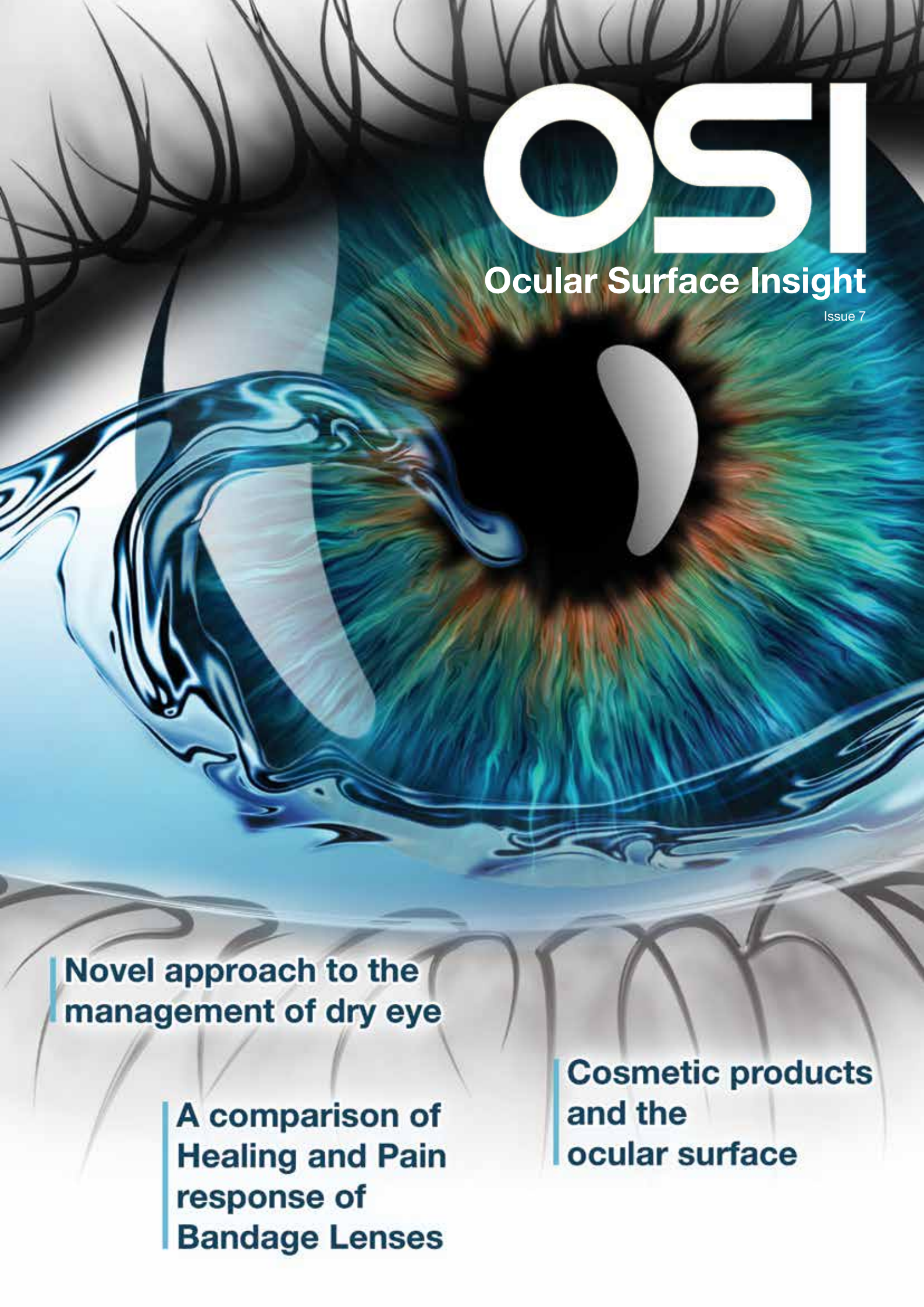

# OSI

## Ocular Surface Insight

Issue 7

Novel approach to the management of dry eye

A comparison of Healing and Pain response of Bandage Lenses

Cosmetic products and the ocular surface

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# Ocular Surface Insight

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Roy Bennett

## Welcome to the Autumn issue of OSI.

Welcome to the Autumn issue of the OSI magazine! I am delighted to announce that we will hold the 2nd OSI symposium on the 12th March 2020. Following much positive feedback from our 1st symposium in January this year, we are keen to make the OSI symposium an annual event, where both clinicians and the industry can share best practices in the treatment of the ocular surface.

The symposium will cover a wide range of topics and provide the opportunity for discussion about the most up to date ocular surface treatments. This will appeal to ophthalmologists, trainee ophthalmologists and specialist optometrists. We will introduce a dedicated session on patient compliance and what can be done to improve compliance for best outcomes and experiences for the patients.

In this issue of OSI we have many interesting articles, but I want to make a special mention about cosmetics and their effect on the ocular surface. This is a topic my team and I have been keen to cover for a while as this concern is one of the most frequently asked questions by female patients. There has been a lack of awareness about the ingredients in cosmetics, such as benzalkonium chloride (BAK), in which there has already been a huge drive to be removed from eye drops. The Harry Roberts article is covering various aspect of this and it is something which practitioners should be aware of.

We are also introducing a new concept in managing ocular surface disease which applies to the inflammation of the ocular surface and its microenvironment. This concept will help ophthalmologists to accurately diagnose ocular pathology and treat it appropriately to restore the homeostasis of the ocular surface.

We met with Amy Sullivan from the non-profit making TFOS this summer when she visited London. We agreed to keep highlighting the DEWS II practical tips and messages in the OSI magazine. Therefore in this issue we are publishing the patient focussed summary of the DEWS II report.

*Samer Hamada*

Samer Hamada,
MD, MSc, DO (hons), FRCSEd, FRCOphth

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## Ocular Surface Insight

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If you are interested in submitting an article, please get in touch by emailing: articles@visionduo.com

# Contents




# What's in the news?

## Six months' treatment with lifitegrast in patients with moderate-to-severe symptomatic dry eye: a retrospective chart review

The purpose of this study was to evaluate 6-month treatment benefits with lifitegrast ophthalmic solution 5% in symptomatic dry eye patients.

A retrospective chart review was conducted in 168 patients (111 females and 57 males) who presented with symptoms of chronic dry eye disease and were treated with lifitegrast 5% ophthalmic solution for 6 months. Collected symptom data included improvement of eye dryness, tearing, eye pain, fluctuation in vision, foreign body sensation, itching, grittiness, burning and contact lens intolerance if applicable. Collected clinical signs included changes in superficial punctate keratitis, corneal fluorescein staining, conjunctival hyperemia and presence of tear debris.

The results showed that treatment with lifitegrast ophthalmic solution 5% twice daily for 6 months significantly improved majority of dry eye symptoms reported by patients. Improvements were also observed in corneal and conjunctival staining and tear debris for most of the patients reviewed. The authors concluded that treatment with lifitegrast twice a day for 6 months improved both signs and symptoms of chronic dry eye.

Authors: Atallah RT, Castanos MV, Najac R, Donnenfeld E
Clin Ophthalmol. 2019 Jun 19;13:1033-1037. doi: 10.2147/OPTH.S191635.

## Reduction of Ocular Surface Damage and Bacterial Survival Using 0.05% Povidone-Iodine Ocular Surface Irrigation before Cataract Surgery

This study aimed to investigate the effects of 0.05% povidone-iodine (PI) irrigation on the ocular surface structure and bacterial survival rate in patients with cataract.

Ninety eyes of 90 patients with cataract were included. Before surgery, the operative field was irrigated with 0.05% PI and divided into 30-s, 1 and 2-min groups. Anterior chamber fluid was cultured bacteriologically. Tear film breakup time (BUT), corneal fluorescein staining (CFS), lacrimal river height (LRH) and Schirmer test I (STI) were conducted to assess ocular surface.

In all groups, the patients had significantly shorter postoperative BUT at 1 day, 3 days and 1 week postoperatively than preoperatively. In addition, there was still lower BUT at 1 month postoperatively in the 1- and 2-min groups. STI and LRH were all decreased postoperatively at different time points (1 day, 3 days, 1 week), while CFS was increased. With the extension of time preoperatively (1 and 3 months), the ocular surface indicators returned to the preoperative level. The bacterial cultures after eye irrigating were negative in all groups.

The conclusion reached was that 0.05% PI irrigating the conjunctival sac for 30 s can achieve a low bacterial contamination rate. Importantly, it reduced the damage of ocular surface, which is beneficial to the recovery of ocular surface function.

Authors: Fan F, Zhao Z, Zhao X, Ma Q, Li K, Fu W, Jia Z. Ophthalmic Res. 2019 Jul 26:1-7. doi: 10.1159/000501373.

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**Date of last revision of Prescribing Information:** 17/07/2019.

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1. Baudouin C et al. Br J Ophthalmol 2014;98:1168 - 1176
2. Craig J et al. Ocul Surf 2017;15(4):802 - 812
3. Leonardi A et al. Eur J Ophthalmol 2016;26(4):287 - 296.


**Date of preparation:** July 2019 **Job code:** PP-IKERVI-UK-0208

# What's in the news?

## Prevalence and antibiotic susceptibility of bacteria isolated in patients affected with blepharitis in a tertiary eye centre in Spain

To describe which bacteria can be found on lid margins in patients affected with blepharitis, to show their antibiotic susceptibility pattern and to evaluate the antibiotic resistance trend of coagulase-negative Staphylococcus through time.

Consecutive cases of 198 eyes affected with blepharitis between 2012 and 2018 were reviewed. A sample was collected by rubbing a swab against the base of the eye-lashes of both the eyes of all patients. The samples were inoculated in blood agar and chocolate agar. The susceptibility of the identified bacteria to common antibiotics was tested. In addition, the antibiotic susceptibility pattern of coagulase-negative Staphylococcus detected from year 2016 to 2018 was compared with that of 4 years before.

The most common isolated bacterium was coagulase-negative Staphylococcus (89%) and Staphylococcus aureus (28%). Coagulase-negative Staphylococcus showed highest susceptibility to vancomycin (100%), neomycin (94%) and chloramphenicol (91%). Coagulase-negative Staphylococcus and Staphylococcus aureus were the most resistant to penicillin and erythromycin (resistance in 92%, 91% for coagulase-negative Staphylococcus, 86% and 43% of eyes for Staphylococcus aureus). Corynebacterium was resistant to oxacillin and erythromycin. Streptococcus viridans showed resistance to gentamycin and tobramycin. Moraxella was susceptible to most antibiotics. Bacillus was resistant to oxacillin. The antibiotic resistance trend of coagulase-negative Staphylococcus showed that the resistance to rifampicin increased through the years 2012-2018.

The authors reached the conclusion that Coagulase-negative Staphylococcus and Staphylococcus aureus were the most isolated bacteria in patients affected by blepharitis in the tertiary eye centre. Both bacteria were resistant to erythromycin. Through the years, it seems that coagulase-negative Staphylococcus gained resistance to penicillin, erythromycin, ciprofloxacin and rifampicin.

Authors: de Paula A, Oliva G, Barraquer RI, de la Paz MF. Eur J Ophthalmol. 2019 Jun 24: 1120672119854985. doi: 10.1177/1120672119854985.

## Combined low level light therapy and intense pulsed light therapy for the treatment of meibomian gland dysfunction

This multi-centre study set out to evaluate the effects of combined intense pulsed light therapy (IPL) and low-level light therapy (LLLT) on clinical measures of dry eye related to severe meibomian gland disease (MGD) in subjects unresponsive to previous medical management.

This was a retrospective chart review of patients treated by four physicians at three centres. All patients were documented treatment failures with traditional pharmaceutical therapy. They all had their MGD evaluated before treatment using a grading scale (0-4), tear breakup time in seconds and the Ocular Surface Disease Index (OSDI) questionnaire. To be included, all patients had to have had a short course of adjunct pharmaceutical or device-related therapy, along with a combined IPL/LLLT treatment. As well, a second MGD evaluation with the same three measures had to have been conducted 1-3 months post treatment.

A total of 460 eyes of 230 patients were identified for inclusion in the data set. Mean OSDI scores were significantly lower after treatment; 70.4% of patients had pre-treatment OSDI scores indicative of dry eye; this dropped to 29.1% of patients after treatment. A 1-step or greater reduction in MGD grading was observed in 70% of eyes, with 28% of eyes having a 2-step or greater reduction. Tear breakup time was ≤6 seconds in 86.7% of eyes pre-treatment, dropping to 33.9% of eyes after treatment. There were no ocular or facial adverse events or side effects related to the combined light treatment.

Having reviewed all the data they concluded that the use of combined IPL/LLLT for the treatment of severe MGD appears to be beneficial in patients who have failed topical and/or systemic therapy.

Authors: Stonecipher K, Abell TG, Chotiner B, Chotiner E, Potvin R. Clin Ophthalmol. 2019 Jun 11;13:993-999. doi: 10.2147/OPTH.S213664. eCollection 2019.

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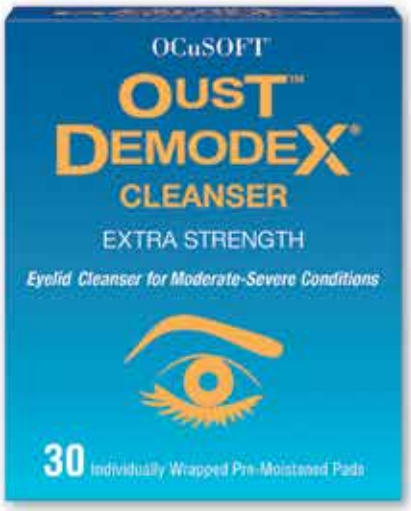


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# Cosmetic products and the ocular surface

by **Harry Roberts**

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Corneal ASTO, Norfolk & Norwich University Hospital

Acknowledgements: Carolyn Cates.

Ocular cosmetics (chiefly mascara, eye-liner and eye shadow) are commonly used world-wide and by predominantly females of all ages and cultures. Unfortunately they are known to be detrimental to the function of the ocular surface via various mechanisms[1,2]. While there is less evidence on the effects of make up removers (MURs), these are also likely to have negative effects on the ocular surface.

Despite the intended external application of ocular cosmetics, migration of the products onto the posterior lid margin and into the tear film has been well documented[2]. Migration of the make up to the posterior lid margin is a common sign on slit lamp examination of make-up users, this may result in increased meibomian gland plugging and disruption of the lipid layer leading to tear film instability and evaporative dry eye symptoms[3]. Within the tear film, several mechanisms relating to secondary ocular surface insult have been hypothesized, including the detergent and cytotoxic effects of preservatives such as benzylammonium chloride (BAK), toxicity of metallic pigments in the product, or the destabilising effects to the lipid layer of lipophilic pigments within the cosmetic[2,4]. Furthermore there may be direct pro-inflammatory effects via an increase in tear film osmolarity as any hydrophilic components dissolve into the aqueous layer[2].

In contrast, there is a paucity of evidence on the effects to the ocular surface of the constituents of MURs. Generally speaking, the mechanism of action of MURs is to remove the lipophyllic cosmetic from the epidermis and they can be oil-based, water-based with surfactants or micelle-based[5]. Due to their mechanism of action, they are known to destabilise the tear film and increase evaporation. A common type of MUR are make-up remover wipes (MURWs). These are popular due to their convenience, portability, efficacy and cost-effectiveness and there is a predicted growth in their use (global growth of USD 3.71 Billion between 2018-2022) (cite the website https://www.technavio.com/report/global-facial-wipes-market-analysis-share-2018).

MURWs contain surfactants to dissolve the cosmetic, solubilisers and emulsifiers to promote adsorbtion to the cloth and preservatives to prevent bacterial or fungal contamination of this product in its resealable packaging. Possible harms of MURWs may include allergy or toxicity of any of the chemical constituents including the preservative.

Surfactants solubilising the skin sebum may lead to drying of the skin and peri-ocular
dermatitis as well as disrupting the tear film lipid layer. The residue of the remaining solution and the cosmetic on the skin and lid margin may lead to bacterial overgrowth, clogging of the Meibomian glands, or migration onto the ocular surface with similar effects as above. Preservatives in MURWs may include BAK, formaldehyde-releasing agents and isothiazolinones. BAK has pro-inflammatory, cytotoxic and surfactant properties[6]. Formaldehyde, a known carcinogen, is pro-allergenic and associated with increased blinking frequency, conjunctival hyperaemia and conjunctival epithelial cell reduced survivability[7,8]. Isothiazolinones have received significant negative attention in the dermatological literature, but there is a paucity of research on their effects on the ocular surface[9,10]. It is known however that there are relatively high prevalence rates of sensitisation to isothiazolinone across developed nations (1.0-8.4%)[11]. In the absence of better evidence, it seems prudent to recommend to our patients to avoid

products containing isothiazolinones. Toxic conjunctival reaction to ocular cosmetics and/or MURWs has been previously reported as presenting with epiphora in the absence of other allergic symptoms such as itch[12]. We have previously identified a similar cohort of patients where we have suspected that the patient's use of MURWs has contributed to the clinical picture of bilateral frank epiphora, usually associated with a chronic tarsal conjunctivitis. In these patients we observed that the ocular cosmetics used varied between patients (mascara, eyeliner, eye shadow) whereas the patients were unified by the use of MURWs without the use of make-up remover liquids or suspensions. This led us to believe that there must be a common substance or mechanism within many MURWs which can be toxic to the ocular surface and/or exacerbate concurrent ocular surface disease (OSD).

Identification of the role of cosmetics and cosmetic remover in OSD patients is important, because once identified, treatment (i.e. cessation of the product) is relatively simple. Early suspicion of conjunctival toxicity is important in young females with bilateral symmetrical symptoms, thus avoiding unnecessary invasive investigations or treatments. Many patients are not overjoyed to be told to limit their use of cosmetics and the effects of ocular cosmetics on self-confidence have been previously reported[13]. In these instances, it is important to promote reduction rather than abstinence (depending on the clinical picture) and micellar water may offer less ocular surface toxicity than MURWs, albeit in the absence of specific peer-reviewed evidence. The mechanism of action of micellar water is that it encapsulates insoluble residues on the skin within micelles of surfactant which are subsequently removed, avoiding the use of solvents such as alcohol or requiring rubbing of the skin and associated trauma[14]. It is perhaps even more important to stress the need to remove any residue from MURs with dry adsorbent pads. A course of topical steroids is effective in masking the toxicity from these products, however cessation ought to be considered as the first line treatment in cases where cosmetics are felt to be exacerbating OSD[12].

There are some confounding hurdles in evaluating the role of cosmetics and cosmetic remover in our OSD patients.

Users may vary their choice of cosmetics on a daily basis and in all cases, there is a confounding concurrent use of ocular cosmetics with a cosmetic remover, where there may be an interaction between ingredients of each. Furthermore a cosmetic product is a mixture of many ingredients, each with their own effects on the lid margin and tear film. MURs are first and foremost designed for the skin, which has significantly different local chemistry from the tear film and mucous membrane of the ocular surface, but it remains unknown whether specifically formulated eye make up removers convey an advantage. Despite the negative effects of cosmetics and their removers, there may be a confounding effect when used judiciously with efficacious removal acting as effective lid hygiene which may promote better ocular surface health.

OSD Patients need to be counselled as to the effects of their choice to use ocular cosmetics so they may make a balanced decision. Evaluating the specific effects to the ocular surface in a scientific manner is hampered by the range of products available and the panoply of ingredients within each product.

There are some confounding hurdles in evaluating the role of cosmetics and cosmetic remover in our OSD patients. Users may vary their choice of cosmetics on a daily basis and in all cases, there is a confounding concurrent use of ocular cosmetics with a cosmetic remover, where there may be an interaction between ingredients of each.

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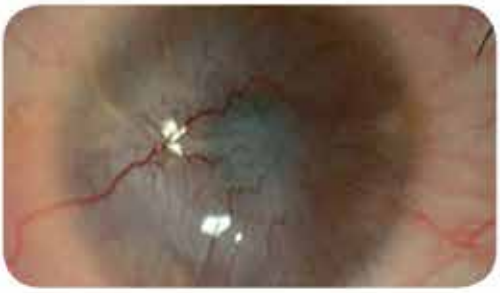



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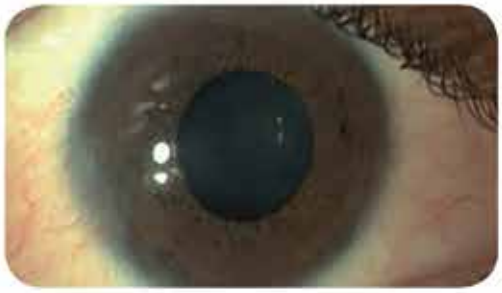



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**Presentation:** *Ex vivo* expanded autologous human corneal epithelial cells containing stem cells. Each Holoclar transparent circular sheet consists of 300,000 to 1,200,000 viable autologous human corneal epithelial cells (79,000 - 316,000 cells/$cm^2$), including on average 3.5% (0.4 to 16%) limbal stem cells, and stem cell-derived transient amplifying and terminally differentiated cells, attached on a supportive 2.2 cm diameter fibrin layer and maintained in the transport medium. **Indications:** Treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1 - 2 $mm^2$ of undamaged limbus is required for biopsy. **Posology:** This medicinal product is intended for autologous use only. Holoclar must be administered by an appropriately trained and qualified surgeon and is restricted to hospital use only. The amount of cells to be administered is dependent on the size (surface in $cm^2$) of the corneal surface. Each preparation of Holoclar contains an individual treatment dose with sufficient number of cells to cover the entire corneal surface. The recommended dose of Holoclar is 79,000 - 316,000 cells/$cm^2$, corresponding to 1 $cm^2$ of product/$cm^2$ of defect. Each preparation is intended as a single treatment. Treatment may be repeated if considered indicated by the treating physician. The administration should be followed by an appropriate antibiotic and anti-inflammatory treatment schedule, as discussed in the SPC. *Elderly:* data on use limited. No recommendation on posology can be made. *Hepatic and renal impairment:* data not available. *Paediatric population:* safety and efficacy in children and adolescents aged 0 to 18 years has not yet been established. **Contraindications:** Hypersensitivity to any of the excipients or to bovine serum and murine 3T3-J2 cells. **Warnings and precautions:** Holoclar is an autologous product and should under no circumstances be administered to anyone other than the donor patient. Holoclar contains lethally-irradiated murine 3T3 fibroblast cells and may contain traces of foetal bovine serum. Patients with a known hypersensitivity to mice or foetal bovine serum must not be treated. Holoclar could contain potentially infected biological material. Concomitant eyelids malposition, conjunctival scarring with fornix shortening, corneal anaesthesia and/or conjunctival anaesthesia or severe hypoaesthesia, pterygium and severe dry eye are potential complicating factors. When possible, concomitant eye problems should be corrected prior to implantation. Patients with acute ocular inflammation or infections should be deferred until recovery has been documented since inflammation may compromise treatment success. The procedure of Holoclar administration includes the use of antibiotics and corticosteroids. For relevant safety information, physicians should consult the SPC of these medicinal products. **Interactions:** No interaction studies have been performed. Eye-drops containing benzalkonium chloride, and/or other preservatives, must be avoided. Benzalkonium chloride (as well as other quaternary ammonium compounds) is cytotoxic and eye drops containing this preservative may damage the newly-regenerated corneal epithelium. Other cytotoxic agents must be avoided. No interactions with post-biopsy/post-operative treatment reported. **Fertility, pregnancy and lactation:** No data for use in pregnancy. Animal studies not available with respect to reproductive toxicity. As a precautionary measure and in light of requirement of post-operative pharmacological treatment, it is preferable to avoid the use of Holoclar during pregnancy. Holoclar is not recommended for implant during breast-feeding. No clinical data on effects on fertility available. **Effects on driving and operating machinery:** The surgical nature of the underlying implantation procedure has a major influence on the ability to drive and use machines. Therefore, driving and using machines must be limited and patients should follow the advice of the treating physician. **Side effects:** *Very common:* blepharitis. *Common:* conjunctival haemorrhage, eye haemorrhage, corneal epithelium defect, eye pain, glaucoma/intraocular pressure increased, ulcerative keratitis. *Uncommon:* corneal infection, syncope vasovagal, conjunctival adhesion, conjunctival hyperaemia, corneal oedema, corneal perforation, eye irritation, photophobia, haemorrhage subcutaneous, metaplasia of the implant, suture rupture (Refer to SPC for full list of side effects). **Legal category:** POM **Price and Procedure:** £80,000 per individual treatment per eye. **Marketing authorisation (MA) No:** EU/1/14/987/001. **UK Distributor:** Chiesi Limited, 333 Styal Road, Manchester, M22 5LG. **Date of Preparation:** May 2018

**Prior to prescribing Holoclar, please contact Chiesi Medical Information on 0800 0092329 (UK) or 1800 817459 (IE).**

**Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Chiesi Limited on 0800 0092329 (UK), 1800 817459 (IE) or PV.UK@Chiesi.com.**

**▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.**


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UK-HOL-1900008

Date of Preparation: February 2019

# Dry eye and Omega 3 – essentials about the essentials

by **Saj Kahn**

For more than the last quarter of a century, the awareness of the prevalence and significance of the condition often dismissively referred to as 'mere' dry eye has been increasing at an exponential rate.

As a condition that afflicts hundreds of millions of people throughout the world, affects quality of life on a par with angina(1) and increases the risk of anxiety/depression by 50% (2), dry eye disease (DED) is one of the most frequent causes of patient visits to eye care practitioners.

Even before the 1995 NEI/Industry Workshop on Clinical Trials in Dry Eye, dedicated groups of ophthalmic practitioners and scientists have been attempting to produce a universally agreed definition, classification and management plan for DED. As the collaborations and focus of these groups have evolved, most notably resulting in the publishing of the first and second reports of the Dry Eye Workshop (DEWS 1 & 2) of the Tear Film and Ocular Surface Society (TFOS) in 2007 and 2017 respectively, so too has the evidence base and congruity of approach.
The most recent definition of dry eye from DEWS 2 states "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".

If we take a moment not to be put off by the length of the statement, this is less restrictive than earlier definitions but with a more comprehensive acknowledgement of the causal role of factors such as hyperosmolarity and ocular surface inflammation.

In between DEWS 1 and 2, the opening sentence of the report of the 2011 International Workshop on Meibomian Gland Dysfunction(MGD) states "Meibomian gland dysfunction (MGD) may well be the leading cause of dry eye disease throughout the world", though only tentatively touching on the association of inflammation as a causative factor., whilst Badouin et al. identify a much stronger association at several points within the vicious circle of dry eye disease (3).
The consistent theme above is of inflammation, of various structures and at different stages of the pathophysiological process, being a pivotal root cause in the etiology of dry eye.

This is not new information.

The literature is strewn with a plethora of publications and references, but still today, despite this enhanced knowledge supported by an array of diagnostic tools and guidelines, I am surprised and disappointed on a weekly basis by how few patients with chronic, significant dry eye problems have been made aware of this basic fact. Sadly, most treatment for dry eyes is still advised as a reactive measure rather than being proactive and is focused as a local ocular treatment and not necessarily attempting to address some of the fundamental underlying issues.

Despite the DEWS reports having succinctly refined and provided a clear, systematic, 4 step approach to treatment, the lack of patient education is a failure of the first part of the first step – having always been taught that the easiest way to follow a path is to start at the beginning so you can only follow it in the right direction, this does not bode well – either for patient understanding/compliance, or for appropriate/successful treatment being provided by the practitioner.

In the absence of a direct local trigger such as trauma, inflammation anywhere in the body is fundamentally a

systemic process and one that is essentially determined by the balance of essential fatty acids (EFAs) in our system: omega 3 and omega 6.

In the context of MGD and dry eyes, inflammation will cause meibum to become thick and block the meibomian glands. The blocked glands become inflamed. As the blocked glands are not releasing healthy meibum to form the lipid layer of the tears, an evaporative dry eye results in irritation and inflammation of the ocular surface, which in turn also generates increased friction with the inflamed eyelid to propagate the vicious cycle of dry eye disease.

Essential fatty acids are essential in that they are not able to be produced or stored by the body and must therefore be consumed. Though both are needed for the body to function normally, omega 3 has anti-inflammatory properties whilst omega 6 is pro-inflammatory and thus the ratio of these 2 EFAs is crucial to good health – a fact long recognised by our colleagues taking care of patients with cardiovascular, joint, cognitive and skin problems amongst others.

Good sources of omega 3 are oily fish, flaxseed, nuts and dark leafy vegetables. There are different types of omega 3 but the most common are eicosapentaenoic acid(EPA), docosahexaenoic acid(DHA) and alphalinoleic acid(ALA), with EPA and DHA being the most important ones.

Omega 6 sources include vegetable oil, butter, mayonnaise and fast/ processed foods, which typically means most people will ingest more omega 6 than omega 3 on a daily basis. The pro-inflammatory effects of omega 6 are important in the healthy functioning of our immune and defence systems, but in excess those same properties become detrimental.

In an ideal scenario, the ratio of omega 3:6 should be close to 1:1. However, with modern western diets these ratios can be found as high as 1:25 and even 1:50. It is therefore important for patients with DED to supplement with high dose, high quality omega 3 supplements in order to restore the more optimal ratio and reduce the undesirable pro-inflammatory effects.

Patients suffering from dry eye and treated with high dose oral omega 3 supplements demonstrate clinical improvements in symtoms, meibum quality, ocular surface staining(4).

However it is important to understand that not all omega 3 supplements are the same. Omega 3 supplements are most commonly found in ethyl-ester form, as this is associated with cheaper production costs, but is recognised as being less bioavailable than the re-esterified triglyceride form which undergo an extra manufacturing step to remove the ethanol molecules from the ethyl-ester form (5,6).

In ethyl-ester form the body relies on pancreatic lipase enzymes to covert it into the triglyceride form to enable absorption – in the absence of this step the re-esterified triglyceride form is more easily absorbed and thus achieves between 3 and 6 fold greater bioavailability, which will typically translate to greater clinical efficacy.

In my own clinical practice I explain the above and recommend to all patients with clinically significant dry eye that they should commence regular oral re-esterifed omega 3 supplements, with the assumption that they will maintain supplementation, often at a reduced dose once controlled, for life. It is imperative that they understand the need for consistent and regular ingestion and that the effect will take a few weeks to build up gradually. Despite this, it is not uncommon to have patients commence treatment and then stop after a few weeks because they can not feel the benefit – until they stop taking the supplements and notice a more obvious deterioration of the improved symptoms.

As a long term (>25 years) dry eye sufferer myself, re-esterified oral omega 3 supplements, initially PRN Omega Eye and more recently at a lower dose with Optase Omega Vision, have been the foundation of my dry eye control for almost a decade – the consistency allowing me to be more flexible with my lid hygiene and lubrication regimes.

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**Eylamdo (dorzolamide/ timolol) Eye Drops Prescribing Information (please refer to the full SmPC before prescribing) Indications:** Elevated intraocular pressure (IOP) in patients with open-angle glaucoma or pseudoexfoliative glaucoma when topical beta-blocker monotherapy insufficient. **Available strength:** 20mg/ml dorzolamide + 5mg/ml timolol Eye Drops, in 5ml solution. **Dosage and method of use:** One drop in affected eye(s) twice daily. If another topical ophthalmic agent used, administer at least ten minutes apart. It is a sterile solution with no preservatives, which can be used for up to 28 days after first opening. Advise patients to wash their hands before use and avoid allowing the container tip to contact the eye. If handled improperly, contamination of ocular solutions can cause ocular infections. **Paediatrics:** Efficacy in paediatrics and safety below the age of 2 years has not been established. **Contraindications:** Patients with reactive airway disease, including bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease (COPD), sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with pacemaker, overt cardiac failure, cardiogenic shock, severe renal impairment (CrCl < 30ml/min) or hyperchloraemic acidosis and hypersensitivity to one or both active substances or excipients. **Special warnings and precautions for use:** Patients with cardiovascular diseases and hypotension therapy with beta-blockers should be assessed and therapy with other active substances considered. Due to its negative effect on conduction time, use with caution in patients with first degree heart block. Use with caution in patients with severe peripheral circulatory disturbance, mild/moderate COPD, hepatic impairment. Respiratory reactions, including death due to bronchospasm in patients with asthma reported following administration of some ophthalmic beta-blockers. As dorzolamide contains a sulfonamido group, which is absorbed systemically, adverse reactions can include Stevens-Johnson syndrome and toxic epidermal necrolysis. Discontinue Eylamdo if signs of serious reactions or hypersensitivity occur. When on beta-blockers, patients with history of atopy or severe anaphylactic reaction may be more reactive to repeated challenge with allergens and unresponsive to usual doses of adrenaline used to treat anaphylactic reactions. Use of two topical beta-adrenergic blocking agents not recommended. Use with oral carbonic anhydrase inhibitors not recommended. If discontinuation needed in patients with coronary heart disease, withdraw therapy gradually. Administer with caution in patients subject to spontaneous hypoglycaemia or labile diabetes, as beta-blockers may mask signs and symptoms of acute hypoglycaemia. May mask signs of hyperthyroidism so withdraw slowly to avoid worsening of symptoms. Caution in patients with corneal diseases as dryness of eyes may occur. May block systemic beta-agonist effects of adrenaline (for surgery, anaesthetist should be informed). Symptoms of myasthenia gravis may be aggravated. Patients with prior history of renal calculi may be at increased risk of urolithiasis. No studies in patients with acute angle-closure glaucoma. Use with caution in patients with pre-existing chronic corneal defects and/or a history of intraocular surgery. Choroidal detachment reported with administration of aqueous suppressant therapies after filtration procedures. Diminished responsiveness after prolonged therapy reported. Should not be used if contact hypersensitivity to silver as dispensed drops may contain traces of silver from container. No studies in patients wearing contact lenses. **Interactions:** Potential for additive effects resulting in hypotension and/or marked bradycardia when administered concomitantly with oral calcium channel blockers, catecholamine-depleting medicines or beta-adrenergic blocking agents, antiarrhythmics, digitalis glycosides, parasympathomimetics, guanethidine, narcotics, and monoamine oxidase (MAO) inhibitors. Potentiated systemic beta-blockade reported during combined treatment with CYP2D6 inhibitors. Mydriasis resulting from concomitant use with adrenaline has been reported. May increase hypoglycaemic effect of antidiabetic agents. May exacerbate rebound hypertension following withdrawal of clonidine. **Pregnancy & Lactation:** Should not be used during pregnancy or lactation. If administered until delivery, monitor neonate carefully during first days of life. **Side effects:** For full list of side effects consult SmPC. 'Very Common' 'Common' and 'Serious' side effects included. Very common (≥1/10) side effects: burning, stinging and dysgeusia. Common (≥1/100 to <1/10) side effects: headache, conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing, eyelid inflammation, eyelid irritation, signs and symptoms of ocular irritation including blepharitis, keratitis, decreased corneal sensitivity, dry eyes, sinusitis, nausea, asthenia/ fatigue. Uncommon Serious (≥1/1000 to <1/100) side effects: depression, iridocyclitis, bradycardia, dyspnoea, urolithiasis. Rare Serious (≥1/10000 to <1/1000) side effects: angioedema, anaphylaxis, myasthenia gravis exacerbation, cerebrovascular accident, cerebral ischaemia, corneal oedema, congestive heart failure, cardiac arrest, heart block, Raynaud's phenomenon, respiratory failure, bronchospasm, Stevens-Johnson syndrome, toxic epidermal necrolysis, systemic lupus erythematosus, choroidal detachment following filtration surgery. Frequency not known Serious (frequency cannot be estimated) side effects: atrioventricular block, cardiac failure. **MA number:** PL35533/0117 **Cost:** £14.29 for 20mg/ml dorzolamide + 5mg/ml timolol x 5ml. **MAH:** Aspire Pharma Ltd, Unit 4, Rotherbrook Court, Bedford Road, Petersfield, Hampshire, GU32 3QG. **Legal category:** POM. **Date reviewed:** September 2019. **Version number:** 1010368208 v 4.0

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ASPIRE PHARMA

# Global Effort To Increase Understanding Of Dry Eye Disease[1]

by **Amy Gallant Sullivan** and **TFOS**

To increase our understanding of dry eye disease, the Tear Film & Ocular Surface Society (TFOS) launched the Dry Eye Workshop II (TFOS DEWS II) in March 2015, which lasted for more than two years and involved the efforts of over 150 eye doctors and researchers around the world. The reason that TFOS sponsored and organized this initiative is because TFOS is a non-profit organization with a mission to advance eye and tear film research, knowledge and education. The goal of TFOS DEWS II was to achieve consensus among the diverse members to 1) update the definition and classification of dry eye; 2) clarify the patterns, causes and effects of the disease; 3) provide recommendations for the diagnosis, management and treatment of dry eye and 4) delineate clinical trial design for testing new therapies for dry eye. The entire TFOS DEWS II report is available on the TFOS website (http://www.TearFilm.org) and the TFOS DEWS II App (http://www.tearfilm.org/dettnews-download_the_tfos_dews_ii_app__view_tfos_dews_ii_videos/5602_16/eng/). This article presents a patient-focused Executive Summary of the conclusions and recommendations of the TFOS DEWS II Subcommittee reports. A glossary of terms appears at the end of this article. The authors of this Summary are cited in the reference list.[2]

## Classification And Definition Of Dry Eye Disease[3]

Evidence supports a classification scheme that accounts for elements of both aqueous deficient and evaporative types of dry eye in the diagnosis and management of the disease. Aqueous deficient dry eye refers to lacrimal gland dysfunction and evaporative dry eye includes both eyelid-related causes such as meibomian gland dysfunction (MGD), inadequate lid closure during sleep (nocturnal lagophthalmos) and blink-related problems and conditions related to the surface of the eye (e.g. changes to mucins or lipids).

Dry eye has both symptoms experienced by the patient and signs detected during clinic-based testing and can be differentiated from other eye diseases by a careful examination of tell-tale signs. Symptoms may include changes in vision as well as symptoms of discomfort, such as dryness, grittiness and burning. **Figure 1** represents a clinical decision-making tree or flow chart, which begins with an assessment of patient symptoms and is followed by the identification of signs of eye surface disease.

The lower portion of **Figure 1** highlights the two main dry eye categories: aqueous deficient and evaporative. Evidence suggests that dry eye is mostly evaporative in nature. While it is possible that either type can occur without obvious signs of the other, as the disease progresses, it is increasingly likely that characteristics of both types of dry eye will become evident.

The goal was to create an updated and evidence-based definition and a contemporary classification of dry eye disease to help guide clinical management and future research. The new definition is *"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."*

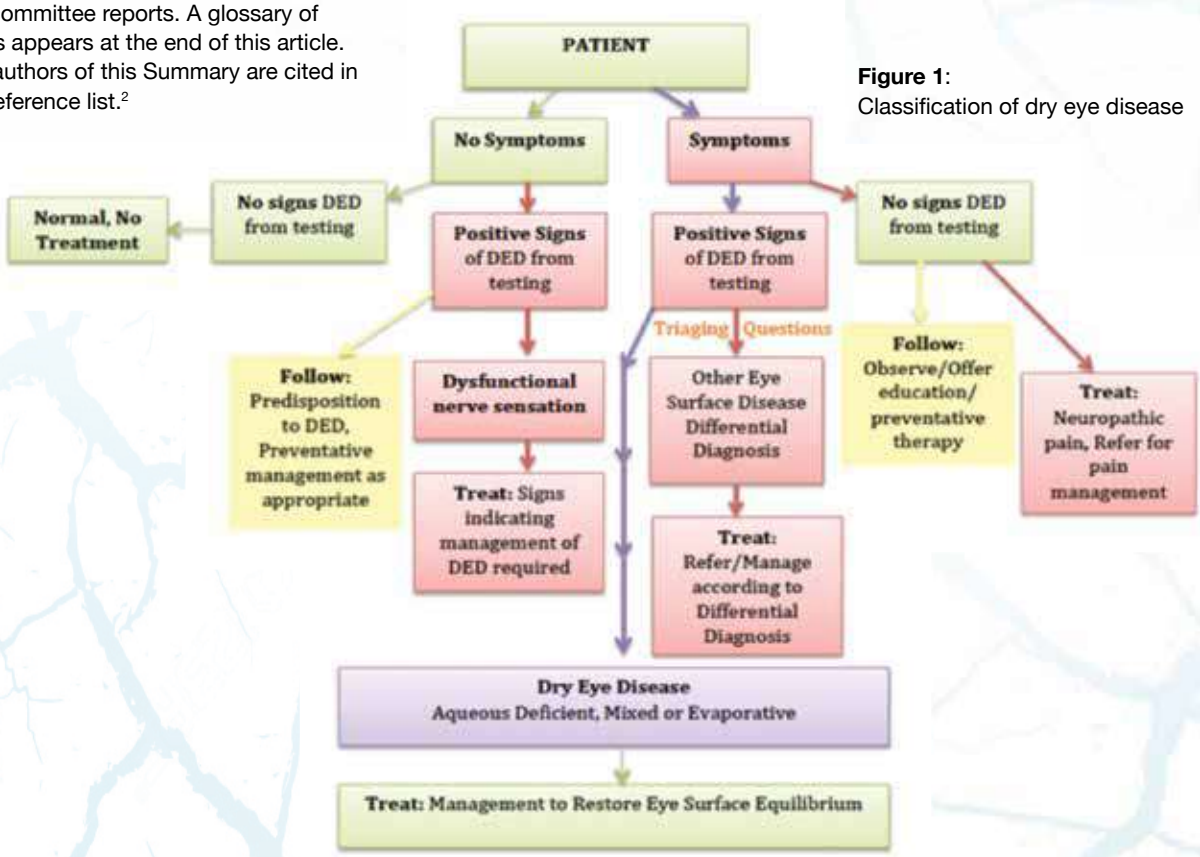



**Figure 1**:
Classification of dry eye disease

Homeostasis refers to balance, hyperosmolarity to the tear film being more concentrated (i.e. too salty), neurosensory abnormalities to change in the sensitivity of the ocular surface caused by the damage, with etiological roles indicating what causes dry eye.

Epidemiology Of Dry Eye Disease4
The overall prevalence of dry eye with and without symptoms ranges from 5% to 50%, while the prevalence based on signs of eye surface disease alone is generally higher and more variable, reaching up to 75% in some populations.

Risk factors for having dry eye are summarized in **Table 1**.

Table 1: **DRY EYE DISEASE RISK FACTOR CATEGORIZATION**

| Consistent | Probable | Inconclusive |
|---|---|---|
| Aging | Diabetes | Hispanic ethnicity |
| Female sex | Rosacea | Menopause |
| Asian race | Viral infection | Acne |
| Meibomian gland dysfunction | Thyroid disease | Sarcoidosis |
| Connective tissue disease | Psychiatric conditions | Smoking |
| Sjögren syndrome | Pterygium | Alcohol |
| Androgen deficiency | Low fatty acid intake | Pregnancy |
| Computer use | Refractive surgery | Demodex infestation |
| Contact lens wear | Allergic conjunctivitis | Botulinum toxin injection |
| Use of medications, such a, antihistamines, antidepressants, anxiolytics, and isotretinoin | Medications (for example, anti-cholinergics, diuretics, ? diuretics | Multivitamins |
| | | Oral contraceptives |
| Estrogen replacement therapy | | |
| Hematopoietic stem cell transplantation | | |
| Environmental conditions, such as pollution, low humidity, and sick building syndrome | | |

The signs and symptoms of dry eye increase with age, however the presence of signs detected through eye testing show a greater increase per decade of life than symptoms. Few studies have been conducted in populations under the age of 40 where dry eye is also present and some signs of dry eye may be related to normal aging. Higher rates of dry eye occur in women than men, although the differences generally only become significant with increasing age.

The influence of dry eye on the individual is considerable given its detrimental effect on vision, quality of life, work productivity, as well as the psychological and physical effects of pain. The financial burden of dry eye on the individual and society is substantial, the most significant impact being indirect costs due to reduced work productivity.

Future research needs to include better evaluation of the prevalence of dry eye of differing severity and in youth, the incidence in varied populations, the impact of modifiable risk factors such as mobile device usage, the influence of climate, environment and socioeconomic factors and the natural history of both treated and untreated dry eye disease.

## Role Of Sex, Gender And Hormones In Dry Eye Disease[5]

One of the most compelling features of dry eye disease is that it occurs more frequently in women, such that being of female sex significantly increases the risk factor of dry eye.

Many reported sex-related differences are attributed to the effects of androgens (hormones), as they are extremely important in regulation of the eye surface and surrounding tissues; their androgen deficiency can lead to development of both types of dry eye. Sex-related differences may also be attributed to the genes on the sex chromosomes.

It is important to note that the word “sex” is used for a reason. “Sex” refers to the classification of living things, generally as male or female, according to their reproductive organs and functions assigned by chromosomes. “Gender,” on the other hand, refers to a person’s self-representation as a man or woman, or how social institutions respond to that person based on the individual’s gender presentation.

Both sex (female/male) and gender (feminine/masculine) affect dry eye risk, how dry eye presents, the immune system’s response, perceived pain level, care-seeking behavior and interactions with eye care professionals.

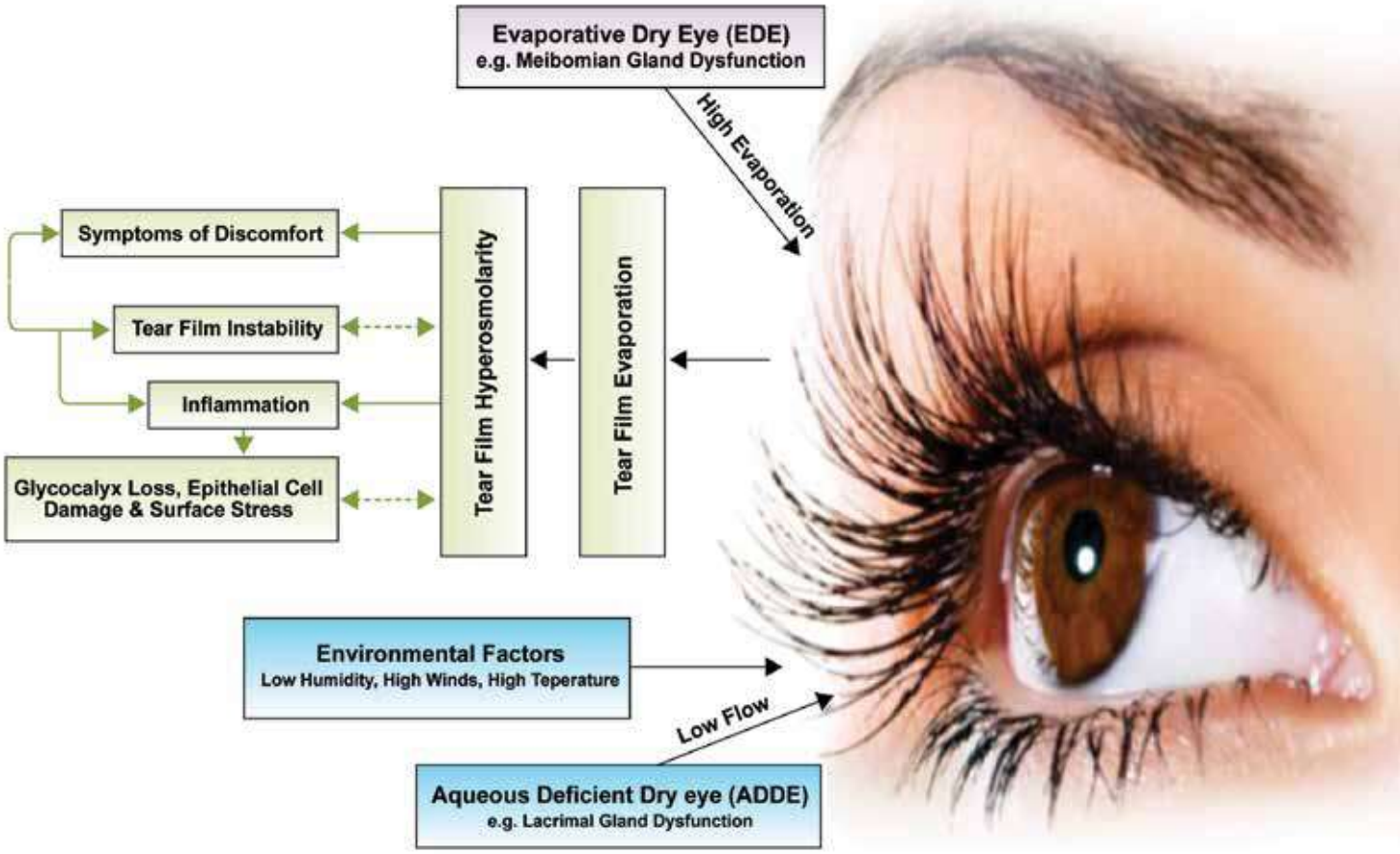
## Pathophysiology Of Dry Eye Disease[6]

The core mechanism of dry eye disease is evaporation-induced tear hyperosmolarity (higher salt concentration than normal), which is the trigger for a cascade of events leading to eye surface damage and inflammation.

Two forms of dry eye are recognized, aqueous deficient resulting from reduced tear secretion and evaporative resulting from excessive tear evaporation due to a dysfunctional tear film (e.g. changes to lipids on the surface of the tear film).

Tear film instability can be initiated by conditions that affect the surface of the eye, such as vitamin A deficiency, eye allergies, use of preservatives in topical medications, contact lens wear, certain cosmetics, low humidity, blowing air and computer vision syndrome (see Tables 1 and 2).

**Figure 2**. Pathophysiology of dry eye disease




Aqueous deficient dry eye may result from blocking the sensory drive to the lacrimal gland, chronic topical anesthetic use, reduced reflex tearing due to nerve damage or refractive surgery (such as LASIK surgery), obstruction to the lacrimal ducts, a number of systemic drugs such as antihistamines, b-blockers, bladder and bowel antispasmodic agents, diuretics and specific psychotropic drugs, or aqueous tear reduction due to aging.

In the Western world the most common cause of aqueous deficient dry eye is inflammation of the lacrimal gland, as seen in autoimmune disorders such as Sjögren syndrome.

The most common cause of evaporative dry eye is MGD, which results in low delivery of lipid to the surface of the eye. The most common cause of MGD, in turn, is obstruction of the meibomian gland's external duct, which leads to tear film instability, increased tear evaporation and ultimately to evaporative dry eye.

The prevalence of MGD increases after the age of 50 years, a process that may be linked to a decrease in bioavailable androgens (hormones). Use of cis-retinoic acid (for example, isotretinoin or retinoic acid treatment of acne vulgaris) and certain anti-glaucoma eye drops may induce MGD. A variety of disorders, such as acne rosacea and psoriasis, are associated with MGD.

Both evaporative and aqueous deficient dry eye can lead to friction-related symptoms and ocular surface damage.

## Tear Film In Dry Eye Disease[7]

Evidence supports a two-layered model of the tear film, involving a thin surface lipid layer overlying a thicker mucous-aqueous mixed layer. The mucin component of this latter layer helps to wet the eye's surface, which in turn allows the watery aqueous component to spread over an otherwise non-wetting surface.

While the extent of the role of the tear film lipid layer alone in preventing evaporation and breakup of tears is unclear, it is likely that interactions of the whole tear film, including lipids, mucins, proteins and salts, prevent evaporation and collapse of the tear film. Several studies have attempted to correlate changes in tear lipid biochemistry with dry eye, but no definitive links.

Tear hyperosmolarity is the hallmark of dry eye disease, Tear film osmolarity increases with dry eye severity.

A holistic approach to understanding tear film structure and function, together with improvements in characterizing tear film biochemistry, are expected to lead to identification of new markers that can be used to diagnose, potentially predict and even treat dry eye.

## Pain And Sensation In Dry Eye Disease[8]

Pain is differentiated into two types. The first type is nociceptive, which is pain in response to actual damage to tissues. Pain when you burn your hand on the stovetop is nociceptive pain.

The second type of pain is neuropathic, which is pain due to an abnormality anywhere along the pathway of nervous system that conducts sensation. Phantom limb pain is an example neuropathic pain.

Pain associated with dry eye is transmitted via nerve pathways from the ocular surface to the brain.

Tear evaporation between blinks causes distinct cooling of the eye and increases the osmolarity of tears. This increased osmolarity triggers the activity of cold-sensing nerve receptors in the cornea and contributes to the reflex control of tear production and eye blinking. Specific regions in the brain stem play a dominant role in sensing the osmolarity of tears and ocular pain, which encourages maintenance of tear film stability, which in turn helps to alleviate eye pain.

Reduced tear secretion in dry eye leaves the cornea exposed to adverse environmental conditions, which can lead to varying levels of inflammation and to nerve damage.

## Iatrogenic Dry Eye Disease[9]

Dry eye disease can be caused by a variety of medical interventions (termed iatrogenic), including the use of topical and systemic drugs, preservatives, contact lenses and exposure to ophthalmic surgical and non-surgical procedures.

Table 2: **TOPICAL AND SYSTEMIC MEDICATIONS THAT MAY INDUCE OR WORSEN DRY EYE DISEASE**

| Topical Medication Categories | Systemic Medication Categories and Sub-Categories |
|---|---|
| Adrenergic agonists | Analgesics: Antirheumatic, Cannabinoid, Opioid |
| Antiallergics | Anticholinergic (antimuscarinics): Antiarrythmic/Bronchodilating, Antihistamine, Antidepressant, AntiParkinson's, Antipsychotic, |
| Antivirals | |
| b?Adrenergic receptor blockers | |
| Carbonic anhydrase inhibitors | Antispasmodic, Decongestant |
| Cholinergic agonists | Antihypertensives: Adrenergic blocking Na+Cl- Co-transporter (diuretic) |
| Decongestants | Hormonal: Antiandrogen/Estrogen replacement |
| Miotics | Anesthesia |
| Mydriatics & cyclopegics | Antileprosy |
| Prostaglandins | Antimalarial |
| Topical and local anesthetics | Antineoplastic |
| Topical ocular non-steroidal anti-inflammatory drugs | Anxiolytic/hypnotic |
| | Chelator/Calcium Regulator |
| | Depressant |
| | Herbal and Vitamins |
| | Neurotoxin |
| | Sedative |

Contact lens wear has been identified as causing or being associated with dry eye. Changes to the tear film in contact lens wearers with dry eye include lipid layer thinning, tear film instability, lower tear turnover and a decreased volume of tears on the ocular surface.

Corneal refractive surgery, corneal transplantation, cataract surgery, eyelid surgery, cosmetic procedures and botulinum toxin application may cause or aggravate dry eye.

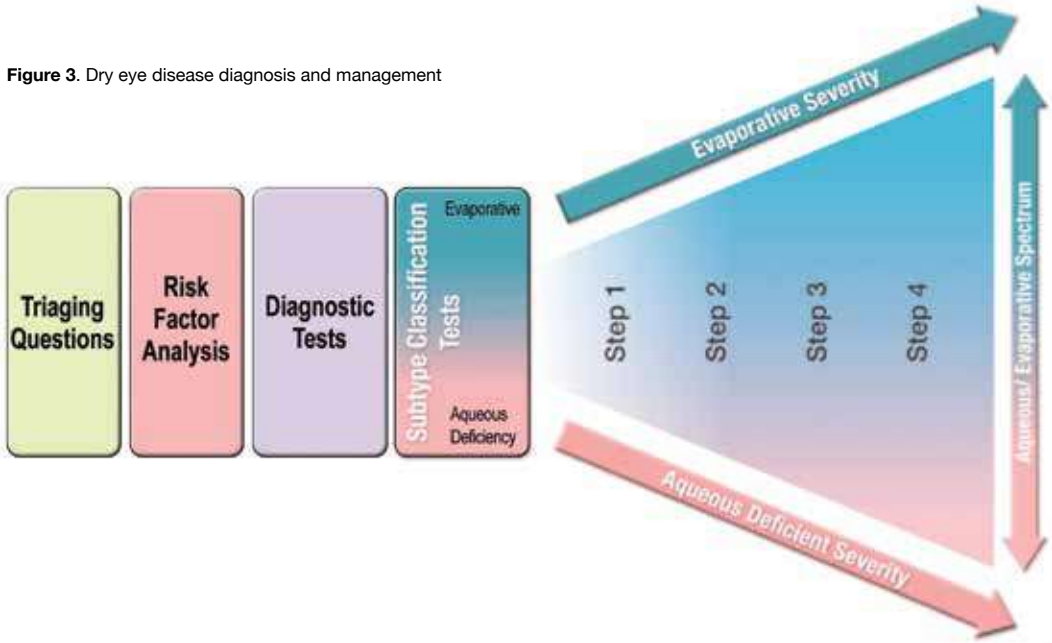
Topical and systemic medications and drug groups that may induce or worsen dry eye are listed in **Table 2**.

More research is needed to identify dry eye risk factors, detect early dry eye prior to eye surgery, determine the benefits of proactive pretreatment and to develop less toxic medications and less disruptive eye surgeries.

## Diagnosis of Dry Eye Disease[10]

A recommended sequence of tests for the diagnosis of dry eye disease and an assessment of its severity and the relative contributions of the aqueous deficient or evaporative dry eye subtypes are shown in **Figure 3** below.

**Figure 3**. Dry eye disease diagnosis and management




This diagnostic process first utilizes questions to exclude conditions that mimic dry eye. A dry eye diagnosis then requires a positive score on one of two specific symptom questionnaires, followed by at least one positive clinical sign indicating a reduced non-invasive tear break-up time (a measure of tear film stability), an elevated or a large inter-eye disparity in osmolarity (tear saltiness), or ocular surface damage indicated by dye staining.

After confirming that the condition is dry eye, further subtype classification tests such as imaging the meibomian glands, observing the lipid layer on the surface of the tears and tear volume measurement should be performed to determine: [a] where the dry eye falls on the spectrum between aqueous deficient and evaporative and [b] the severity of dry eye, as these help to guide treatment.

## Management and Therapy of Dry Eye Disease[11]

The management of dry eye disease can be challenging due to its multifactorial etiology. Determining the major causative factors behind the dry eye is critical to selecting the appropriate management.
The ultimate goal of dry eye management is to restore the homeostasis of the surface of the eye and tear film. While certain treatments may be specifically indicated for one aspect of a patient's condition, a number of therapies may be appropriate to manage a patient presenting with dry eye.

Although a priority is to identify and manage the primary source of the disease, the management of dry eye invariably involves prolonged therapy to address chronic signs and symptoms.

Scientific evidence, as well as risk/benefit and cost considerations, will also contribute to decisions made in choosing between multiple treatment options.

While there is strong evidence that individual treatments are more effective at managing dry eye than no treatment, there is little information to suggest the dry eye subtype and severity for which they are most beneficial. This is therefore the focus of ongoing research.

The evidence supports a staged management and treatment of dry eye (**Table 3 on the next page**).

The anticipated therapy duration is related to the individual's compliance and response and to the treatment being considered. Most often, therapeutic effects are observed within one to three months, although some treatments (e.g. cyclosporine A) may take longer. Overall, the treatment of dry eye remains something of an art, requiring an individualized approach for affected patients. There is no single approach to dry eye management that will suit all patients.

## Design Of Clinical Trials For Dry Eye Disease Treatment[12]

In order to improve the quality of dry eye clinical trials, to optimize resources and to improve patient access to novel treatments, the following recommendations are made:

- Studies should be conducted under Good Clinical Practice guidelines, which requires compliance with appropriate regulatory requirements.
- The Consolidated Standards of Reporting Trials (CONSORT; http://www.consort-statement.org/) statement is useful to review prior to planning and starting a study.
- The trial design and sample size should align with the type of treatment under investigation, the purpose of the study and the stage of development.
- The dose of a therapy must be non-toxic, but be sufficiently strong and frequently administered to achieve the optimal therapeutic results.
- The duration of treatment, at least for a pivotal study (which is one that provides evidence for getting regulatory approval to commercialize a drug), should correspond with the drug's mechanism of action and the time taken to achieve its desired effect.

## Table 3: **RECOMMENDATIONS FOR THE STAGED MANAGEMENT OF DRY EYE DISEASE**

**Step 1:**

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

**Step 2:**

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

**Step 3:**

**If above options are inadequate consider:**

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

**Step 4:**

**If above options are inadequate consider:**

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


- For pivotal studies, number of trial subjects is key to the potential validity of the study.
- Test choice is critical in confirming how well a treatment works. If possible, test procedures should be minimally invasive and non-operator dependent, to avoid biasing the results, as well as being relevant to the changes that are anticipated to occur with administration of the treatment.
- Exploration of novel ways to evaluate dry eye disease, such as biomarker evaluation, may lead to improvement in dry eye clinical trial design and increased clarity on the efficacy of new treatments.

## Glossary Of Highlighted Terms

**Allogeneic** - of cells or tissues obtained from a genetically similar, but not identical, donor Anterior blepharitis - inflammation around the eyelid skin, lashes and lash follicles
**Antispasmodic agents** – medicines used to treat symptoms such as tummy pain and cramp (spasm). They are most commonly used for symptoms of irritable bowel syndrome
**Autologous** - of cells or tissues obtained from the same individual
**Bioavailable** - the proportion of a drug or other substance that enters the circulation when introduced into the body and so is able to have an active effect
**Epidemiology** – the branch of medicine relating the incidence, distribution and possible control of diseases and other factors relating to health
**Etiology** - the cause of a disease
**Evidence-based** - any concept or strategy that is derived from or informed by unbiased scientific evidence
**Homeostasis** - the tendency of the body to seek and maintain a condition of balance within its internal environment
**Hyperosmolar or Hyperosmolarity** – referring to the increased osmolar concentration (saltiness) of body fluids
**Iatrogenic** - relating to illness caused by medical examination or treatment
**Lipid Layer** - a blanket of fats or oils that helps slow tear or water evaporation
**Neuropathic** - pain due to an abnormality anywhere along the pathway of nervous system that conducts sensation. Phantom limb pain is classified as a neuropathic pain.
**Nociceptive** - pain in response to actual damage to tissues. Pain when you burn your hand on the stovetop is nociceptive pain.
**Nocturnal lagophthalmos** - refers to the inability of apparently closed lids to exclude air from the ocular surface during sleep. It may be responsible for dry eye symptoms occurring immediately upon rising
**Pathophysiology** - functional changes that accompany a disease Serum - protein-rich liquid that separates out when blood coagulate.

### Dedication

This TFOS DEWS II report is dedicated to the late Professor Juha Holopainen (Helsinki Eye Lab and Department of Ophthalmology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland), who served on the TFOS DEWS II Steering Committee and Tear Film Subcommittee, in recognition of his outstanding scientific contributions to the field of the ocular surface and tear film.

### Acknowledgments

The authors thank all participants of TFOS DEWS II and the TFOS staff and consultants for their contributions to this report.

The TFOS DEWS II was supported by unrestricted donations from Alcon, Novartis, Shire, Allergan, Bausch+Lomb, Akorn, CooperVision, Dompé, Horus Pharma, Lµbris Biopharma, Oculeve, TearLab, Laboratoires Théa, SIFI, Sun Pharma, Johnson & Johnson VisionCare, Carl Zeiss Meditec, Quint Health, Scope Ophthalmics and Senju.

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# All-in one automated measuren interferometry, tear meniscus, non-i

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## PURPOSE

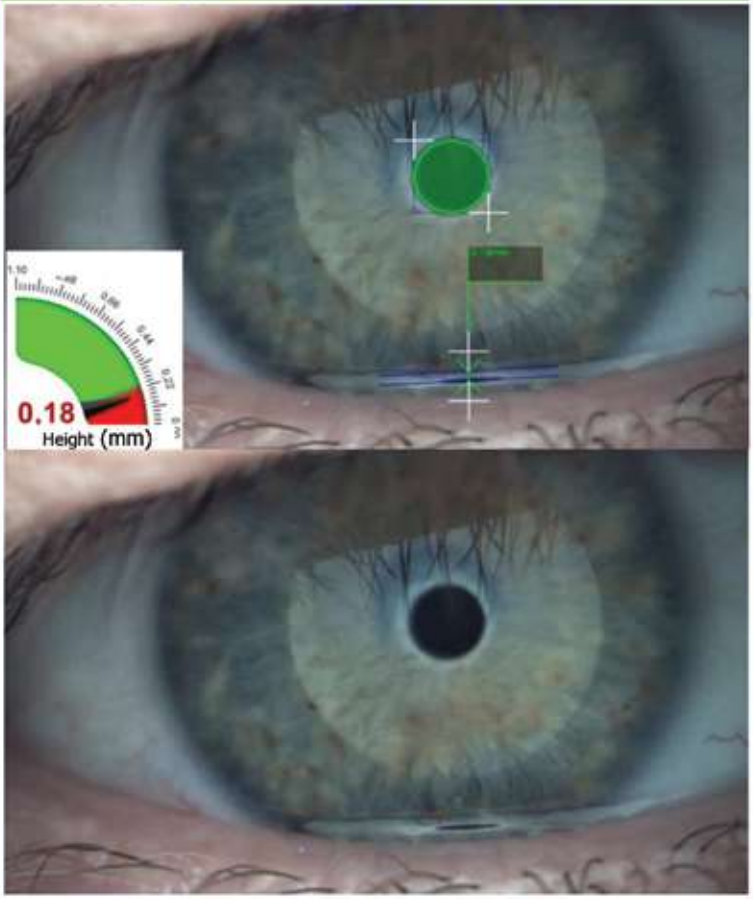
Diagnosis procedures in the dry eye syndrome (DES) are evolving. The experts of the 2017 Dry Eye WorkShop (D time of (BUT) using fluorescein eye drops[3,4]. When instilled, the fluorescein dilutes the natural tears and logica recommended to use a dye-free imaging: the Non-Invasive BUT (NIBUT)[5,6]; 2/ the Schirmer's test measuring th Contact with the paper causes reflex tearing that distorts the test. It is now recommended to use a non-contact im **Aim:** to present a new device that simultaneously measures at least four parameters of the ocular surface ind interferometry and meibography.

## METHODS

LacryDiag (Quantel Medical, Clermont-Ferrand, France) is a new CE marked medical imaging device. We present performed **semi-automatically**: 1/measurement of the **height of tear meniscus**, which is a surrogate crite lacrimal river; 2/ **interferometry** that provided quantitative and qualitative analyze of the lipid layer of the tear f videos; 3/ **meibography** by infrared imaging of Meibomian glands and image analysis (automatic boundaries det by image analysis of placido's disk. A graphic representation (color code) provided rapid interpretation of the 4 test

## RESULTS

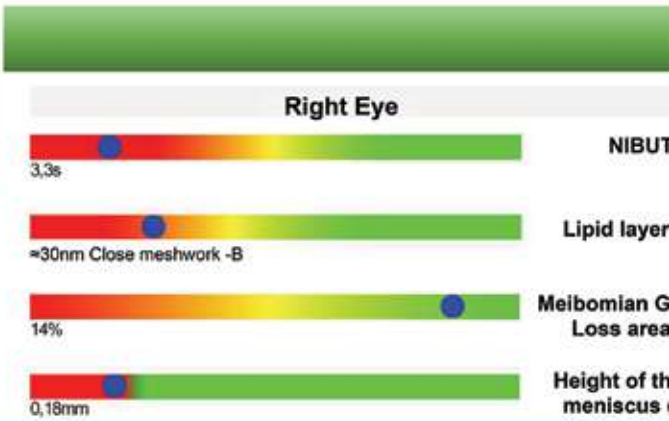
### 1) Height of the tear meniscus




The height of the tear meniscus measurement was 0.18mm.
The lacrimal river was discontinuous and thin.

### 2) Interferometry


An instable lipid layer, shortly visible (around 1/2sec) due to severe tear deficiency was detected (≈30nm: close meshwork).




## CONCLUSIONS

To the best of our knowledge, this new device is the first to perform these 4 measurements simultaneously.
Non-invasive measurements are in conformity with the recent Dry Eye Workshop II recommendations.

# ment of ocular surface parameters: nvasive break-up time and meibography

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biig
biology, engineering and imaging of Corneal Graft

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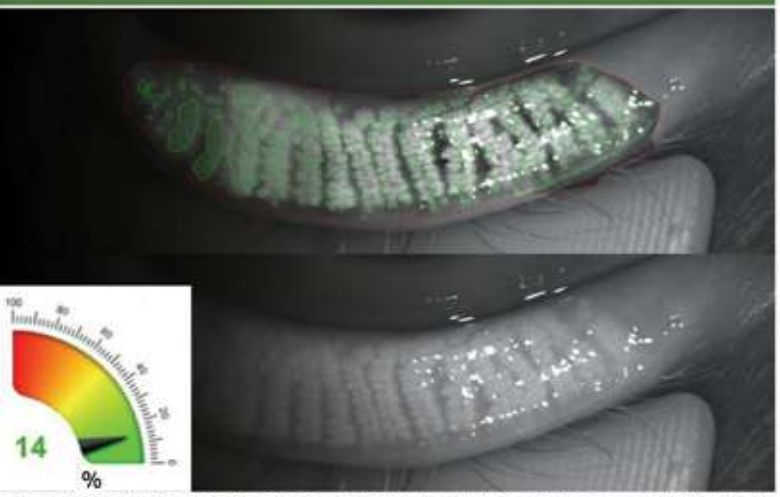
DEWSII 2017)[1,2] proposed to modify two tests: 1/ the classic tear film break-up lly modifies their physical proprieties and thus the BUT evaluation. It is now he length of a strip of blotting paper impregnated by tears after 5 minutes[7,8]. naging method measuring river height or tear meniscus *in situ*.
icated for the diagnosis and monitoring of DES: NIBUT, lacrimal river height,

t the first use in a volunteer patient with known DES. The device sequentially rion for the tear volume, thanks to 2 calipers placed by the observer on the ilm depending on its thickness and regularity, using a comparison with a set of tection + manual corrections whenever necessary); and 4/ **automatic NIBUT** ts.

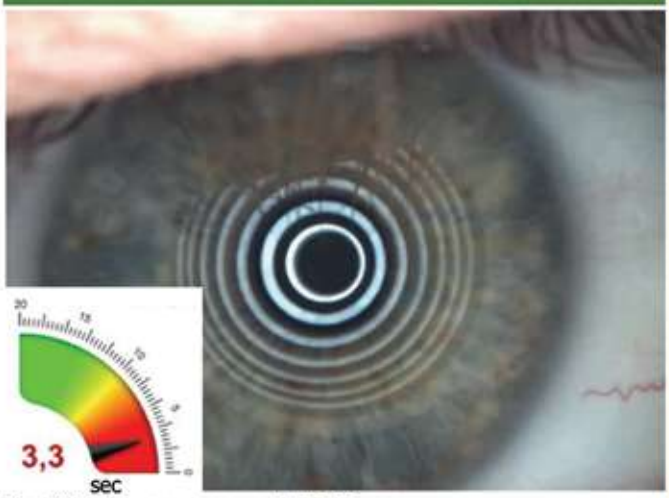
**Figure 1.** The LacryDiag device

## 3) Meibography



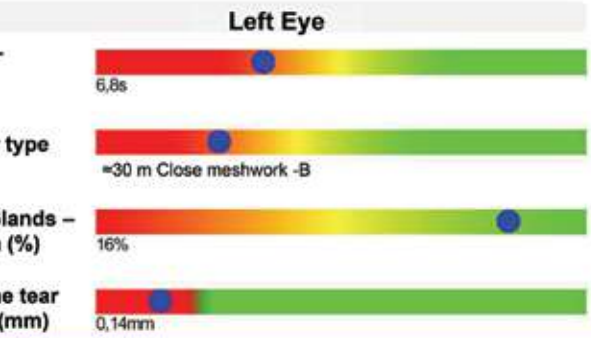

The Meibomian glands were well visible with a low loss, estimated at 14%.

## 4) NIBUT




The NIBUT was measured at 3.3 sec.

## 5) Exam report




The four parameters were obtained on both eyes in 10 minutes. The device allowed diagnosing a DES mainly due to aqueous deficiency without significant Meibomian gland dysfunction.
The graphical representation is intended to help the physician explain the pathology to patients.

The device can also measure the classical BUT and corneal topography.

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# Reduced Visual Quality of Life Associated with Migraine is Most Closely Correlated with Symptoms of Dry Eye

Patients with migraine frequently report ocular or visual symptoms including aura, photophobia and eye pain. Using validated instruments, our group previously reported that due to these symptoms, patients have marked reductions in visual quality of life. In chronic migraine, these reductions can be as substantial as those reported for other neuro-ophthalmic diseases such as multiple sclerosis with optic neuritis and idiopathic intracranial hypertension. Because the instruments take several different dimensions into account, we were unable to determine which ocular symptom(s) contributed to reduced visual quality of life. The purpose of this investigation was to attempt to determine which ocular symptom(s) were driving the observed reduction in visual quality of life.

The authors designed a cross-sectional survey-based study to assess visual quality of life, headache impact, aura, dry eye and photophobia in migraine patients. Subjects were recruited from the Headache Clinic and General Neurology Clinic at a tertiary teaching hospital. Subjects completed validated questionnaires including: The visual functioning questionnaire-25 (VFQ-25), the headache impact test (HIT-6), the visual

aura rating scale (VARS), the ocular surface disease index (OSDI) and the Utah photophobia score (UPSIS-17). Associations between VFQ-25 and OSDI, VFQ-25 and VARS, VFQ-25 and UPSIS-17, HIT-6 and OSDI, HIT-6 and VARS and HIT-6 and UPSIS-17 were calculated.

The results showed that out of the 62 patients who completed all questionnaires, 17 had episodic migraine and 45 had chronic migraine. 23 patients experienced aura and 39 did not report aura. The most striking correlations were observed between the VFQ-25 and the OSDI (-0.678; $P < .001$), between the HIT-6 and UPSIS-17 (0.489; $P < .001$) and between the HIT-6 and OSDI (0.453; $P < .001$).

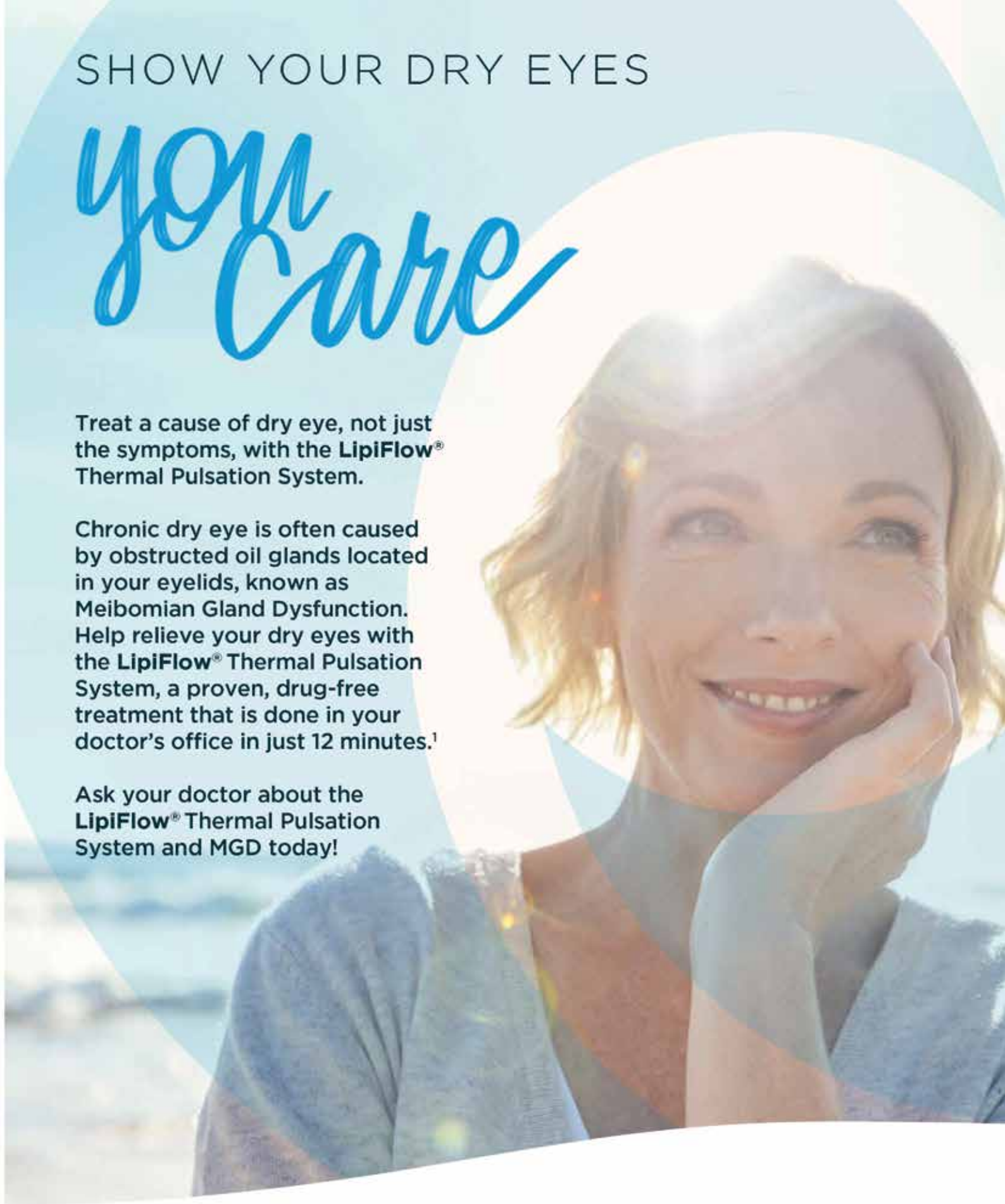
Dry eye seems to be the most important symptom that reduces visual quality of life and worsens headache impact. This symptom may be a form of allodynia, a well-known feature of chronic migraine. Photophobia appears to have modest effects on headache impact. In the future, they hope to determine whether treatment of dry eye symptoms can improve visual quality of life and reduce headache impact.

Authors: Ozudogru S, Neufeld A, Katz BJ, Baggaley S, Pippitt K, Zhang Y, Digre KB

Headache. 2019 Sep 26. doi: 10.1111/head.13662.

# SHOW YOUR DRY EYES

# you Care



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1. LipiFlow® Thermal Pulsation System Instructions For Use. P. 32. Doc. 011390 INT. Rev C, 02/2019. REF2019TS4031.



Johnson & Johnson VISION

# ALL-IN-ONE AUTOMATED MEASUREMENT OF OCULAR SURFACE PARAMETERS

LacryDiag from Quantel Medical simultaneously conducts four essential, noncontact, dye-free exams of the ocular surface for the diagnosis and monitoring of dry eye.

COURRIER E.; TRONE MC.; RENAULT D.; LAMBERT V.; LAZREG S.; THURET G.; GAIN P.

Dry eye syndrome (DES) affects millions of people throughout the world and is one of the most frequent causes of patient visits to eye care practitioners. It is a symptomatic disease, characterized by a vicious cycle of tear film instability and hyperosmolarity, which leads to increased ocular surface inflammation, damage, and neurosensory abnormalities.[1] In most cases, DES can be successfully managed if diagnosed early and properly treated. For patients, DES can be relentlessly uncomfortable, leaving them to a lifetime of applying artificial tears (drops) and ointments daily for temporary relief of dry eye irritations. From a physician's perspective, not having an accurate diagnosis of underlying conditions not only leads to superficial treatment protocols, and some guesswork, but also leaves a greater risk of undiagnosed DES, potentially causing vision loss.

Fortunately, today, diagnostic procedures to detect DES are evolving. To create an evidence-based definition and a contemporary DES classification system, experts of the 2017 Dry Eye Work Shop (DEWS II report) have redefined the diagnostic methodology to include a comprehensive ocular surface examination specific for diagnosing DES (Figure 1).[2] There are two phases of this methodology.

The first phase is to determine DES and homeostasis through one of three tests: Non-Invasive Break-Up Time (NIBUT), ocular surface staining, or osmolarity tests. Once this is complete, the second phase aims to determine the subtype of DES. For this, several different exams are required to identify an evaporative form using interferometry and meibography or to identify aqueous deficiency using tear meniscus height.[2]

In order to provide a more accurate diagnosis of DES, and to determine the underlying deficiencies, the experts proposed the modification of two tests: the classic tear film break-up time using fluorescein eye drops[3,4] and the Schirmer test.[5,6]

In tear film break-up time, the fluorescein dilutes the natural tears and logically modifies their physical proprieties providing an inaccurate tear film break-up time evaluation. To address this issue, it is now recommended to use dye-free imaging known as the NIBUT test (Figure 2).[7,8] The Schirmer test uses paper strips inserted into the eye for approximately 5 minutes to determine

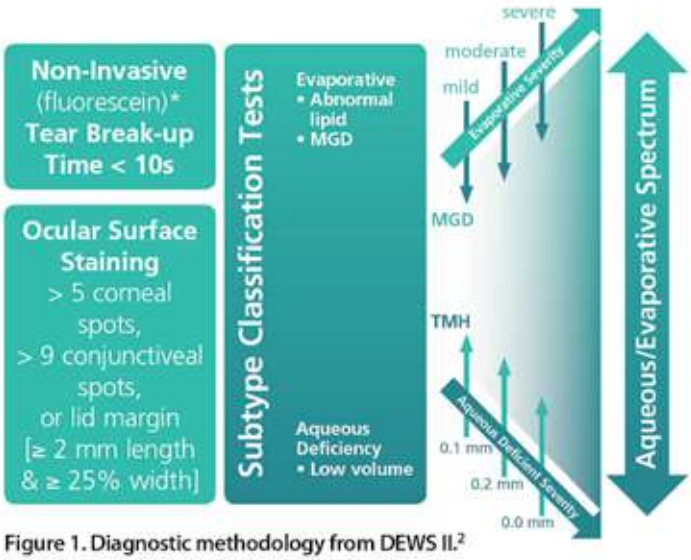


Figure 1. Diagnostic methodology from DEWS II.[2]

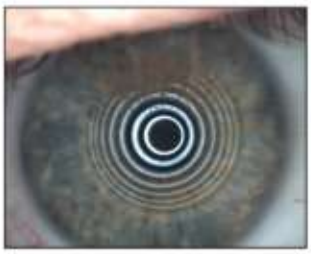

Figure 2. NIBUT test.

Figure 3. Noncontact tear meniscus.

the production of tears. One issue is that eye contact with the paper causes reflex tearing that can distort the test and provide an inaccurate reading. For more accurate readings, it is recommended to use a noncontact imaging method measuring river height or if tear meniscus is present (Figure 3).

## A New, Innovative Diagnostic Tool

With an aim to introduce a dye-free, noncontact method to diagnosing DES, a new ocular surface analyzer and medical imaging device–LacryDiag (Quantel Medical)–emerged. LacryDiag simultaneously conducts four essential, noncontact, dye-free exams of the ocular surface for the diagnosis and monitoring of DES: they are

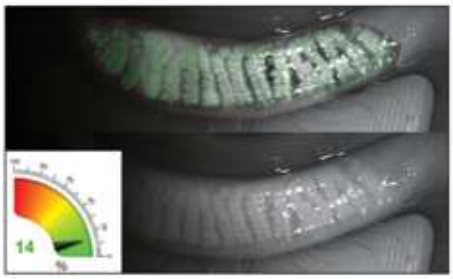


Figure 4. Meibography.

NIBUT, tear meniscus, interferometry, and meibography.

Noncontact meibography is an imaging study for the purpose of observing the morphology of meibomian glands in real time.[9] The meibomian glands in the eyelids secrete meibum, a lipid complex that forms the lipid layer of the tear film. The lipid layer prevents evaporation of aqueous tears and subsequent drying. Lipid deficiency due to meibomian gland dysfunction is the most common cause of symptoms associated with DES.[10] A unique feature of the LacryDiag is the ability to classify various levels of meibomian gland dysfunction automatically (Figure 4).

Thanks to its yellow filter and blue light, LacryDiag can also perform ocular staining exams with fluorescein; blepharitis and demodex imaging can also be analyzed with this product.

## Case Study

In the following case, a volunteer patient with previously diagnosed DES was examined using the LacryDiag. The device sequentially performed the following four, noncontact tests semi-automatically and produced a rapid, graphic representation (color coded) of all four tests (Figure 5).

## The Results of the Test Are as Follows:

1. In this case, the height of the tear meniscus measurement was 0.18 mm in the right eye and 0.14 mm in the left eye. Measurement of the height of tear meniscus, which is a surrogate criterion for the tear volume, was achieved thanks to two calipers placed by the observer on the lacrimal river. The lacrimal river was discontinuous and thin.
2. Interferometry detected an instable lipid layer of the tear film, shortly visible (1 or 2 seconds) due to severe tear deficiency (≈ 30 nm: close meshwork for both eyes).
3. Meibography by infrared imaging of meibomian glands and image analysis detected the glands were visible with a low loss, estimated at 14% in the right eye and 16% in the left eye.
4. The NIBUT was measured at 3.3 seconds in the right eye and 6.8 seconds in the left eye.

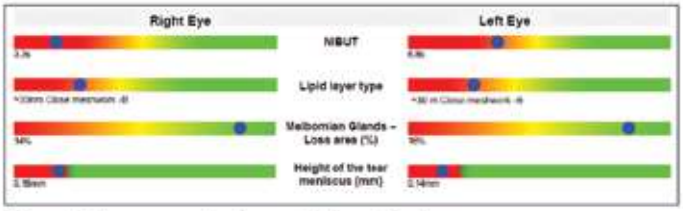


Figure 5. Exam report of case study patient.

## Results

The four parameters were obtained on both eyes within 10 minutes. From the exam report, we determined this patient's DES was mainly due to aqueous deficiency without significant meibomian gland dysfunction. Enhancing our patient education protocols, the graphical representation helped illustrate and explain the pathology to this patient. If needed, the device can also measure the classical BUT and corneal topography.

## Conclusions

To the best of our knowledge, the LacryDiag is the first noncontact ocular surface analyzer and medical imaging device to perform the four necessary exams simultaneously to comprehensively detect and diagnose DES. ■

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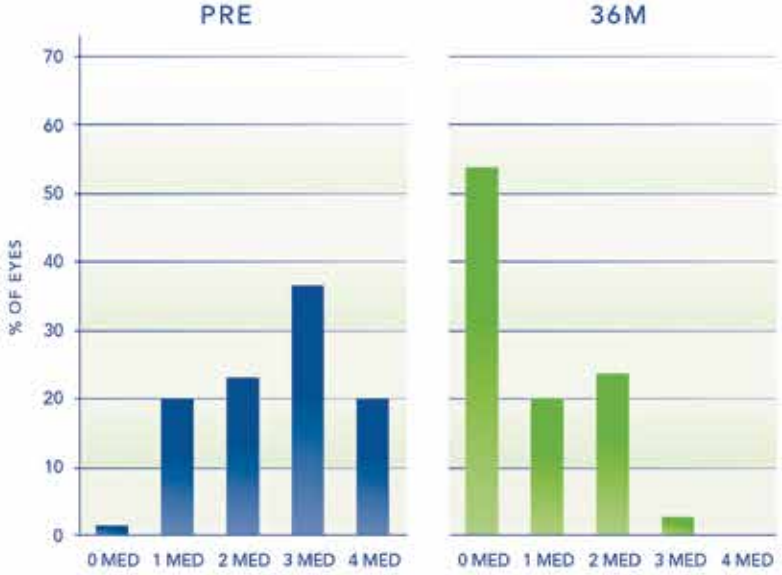


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The device may also be implanted in patients who continue to have elevated intraocular pressure despite prior treatment with glaucoma medications and conventional glaucoma surgery.

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PM-EU-0047

# Treatment with pulsed light for alteration of tear film due to Meibomian Gland Disease

by **Mr Francesco Carones**

Dry Eye Disease is an increasingly frequent condition nowadays and probably due to changes in life and work habits as well as changes in the surrounding environment. Intense and prolonged use of PCs, tablets, smartphones, air pollution, stressful lifestyles and eating disorders and poor diet can all play a role in altering the tear film and therefore cause the discomforts associated with dry eye [1-3].

The discomforts caused by dry eye can become so severe that they negatively impact daily life and require the intervention of an ophthalmologist for appropriate therapy [4].

Fig 1. Schirmer test

Fig 2. Osmolarity test

Fig 3. Break Up Time test (BUT)

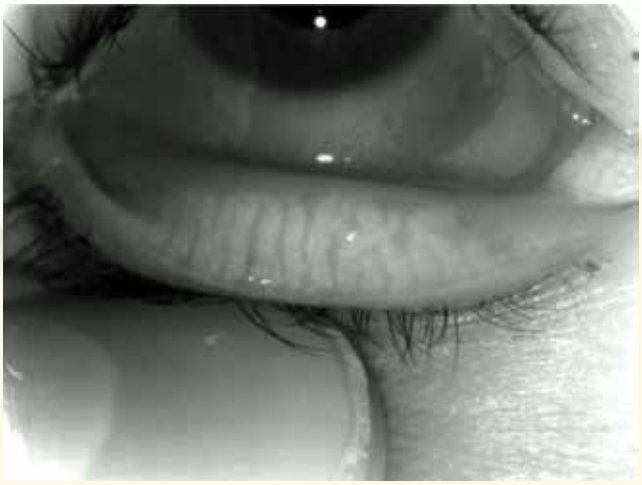

Fig 4. Meibomian glands

Environmental, immunological, metabolic and hormonal [5-6] conditions can lie at the base of the disease and the alteration of the tear film can last a long time and require a multidisciplinary approach for adequate diagnosis and treatment.

Dry eye disease is the pathological condition that results from a chronic alteration of the tear film. This can be caused by insufficient tear production by the lacrimal gland or by the production of a poor quality tear film which tends to evaporate quickly from the surface of the eye. This tear film does not give adequate nutrition and protection to the ocular surface.

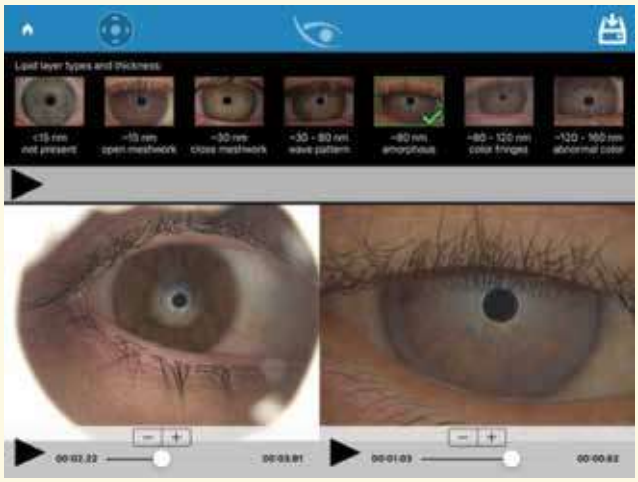

Fig 5. Evaluation of the lipid layer

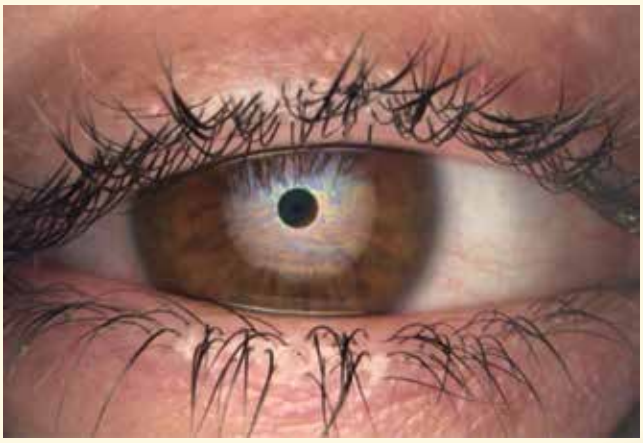

Fig 6. Lipid layer in the tear film

The tear film plays a fundamental role in maintaining the integrity of the ocular surface. Quantitative and qualitative alterations to the tear film can cause stress to the the corneal surface with associated symptoms such as burning, foreign body sensation, photophobia, itching, up to a worsening of the visus and a change to biometric values that can play a crucial role in pre-surgical measurements in cases of refractive and cataract surgery [7-8].

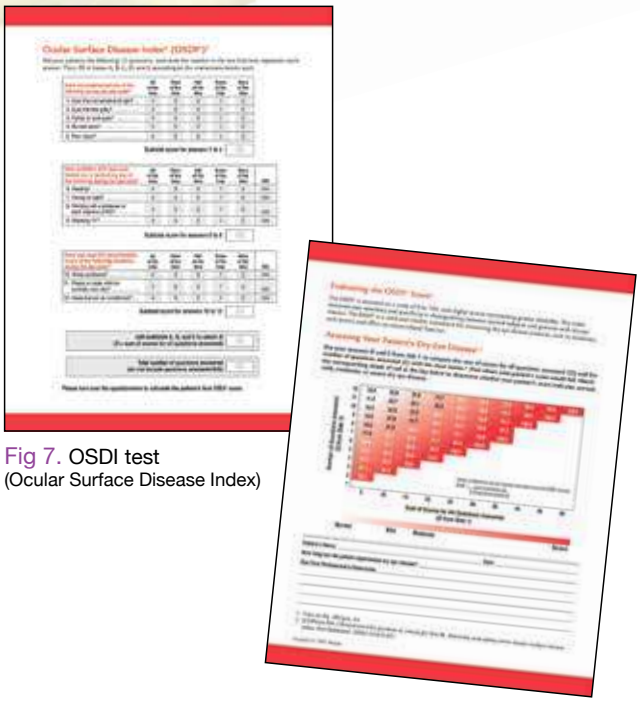

Fig 7. OSDI test
(Ocular Surface Disease Index)

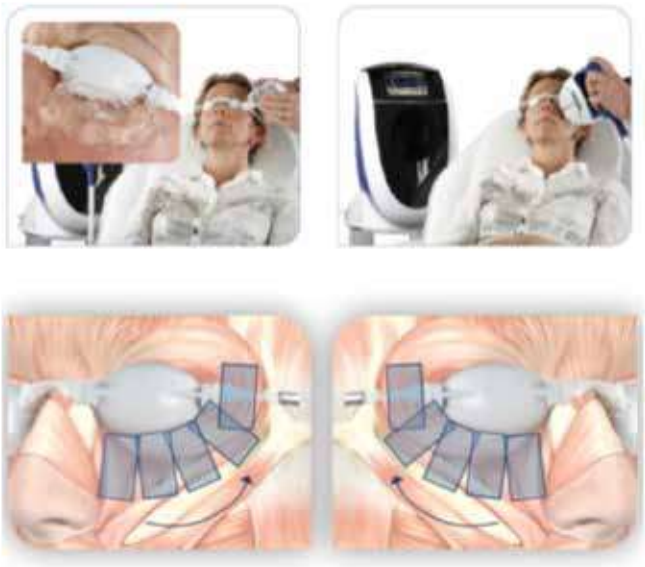

Fig 8. Treatment with pulsed IRPL light

Therefore it is important to have an intact tear film to reduce or eliminate the patient's subjective symptoms and to improve the outcomes of corneal and cataract surgery.

There are several tests that can be performed to investigate tear film alterations and to evaluate the condition of dry eye disease: Schirmer test (Figure 1), Osmolarity test (Tear Lab) (Figure 2) , BUT (Break Up Time) (Figure 3), Meibomian gland analysis (Figure 4) and Lipid Layer Analysis (Figures 5-6), Staining and Ferning tests and standardized questionnaires to be filled in by the patient (Ocular Surface Disease Index: OSDI) (Figure 7). The execution of these tests allows us to understand the origin of this condition, its severity and to provide the patient with a specific therapy.
One of the most common forms of Dry Eye Disease is the evaporative form and is determined by dysfunction of the

meibomian glands (MGD). The reduced production of the lipid component in the tear makes the tear film less stable on the ocular surface causing its rapid evaporation.
Age, hormonal and metabolic disorders are commonly the cause of this dysfunction which results in excessive reflex tearing (but with the patient's perception of dry eye symptoms) and the onset of blepharitis and chronic blepharitis which are often difficult to treat.

There are several treatments that can be useful and effective and that can be combined to improve the patient's symptoms and clinical conditions: warm compresses, eye washes, omega-three supplements, artificial tears with lipids, steroids and antibiotic combinations both as eye drops and ointments (especially tetracyclines) 9. These medicines must be used chronically or cyclically by the patient to improve symptoms and reach a condition of well-being, although sometimes transitory. Among these treatments are therapies with Intense Pulsed Light or IRPL. This type of treatment can give more relief and lasts for a longer time.

IRPL treatment (Figure 8-9) consists of the application of a flashing light using a xenon lamp with a broad range spectrum ranging from 580 nm to 1200 nm. In each IRPL treatment, 4 overlapping flashes are applied in the area under the lower eyelid plus a side flash for each eye. During treatment the eyes are protected with opaque glasses and a protective gel is applied to the treatment area to allow optimal transmission of light and heat.The energy intensity varies between 9.8 J / cm 2 and 13J / cm2 depending on the type of skin according to the Fitzpatrick classification. In order to obtain optimal and lasting results a cycle of 3 or 4 sessions is required over a period of two months. The main mechanism of action of the IRPL treatment its effect on the parasympathetic nervous system which stimulates the meibomian glands to return to normal functioning. There are also other possible mechanisms by which IRPL treatment can help patients with MGD. The instrument is able to produce an intense heat that dissolves the secretions in the glandular ducts. The energy produced is also absorbed by the hemoglobin resulting in a reduction in inflammation of the eyelid border and conjunctiva. Furthermore IRPL treatment seems to be able to balance the oxidation and anti-oxidation processes, thus improving the microbiome of the eyelid margin and meibomian glands [10].

Fig 9. IRPL pulsed light equipment.

After performing all diagnostic analysis of the dry eye condition of the patient IRPL can be used to treat evaporative dry eye, blepharitis and blepharoconjunctivitis and patients suffering from all types of MGD.
In our clinic in Milan (Centro Oftalmo-Chirurgico Carones) we have so far treated 82 patients with IRPL, with at least 3 sessions each. The results were a significant improvement in the patient's objective parameters and subjective symptoms(OSDI tests) in 87% of cases. We also noted a significant decrease in osmolarity values, an improvement of the lipid layer in the tear film and an increase in the tear residence time on the ocular surface (BUT).

These values were measured at one month after the third session, that is 75 days after the first treatment. The subjective improvements were reported by the patients after each session and with a cumulative effect.

The decrease in osmolarity values 11 and the presence of a more stable tear film improves the condition of the ocular surface and allows for more precise detection of biometric values prior to surgery. The results have been better visual outcomes and a reduction of post-operative disorders that effect patients after corneal surgery.

Treatment with IRPL light in appropriately selected patients (most patients with dry eye disease are eligible), in association with the use of other treatments (omega 3 supplements, artificial tears with lipids, steroid and antibiotic therapy) is effective in improving the objective parameters and subjective symptomatology of patients for a prolonged period. A further treatment may be necessary after 6-7 months or after more than a year an entire cycle of treatments may be necessary in order to continue to enjoy the benefits obtained with IRPL.

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# Novel approach to the management of dry eye

by **Vivian Ho** and **Samer Hamada**

Dry eye disease is a global problem, afflicting over 344 million people worldwide and is one of the most frequent causes of patient visits to eye care practitioners.
According to DEWS 2007 report, dry eye disease affects between 5 to 30% in those over the age of 50 years.
The new definition of dry eye disease is: "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." (DEWS II 2017)

Dry eye disease has been historically classified into two types: aqueous tear-deficient dry eye and evaporative dry eye. Aqueous deficient is further divided into Sjogren (primary or secondary) or non - Sjogren dry eye. Evaporative dry eye on the other hand can be intrinsic, where the regulation of evaporative loss from tear film is affected by e.g. meibomian gland dysfunction, poor blinking; or extrinsic, where evaporation is increased due to the use of topical drug preservative, contact lens wear or affected by ocular surface disease. The classification has also formed the basis of most dry eye management. These include patient education, adopting a certain lifestyle measures, warm compressed, lid hygiene, the use of artificial tears and anti-inflammatory or immodulatory treatments.

Zhang et al. (Zhang 2017) however came up with a new approach in the diagnosis and management of dry eye disease. They introduced the concept of ocular surface microenvironment, which may alter in dry eye patients. In that the cornea, conjunctiva, meibomian glands, lacrimal glands, the neural network and other components such as immune cells, matrix cells, hormones and microbiome all regulate the homestasis of the ocular surface. If there are any changes of these components, the homeostasis of the ocular surface can be compromised, resulting in dry eye.

The authors took each individual component and discussed their functions in maintaining the health of ocular surface, as well as how dry eye can affect them.

## 1) Cornea

The epithelium resists the entry of harmful pathogens by maintaining tight intracellular junctions. The microvilli also supports in the anchorage of the tear film. Epithelial cells have signaling mechanism involved in wound healing whereas the keratocytes are capable of synthesizing collagen and glycosaminoglycans, to maintain the extracellular matrix. Limbal stromal cells control proliferation and differentiation of limbal stem cells. Corneal endothelium acts as a barrier between the stroma and the aqueous humor in the anterior chamber.

In dry eye disease (DED), there is a reduction of corneal epithelial microvilli and a conversion of corneal epithelial phenotype to keratin 10 positive epidermal phenotype resulting in tear film instability. Endothelium cells are also significantly decreased in central cornea, in mild to severe dry eye.

## 2) Conjunctiva

Conjunctiva covers two-thirds of the ocular surface. The epithelium acts as a barrier and has an important role in mucin production and immune defence. It also contains mucin producing goblet cells and dendritic Langerhans cells. In mild to severe dry eye disease however, chronic inflammation of the conjunctiva occurs, together with deficiency of tear film and can lead to pathological changes of conjunctiva to squamous metaplasia. Goblet cell density is also reduced in dry eye.

## 3) Lacrimal gland

Lacrimal gland helps to maintain a healthy ocular surface by secreting aqueous tear that consists of water, electrolytes, protein and mucus. Its protein acts as a medium for light refraction between air and the cornea. It also contains microbicidal proteins and IgA secreting plasma cells which protect the ocular surface from invasive pathogens.

Various causes can contribute to lacrimal gland dysfunction such as aging, dry environments, radiation therapy, contact lenses, refractive surgery, hormonal imbalance, ocular cicatrical pemphigoid, Sjogrens syndrome and systemic disorders. All these conditions can cause irreversible changes in the lacrimal gland, causing loss of secretory acinar cells, fibrosis and gland atrophy, affecting the quantity and quality of the secretion resulting in severe aqueous deficient dry eye.

## 4) Meibomian gland

These specialized glands are composed of meibocytes forming the acini that undertake the process of lipogenesis and production of meibum. Changes in lipids present in meibum, can alter the quality of tear film leading to evaporative dry eye. Progressive obstruction of the ducts due to intraglandular cystic dilatation and hyper-keratinization, can widen the duct leading to gland drop out, tear film instability, excessive evaporation, hyperosmolarity and desiccating stress.

## 5) Eyelids

Our lid consists of a mobile mucosal lining. This forms a physical barrier, as well as distributing glandular secretion into the tear film. Reduction in blinking frequency lessened the thickness of the lipid layer, resulting in an increased evaporation of the aqueous layer. Altered lid laxity also alters the pressure over the meibomian glands to release meibum, resulting in meibomian gland dysfunction.

## 6) Tear film

Every layer of the tear film has an important role in the homeostasis of ocular surface microenvironment. Lipids maintain the surface tension and minimize evaporation of underlying aqueous. The aqueous helps to lubricate the ocular surface and contains proteins which are essential in cell signaling and rehabilitation. Mucus acts as a surfactant, spreading tear film on the surface. Changes in the quality and quantity of any layer of the tear components can disrupt the ocular surface health.

## 7) Immune cells

The ocular surface immune system is tightly regulated by both innate and adaptive responses. The innate immune system is the first-line of protection and functions to control infection and initiates the adaptive immune response. The adaptive immunity of the ocular surface depends on the cellular defense mediated by the T cells and the humoral defense mediated by the immunoglobulins secreted by the plasma cells. In DED, the ocular surface microenvironment experiences failure of immunohomeostasis, resulting in chronic inflammation.

## 8) Nerve supply of ocular surface

The ocular surface is populated with nerve fibers that are derived from the branches of the trigeminal nerve. They provide the action of blinking and tear reflex. Nerve endings secrete neurotransmitters and nerve growth factors which is essential in maintaining the epithelial integrity, proliferation and wound healing. The lacrimal gland is supplied by the preganglionic parsympathetic nerve. In dry eye disease however, there are reductions in the suprabasal density and altered morphology of cornea nerve supply.

## 9) Systemic hormones

Lacrimal and meibomian glands contain the sex hormone receptors. Androgens are capable of eliciting a major effect on the gene expression, protein synthesis

| Components of OSM | Normal Function | Changes in Dry Eye | Targeting Therapy |
|---|---|---|---|
| Cornea | Normal barrier function<br>Growth factors & cytokines<br>Quiescent keratocytes | Scarring & ulcer<br>Opacification<br>Neovascularization<br>Pannus formation<br>Squamous meteplasia<br>Extracellular matrix degradation<br>↓Endothelial cell number | Lubricants<br>Autologous serum<br>Growth factors<br>Amniotic membrane extract<br>Amniotic membrane<br>Contact lens<br>MMP-9 inhibitors |
| Conjunctiva | Immune defence<br>Secretes mucin | Squamous metaplasia<br>↓Goblet cell density<br>Chronic inflammation<br>Conjunctivochalasis | Autologous serum<br>Amniotic membrane<br>Vitamin A<br>MM-9 inhibitor<br>Growth factors<br>Rebamipide<br>Gefarnate<br>Diquafosol tetrasodium<br>Hydroxyeicosatetraenoic acid |
| Lacrimal Gland | Secretes:<br>Fluid<br>Mucopolysaccharides<br>Electrolyte<br>Microbial and proteins<br>Mucin | ↓Aqueous tear<br>↓Acinar and ductal cells<br>Fibrosis<br>Apoptosis<br>Inflammation | Lubricants<br>Immunomodulators<br>Secretagogue<br>Neurostimulation<br>Cyclosporin A |
| Meibomian Gland | Accomplishes lipogenisis<br>Secretes meibum<br>Maintains tear film stability<br>Prevents tear film evaporation | ↓Meibum<br>↑Tear evaporation<br>↑Keratinization<br>Apoptosis<br>Inflammation | Warm compress<br>Lid hygiene<br>Lipiflow System™<br>Intense Pulsed Light<br>w-3 fatty acid<br>Liposomal sprays |
| Eyelid | Physical defence<br>Meibum distribution<br>Prevents tear film evaporation | ↓Eyelid laxity<br>↑Tear evaporation<br>Corneal ulcer<br>Epithelial defect<br>Inflammation<br>Infrequent/ineffective blinking | Warm compress<br>Lid hygiene<br>Antibiotics<br>Surgery |

and immune response of the cornea, conjunctiva and the control of secretory functions of the lacrimal and meibomian gland. Androgen deficiency could lead to obstructive meibomium gland dysfunction with a lack of lipids at the lid margin and in the tear film, changing the lipid profile producing dry eye symptoms. Growth hormone also plays an important role in regulating the size and morphology of meibomian gland and the migration of cornea epithelium except for lacrimal gland.

## 10) Vascular system

The ocular surface vasculature is mainly seen in the conjunctival, episcleral layers and the limbal region. The normal human cornea is avascular but nourished by the components of blood. Arterial supply of conjunctiva originates from the peripheral tarsal arcades, marginal tarsal arcades and the anterior ciliary arteries. The blood and lymphatic vessel formation is primarily maintained by the vascular endothelial growth factors (VEGF). Continuous blood supply is required for the ocular surface, to facilitate the transport of growth factors, immune response and oxygen supply. Moderate to severe DED stimulates neovascularization and corneal pannus.

## 11) Ocular surface microbiome

Twenty-four genera, including pathogenic and non-pathogenic bacteria, have been found in the ocular surface. The microbiome of ocular surface also harbors viruses such as the herpes simplex type 1, hepatitis B virus, hepatitis C virus and Torque teno virus. The ocular flora cohabits with the components of ocular surface, contributing to immune tolerance and eliminating pathogenic microbes. Changes in the ocular microbiome are seen in conditions such as DED,

| Components of OSM | Normal Function | Changes in Dry Eye | Targeting Therapy |
|---|---|---|---|
| Tear Film | Ocular surface homeostasis<br>Moistens & lubricates<br>Transports nutrient & oxygen | Tear hyperosmolarity<br>Tear film instability<br>Excessive tear film evaporation<br>Delayed tear clearance | Compensation of tear<br>Artificial tears/serum<br>Tear stimulation<br>Pilocarpine, Pituitary adenylate cyclase-activating polypeptide, Diquafosol tetrasodium, Oculeve<br>Intranasal neurostimulation device<br>Controlling tear evaporation<br>Moisture-retaining eyeglasses, Swimming goggles, Prosthetic Replacement of the Ocular Surface Ecosystems, Castor oil eye drops<br>Regulating excessive nasolacrimal drainage<br>Punctal plugs |
| Inflammation | Immune homeostasis | Chronic inflammation<br>↑Pro-inflammatory cytokine<br>↑Chemokine<br>↓Glandular secretion<br>↑Reactive oxygen species<br>↑Apoptosis<br>CD4+ T cells-medicated pathogensis | Corticosteroids<br>Nonsteroidal anti-inflammatory drugs<br>Doxycycline<br>Azithromycin<br>Cyclosporin A<br>FK506<br>Lifitegrast<br>Tofacitinib<br>Fatty acids |
| Nerve | Secretes neurotransmitters & nerve growth factors<br>Controls tear reflex & landular secretions | ↓Neuronal stimuli<br>↓Corneal sensitivity<br>Altered nerve morphology | Neurostimulation<br>Nerve growth factor |
| Systemic hormones | Ocular surface homeostasis<br>Regulates meibomian gland & Lacrimal gland | Androgen deficiency<br>Estrogen deficiency<br>Thyroid hormones state disorder | Hormonal supplementation<br>Androgen & estrogen receptor inhibitors |
| Vascular and Lymphatic systems | Transports growth factors<br>Immune response<br>Oxygen supply<br>Lipogenesis | Lymphangiogeneisi<br>Hemangiogenesis | Anti lymphangiogenic agents |
| Ocular surface microbiome | Immune tolerance<br>Eliminates pathogens<br>Mucin turnover | Colonization of normal flora<br>Opportunistic pathogen<br>Drug resistance<br>Infectious keratitis<br>Conjunctivitis | Topical antibiotics<br>Corticosteroids |
| | ↓ decreased | ↑ increased | |

contact lens wear, keratoprosthesis, antibiotic exposure and infection. The ocular surface integrity is compromised in DED, encouraging the flora to exert its pathogenic effect, triggering the innate immune response.

hyperkeratinization of epithelium, squamous metaplasia and decreased conjunctival goblet cells. Topical vitamin A is found to improve the tear film stability by enhancing mucin production, hence maintaining the functionality of

> "In DED, the ocular surface microenvironment experiences failure of immunohomeostasis, resulting in chronic inflammation."

## Targeted therapy for dry eye

Zhang et al. introduced the idea of ocular surface microenvironment targeted therapy, to manage dry eye. This is shown in the summary table adapted from their paper (Zhang et al. 2017). In the cornea for example, autologous serum eye drops are loaded with EGF, HGF, vitamin A and fibronectin mimicking the tear film constitute which lubricates and maintains the integrity of the ocular surface. Autologous serum can therefore induce proliferation, migration, restore the tight junctions of the ocular surface epithelial cells, assisting in wound healing. Vitamin A deficiency in the ocular surface leads to ocular surface epithelial cells. Artificial tears on the other hand are the most common initial medical management for DED, as they contain ingredients that mimic the tear to maintain the osmolarity of the depleted tear film. Ocular inflammation can occur in DED resulting in subsequent ocular surface damage. Anti-inflammatory drugs help to disrupt this process and restore the normal ocular homeostasis in DED. Nerve growth factor (NGF) can enhance ocular surface sensitivity, inhibit inflammatory reactions, minimise the apoptosis of corneal epithelium and regulate tear film production by lacrimal gland and goblet cells. NGF can thus be utilised as a novel treatment for dry eye.

In summary the goal of DED management is to restore the ocular surface and tear film to their normal homeostatic state, i.e., the healthy ocular surface microenvironment. A wide range of therapeutics is available in treating DED, but the authors in their paper emphasize the importance of the functions of the OSM component and that we should adopt a target therapy approach to the management of DED. Customized and personalized therapy targeting the OSM will help to promote a healthy ocular surface hence a complete resolution of DED.

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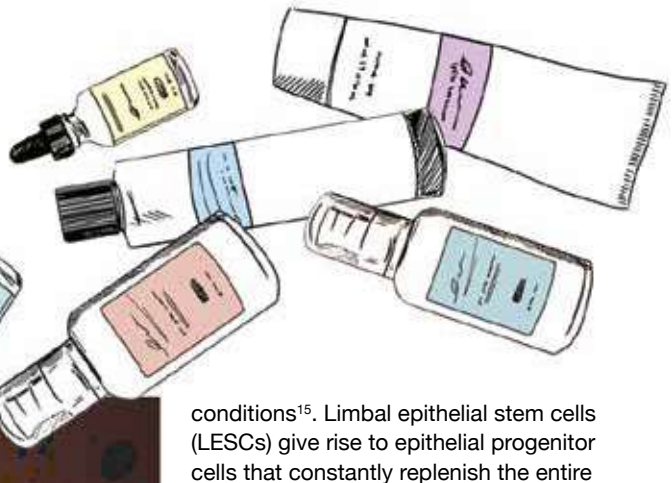
# Systemic medication injuring the cornea

by **Mohamed Elalfy** and **Kareem Sawah**



Homeostasis is a property of cells, tissues and organisms. It allows maintenance and regulation of the tissue stability, needed to function properly. This healthy state is maintained, by the constant adjustment of biochemical and physiological pathways[1]. Homeostasis imbalance occurs when the stable internal environment cannot be maintained and this disturbance results in disease development[1]. Tear film, lacrimal glands, corneal and conjunctival epithelium and Meibomian glands work together as a lacrimal functional unit (LFU), to preserve the integrity and function of the ocular surface[2]. The stability of the ocular surface is necessary for the health and normal function of the eye and vision. Nervous connections and systemic hormones, are also well known factors that maintain the homeostasis of the ocular surface[3,4].

TFOS DEWS II report defined dry eye as a multifactorial disease of the ocular surface characterized by 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[5]. It was found that among the top 100 selling systemic drugs in the US, 22 can cause dry eye[6]. Many systemic drugs are identified by large epidemiological studies and associated with dry eye disease such as nonsteroidal anti-inflammatory drugs, diuretics, vasodilators, analgesics/ antipyretics, antiulcer agents, sulfonylureas, cardiac glycosides, anxiolytics/benzodiazepines, anti-infectives, antidepressants/ antipsychotics, hypotensive agents, and antihistamines[7].

Different mechanisms have been proposed to describe the effect of drugs on dry eye symptoms and are unique to the particular class of drug being administered. Drugs with anticholinergic activity such as antidepressants, antipsychotics or neuroleptics, anti-Parkinson's, antihistamines, decongestants and antispasmodics can affect G-protein coupled muscarinic receptors in the lacrimal gland acini and conjunctival mucus-producing cells, reducing aqueous and mucous production, and tear film stability[8,9]. Amiodarone, aspirin, bisphosphonates, chloroquine, ibuprofen and clofazimine are secreted in the tears which either cause mechanical irritation, or increase evaporative dry eye by the presence of drug crystals in the tears or cornea[10,11].Chemotherapeutic agents such as methotrexate, mitomycin-c and busulfan either alter the quality of tear film, or affect reflex tear secretion[12,13]. Excess retinoic acid causes meibomian gland atrophy which in turn changes lipid secretion, tear osmolality and tear film stability[14].

The regenerative capability of the corneal epithelium helps to maintain its ultra-structure and function both during homeostatic and wound healing conditions[15]. Limbal epithelial stem cells (LESCs) give rise to epithelial progenitor cells that constantly replenish the entire corneal epithelium[16].
Limbal niche is a specialized microenvironment in the limbus which regulates LESCs function[17]. One of the causes of Limbal stem cell deficiency (LSCD) is Steven Johnson Syndrome/ Toxic epidermal necrolysis (SJS/TEN)[18]. It is believed that the most frequent single cause of TEN is drugs (80-95%) and nearly all TEN patients will have ocular involvement[19]. Many drugs have been implicated in the development of SJS such as cotrimoxazole, sulfonamides, allopurinol, carbamazepine, phenytoin, phenobarbital, nevirapine, lamotrigine and pantoprazole[20]. It is suggested that these drugs affect ocular surface by causing cytotoxic cell mediated hypersensitivity reaction, against keratinocytes leading to their apoptosis[21]. The ocular findings include epithelial defects, conjunctival and corneal ulceration, lid margin keratinization and subconjunctival scarring and corneal perforation[22].

A number of systemic drugs induce corneal epithelial changes characterized by deposits presenting as: punctate keratopathy, diffuse epithelial haze, Vortex Keratopathy / Cornea Verticillata, or crystalline precipitates. Drugs that are included in Vortex keratopathy include amiodarone , aminoquinolones, tamoxifen, chlorpromazine, NSAIDs, atovaquone , clofazimine, vandetanib, gold suramin and tilorone[23]. The specific mechanisms underlying corneal epithelial deposition are not completely understood. Lysosomal dysfunction, either from endogenous causes or exogenous causes, is responsible for many corneal epithelial keratopathies. Exogenous lysosomal dysfunction results from administration of drugs that produce corneal phospholipidosis[24]. Two theories are proposed for phospholipidosis: the first is inhibition of specific lysosomal phospholipases that normally would be responsible for catabolizing the lipids[25] and the second is that the some systemic medications share cationic, amphiphilic properties

that allow them to penetrate the lysozymes and form drug-lipid complexes. These complexes are unable to pass from the lysosome or be degraded[24].

Amiodarine is a benzofurane derivative used to treat a variety of cardiac abnormalities. Ocular manifestations of this drug include vortex Keratopathy (corneal verticillata) starting near the inferior pupillary margin, extending toward the limbus, which can occur as early as 6 days after drug initiation, but typically within 3 months of treatment. Severity of keratopathy appears to be dose related (100 –200 - mg/d minimal effect; 400 - 1, 400 mg/d - more advanced keratopathy) and resolves within 6-8 months after discontinuation of drug. Other ocular manifestations include anterior subcapsular cataract[26]. Another systemic drug is aminoquinolines (Chloroquine and hydroxychloroquine) which are antimalarial drugs used to treat rheumatoid arthritis, systemic lupus erythromatosis and other collagen diseases. Corneal manifestations of aminoquinolones start as diffuse punctate deposits that, over time, aggregate into curved linear whorls involving the pupillary zone. The deposits start to gradually disappear on cessation of therapy and resolution may take up to a year. Other ocular manifestations are posterior subcapsular cataract and bull's eye maculopathy[24].

Corneal stromal deposition may develop from a number of medications. These drugs gain access to the cornea via the aqueous humor, the limbal vasculature and tear film. These drugs are clofazimine, phenothiazines, retinoids (Isoretinoin), gold (Chrysiasis) , exogenous immunoglobulins and silver (Argyrosis)[27]. Clofazimine (Lamprene) is a phenazine red dye derivative used in treating leprosy, psoriasis, pyoderma gangrenosum and discoid lupus. Ocular Presentation include fine, granular, brownish, or brownish red lines or a single line resembling a Hudson-Stahli line in the superficial layers of the lower part of the corneas, other ocular manifestations include conjunctival pigmentation[27]. Isoretinoin, a mainstay in the treatment of recalcitrant cystic acne, is frequently associated with adverse ocular manifestation. The most common ocular complications include blepharoconjunctivitis, dry eye, pseudotumor cerebri and corneal opacities. Corneal opacities are typically fine, diffuse gray deposits in the superficial stroma, located in both the central and peripheral cornea. These opacities typically do not interfere with vision and resolve with drug cessation (2–10 months)[28].

Immunoglobulins used exogenously in the management of Pyoderm Gangrenosum are deposited in the midstroma as crystalline deposits in an annual pattern over the corneal mid-periphery[29]. The systemic administration (intramuscular, oral) of colloidal gold salts, most commonly used in the management of rheumatoid arthritis, may lead to the deposition of gold in the skin and cornea, termed chrysiasis. When cumulative doses are greater than 1 g, 67 to 97% of patients demonstrate corneal gold deposition[30]. The deposition is greatest in posterior stroma, sparing endothelium and DM. Ocular chrysiasis may resolve as early as three months, or persist as late as 9 years after drug cessation. This rarely affects visual acuity and so there is no indication to stop therapy[30,31]. Silver can also affect the corneal stroma as greyish brown granular deposits either iatrogenically or from occupational exposure[27].
Although most of these drugs show deposition, either in the corneal epithelium or stroma, endothelial deposition has more recently been described with rifabutin, a derivative of rifampin . Rifabutin is used for the prophylaxis and treatment of Mycobacterium avium complex (MAC) infections, a common disseminated infection in patients with AIDS. It shows bilateral corneal endothelial deposits, in the absence of inflammation. The stellate, refractile endothelial deposits first present in the periphery and may eventually extend to involve the central cornea[32,33]. Other drugs are associated with corneal endothelial dysfunction and corneal edema such as amantadine, ketamine and memantine. These drugs are indicated for Parkinson's disease and show bilateral corneal edema which may lead to permanent endothelial damage. The pathogenesis of end othelial affection is unclear and resolution of symptoms is dependent on complete cessation of treatment[34].

Cannabinoids showed decreased endothelial cell density in a study done in 2017[35]. Large intake of ethyl alcohol has also been shown to cause temporary endothelial cell dysfunction[36]. Dopaminergic drugs (methylphenidate, ropinirole and resiniferatoxin) are all found to cause corneal edema and endothelial dysfunction[37]. Several chemotherapy agents can affect the cornea causing dry eye, Mebomian gland dysfunction, nonhealing corneal epithelium and corneal melt, corneal deposits and conjunctivitis. Examples of these agents are epidermal growth factor receptor (EGFR) inhibitors, human epidermal growth factor receptor 2 (HER2) inhibitor (trastuzumab),BRAF gene inhibitor (vemurafenib), immune checkpoint inhibitor (ipilimumab), small-molecule tyrosine kinase inhibitors (nilotinib, Imatinib, afatinib)[38].

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# A comparison of Healing and Pain response of Bandage lens, LensWista Element BL versus PureVision Bandage lens after LASEK

By **Azher Qasem Aldouri**, FRCS, FEBO, **Michael O'Keeffe**, MD, FRCS


## Purpose:
To evaluate the healing tendency, relative pain and tolerability of 2 different bandage lenses applied after LASEK.

## Setting:
Department Of Ophthalmology, Refractive Surgery Research Centre, Mater Private Hospital, Dublin-Ireland

## Design:
Prospective randomized comparative case series.

## Methods:
Patients having LASEK were randomized to LensWista Element BL (manufactured by LensWista AG, distributed by LensWista or Geuder, polydimethylsiloxane) and PureVision (Bausch &Lomb, Balafilcon A) bandage lens in each eye postoperatively.
Patients were evaluated on 1ST and 3RD day postoperatively and completed a questionnaire rating pain score and cure behaviour.

## Results:
42 patients after bilateral LASEK were enrolled over a 6-month period (Total 84 eyes-48 female eyes & 36 male eyes, 57.14% of the patients were women, age (20-69 years old with a mean age of 37.261 year +-14.817 STDEV) and the range of refraction was (from +0.50/-2.35*85 to -7.25/-0.75*140) with a mean spherical equivalent (MSE) of 2.885 +- 2.380 STDEV.
At 1ST and 3RD day postoperatively, eyes with the LensWista bandage lens experienced less pain and discomfort. The healing tendency of both lenses was almost identical and 77 eyes (91.6%) showed 95%-100% epithelial healing at day 3 postoperatively.
6 eyes experienced lost bandage lenses (2 LensWista vs 4 PureVision) and therefore needed replacement.
While 7 PureVision (Bausch&Lomb) needed exchange at 3rd day, due to incomplete corneal epithelial healing of less than 95%.

## Conclusion:
LensWista bandage lens (manufactured by LensWista AG, distributed by LensWista or Geuder) showed better tolerability for postoperative pain compared to Bausch &Lomb lenses, but the postoperative epithelial healing tendency was almost the same on 3rd day postoperatively.



## Financial Disclosure:
The authors have no proprietary or financial interest in any material or method mentioned.


## Introduction:
Despite many advances in refractive surgery, pain post LASEK remains the single biggest immediate postoperative problem.[1]
There are many strategies which have been adopted, including analgesia, sleeping tablets, systemic and topical anti-inflammatory agents.[2]
A bandage lens produces a physical barrier to the mechanical stimulation of the ocular surface nociceptors, from blinking. [3, 4]
Bandage lenses are universally used in the management of corneal epithelial defects, wound leaking and recurrent corneal erosions. They are commonly used after Laser Assisted Sub-Epithelial Keratectomy (LASEK).[5]
In this prospective randomized comparative study, we report on relative pain, corneal epithelial healing tendency and tolerability of two different types of bandage lens. We obtained institutional approval and the study fulfilled the tenets of Helsinki agreement of ethical principles for medical research. The patients were recruited after detailed discussion and all signed a consent form agreeing to take part in the study.

## Patients and Methods:

### Inclusion criteria:
Included all patients meeting administrative and medical requirements for LASEK treatment at the Department of Ophthalmology, Refractive Surgery Research Centre, Mater Private Hospital, Dublin-Ireland.

### Exclusion criteria:
Patients requiring a unilateral treatment, retreatment (enhancement), patients undergoing corneal crosslinking and patients with dry eyes or poor ocular environment ie: blepharitis, meibomian gland dysfunction, abnormal Tear Film Break Up Time (TFBUT), were excluded.

Eyes were randomised to compare 2 different bandage lenses (new product LensWista Element BL by LensWista and PureVision by Bausch&Lomb).
Patients were treated according to the standard LASEK protocol at the laser centre, with the removal of epithelium using diluted alcohol (20% Ethanol) in an 8.5mm area for 30 seconds. Excimer-surface laser ablation was performed and each eye was then rinsed with a cold balanced salt solution and 2 drops of chloramphenicol were installed directly on the cornea. The bandage lens was selected and placed on the cornea in a randomised fashion.

Postoperative management during the first 5 days included topical chloramphenicol (2 drops every hour on the day of surgery, then 4-times daily for 6 days). Intensive preservative-free artificial tears and maxidex (started on the 5th day -1 drop 4 times daily for 3 weeks

then twice a day for 3 weeks). Diclac (Difene Retard 75 mg was given orally twice per day) , paracetamol 1g 4 times daily for 3 days and dalmane (sleeping tablet) 30 mg at night, for 3 nights post-surgery. According to the standard protocol, patients were evaluated 1st and 3rd day postoperatively. At these visits, patients completed a pain evaluation form (patient questionnaire), pain scaleform, and the eye surgeon completed a cure behaviour form. The bandage lenses were removed at 3rd postoperative day.

## Results:

42 patients were enrolled over a 6-month period. Total of 84 eyes - 48 female eyes & 36 male eyes, 57.14% of the patients were women, age (20-69 years old with a mean age of 37.261 year +-14.817 STDEV) and the range of refraction was (from +0.50/-2.35*85 to -7.25/-0.75*140) with a mean spherical equivalent (MSE) of 2.885 +-2.380 STDEV.

At 1st and 3rd day postoperatively, eyes with the LensWista bandage lens experienced less pain and discomfort. The healing tendency of both lenses was almost identical (95%-100% of the epithelium healed by day 3 postoperatively). Two LensWista lenses were lost, compared to four Pur-Vision during the first 72 hours postoperatively. On the other hand, seven PureVision lenses needed exchange at 3rd day, due to incomplete corneal epithelial healing. Table 1, chart 1-a, b.
Pain response and tolerability after LASEK was assessed in 84 eyes, which were divided into 5 pain management groups.
Pain at its worst, was measured using a pain evaluation form (patient questionnaire) & pain scale form. The groups are arranged in order, group 5 having experienced the most unbearable pain and group 1 with no pain & no foreign body sensation:
Group-5 was dramatically better than any other group. In fact, only 3.57% (3 eyes) of group-5 patients with PureVision bandage lenses had unbearable pain at the 1st postoperative day.

At day 1 & day 3 after surgery, group-2 showed better tolerability with no pain but some discomfort in 23.80% (20 eyes)and 22.61% (19 eyes) with LensWista, compared to 1.19% ( 1 eye) and 23.80%(20 eyes) with PureVision lens at 1st & 3rd post-operative day respectively.Table1, chart 1-a.

## Discussion

The efficacy of the bandage lenses in controlling the pain is evident clinically by the intense pain commonly reported by patients, after a lens is lost during the early 72-hours postoperatively.[5]
We used two different types of bandage lens, LensWista Element BL (distributed by LensWista or Geuder) and PureVision (Bausch&Lomb).

The LensWista Element BL consists of polydimethylsiloxane, while PureVision bandage lens is composed of flurosilicone hydrogel material. Both lenses differ in several ways, such as water content, edge profile, thickness, oxygen permeability and oxygen transmissibility.
The LensWista has nearly 10-times higher oxygen permeability compared to PureVision lens and its biocompatible pure silicone material have contributed to the fast wound healing and significant pain relief. Table 2

Moreover, the new surface technology gives LensWista a maximum and durable hydrophility. The aspherical inner surface of the lens reduces noticeably the pressure on the cornea, to provide the patient with maximum tolerability and comfort without any visual impairment. Deposits of lipids or mucin material within the lens and potential risk of infections, are also significantly reduced.
LensWista is approved as a medical device for a seven day long-wear period, according to Council Directive 93/42/European Economic Community (EEC).
Several variables related to lens architecture and lens material, may have contributed to the relative differences in pain experienced. Oxygen permeability, oxygen transmissibility, thickness and water content are all related entities. Oxygen permeability (DK) is the product of oxygen diffusion and oxygen solubility and is intrinsic to the lens material used. [6]
Lens manufacturers strive for materials with high DK values, because these materials maximize oxygen transmissibility (DK/t) at a given lens thickness (t).[7]
For hydrogel lens, the DK increases as the percentage of water increases [7] , while for pure silicon (LensWista), the inverse is true.
This tendency is driven by the fact that a silicone lens is more permeable to oxygen than water, which in turn is more permeable than hydrogel material.[7]
The United States Food and Drug Administration (FDA) approved PureVision (Bausch&Lomb) soft contact lens to be used as a bandage lens for wound healing after LASEK.[7] This lens is made with silicone hydrogel material (Balafilcon A) compared to LensWista which is made by pure silicone and is currently not approved by FDA.

Oxygen transmissibility, is a measure of the oxygen that reaches the cornea in the presence of the contact lens in situ. In a bandage lens high transmissibility is essential, because the cornea depends on atmospheric oxygen to maintain aerobic metabolism for epithelial regeneration and wound healing.[8]
The PureVision (Bausch&Lomb) lens has a lower DK value and a greater thickness than LensWista. The increased thickness causes a reduction in the amount of oxygen reaching the cornea (DK/t), which could delay wound healing and be associated with discomfort.[9]
In addition, the difference in thickness between the PureVision (Bausch&Lomb) lens and LensWista may lead to discomfort.

Based on our findings, the PureVision is more rigid than the thinner LensWista when manipulated. A thinner bandage lens with less resistance to deformation, might be expected to completely cover the surface of the eye and likely contribute to a decreased foreign body sensation.Table 2
Lens diameter and base curve, are other factors that differ between the 2 lenses. The lens diameter ranged from LensWista 13.40 mm and PureVision 14.00 mm and the base curves are 8.6 mm and 8.3 mm for PureVision and 7.9 mm, 8.1 mm and 8.3 mm for LensWista Element BL.
These variables were matched as closely as possible, within manufacturer limitations. The impact of lens diameter and base curve on patient comfort is not clear from this study, however, these factors may be patient dependent, varying with patient keratometry and corneal diameter. It might be possible that ocular pain further improved, by fitting the bandage lens to the postoperative keratometry instead of using a standard size for every patient. Therefore, this hypothesis requires further study.

These factors are beyond the scope of this study, however, extensive research has shown that hydrophilicity and lubricity play important roles in ocular comfort.[9]

Hydrophilicity and surface smoothness are documented factors that may contribute to ocular comfort.[10, 11]
Surface smoothness has been shown to vary based on the material. Increased hydrophilicity results in better lens-surface lubrication and improved comfort. [12]
The last lens characteristic that may explain the difference in comfort between the two lenses, is the edge profile. It has been noted the edge profile of a contact lens is associated with comfort [13]

Although compared with lubricity or oxygen permeability, the edge profile may play only a small role in differentiating the comfort of the two lenses.

The LensWista Element BL (Polydimethylsiloxane) appears to have a much sharper, and thinner edge than the PureVision (Balafilcon A; Bausch &Lomb). By contrast, the PureVision has a much thicker edge, which is blunted and curved.

The tapered, thin edge of the LensWista lens creates less perceptible transition from the ocular surface to the bandage lens, as the eyelid crosses the interface when blinking. A smoother transition likely decreases movement of the bandage lens during blinking, which may contribute to less pain. Table 2

Previous study by Grentzelos, compared the efficacy of 2 types of silicone hydrogel bandage lenses with high oxygen transmissibility, after photorefractive keratectomy (PRK).
This prospective study enrolled 44 patients (88 eyes), 1 eye of patients having bilateral PRK was randomly fitted with a bandage lens of lotrafilcon A (day&night) and the fellow eye, with a bandage lens of lotrafilcon B (O2 Optix). The mean epithelial defect size immediately after surgery was 4.7 mm with both types of bandage lenses. There was no statistically significant difference in epithelial defect size between the 2 lenses, at any postoperative visit.
Three days postoperatively, re-epithelialization was complete in 75.0% of eyes in the lotrafilcon A-group and 72.7% of the eyes in the lotrafilcon B-group. [14]

Another study by Taylor KR, compared 3-FDA approved different silicon hydrogel bandage lenses for pain control at day 1 & 4 post photorefractive keratectomy (PRK)[16]. The study enrolled 54 patients having PRK, who were randomized to a senoflicon A (Acuvue Qasys), balafilcon A (PureVision), or lotrafilcon A (Air Optix) bandage soft lens in each eye postoperatively.
At 1 and 4 days, eyes with the senofilcon A lens had the lowest pain scores, followed by eyes with the lotrafilcon A lens then eyes with the balafilcon A lens. Averaging qualitative results showed that eyes with balafilcon lens (by Bausch&Lomb) were the least comfortable.

Advances in bandage lens design and material, have dramatically improved the comfort experienced with their wear as well as their efficacy in use postoperatively. Several factors likely contributed to the efficacy of each lens and continued advances in contact lens design will hopefully provide greater comfort not only with bandage lenses, but also with contact lenses used to correct refractive errors.
A possible drawback to our study was the use of topical and oral painkillers. We did not restrict pain medication use, due to potential ethical concerns. The oral pain medication is universally used. The administration of topical proxymethacaine was very limited, because it was only recommended as a last line of treatment to relieve pain and discomfort.

> “Patients that require bandage lenses for other indications may find the LensWista to be more comfortable than the PureVision lens. However, it’s the surgeon’s decision whether the benefits of LensWista are good enough to justify its cost.”

In conclusion, our findings have shown that the pure silicone LensWista Element BL bandage lens (manufactured by LensWista AG; distributed by LensWista or Geuder) is more comfortable than the BalafilconA Bausch& Lomb), specifically within the first 48 hours after surgery.
Patients that require bandage lenses for other indications may find the LensWista to be more comfortable than the PureVision lens.
However, it’s the surgeon’s decision whether the benefits of LensWista are good enough to justify its cost.

A study by Cherry PMH, assessed the additive effect of local anaesthetic drops, topical diclofenac and bandage soft lens in the treatment of pain following excimer laser photorefractive keratectomy (PRK). Pain control after excimer laser PRK was assessed in 112 eyes. This study determined that difference in pain of 30% or more, tends to be clinically significant.[15]

## What was known

Different types of contact lenses are FDA approved for use as bandage soft lenses after refractive surgery.

## What this study provides

The LensWista bandage soft lens was clinically significantly more comfortable than the PureVision BSCL post LASEK.

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**Table 1 (Post- Operative days & Levels of pain response, healing tendency)**

| Post- Operative days | Level 1. No pain, No foreign body sensation | Level 2. No pain, some discomfort | Level 3. Bearable pain/ Some discomfort | Level 4. Severe pain | Level 5. Unbearable Pain | Healing Tendency (Epithelial closure/Erosion zone) | | |
|---|---|---|---|---|---|---|---|---|
| 1st day postop.- LensWista Bandage Lens (Geuder) | 9 | 20 | 12 | 1 | 0 | Less than 95% | More than 95% | 100% |
| | | | | | | 42 | 0 | 0 |
| 1st day post op- PureVision Bandage Lens (Bausch&Lomb). | 0 | 1 | 22 | 16 | 3 | Less than 95% | More than 95% | 100% |
| | | | | | | 42 | 0 | 0 |
| 3rd day post op- LensWista Bandage Lens (Geuder) | 21 | 19 | 2 | 0 | 0 | Less than 95% | More than 95% | 100% |
| | | | | | | 0 | 7 | 35 |
| 3rd day post op .- PureVision Bandage Lens (Bausch&Lomb). | 4 | 20 | 18 | 0 | 0 | Less than 95% | More than 95% | 100% |
| | | | | | | 7 | 9 | 26 |
| | | | | | | 7 Lenses needed exchange | | |

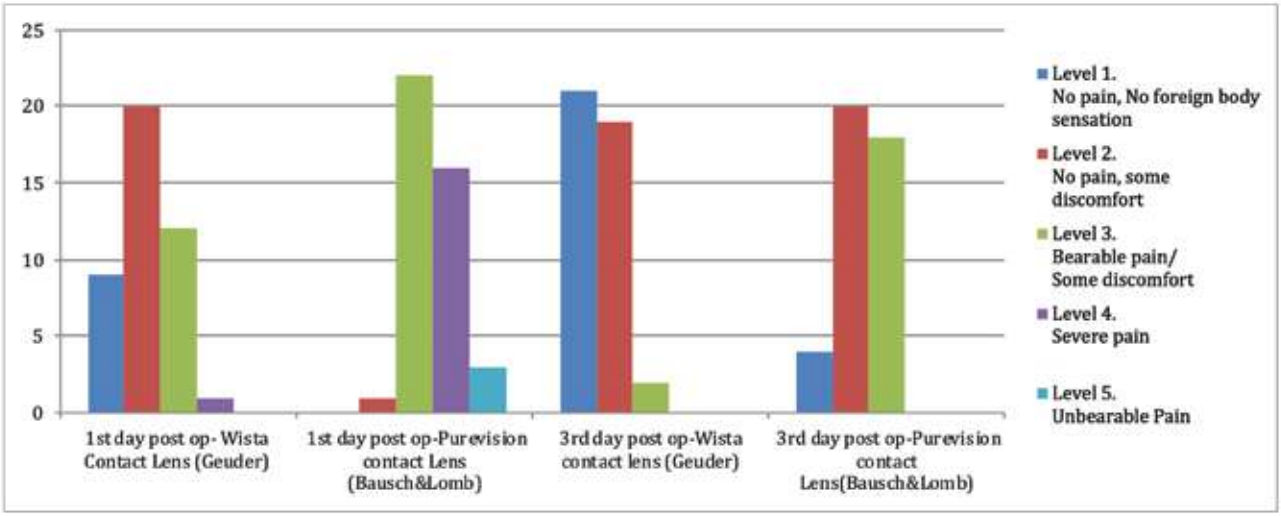


**Chart 1-a (Post- Operative days & Levels of pain response)**

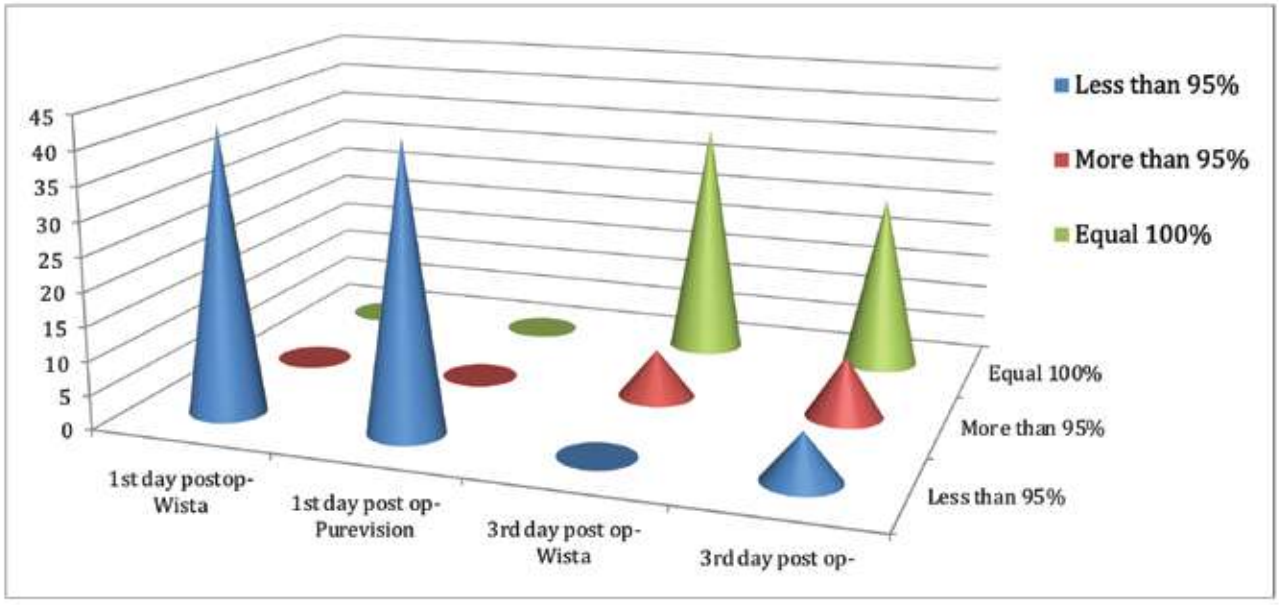


**Chart 1-b (Post- Operative days & Levels of pain Healing Tendency - Epithelial closure/Erosion zone)**

**Table 2 (Manufacturer Specifications for the 2 bandage contact lenses used.)**

| Lens | Material | DK= Oxygen permeability | DKt=Oxygen Transmissibility at the given lens thickness | Thickness(Micromete) | Water % | Diameter (mm) | Radius BC (mm) |
|---|---|---|---|---|---|---|---|
| PureVision (Bausch& Lomb) | Balafilcon A | 91 | 33 | 275 | 36 | 14.00 | 8.6 |
| LensWista Element BL (currently is not approved by FDA) | Polydimethil siloxane, pure silicone | 938 | 520 | 180 | 0% | 13.4 | 8.3 |

**DK=Oxygen permeability, DKt=Oxygen Transmissibility at the given lens thickness (t).**
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