-122-a

preservative-free 0.5% timolol+0.2% brimonidine

+2.0% dorzolamide fixed combination

Group 2-Sequence B (n=27)</td>
<td>-IOP

-Ocular findings (TBUT, chemosis, hyperaemia, tearing and burning sensation)

-VF-14 index

-Questionnaire

-AEs</td>
<td>Base IOP (mmHg)

<table>
<tr><th></th><th>Sequence A</th><th>Sequence B</th></tr>
<tr><td>Baseline</td><td>13.60 ± 2.9</td><td>12.13 ± 1.8</td></tr>
<tr><td>Day 1-30</td><td>13.19 ± 3.2</td><td>11.80 ± 2.1</td></tr>
<tr><td>Day 31-60</td><td>12.60 ± 3.0</td><td>11.24 ± 1.6</td></tr>
</table>

Peak IOP

Mean Peak IOP higher for Sequence B than Sequence A across all time points, but no significant difference in change in peak IOP at baseline vs. crossover, with adjusted differences between sequences.

A sequence Ocular findings (n=48)

<table>
<tr><th></th><th>Base-line</th><th>Week 4</th><th>Week 8</th></tr>
<tr><td>TBUT (s)</td><td>6.46 ± 3.3</td><td>6.65 ± 2.9</td><td>6.08 ± 1.7</td></tr>
<tr><td>Conjunctival Hyperaemia (n)</td><td>19</td><td>18</td><td>10</td></tr>
<tr><td>Tearing (n)</td><td>9</td><td>8</td><td>7</td></tr>
</table>
</td>
<td>-PRO-122 not inferior to KOF; both sustained a reduced IOP during the course of the treatment.

-PRO-122 and KOF equally tolerable and safe to use, however, short study duration limits this finding.</td>
</tr>
</table>

				-received KOF-preserved version of 0.5% timolol+ 0.2% brimonidine+ 2.0% dorzolamide fixed combination 2. Apply 1 drop of designated medication to each eye morning and night. Drops to be used from day 1 to 30. 3. At this crossover visit, patients were changed to the other treatment type (PRO-122				

Chemosis (n)	0	0	0
Eye burning (n)	16	12	14
FB sensation (n)	14	14	5

B sequence ocular findings (n=54)

	Base-line	**Week 4**	**Week 8**
TBUT (s)	7.30 ± 1.8	6.41 ± 1.4	6.74 ± 2.4
Conjunctival Hyperaemia (n)	6	14	7
Tearing (n)	2	9	9
Chemosis (n)	2	2	0
Eye burning (n)	18	18	19
FB sensation (n)	14	16	7

<table>
<tr>
<td></td>
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<td></td>
<td>TO KOF in Sequence A, and KOF to PRO-122 for Sequence B). No washout period, so treatment started from day 31.

4. Final visit after another 30 days of alternate treatment.</td>
<td></td>
<td>Adverse Events
In total, 29 cases of AEs reported. However, no difference in incidence of AEs between the two groups.

VF-14/Questionnaire

VF-14 index showed no differences between sequences during the first, crossover or final visit.

The scores on the questionnaire were low overall, indicating low discomfort, and no differences were observed between the two treatments.</td>
<td></td>
</tr>
<tr>
<td>(Kumar et al., 2018a)</td>
<td>India</td>
<td>-46 patients

Recruited</td>
<td>Group 1

Mean age= 42years</td>
<td>Group 1 Preserved Latanoprost

LATOPROST-</td>
<td>1º Outcome

-IOP

2º Outcome</td>
<td>Mean IOP (mmHg)
<table><tr><th>Visit</th><th>Group 1 Preserved</th><th>Group 2

PF</th></tr></table></td>
<td>-Randomisation using the envelope method.</td>
</tr>
</table>

		-44 patients completed the study= PP	(range 25 to 66 years) -13 male, 10 female **Group 2** Mean age=43.61 (range 23 to 70 years) -13 male, 10 female	0.005% latanoprost, preservative: benzalkonium chloride 0.02%; SUN pharma laboratories Ltd. Mumbai) **Group 2 PF Latanoprost** LACOMA- 0.005% latanoprost, Ajanta pharma Ltd., Mumbai). -1 drop to be instilled once a day on an evening in both	-TBUT -Hyperaemia		-Preserved and PF formulations were equally effective at lowering IOP. -Long term Preserved Latanoprost may lead to OSD especially in ocular surface compromised patients. -Hyperaemia differences were significant between the groups at week 2, but at baseline and by week 12, these

Baseline	26.25	25.36
Week 2	18.00	18.32
Week 4	17.42	17.7
Week 6	17.07	17.46
Week 12	16.97	17.26

Mean Hyperaemia Score

Visit	Group 1 Preserved	Group 2 PF
Baseline	0.39	0.41
Week 2	0.68	0.45
Week 12	0.47	0.43

Mean TBUT (seconds)

Visit	Group 1 Preserved	Group 2 PF
Baseline	12	11.91

				eyes for 3 months.		**Week 4**	10.43	11.68	differences were insignificant. -TBUT decreased across weeks 4 and 12 for both groups, but significantly for Group 1 and insignificantly for Group 2. -There was a significant difference in mean TBUT between the groups at weeks 4 and 12.
						Week 12	8.02	11.63	

<table>
<tr>
<td>(Stevens et al., 2012)</td>
<td>Not specified</td>
<td>-28 patients with untreat-ed OHT

-2 excluded from final analysis for 1)poor adherenc e and 2)intra-ocular inflamma -tion at baseline.</td>
<td>-Mean age 62 years old (range 42-74 years)

-9 Female, 17 Male</td>
<td>-BAK preserved Timolol Maleate (0.5%) in one eye and PF Timolol Maleate (0.5%) in the other eye.

-Instillation 2x a day for both formulations.</td>
<td>-Flare intensity measured using The Laser-Cell-Flare-Meter

-IOP</td>
<td>Mean IOP (mmHg)

<table>
<tr><th></th><th>PF Timolol</th><th>Preserved Timolol</th></tr>
<tr><td>Pre treatment</td><td>22.88</td><td>23.00</td></tr>
<tr><td>After 1 month</td><td>16.50</td><td>16.83</td></tr>
</table>

Flare Intensity (ph/ms)

<table>
<tr><th>Flare</th><th>PF Timolol</th><th>Preserved Timolol</th></tr>
<tr><td>At baseline</td><td>5.29</td><td>5.65</td></tr>
<tr><td>At 1 month</td><td>6.81</td><td>8.02</td></tr>
<tr><td>Flare Increase</td><td>1.51</td><td>2.37</td></tr>
<tr><td>Difference in Flare increase</td><td colspan="2">0.86</td></tr>
</table>
</td>
<td>-Computer generated randomisation using a list of numbers

-Both treatments significantly increased the flare intensity.

-Preserved Timolol increased the flare significantly more than the PF Timolol.

-Previous studies support the hypothesis that BAK</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>increases flare, rather than an increased penetration of the active Timolol compound due to BAK.

-Cannot rule out ‘flow-over effect’; systemic effects of BAK to the contralateral eye.</td></tr>
<tr><td>(Mohammed et al., 2020)</td><td>United Kingdom</td><td>36 patients, 1 dropout after baseline</td><td>PF

Male/Female= ¾

Mean age 67.9

PQ</td><td>PF

-Latanoprost 0.005%

-Timolol 0.5%

-Dorzolamide 2%</td><td>-Impression cytology

-Tear analysis

-OSDI questionnaires</td><td>IOP (mmHg)

<table><tr><th></th><th>Baseline</th><th>Month 24</th></tr><tr><td>PF</td><td>25.2</td><td>16.0</td></tr><tr><td>PQ</td><td>28.7</td><td>18.3</td></tr><tr><td>BAK</td><td>27.1</td><td>15.3</td></tr></table></td><td>-Randomisation determined using computer process by the Clinical Trials Unit of the</td></tr>
</table>

			Male/Female= 2/6 Mean age 70.3 **BAK** Male/Female= 6/3 Mean age 63.9 -All treatment naïve Glaucoma patients	**PQ** -Travoprost 0.004% monotherapy -Travoprost 0.004%/Timolol 0.5% combination therapy **BAK** -Bimatoprost 0.01% -Travoprost 0.04%	-IOP	**IC** **Interleukin 6** **BAK:** >2fold increase in 7/9 samples at all time points, but no significant difference compared to PQ and PF. **PQ:** 'modestly increased' across all time points but not significant compared to baseline. **PF:** 'modestly increased' across all time points but not significant compared to baseline. **Interleukin 8** **BAK:** Increased 4 fold at month 1 and significant increases at month 3 and month 6. **PQ:** No significant change to baseline at any time points. **PF:** No significant change to baseline at any time points.	University of Nottingham. -Masking of patients and clinicians not possible. -Pro-3 way evaluation of naïve patients. -Small sample size -11 of 35 IC samples could not be used due to low quantity and/or quality. -8 of 35 tear samples of low volume and so

						Interleukin 1β **BAK:** increased in time dependent manner from month 3 onwards. This increase was significant at month 6 (p=0.0023). High levels remained throughout until month 24, compared to baseline, PQ and PF. **PQ:** 2.92-fold increase at 24 months. **PF:** No change across all time points. **Interleukin 10** **BAK:** Some increase from month 3 onwards, but no statistical difference between baseline, PQ or PF. **PQ:** Reduction in levels until month 12, with some elevation by month 24. **PF:** 1.5-fold increase from month 1, sustaining these levels up to month 24. **TNF-α & IL-12a**	could not be analysed. -Inconsistencies between patients on number of eye drops they are on, as more drops were added if desired IOP was not achieved in the course of the study. Additional drops had the same preservatives in too, and if not available, then PF version added.

						No significant changes in any groups **Tear samples** **Interleukin 6** **BAK:** Increase from month 6, with a significant elevation at month 24 (p=0.0368). **PQ:** Non-significant increase from month 6, maintained at similar levels until month 24. **PF:** Not stated, though the graph shows a slight decline at month 24 from baseline. **Interleukin 8** **BAK:** Increase from month 3 onwards, which stayed elevated until month 24 compared to PF. **PQ:** Some increase, but insignificant, across all time-points compared to PF. **PF:** Not stated, but graph shows some decline over the 24 month period.	-Different drugs used in each preservative group could be a confounding factor as effects could be down to the active ingredient.

						Interleukin 1β **BAK:** Significant increase from month 3 (p=0.0243), and a significant increase compared to PF at month 24 (p=0.0187). **PQ:** Some elevation across all time points. **PF:** Not stated, and the graph only shows data for the 24-month time-point. **OSDI** **BAK:** Mean score >20 at 12 months for 5/9 patients and >30 for 3/9 patients at 24 months. **PQ:** Mean score >12 for 4/8 patients from 6 months on. 1 patient scored >20 at 24 months. **PF:** Mean score <12 for 6/7 patients, at all time points. **OSDI shows significant correlation with the markers IC IL 1β, IC IL10 and tear IL 1β.**	

<table>
<tr>
<td>(Duru and Ozsaygili, 2020)</td>
<td>Turkey</td>
<td>-21 patients

-42 eyes</td>
<td>-7 male, 14 female

-Mean age 44.85±13.35 years

-All treatment naïve patients</td>
<td>-Preserved Brimonidine 0.15% (Alphagan-P)
-PF Brimonidine 0.15% (Brimogut)

-Instillation twice a day, at 8am and 8pm, for 4 weeks.</td>
<td>-IOP

-Ocular discomfort score

-TBUT

-Schirmer</td>
<td>IOP (mmHg)

<table><tr><th></th><th>Baseline</th><th>Week 4</th></tr><tr><td>Preserved</td><td>23.09±1.86</td><td>17.8±2.06</td></tr><tr><td>PF</td><td>23.85±1.74</td><td>18.09±1.97</td></tr></table>
Reduction in IOPs in both groups significant (p<0.001) from baseline to endpoint.

TBUT (seconds)

<table><tr><th></th><th>Baseline</th><th>Week 4</th></tr><tr><td>Preserved</td><td>9.38±2.83</td><td>5.76±1.78</td></tr><tr><td>PF</td><td>9.95±2.06</td><td>6.38±1.77*</td></tr></table>
*error in article->both values are stated as preserved at week 4. For the purpose of this review, values have been taken respectively as has been reported for all other test results.

Mean Schirmer Score (mm)

<table><tr><th></th><th>Baseline</th><th>Week 4</th></tr><tr><td>Preserved</td><td>11.80±9.08</td><td>10.71±8.40</td></tr><tr><td>PF</td><td>12.23±9.54</td><td>11.33±8.91</td></tr></table></td>
<td>-IOP reduction similar in both groups.

-Only significant difference in ocular symptoms was stinging on instillation, but this could be down to small sample size and short study duration.

-Negative change in tear parameters over the course of the study for both preserved and PF formulations</td>
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<td>
Mean symptom score upon instillation
<table>
<tr><th>Symptoms</th><th>Preserved</th><th>PF</th></tr>
<tr><td>Pain</td><td>0.42±1.20</td><td>0.57±1.32</td></tr>
<tr><td>Blurred Vision</td><td>0.61±1.16</td><td>0.42±1.20</td></tr>
<tr><td>Stinging</td><td>0.66±1.19</td><td>0.61±1.20</td></tr>
<tr><td>Burning</td><td>0.52±0.92</td><td>1.19±1.20</td></tr>
</table>
Significant difference between formulations for stinging on instillation (p=0.01)
Mean symptom score between instillations
<table>
<tr><th>Symptoms</th><th>Preserved</th><th>PF</th></tr>
<tr><td>Itching</td><td>0.33±0.57</td><td>0.23±0.53</td></tr>
<tr><td>Tearing</td><td>0.47±0.92</td><td>0.61±0.97</td></tr>
<tr><td>Photophobia</td><td>0.52±0.67</td><td>0.42±0.67</td></tr>
<tr><td>Burning</td><td>0.80±0.81</td><td>0.76±0.70</td></tr>
<tr><td>Stinging</td><td>0.47±0.60</td><td>0.23±0.43</td></tr>
</table>
</td>
<td>suggest that such changes could be linked to not only the preservatives, but also the active ingredient and excipients.

-Long term data is needed to look at this efficacy and tolerance between preserved and PF formulations.

-No washout period, 21 eyes randomised to receive PF, and</td>
</tr>
</table>

							the other 21 received preserved formulations.

3. Current clinical approaches to ocular surface disease (OSD) in UK glaucoma clinics: Survey questions

All about you

1. **What is your age?**
   □21-30 y/o □31-40 y/o □41-50y/o □51-60 y/o □over 60 y/o

2. **How long have you been qualified?**
   □0-5 years □6-10 years □11-15 years □over 15 years

3. **What is your job title?**
   □Consultant ophthalmologist □Ophthalmologist □optometrist
   □nurse prescriber □other (please specify)_____

4. **What is your specialism?**
   □Glaucoma □Corneal □Medical retina □Vitreoretina □Oculoplastics
   □Paediatric ophthalmology □other (please specify)_____

The glaucoma clinics you work in

1. **What is your first line treatment of Glaucoma/Ocular hypertension on a new patient? Please select your top 3 preferences in order from below.**

	1st choice	2nd choice	3rd choice
Alphagan			
Azarga			
Azopt			
Betagan			
Betagan PF			
Betopic			
Betopic PF			
Combigan			
Cosopt			
Cosopt PF			

Duotrav			
Ganfort			
Iopidine			
Iopidine PF			
Latanoprost			
Lumigan			
Lumigan UD PF			
Monopost			
Pilocarpine			
Pilogel			
Saflutan PF			
Simbrinza			
Timoptol			
Timoptol PF			
Tiopex PF			
Travatan			
Trusopt			
Trusopt PF			
Xalacom			
Xalatan			

Other_____

2. **Do you examine the ocular surface of (tick all that apply):**
   □all new patients □new glaucoma patients □new patients who complain of dryness symptoms □existing patients on glaucoma drops □existing patients who complain of dryness symptoms □patients of known dry eyes

3. **Of what importance does the role of ocular surface disease (OSD) play in your initial prescribing/ management of glaucoma in a new patient?**
   1. Extremely important 2.Very important 3. Somewhat important
   4. Not so important 5. Not at all important

4. **How do you examine the ocular surface? (Tick all that apply)**

- o Tear break up time (with fluorescein)
- o Non invasive tear break up time
- o Tear meniscus height
- o Schirmer's test
- o Tear osmolarity testing
- o Fluorescein Corneal staining without grading
- o Fluorescein Corneal staining with grading
- o Lissamine Green Conjunctival staining without grading
- o Lissamine Green Conjunctival staining with grading
- o Conjunctival/Bulbar redness and grading
- o Lid margin assessments
- o Meibomian gland imaging
- o Other _____

5. **Are newly diagnosed patients taught about drop instillation in your clinics?**
   □No □Yes, by the nurse □Yes, by the ECLO □Yes, by myself
   □Yes, by someone else (please specify)_____

6. **Do you provide a leaflet on the anti-glaucoma drops when they are prescribed for the first time?**
   □Yes, I provide information on the drops and how to instil them
   □Yes, I provide information on the drops, how to instil them and how often to instil them
   □Only sometimes, if one is available □No, I only provide the prescription to obtain the drops

7. **What percentage of your glaucoma patients may have concurrent dry eyes/ocular surface disease?**
   □>50% □25-50% □<25% □Not sure □Other (please specify)_____

8. **What percentage of your glaucoma patients do you concurrently prescribe ocular lubricants?**
   □<10% □10% □20% □30% □40% □50% □>50% □not sure □not applicable

The use of preservative free medicine in glaucoma

1. When would you consider prescribing preservative free medication? (tick all that apply)

□First line treatment □in patients reporting dryness symptoms □in patients showing clinical signs of dryness □Post surgery □Prior to surgery □when you suspect poor compliance □not at all

2. Would you consider PF drops in a patient without OSD?

□Yes □No

3. If no, why not? □Cost □Not on formulary □Not beneficial □Not effective □N/A □other (please specify)_____

4. Do you consider age an important factor when prescribing PF medication?

□Yes □No

5. Roughly how many patients on average complain of intolerance/allergy/discomfort to drops on a follow up appointment?

□1 in 5 □1 in 4 □1 in 3 □1 in 2 □more than 1 in 2 □other (please specify)_____

4. Current clinical approaches to ocular surface disease (OSD) in UK glaucoma clinics

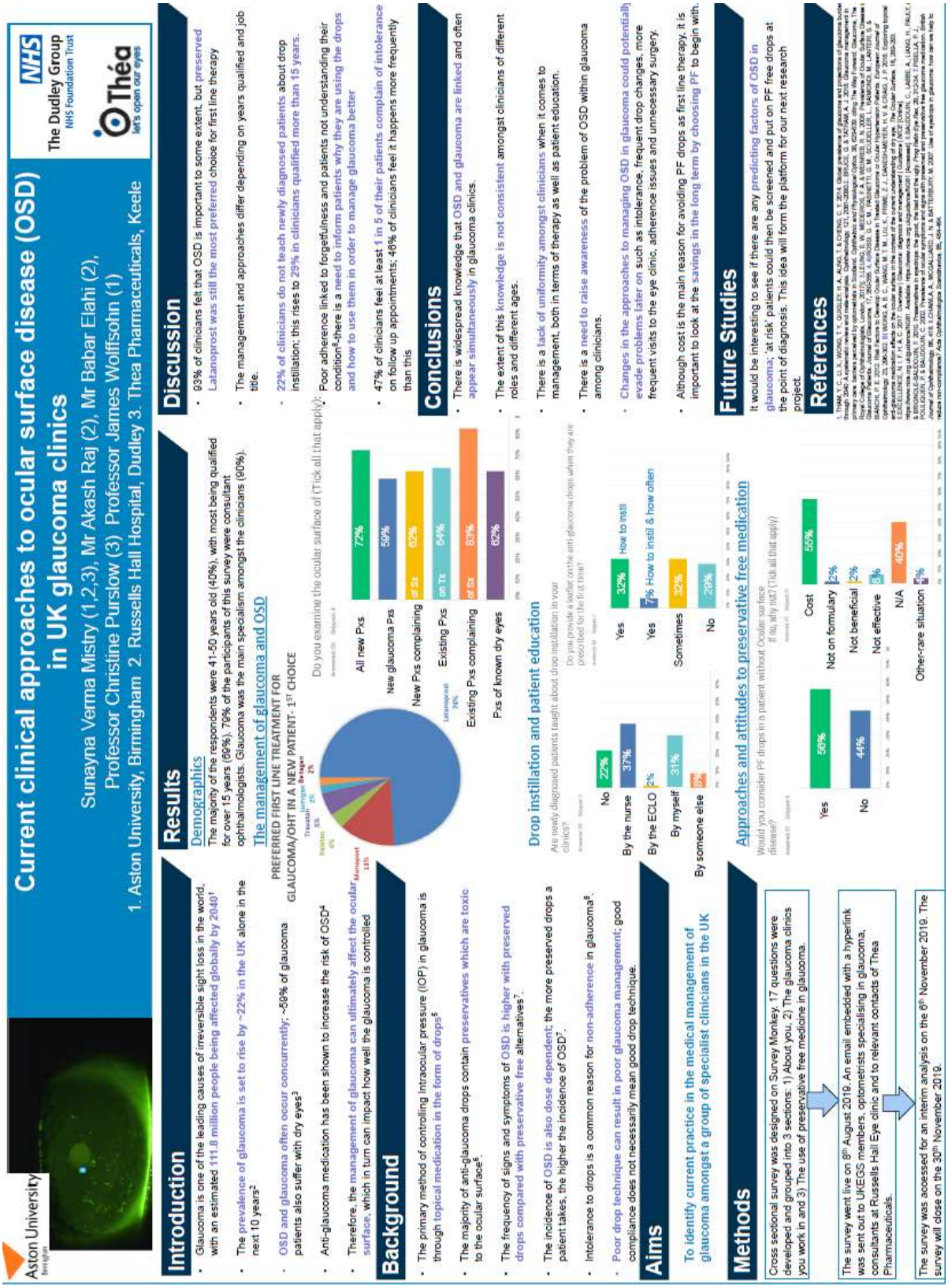
The following abstract was submitted to the UK and Eire Glaucoma Society (UKEGS) following an interim analysis and accepted in September 2019 for a poster presentation. The results of this study were presented at the UKEGS national congress on the 21st and 22nd of November 2019. The poster presented at this conference is included in Appendix 5.

Abstract

First Author: Sunayna Verma Mistry (1, 2, 3)
Co-Authors: Mr Akash Raj (1), Prof. James S. Wolffsohn (2), Mr Babar Elahi (1), Prof. Christine Purslow (2, 3)
Affiliations:
1. Russells Hall Hospital, Dudley
2. Aston University, Birmingham
3. Thea' Pharmaceuticals, Keele
Title: Current clinical approaches to ocular surface disease (OSD) in UK glaucoma clinics
Purpose: To study the current practices of ocular surface management for glaucoma patients in the UK as well as current approaches to patient education on drop instillation.
Design: Cross Sectional Survey
Methods: A survey monkey survey questionnaire of 18 questions was sent using a web link to all UKEGS members, IP registered optometrists with specialist prescribing in glaucoma, Thea Pharmaceutical glaucoma contacts and also by individual emails to glaucoma consultant colleagues.
Results: 47 clinicians responded within the first 2 weeks of distribution of the survey. The majority of the responses were from glaucoma consultant ophthalmologists with over 15 years' experience. Though 91% of clinicians thought the ocular surface plays an important part in prescribing and managing glaucoma in new patients, 76% of clinicians would still prescribe preserved Latanoprost as first line therapy. For the majority of clinicians, preservative-free drops would only be considered if signs or symptoms are present and cost seems to be the main obstacle when it comes to prescribing preservative-free drops. 25% of patients are not advised regarding drop instillation.
Conclusions: There is a strong relationship between ocular surface disease and glaucoma treatment and though there is an awareness of this amongst clinicians, there are still some

barriers when it comes to prescribing preservative-free medication. There is also room for improvement in patient education on drop instillation.

5. Current clinical approaches to ocular surface disease in UK glaucoma clinics-Poster



6. Patient survey investigating adherence to glaucoma treatment

Thea — Aston University — NHS The Dudley Group NHS Foundation Trust

Clinical Audit investigating adherence to Glaucoma treatment

Section 1: All about you

1. What is your age? ◯ Under 18 ◯ 18-24 ◯ 25-34 ◯ 35-44 ◯ 45-54 ◯ 55-64 ◯ 65 and over

2. What is your ethnicity?

◯ Caucasian/White/English/Welsh/ Scottish/Northern Irish/British/Irish

◯ Mixed/Multiple ethnic group/White and Black Caribbean/White and Black African/White and Asian

◯ Asian/Asian British/Indian/Pakistani/Bangladeshi/Chinese/Any other Asian background

◯ Black/African/Caribbean/Black British

◯ Other ethnic group/Arab/Any other ethnic group

3. How long have you been on Glaucoma/Ocular hypertension eye drops? ____years

Section 2: Medication information

4. What eye drops are you taking at the moment for your Glaucoma/Ocular Hypertension?

◯Alphagan	◯Combigan	◯Ganfort	◯Saflutan/Tafluprost	◯Trusopt
◯Azarga	◯Cosopt	◯Iopidine	◯Teoptic	◯Xalacom
◯Azopt	◯Diamox	◯Lumigan/Bimatoprost	◯Timoptol/Timolol	◯Xalatan/Latanoprost
◯Betagan	◯Dorzolamide	◯Monopost	◯Tiopex	
◯Betoptic	◯Duotrav	◯Pilocarpine/Pilogel	◯Travatan/Travoprost	

◯Other (please specify) _____

5. Were you given written information about Glaucoma/Ocular Hypertension at the start of your treatment? ◯ Yes ◯ No

6. Do you feel you had sufficient information about your condition from your consultant prior to starting treatment? ◯ Yes ◯ No

Section 3: Drop instillation information

7. Who instils your drops? ◯ Myself ◯ My partner ◯ My carer ◯ My nurse ◯Other (please specify) _____

8. On a scale of 1 to 10, with 1 being very easy and 10 being very hard, how easy do you find it to instil your drops? _____

9. Did someone at the hospital teach you how to instil the drops?

◯ No ◯Yes, the Glaucoma consultant ◯Yes, the Nurse

◯Yes, the Eye Clinic Liaison Officer ◯Yes, the Ophthalmic Technician

10. Were you issued with written instructions on how to instil your drops at the start of your treatment? ◯Yes ◯No

11. Do you have a system in place to remind you to instil the drops?

◯No ◯Yes, a mobile phone/tablet app ◯Yes, a Paper chart

◯Yes, a mobile phone/tablet alarm ◯Other (please specify) _____

Section 4: Adherence and Glaucoma

12. Do you have any of the following symptoms on instillation of your drops? (tick all that apply) ◯Burning ◯Stinging ◯Pain ◯Watery eyes ◯Red eyes ◯None

13. How long do these symptoms last? _____minutes

14. How often a week do you miss instilling your eye drops? _____times a week

15. What are the reasons you might miss instilling your drops? (tick all that apply)

◯Forgetfulness ◯Complicated routine/too many drops to take

◯Difficulty handling the bottles/vials of medication to squeeze out the drops

◯Side effects of drops e.g. stinging, burning ◯Running out of drops

◯Not understanding why you have to take the drops

◯Other (please specify) _____

16. Are you using dry eye drops/artificial tears? ◯Yes ◯No

17. If so, when did you start using them?

◯Not using any

◯Started using **before** being diagnosed with Glaucoma/Ocular hypertension

◯Started using **after** being diagnosed with Glaucoma/Ocular Hypertension

18. How often do you use dry eye drops/artificial tears?

◯Few times a day ◯Once a day ◯Few times a week ◯ As and when ◯Not at all

19. Have you had any eye surgery in the past? This includes, but is not limited to, Glaucoma and Cataract surgery. ◯Yes ◯No

THANK YOU FOR TAKING PART, YOUR INPUT IS MUCH APPRECIATED

7. Consent form and PIS for patient survey

Clinical audit investigating adherence to Glaucoma treatment Patient Consent Form

Name of Chief Investigator:

Please initial boxes

1.	I confirm that I have read and understand the Participant Information Sheet (V1, dated 16/12/2020) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my legal rights being affected.	
3.	I agree to my personal data and data relating to me collected during the study being processed as described in the Participant Information Sheet.	
4.	I understand that if during the study I tell the research team something that causes them to have concerns in relation to my health and/or welfare they may need to breach my confidentiality.	
5.	I agree to my anonymised data being used by research teams for future research.	
6.	I agree to take part in this study.	

Name of participant (Print)	Date	Signature
Name of Investigator (Print)	Date	Signature

1728, V1, 20201216

Aston University

NHS
The Dudley Group
NHS Foundation Trust

Clinical audit investigating adherence to Glaucoma treatment

Participant Information Sheet

Invitation

We would like to invite you to take part in a clinical audit.

Before you decide if you would like to participate, take time to read the following information carefully and, if you wish, discuss it with others such as your family, friends or colleagues.

Please ask a member of the audit team, whose contact details can be found at the end of this information sheet, if there is anything that is not clear or if you would like more information before you make your decision.

What is the purpose of the study?

We are carrying out a quality audit to assess how Glaucoma/Ocular Hypertension affects individuals and the problems you may encounter in the course of your treatment. We are hoping that this will highlight areas that may need development, and aim to use the results of this audit to improve the overall care in the Glaucoma clinics at Russells Hall Hospital and Corbett Hospital. We would appreciate your input by participating in this short questionnaire. Participation is voluntary and will not affect your treatment or the care you receive. Please be as honest as possible when answering the questions; the results are anonymous and will not be shared with your clinician.

Why have I been chosen?

You are being invited to take part in this study because:

- You have been diagnosed with Glaucoma/Ocular hypertension
- You have been prescribed eye drops to treat the Glaucoma/Ocular hypertension
- You are aged between 18-95

What will happen to me if I take part?

You will be provided with a 19 question, questionnaire covering areas such as the Glaucoma eye drops you take, the side effects you may be experiencing and the reasons for not using your drops. The questionnaire should take only a few minutes to complete. The questionnaire can be filled in before or after your routine appointment, and you can put it in the sealed box in the eye clinic once finished. You will not be asked any personal information, and so your participation is anonymous.

We will provide you with contact details of our Audit team, so you can get in touch with us to find out the results of this audit.

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Do I have to take part?

No. It is up to you to decide whether or not you wish to take part.

If you do decide to participate, you will be asked to sign and date a consent form. You would still be free to withdraw from the study at any time without giving a reason.

Will my taking part in this study be kept confidential?

Yes. A code will be attached to all the data you provide to maintain confidentiality.

Your personal data (name) will only be needed to take consent. Analysis of your data will be undertaken using coded data.

The data we collect will be stored in a secure document store (paper records) or electronically on a secure encrypted mobile device, password protected computer server or secure cloud storage device.

To ensure the quality of the audit, Aston University and the NHS Organisation supporting the study may need to access your data to check that the data has been recorded accurately. If this is required your personal data will be treated as confidential by the individuals accessing your data.

What are the possible benefits of taking part?

This audit is assessing the quality of care in the Glaucoma clinics. By participating, you will help to highlight any areas where improvements are needed. This may be in the form of better education about the drops or the condition, or it may inform clinicians the need to manage side effects of medication better. We hope that this audit will help to improve the overall care in the Glaucoma clinics.

What are the possible risks and burdens of taking part?

The main issue associated with taking part in this study is that it will require some of your time during you normal visit to the eye clinic. We have tried to address this by keeping the questionnaire short, so it only requires a few minutes to complete.

Some of the questions also ask your reasons for not using the Glaucoma drops as instructed and whether you feel that your consultant gave you enough information about your condition and the treatment. Though this might seem conflicting, please answer as honestly as possible. Your answers will not be shared with your consultant, and your participation is anonymous. Please be

assured that your ongoing treatment and care will continue as normal regardless of your answers and whether you choose to participate or not.

What will happen to the results of the study?

The results of this study may be published in scientific journals and/or presented at conferences. If the results of the study are published, your identity will remain confidential.

A lay summary of the results of the study will be available for participants when the study has been completed and the auditors will ask if you would like to receive a copy.

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The anonymised results of the study will also be used in Mrs Sunayna Verma Mistry's PhD thesis.

The anonymised results may be shared with the company funding some of the staffing for this study. The anonymised results may be used for research by other research teams as described in Appendix A.

Expenses and payments

There will be no expenses/payments.

Who is funding the audit ?

The study is being funded by Aston University, but some of the funding for the PhD was received by Thea Pharmaceuticals.

Who is organising this study and acting as data controller for the study?

Aston University is organising this study and acting as data controller for the study. You can find out more about how we use your information in Appendix A.

Who has reviewed the study?

This study was given a favorable ethical opinion by the Aston Research Ethics Committee.

What if I have a concern about my participation in the study?

If you have any concerns about your participation in this study, please speak to the audit team and they will do their best to answer your questions. Contact details can be found at the end of this information sheet.

If the research team are unable to address your concerns or you wish to make a complaint about how the study is being conducted you should contact the Aston University Research Integrity Office at research_governance@aston.ac.uk or telephone 0121 204 3000.

Audit Team

Mr Babar Elahi	Tel: 01384 456111 Ext 5815	Email: babar.elahi@nhs.net
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Dr Gurpreet Bhogal-Bhamra	Tel: 0121 204 4874	Email: g.bhogal-bhamra@aston.ac.uk

Thank you for taking time to read this information sheet. If you have any questions regarding the study please don't hesitate to ask one of the audit team.

1728, V1, 20201216

Appendix A: Transparency statement

Aston University takes its obligations under data and privacy law seriously and complies with the General Data Protection Regulation ("GDPR") and the Data Protection Act 2018 ("DPA").

Aston University is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study. Aston University will process your personal data in order to register you as a participant and to manage your participation in the study. It will process your personal data on the grounds that it is necessary for the performance of a task carried out in the public interest (GDPR Article 6(1)(e). Aston University may process special categories of data about you which includes details about your health. Aston University will process this data on the grounds that it is necessary for statistical or research purposes (GDPR Article 9(2)(j)). . Aston University will keep identifiable information about you for 6 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

You can find out more about how we use your information at www.aston.ac.uk/dataprotection or by contacting our Data Protection Officer at dp_officer@aston.ac.uk.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

When you agree to take part in a research study, the information about you may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of research, and cannot be used to contact you.

8. Reasons for missing drops- 'other' option

- "Only once when pharmacist couldn't get stock"
- "I never forget"
- "Forgetfulness is always linked to household/family crises that take priority"
- "I would never miss instilling the drops"
- "Busy or at theatre"
- "0"
- "Severe Depression"
- "Had so many different drops & eye ops in past 2 years but have coped with all the drops every 2 hrs etc."
- "Being too ill from other problems"

9. 'Other' comments for reminders for drop instillation

National cohort

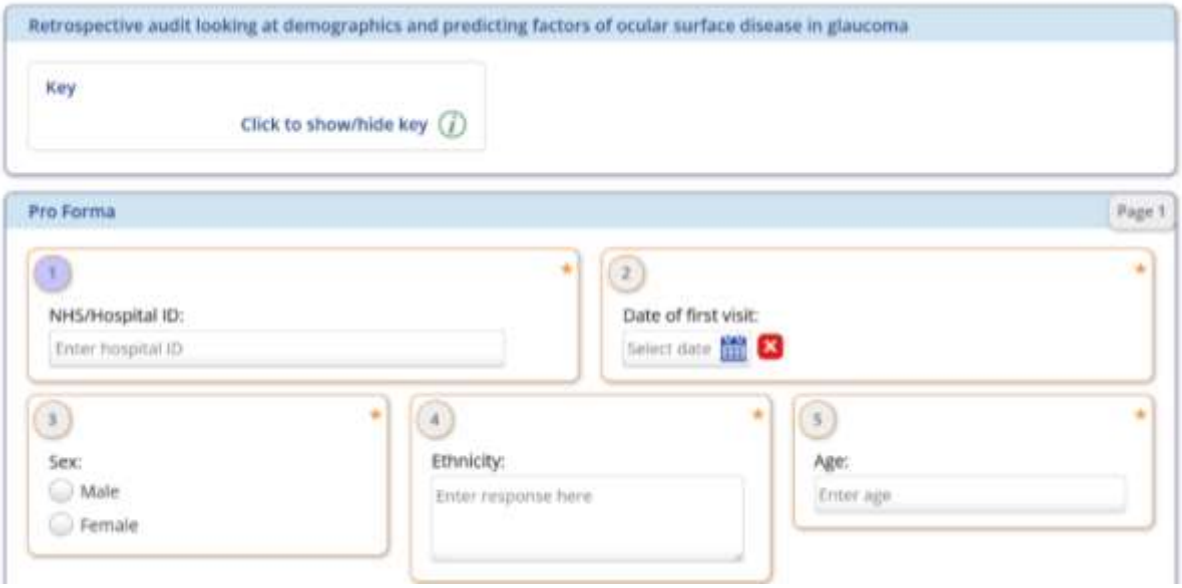
- "Partly for the Ganfort which is once a day the dorzolamide is so regular it is now part of my daily routine"
- "Cosopt an hour before bed and then same time in the morning. Lumigan just before bed"
- "Routine"
- "Linked to set points in daily routine (3x / day)"
- "Use once a day at bedtime so don`t need a reminder"
- "Routine/good memory"
- "Before bed - leave them out as a reminder"
- "I take other medication twice a day already, so the drops have become part of an established routine"
- "a wife"
- "on my bedside table"
- "My parner /carer does this for me 4 times daily"
- "a written reminder on a card in prominent place"
- "I take other medication at same time so it reminds me"
- "I do it first thing in the morning & around 2.00pm then just before going to sleep"
- "Memory"
- "Left in bedside table. Insert last thing at night"

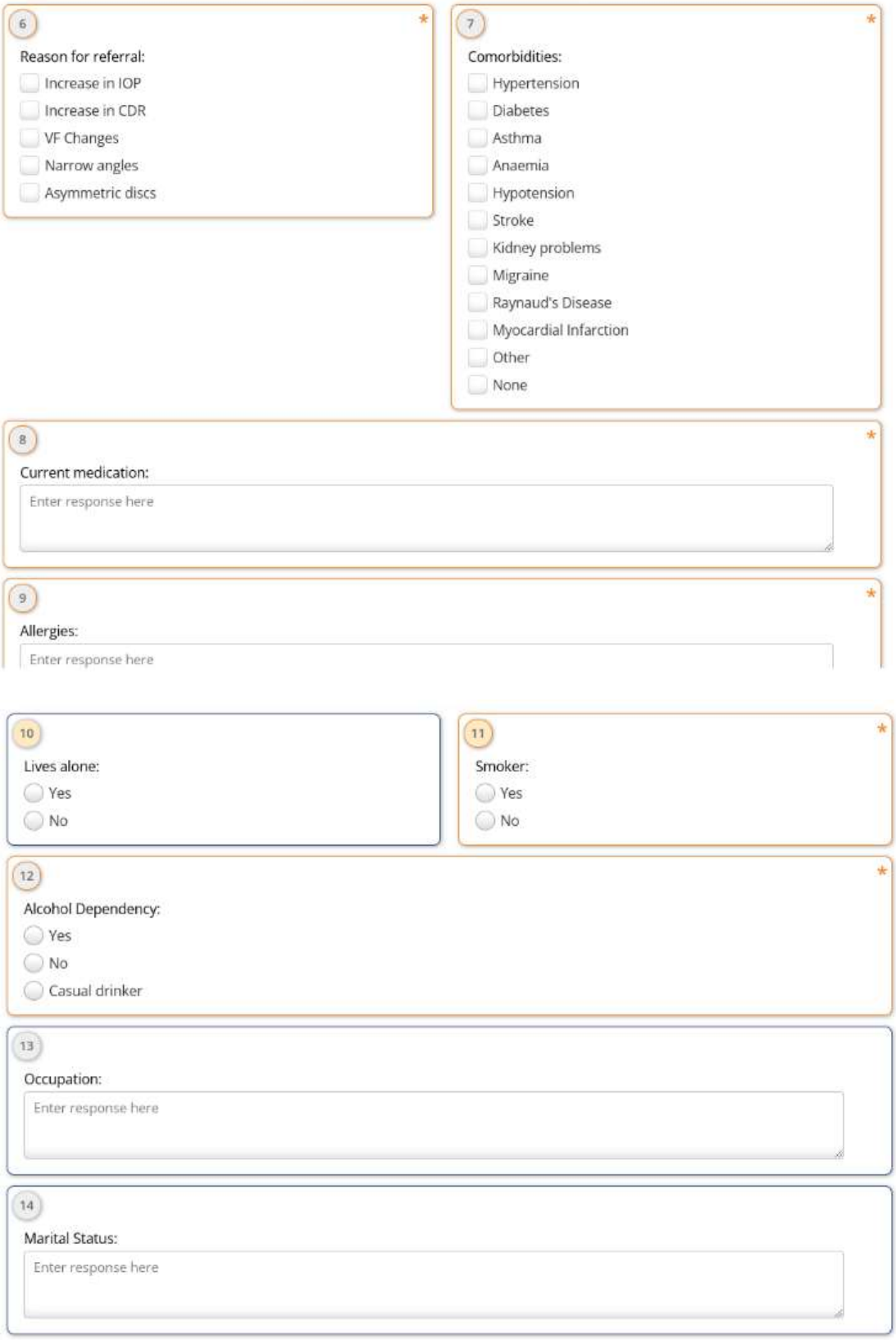
Hospital cohort

- "Set time each day"
- "Alexa"

- “Partner does it”
- “Drops at bedside table”
- “Each night before bed”
- “Morning and night”
- “Bottle by bed”
- “Don't have a kiss at night till it's done”
- “Evening habit, preparing medication for myself and husband”
- “Part of evening routine before getting into bed”
- “Before I retire each night”

10. Pro-forma for the retrospective audit as set out on AMaT




6
*
Reason for referral:
Increase in IOP
Increase in CDR
VF Changes
Narrow angles
Asymmetric discs
7
*
Comorbidities:
Hypertension
Diabetes
Asthma
Anaemia
Hypotension
Stroke
Kidney problems
Migraine
Raynaud's Disease
Myocardial Infarction
Other
None
8
*
Current medication:
Enter response here
9
*
Allergies:
Enter response here
10
Lives alone:
Yes
No
11
*
Smoker:
Yes
No
12
*
Alcohol Dependency:
Yes
No
Casual drinker
13
Occupation:
Enter response here
14
Marital Status:
Enter response here

15 *

Family history of glaucoma:

- [ ] Mother
- [ ] Father
- [ ] Brother
- [ ] Sister
- [ ] Grandparent
- [ ] None

16 *

Central Corneal Thickness RE:

17 *

Central Corneal Thickness LE:

18 *

Visual Fields RE (VFI):

Enter response here

19 *

Visual Fields LE (VFI):

Enter response here

20 *

GAT RE:

21 *

GAT LE:

22 *

Gonioscopy RE:

- [ ] Grade 1
- [ ] Grade 2
- [ ] Grade 3
- [ ] Grade 4
- [ ] not performed

23 *

Gonioscopy LE:

- [ ] Grade 1
- [ ] Grade 2
- [ ] Grade 3
- [ ] Grade 4
- [ ] not performed

24 *

CD ratio RE:

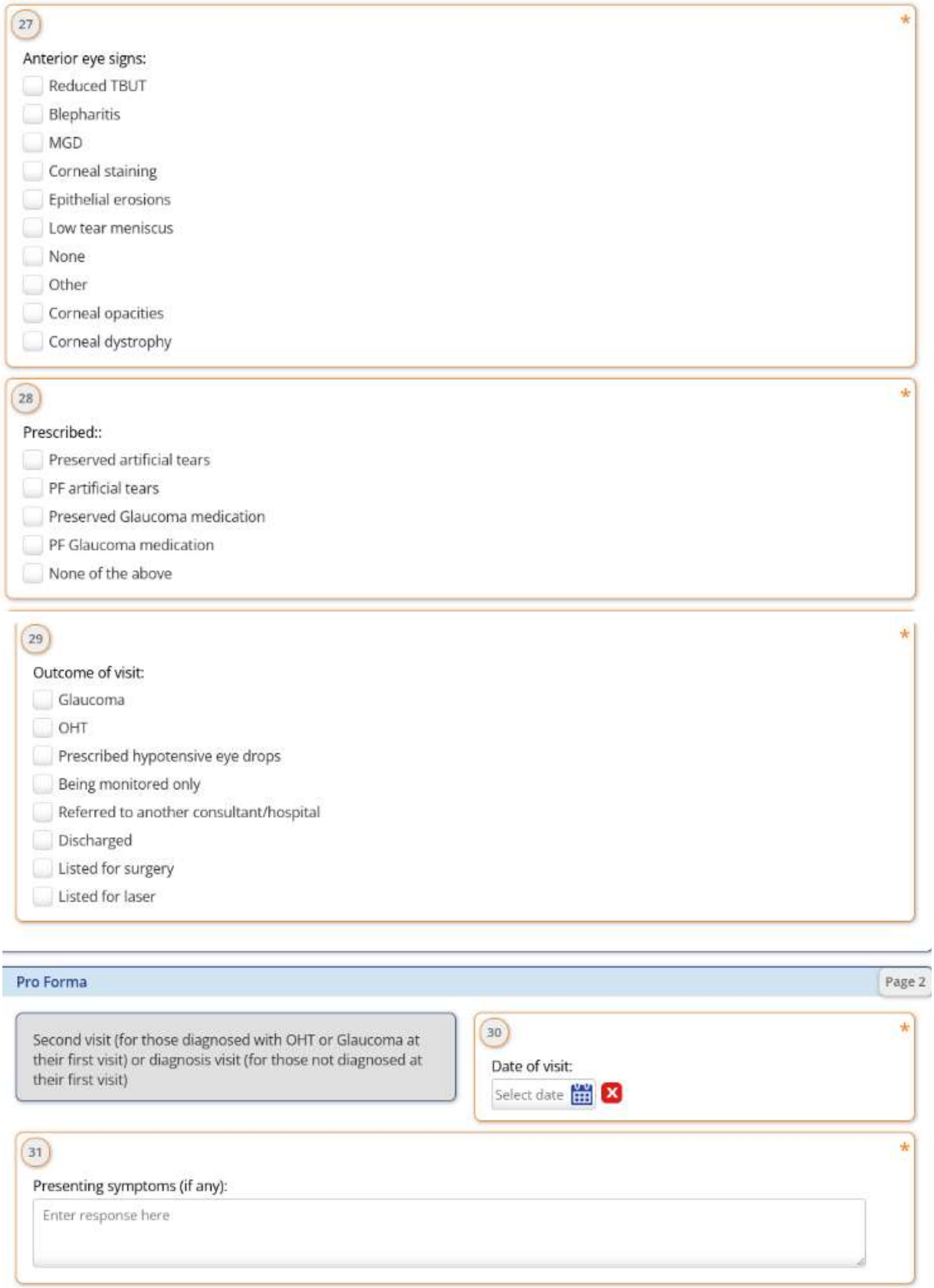
25 *

CR ratio LE:

26 *

Ocular surface disease/dry eyes recorded/diagnosed?:

- ( ) Yes
- ( ) No


27
*
Anterior eye signs:
Reduced TBUT
Blepharitis
MGD
Corneal staining
Epithelial erosions
Low tear meniscus
None
Other
Corneal opacities
Corneal dystrophy
28
*
Prescribed::
Preserved artificial tears
PF artificial tears
Preserved Glaucoma medication
PF Glaucoma medication
None of the above
29
*
Outcome of visit:
Glaucoma
OHT
Prescribed hypotensive eye drops
Being monitored only
Referred to another consultant/hospital
Discharged
Listed for surgery
Listed for laser
Pro Forma
Page 2
Second visit (for those diagnosed with OHT or Glaucoma at their first visit) or diagnosis visit (for those not diagnosed at their first visit)
30
*
Date of visit:
Select date
31
*
Presenting symptoms (if any):
Enter response here

32 *

Anterior eye signs:

- [ ] Reduced TBUT
- [ ] Blepharitis
- [ ] MGD
- [ ] Corneal staining
- [ ] Epithelial erosions
- [ ] Low tear meniscus
- [ ] None
- [ ] Other

33 *

Ocular surface disease/dry eyes recorded/diagnosed:

- ( ) Yes
- ( ) No

34 *

Prescribed::

- [ ] Preserved artificial tears
- [ ] PF artificial tears
- [ ] Preserved Glaucoma medication
- [ ] PF Glaucoma medication
- [ ] None of the above

35 *

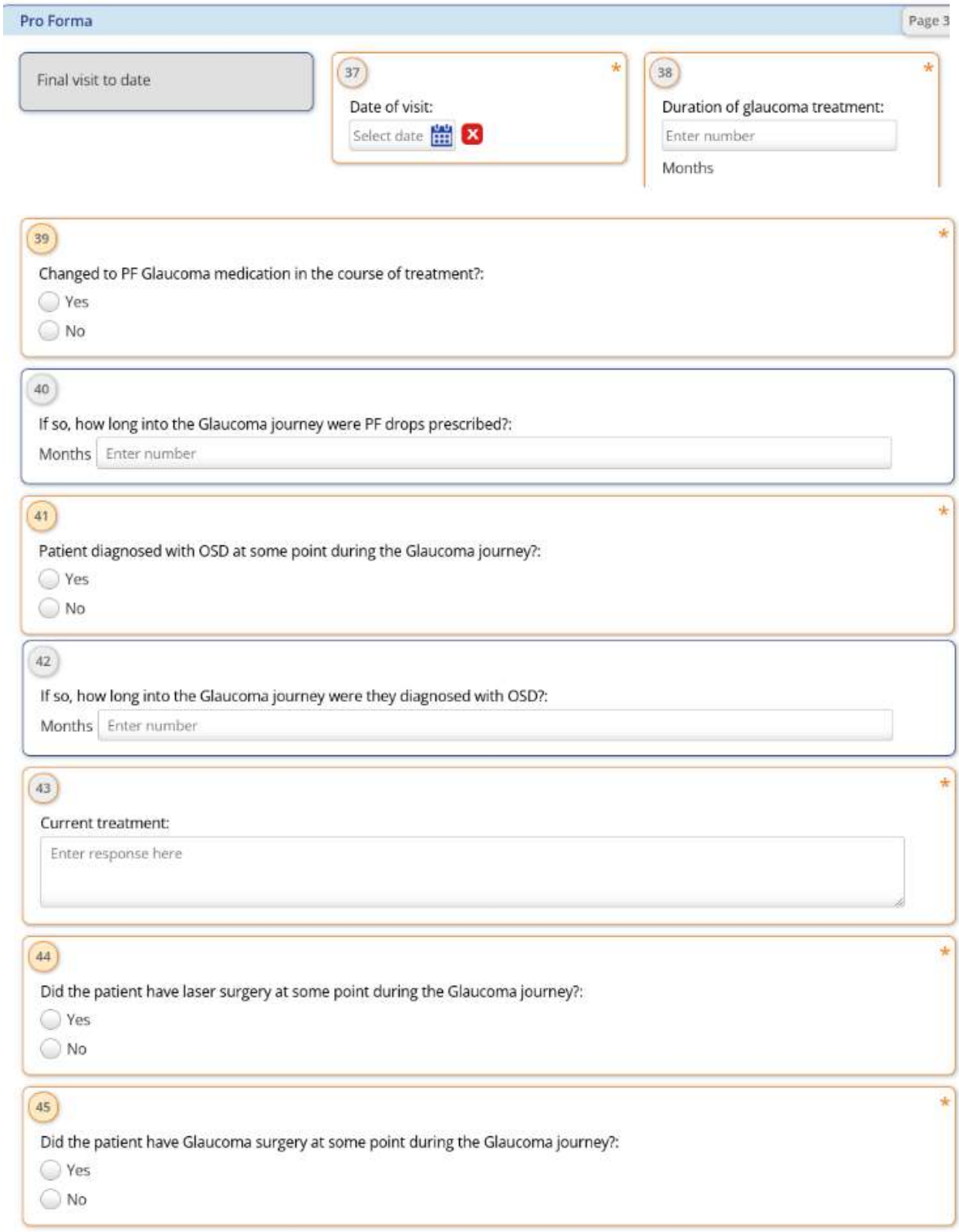
Outcome of visit:

- [ ] Glaucoma
- [ ] OHT
- [ ] Prescribed hypotensive drops
- [ ] Being monitored only
- [ ] Referred to another consultant/hospital
- [ ] Discharged
- [ ] Listed for surgery
- [ ] Listed for laser

36

First line therapy in those prescribed hypotensive drops:

Enter response here


Pro Forma
Page 3
Final visit to date
37
Date of visit:
Select date
38
Duration of glaucoma treatment:
Enter number
Months
39
Changed to PF Glaucoma medication in the course of treatment?:
Yes
No
40
If so, how long into the Glaucoma journey were PF drops prescribed?:
Months
Enter number
41
Patient diagnosed with OSD at some point during the Glaucoma journey?:
Yes
No
42
If so, how long into the Glaucoma journey were they diagnosed with OSD?:
Months
Enter number
43
Current treatment:
Enter response here
44
Did the patient have laser surgery at some point during the Glaucoma journey?:
Yes
No
45
Did the patient have Glaucoma surgery at some point during the Glaucoma journey?:
Yes
No

11. OSDI

OCULAR SURFACE DISEASE INDEX©

Please answer the following questions by checking the box that best represents your answer.

Have you experienced any of the following during **the last week**:

	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?	☐	☐	☐	☐	☐
2. Eyes that feel gritty?	☐	☐	☐	☐	☐
3. Painful or sore eyes?	☐	☐	☐	☐	☐
4. Blurred vision?	☐	☐	☐	☐	☐
5. Poor vision?	☐	☐	☐	☐	☐

Have problems with your eyes limited you in performing any of the following during **the last week**:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?	☐	☐	☐	☐	☐	☐
7. Driving at night?	☐	☐	☐	☐	☐	☐
8. Working with a computer or bank machine (ATM)?	☐	☐	☐	☐	☐	☐
9. Watching TV?	☐	☐	☐	☐	☐	☐

Have your eyes felt uncomfortable in any of the following situations during **the last week**:

	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?	☐	☐	☐	☐	☐	☐
11. Places or areas with low humidity (very dry)?	☐	☐	☐	☐	☐	☐
12. Areas that are air conditioned?	☐	☐	☐	☐	☐	☐

Scoring Instructions

Item scoring

The total OSDI score is calculated based on the following formula:

$$\text{OSDI} = \frac{(\text{sum of severity for all questions answered}) \times (100)}{(\text{total \# of questions answered}) \times (4)}$$

where the severity was graded on a scale of

0 = none of the time,
1 = some of the time,
2 = half of the time,
3 = most of the time,
4 = all of the time.

Interpretation

A score of 100 corresponds to complete disability (a response of "all of the time" to all questions answered), while a score of 0 corresponds to no disability (a response of "none of the time" to all questions answered). Therefore, change from baseline of –12.5 corresponds to an improvement by at least one category in half of the questions answered.

Subscale Scoring

Subscales scores are computed similarly with only the questions from each subscale used to generate its own score. Therefore, any subscales analyzed separately would also have a maximum possible score of 100.

The three subscales (vision-related function, ocular symptoms and environmental triggers) are broken out as follows:

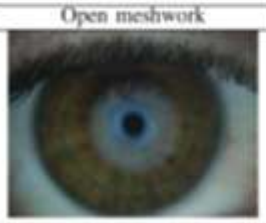
Subscale	Questions
Vision-Related Function	4, 5, 6, 7, 8, 9
Ocular Symptoms	1, 2, 3
Enviromental Triggers	10, 11, 12

Ocular Surface Disease Index (OSDI©) from the TFOS DEWS II Diagnostic Methodology report (Wolffsohn et al., 2017). Original source 1995 Allergan Inc. Irvine, CA, USA.

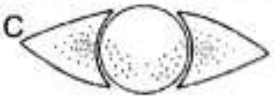
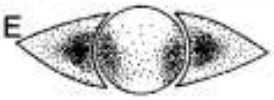
12. Fringe pattern images used for comparison in the EGC clinic

Images are from a study by Bolón-Canedo and colleagues (2012) and based on the grading scale of the Guillon categories: Grade 1 Open Meshwork, Grade 2 Closed Meshwork, Grade 3 Wave and Grade 4 Coloured fringes. The amorphous category was omitted due to its uncommon nature, and thus, the lack of available images to compare to this category (Bolón-Canedo et al., 2012, Guillon, 1998)

TABLE I
LIPID LAYER INTERFERENCE PATTERNS.

	Open meshwork	Closed meshwork	Wave	Colour fringe
Original image				
Appearance	Grey appearance of low reflectivity and meshwork pattern faintly visible.	More compact meshwork pattern with grey appearance of average reflectivity and more lipid than open meshwork.	Vertical or horizontal grey waves of good visibility.	Discrete brown and blue well-spread lipid layer interference fringes superimposed on a whitish background.
Estimated thickness	13-15 nm	30-50 nm	50-80 nm	90-140 nm

13. Oxford grading scale

PANEL	GRADE	CRITERIA	DOT COUNT	LOG	VERBAL DESCRIPTOR
A 	0	Equal to or less than panel A	1	0	Absent
B 	I	Equal to or less than panel B, greater than A	10	1.0	Minimal
C 	II	Equal to or less than panel C, greater than B	32	1.5	Mild
D 	III	Equal to or less than panel D, greater than C	100	2.0	Moderate
E 	IV	Equal to or less than panel E, greater than D	316	2.5	Marked
>E	V	Greater than panel E	>316	>2.5	Severe

The Oxford grading scale for corneal and conjunctival staining (Bron et al., 2003)

14. Follow up questionnaire used in the Pilot study

CLINICAL STUDY FOLLOW UP QUESTIONNAIRE

Px ID:

Start date of treatment:

Date:

Drops used:

Frequency of drops:

Tell me in your own words what your understanding and concerns about glaucoma are:

No. of drops missed since start:

Reasons for missing drop instillation:

Ease of handling drops (1=very easy, 10=very hard):

Any problems with drops/side effects:

Happy to continue with treatment? Y/N

Need to book Px in earlier to review problems?

Additional comments:

OSDI questionnaire completed? Y/N

Representation of the follow up questionnaire used for telephone consultations