Dry Eye – Can You Cry?

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Ocular surface discomfort is often attributed to the symptoms of dry eye, but conditions affecting the lacrimal gland are uncommon. Meibomian gland dysfunction (MGD) is extremely common and is a characteristic feature of many patients with dry eye symptoms. Most ophthalmologists choose some type of lubricant artificial tear drop as first-line treatment for dry eye symptoms, but this paper questions the rationale for this decision. Patients who can cry, or produce tears from any stimulus, demonstrate lacrimal gland function. This paper considers the rationale for employing a safe, effective, biodegradable warm compress as first-line treatment for MGD and associated dry eye symptoms.

Keywords

Dry eye, meibomian gland dysfunction, Sjögren syndrome, blepharitis, warm compress, EyeBag®, anthropocene

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Ocular surface discomfort is probably the most common complaint made by patients visiting the ophthalmologist or optometrist. Although the symptoms of dry eye are well recognised by eye care professionals, there is much debate and discussion about how best to manage dry eye in routine clinical practice.

In 2017, 10 years after the first Dry Eye WorkShop (DEWS) report,[1] the Tear Film and Ocular Surface Society (TFOS) published the findings of their second DEWS, known internationally as TFOS DEWS II.[2] The report redefines dry eye, stating that, '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.'[2] The entire report is divided into 11 sections which, between them, cover all aspects of dry eye research and current thinking on this subject.

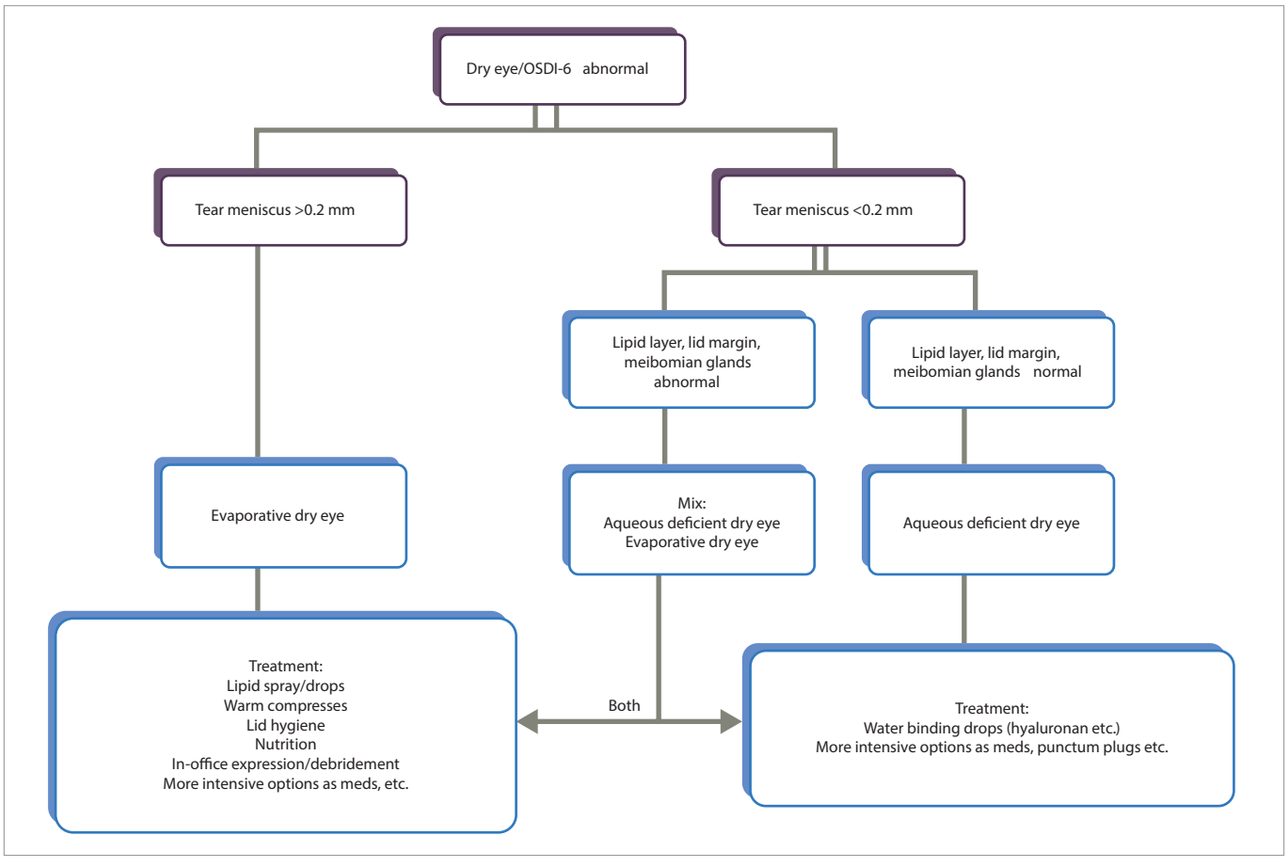
For the first time, this new definition of dry eye includes the phrase 'loss of homeostasis of the tear film'. It also acknowledges that neuro-sensory abnormalities play a significant role in patients with dry eye symptoms.

Lacrimal gland or meibomian gland – or both?

Most patients with dry eye symptoms have a disturbance of the lipid layer of the precorneal tear film which leads to rapid breakup of the lipid layer. This results in an increased rate of evaporation of the watery element of the tear film, which in turn causes an increase in tear film osmolarity. The hyperosmolar tear liquid likely causes local cellular damage of the lid margins and ocular surface, and may initiate local inflammatory responses. Once this inflammatory process has been established it becomes self-perpetuating and a vicious cycle of meibomian gland dysfunction (MGD), poor lipid layer, increased evaporation, hyperosmolarity and lid margin inflammation leads to further obstruction of the terminal ducts and orifices of the meibomian glands exacerbating the MGD.[3] Effective dry eye therapy depends on strategies to break this vicious cycle and efforts to re-establish the tear film homeostasis. It is evident that although around 20 million people – roughly one-third of the population – in the UK have MGD, fewer than 20,000 people actually have lacrimal gland failure.[4] These data suggest that lacrimal gland failure is the primary cause of dry eye in less than 1 in 1,000 patients with dry eye.

Lacrimal gland failure is the end result of the progressive dysfunction of the gland. Progressive lacrimal gland dysfunction eventually leads to lacrimal gland failure. True lacrimal gland dysfunction (LGD) is rare. The most common cause is Sjögren's syndrome, although the condition itself is not common and population prevalence is probably over-estimated at 1%.[5] Primary Sjögren's syndrome is much less common than secondary Sjögren's syndrome, occurring as a consequence of connective tissue diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (*Figure 3*).[6] Most patients with Sjögren's syndrome will already have another systemic condition, usually managed by a rheumatologist. These patients are also much more likely to develop lymphoma. Different national and international rheumatology groups have published criteria for the diagnosis of Sjögren's syndrome. The prevalence of Ro and La antibody positive Sjögren's syndrome is even lower.[7]

Figure 1: Tear meniscus height workflow



OSDI = Ocular Surface Disease Index.
Courtesy of Heiko Pult, MD.

In the UK, some estimates suggest that about one-third of all patients attending a regular sight test have MGD; while the website of the British Sjögren's Syndrome Association states there are only 1,800 members, some of whom do not have Sjögren's syndrome.[8] It is difficult to know for certain the true incidence and prevalence of Ro/La-positive Sjögren's syndrome, but it is possible that it has been decreasing since year 2000 with the advent of biologic, disease-modifying drugs which are now being widely used for many of these rheumatological conditions.

Other causes of LGD, such as sarcoid and graft versus host disease, are even more rare than Sjögren's syndrome.

Onions and tongues

Along with lacrimal gland failure, patients with Sjögren's syndrome also have salivary gland dysfunction which results in a very dry mouth and tongue (*Figure 4*). The typical Sjögren's tongue is dry and fissured. Patients with true Sjögren's syndrome are unable to eat certain foods such as dry biscuits and crisps (potato chips) and this can easily be established by asking direct questions during the consultation.

Because the vast majority of patients with dry eye have good lacrimal gland function, they are able to weep, cry and produce tears in response to appropriate stimuli. The preparation and chopping of onions or shallots in the kitchen usually provokes reactive eye watering but there are many other epiphora genic stimuli which can cause weeping. Any evidence of tear production confirms that the lacrimal glands are functional and that treatment strategies are best targeted at improving MGD. Furthermore, patients with true Sjögren's syndrome usually have co-existing MGD.

Tear meniscus height as a proxy for tear volume

In most patients with dry eye, the tear meniscus height is normal, but in those rare patients with LGD, the total pre-corneal tear volume is markedly reduced so the meniscus height is reduced accordingly. The height of the inferior meniscus is therefore an objective, non-interventional metric which functions as a proxy for total tear volume. The meniscus is typically <0.2 mm high in established Sjögren's syndrome but ≥0.3 mm in dry eye with a normal functional lacrimal gland. One would expect the lipid layer of the pre-corneal tear film to break up rapidly in both MGD and lacrimal gland failure dry eye. Together, the meniscus height and the non-invasive tear film break-up time are useful clinical signs that point to the aetiology of the dry eye symptoms. However, the meniscus height measurement is probably more reliable in routine clinical practice because it is less open to misinterpretation. The meniscus height is useful when considering treatment options (*Figure 1*).

Blinking – a global human experiment

The 'near response' of close attentive gaze is typically said to comprise three features: convergence of the visual axes, accommodation of the lens, and pupillary miosis. However, it is also well known that a fourth feature of the near response is reduced blink rate. The basal blinking rate is controlled by neuro-anatomical nuclei within the basal ganglia – principally, the superior salivary nucleus. Therefore, there is an involuntary reduction in the frequency of blinking during prolonged close attentive staring. This means that the pre-corneal tear film is not refreshed with each blink and the rate of tear evaporation increases while the eyes are wide open during periods of intense concentration in near gaze. Typically, this occurs when staring

Figure 2: Simple dry eye management algorithm

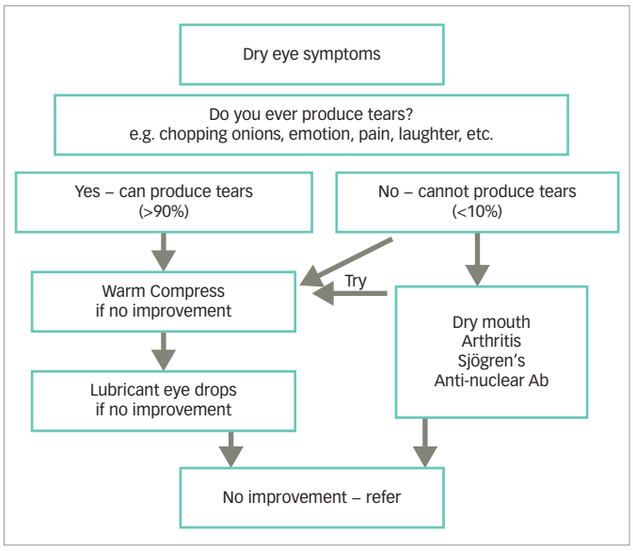
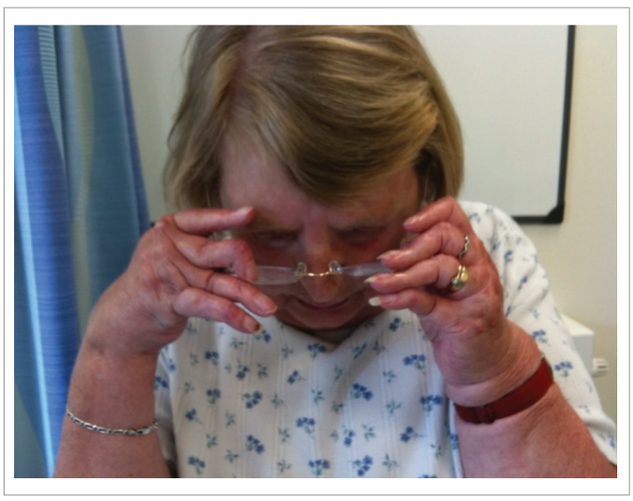


Figure 3: Patient with rheumatoid arthritis with secondary Sjögren syndrome



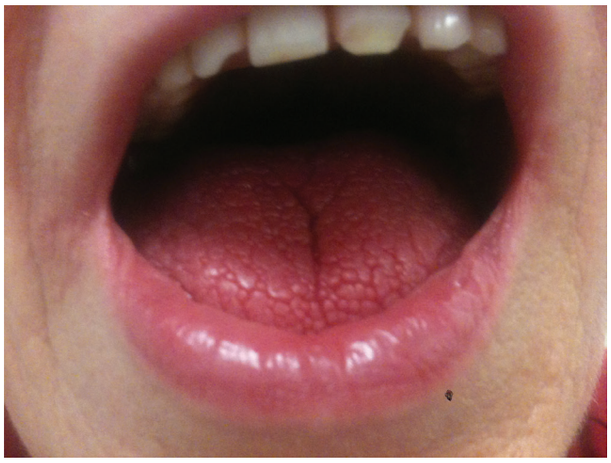
at any close screen, such as a gaming console, or a computer display (laptop or desktop, mobile phone or tablet).

Although smartphones are ubiquitous, being owned by billions of people, they have only been a feature of everyday life for the last decade or so. While the first Sony PlayStation was introduced in December 1994, the Apple iPhone first became available to buy in June 2007. Over the last 25 years, human beings have been spending increasingly prolonged periods of time, often hours on end, in uninterrupted, close, attentive gaze. These prolonged periods of reduced blinking are having a profound effect on the pre-corneal tear film of billions of people. For many, the cycle of ocular surface inflammation may well be instigated by long periods of not blinking while staring at close screens. This really is an uncontrolled global human experiment.

Dry eye treatment – choices and options

The management and therapy section of the TFOS DEWS II report gives a detailed assessment of all the treatments currently available and

Figure 4: Dry tongue and teeth in Sjögren syndrome



discusses the evidence for each intervention, presenting a 'staged management algorithm'.[4] Evidence-based therapeutic interventions are discussed and their use is correlated with the severity of the dry eye condition. Since MGD is approximately 100 times more prevalent than LGD, it seems logical to commence with an effective treatment which will improve the function of the meibomian glands. Artificial tears and ocular lubricating eye drops do not act on the meibomian secretions whereas physical treatments which warm and express those meibomian secretions do address the underlying problem directly. Thus, it is logical for the first therapeutic intervention to be an effective lid-warming therapy for all patients with dry eye. Tear replacement is not required unless there is an LGD, although lubricant eye drops often provide transient symptomatic relief (*Figure 2*).

Ethics and economics

Consider this: if a safe, effective, reusable, biodegradable, warm compress such as the MGDRx EyeBag® (The EyeBag Company, Halifax, West Yorkshire, UK)[9,10,11] costs £10.00,* but it costs £16.58 to carry out a test to prove that dry eye exists, is it not logical and simply better medicine, to give all patients the warm compress treatment first, investigating only those who still have symptoms?

We now understand that tear film osmolarity plays a role in the evolution of dry eye symptoms and probably influences and maintains the vicious dry eye cycle. The National Institute for Health and Care Excellence (NICE) evaluated the TearLab® osmolarity measuring system (TearLab, Escondido, CA, USA) and published a Medtech Innovation Briefing (MIB47) in December 2015.[12] NICE calculated that the cost of measuring tear film osmolarity was £16.58 (£8.29 per eye), but this did not include the cost of the consultation fee of circa £125 (with the UK National Health Service). MIB47 concluded, 'The use of the TearLab osmolarity system is not currently planned into any NICE guidance programme'.[12]

Furthermore, in April 2015, the NICE MIB29 evaluated the LipiFlow® Thermal Pulsation System (TearScience, Morrisville, NC, USA) and calculated the costs to be £453 for one treatment to both eyes, advising 'The use of the LipiFlow system is not currently planned into any NICE guidance programme'.[13] The same cost–benefit argument holds true for intense pulsed light therapy, also discussed in the Management and Therapy section of the TFOS DEWS II Report.

**Annex Part IXA of the UK NHS Drug Tariff – MGDRx Eyebag® Tariff price: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff/drug-tariff-part-ix*

Figure 5: Superficial punctate keratitis – preservative toxicity

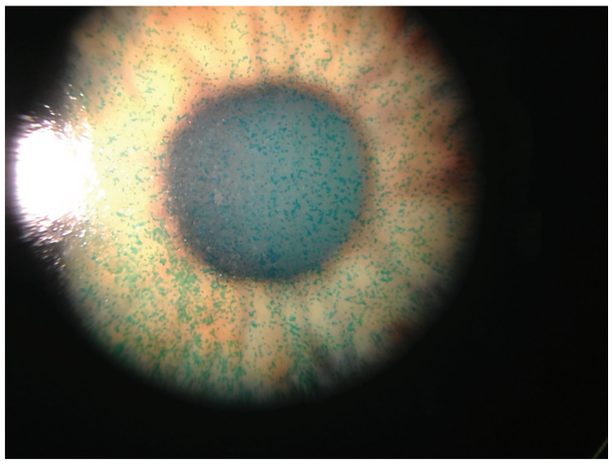
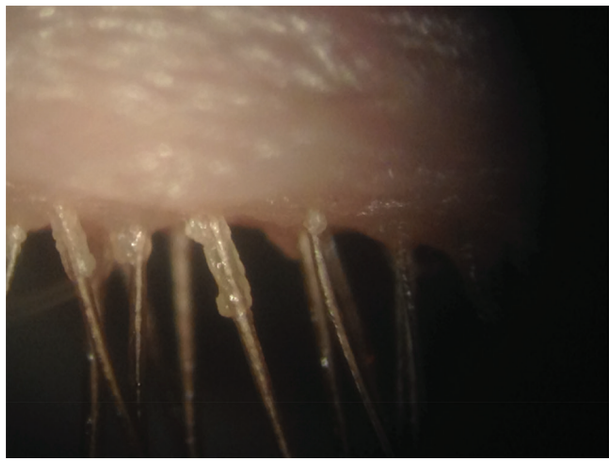


Figure 6: Cylindrical dandruff typical of Demodex anterior blepharitis



Tear replacement

Artificial tears, lubricant gels and eye drops are used extensively in the management of dry eye. Many types are available over the counter (OTC; without a prescription) and their compositions and modes of action are, once again, discussed at length within the management and therapy section of TFOS DEWS II.[9] It is interesting to note the conclusions of the Cochrane review of OTC artificial teardrops carried out by Pucker et al. in which they highlight uncertainty in the comparative effectiveness of products for treating dry eye, as many OTC artificial tears may produce similar symptomatic relief.[14] What is clear, however, is that harm can be caused by certain preservative substances used in many OTC artificial tear preparations, hence the drive to use preservative-free formulations (*Figure 5*).[15–17]

Pharmacologically active eye drops

Steroid eyedrops (topical glucocorticoids) are known to be effective and are widely used to treat many ocular conditions. They can be used to treat dry eye patients with severe lid inflammation, or when symptoms are particularly overwhelming. There is good evidence of efficacy. A well-referenced discussion of the use of steroid eye drops in dry eye management can again be found in the management and therapy section of the TFOS DEWS 2 report by Jones et al.[9] There are several pharmacologically active molecules which have recently been proposed as topical treatments for dry eye. Lifitegrast and cyclosporine are the two agents most widely known and currently available in many territories. Lifiitegrast interferes with T-Lymphocyte migration and the US Food and Drug Administration (FDA) approved a 5% ophthalmic solution called Xiidra® in 2016. Initially created by SARcode Biosciences, Lifitegrast was brought to the USA market by Shire (Lexington, MA, USA). Xiidra® was acquired by the Japanese company Takeda when they bought Shire in 2018. Takeda promptly sold Xiidra® to Novartis for US$3.4 billion six months later in May 2019. Lifitigrast is licensed for the treatment of both signs and symptoms of dry eye disease and is sold in SDU (preservative-free single dose units). Cyclosporine also inhibits T-lymphocyte activity. The systemic use of cyclosporine has been widespread in clinical medicine, since its efficacy in renal transplant patients was first reported by Sir Roy Yorke Calne in Cambridge (UK) in 1978.[18] Topical cyclosporine 0.05% solution has been available as Restasis® (Allergan Inc) since 2003.[19] Restasis® generates billion dollar revenues in the USA but serious questions have been raised about its efficacy.[20] A Cochrane review by de Paiva et al. concluded that the effect of topical cyclosporine 'may not be different from vehicle or artificial tears for the time periods reported in the trials'.[21] While in 2018, Shwartz and Woloshin raised the fundamental question 'does Restasis® work'?[22] They also describe how the Restasis® story took a surprising twist when Allergan recently transferred the six patents on Restasis (cyclosporine ophthalmic emulsion, 0.05%) to the Saint Regis Mohawk Tribe, which will exclusively license the patents back to the company. The deal, which may delay the marketing of generic alternatives to Restasis®, is under legal challenge, amid calls for Congress to ban the strategy Allergan has sought to exploit. Although dequafasol and rebamipide were considered as possible treatments for dry eye, neither has gained FDA approval as topical agents for dry eye. So there is widespread use of topical cyclosporine-A eye drops despite poor evidence of efficacy. Presently there is no pharmacologically active eye drop with indisputable, peer-reviewed, published evidence of superiority in the treatment of dry eye.

Blepharitis and Demodex mites

Posterior blepharitis is synonymous with MGD, while anterior blepharitis is a separate condition. Health professionals who are not eye specialists, often use the word blepharitis to describe any eyelid inflammation. While this is semantically correct, it can lead to confusion because anterior blepharitis is a clinically distinct condition separate from MGD. Anterior blepharitis, presenting with characteristic tubular 'collarettes' or 'cylindrical dandruff' crusts around each eyelash, is typical of *Demodex* infestation (*Figure 6*). Described by Tullos Coston in 1967, *Demodex folliculorum* infestation of the eyelash follicles has long been recognised, but the full significance of the *Demodex* mite is increasingly being appreciated. Anterior blepharitis with 'crusty eyelashes' is usually caused by the *Demodex folliculorum* mite, but these mites are easily overlooked unless the tubular crusts are picked off the lashes where they adhere to the eyelid skin. The mites' tails are best observed protruding from the eyelash follicles using 40X slit lamp magnification but are not well seen at 25X magnification. This explains why health professionals managing inflammatory eyelid conditions have ignored *Demodex* for many years.

There are two distinct approaches to treating *Demodex* infestation of the eyelash follicles: topical and systemic. One molecule, identified in tea tree oil and known as terpinen-4-ol (T4ol), is very effective at killing *Demodex* mites. T4ol is available in two commercially available topical preparations: Cliradex® (Cliradex, Miami, FL, US) and Blephademodex®

Figure 7: Acne rosacea before (left) and after (right) oral Ivermectin

(Théa Pharmaceuticals, Newcastle-under-Lyme, UK). Both of these preparations use T4ol in an appropriate concentration adequate to kill the *Demodex* mites. There are other lid wipes which incorporate tea tree oil extracts but the concentration of T4ol may be too low to ensure *Demodex* death. Oral treatment with ivermectin alone, or given contemporaneously with oral metronidazole, has also been shown to kill demodex mites.[23] This treatment combination is therefore also effective in treating some forms of (acne) rosacea, where *Demodex brevis*, a similar mite, is implicated in the aetiology (*Figure 7*).

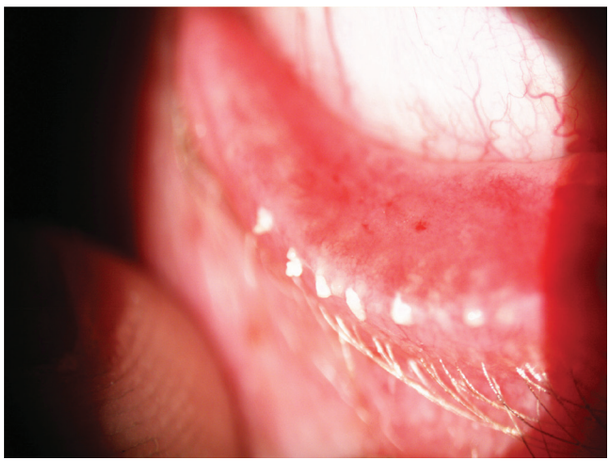
Omega 3 and dietary supplements

Omega 3 fatty acids occur naturally in oily fish but there is no endogenous synthesis in humans. Dietary supplementation with oral preparations of omega 3 polyunsaturated fatty acids is big business, with the dietary supplement market in the US deemed to be worth around US$40 billion.[24] Although many people believed that dietary supplements rich in omega 3 polyunsaturated fatty acids help to alleviate dry eye symptoms, a large multicentre randomised controlled trial (ClinicalTrials.gov Identifier: NCT02128763), known as the DREAM study (DRy Eye Assessment and Management), reported no significant measurable benefit from omega 3 dietary supplements in the study cohort of patients with dry eye.[25] An extension study (ClinicalTrials.gov Identifier: NCT02128763) revealed that patients who used omega 3 supplementation for 12 months, followed by discontinuation of the supplements for another 12 months, did not have significantly worse outcomes compared to those who continued omega 3 supplementation.[26] Presently, the perceived benefits of omega 3 supplements remain anecdotal, since this trial did not show a significant benefit, nor does withdrawal of omega 3 result in worsening of the dry eye.

Neuro-sensory dysfunction and dry eye

Recent work by Chris Hammond's group at St Thomas's hospital in London,[27,28] together with research carried out by Anat Galor and co-workers at the Bascom Palmer Eye Institute in Miami, FL, USA,[29] has drawn attention to altered neuro-sensory pain perception amongst some patients with dry eye. There is a strong correlation between dry eye symptoms and the condition formerly known as fibromyalgia – but now called chronic widespread pain syndrome (CWPS). There are also associations with other conditions where pain perception is enhanced. Concepts such as hyperaesthesia and allodynia do not often feature in the vocabulary of the eye clinic, but we need to become familiar with these concepts to better understand the problems our patients are

Figure 8: Typical meibomian gland dysfunction secretions after expression



experiencing. Understanding the difference between nocioceptive and neuropathic pain opens the door to other treatment strategies, such as systemic medication with serotonin–norepinephrine reuptake inhibitor (SNRI) drugs, including as duloxetine and venlafaxine. There are anecdotal reports of patients with CWPS treated with SNRIs reporting a fortuitous improvement in dry eye symptoms. Cognitive behavioural therapy may also be helpful for some of the problems this patient cohort experience, but these issues require further investigation.

The Anthropocene era – plastic, not so fantastic[30]

There is global concern about the amount of plastic detritus created by humanity, and the impact that plastic is having on the Earth's ecosystem.[31] Sir David Attenborough has thrust this issue into the public spotlight through the BBC nature documentary series called The Blue Planet. Many dry eye treatment options involve the use of plastic, from the humble eye drop bottle containing artificial tears, through to the more complex machines and equipment used to investigate and treat dry eye conditions. It is now preferable to treat as many people as possible using the least amount of plastic possible. Patients with dry eye could commence treatment using a completely biodegradable and compostable product, such as a re-usable warm compress with appropriate eyelid massage. If a significant proportion patients with dry eye can be adequately treated by a plastic-free, safe, effective, re-usable warm eye compress, then the total quantity of plastic generated by dry eye management would diminish accordingly.

Summary

The overwhelming majority of patients with dry eye have healthy lacrimal glands but poor pre-corneal tear film lipid layer which can be improved simply by daily use of a safe, effective, cheap, re-usable warm compress. Artificial tears provide transient symptomatic relief but do not treat MGD (*Figure 8*). Neither topical cyclosporine A, nor systemic omega 3, appear to have much evidence of efficacy. *Demodex* eradication with topical tea tree oil derivatives, or oral ivermectin, seem to improve anterior blepharitis. Dry eye problems are more prevalent in patients who have other conditions which manifest with increased sensitivity to pain. Dry eye symptoms are more common in patients with CWPS and systemic pain management strategies may be more appropriate for this patient cohort once local remedies have failed. Extreme dry eye from exposure keratitis and Sjögren's syndrome is decreasing in prevalence over time. ❑

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