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An Overview of the Current Consensus, Clinical Impact and Management of Dry Eye

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Significance of Dry Eye Disease

Given its widespread prevalence, negative impact on quality of life and financial burden, dry eye disease (DED) is a significant public health concern. The current prevalence of dry eye ranges from 5% to 50%, with up to 30 million afflicted in the U.S., making it one of the most prevalent ocular conditions in clinical practice.[1] In order to define the disease state, provide a better understanding of dry eye pathophysiology and recommend updates to clinical treatment, concerted medical and scientific efforts have been made by several entities, including the NEI workshop (1992), Delphi panel (1995) and the Dry Eye Workshop (DEWS) reports (2007, 2017).[1-4] Despite these efforts, there remains a perceived complexity about management guidelines for dry eye among eye care practitioners.

Dry eye is shown to have a significant impact on visual quality and performance, quality of life and poses a significant economic burden, all of which improve with treatment of the underlying condition.[5,6] Older age, female gender, and the presence of auto-immune disease are commonly associated with dry eye. There are increased reports of dry eye in younger and pediatric populations more recently.[1,7] Other modifiable risk factors that can contribute to dry eye include the use of computers and digital devices, the use of HVAC units, diet and lifestyle.[1] All the above underscore the public health concern with DED and the critical need to address it by healthcare practitioners.

Dry Eye Definition and Subtypes

In the DEWS II report, a revised definition of dry eye recognized the importance of maintaining the delicate homeostasis of the tear film and ocular surface environment, while including patient symptoms as a key part of the diagnostic methodology. The disease was defined as follows:[8]

"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 neuro-sensory abnormalities play etiological roles."

The major sub-types of dry eye, aqueous deficiency dry eye (ADDE) and evaporative dry eye (EDE) are now thought to be on a continuous spectrum of dry eye rather than distinct entities. The DEWS II report also recognizes mixed dry eye when most patients may not present with signs or symptoms of only ADDE or EDE but rather with mixed symptoms of both EDE and ADDE. Management approach for EDE and ADDE are different (lipid vs. aqueous supplementation), however, given that most DED is in a mixed format, both types of treatments are likely necessary. Epidemiological and clinical evidence suggest that the preponderance of DED has an evaporative component, and treatments including lipid-enhanced artificial tears containing phospholipids and mineral oil may be more beneficial at improving patient symptoms, no matter where they fall on the spectrum.[8,9]

The Tear Film

The DEWS II report recommends a two-layer model of the tear film, which has a lipid layer overlying a muco-aqueous phase.[10] The tear film is an approximately 2-5.5µm thick bilayer, with a lipid layer about 42nm thick derived mainly from meibomian gland secretions.[10] The lipid layer mostly consists of non-polar lipids (e.g., wax and cholesterol esters), while amphiphilic (composed of hydrophilic and hydrophobic portions) molecules such as fatty acids and polar lipids including phospholipids, sphingolipids in the lipid layer interface with the tear aqueous phase.[11] The muco-aqueous layer contains secreted mucins (e.g., MUC5AC) from conjunctival goblet cells, membrane-associated mucins (e.g., MUC1 and MUC4) secreted by and attached to the corneal epithelial microplicae in the glycocalyx. The aqueous component of the muco-aqueous layer contains metabolites and electrolytes, antimicrobial peptides, proteins and soluble immunoglobulins that protect the ocular surface from infection and are secreted primarily by the lacrimal gland.[12] The DEWS II report also recognizes that all layers of the tear film are critical for tear stability and for retarding tear film evaporation, although the exact mechanisms are still under investigation.[10]

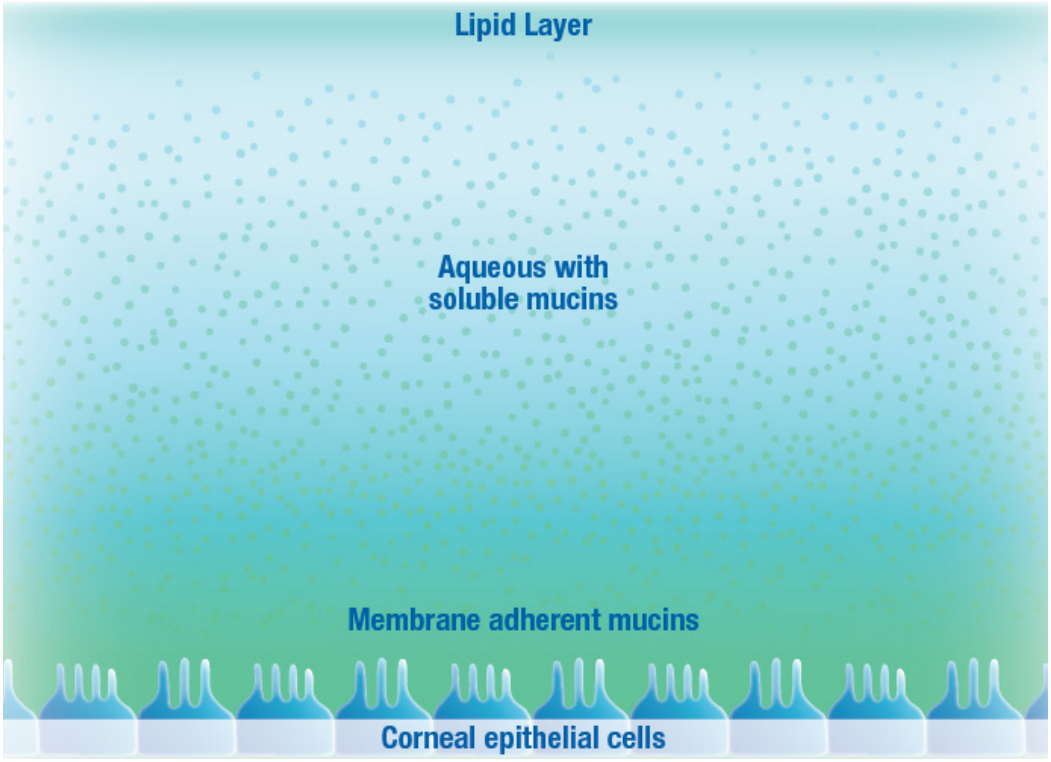


Figure 1: The Two-layered Tear Film Model

Impact on Diagnosis and Clinical Management

The DEWS II report recognized that studies of the sensitivity and specificity of many diagnostic tests for DED are highly dependent on the inclusion criteria and severity of the DED group and the population examined.[13] For the diagnosis of dry eye, the DEWS II report proposes a systematic approach that first involves asking triaging questions to exclude any conditions that mimic DED and a thorough analysis of risk factors to uncover other potential causes.[13] Dry eye diagnosis proceeds to assess the presence of symptoms using questionnaires such as DEQ-5 or OSDI, followed by the presence of at least one of three specified signs of altered tear homeostasis: reduced tear film stability, elevated or large intraocular disparity in osmolarity or ocular surface staining.[14] Non-invasive approaches to assess tear film stability (e.g., tear film interferometry, tearscope, keratograph oculograph) are recommended over conventional fluorescein testing due to its invasive nature.

The extent of patient symptomatology in proportion to clinically observable signs is not linear and very variable. This lack of correlation between patient symptoms and clinical signs in dry eye has long been recognized.[15] The DEWS II report recognized that symptomatic presentation without any signs could indicate pre-clinical dry eye disease wherein patient education and preventative treatment would be beneficial.[13]

Management of Dry Eye Disease

The primary management goal in DED is to achieve homeostasis of the tear film.[1] Management strategies vary depending on the cause or major dry eye sub-type (aqueous-deficient/evaporative/mixed).

Current therapeutic options for dry eye include over-the-counter (OTC) artificial tears, prescription drugs and other medical devices for either increased tear replacement, tear production or tear conservation.[13] The DEWS II report proposed a staged management approach for DED wherein OTC artificial tear drops, gels, ointments or lubricants are recommended as a first-line therapy option while prescription drugs are reserved for more severe disease. Even in moderate to severe disease, artificial tears are recommended as an adjunct therapy for symptomatic relief, to be used alongside prescription regimens or other medical device treatment options.[12] In fact, one study showed that 79%

of patients using artificial tears for DED that were started on topical cyclosporine eye drops reported continued use of artificial tears.[16] Additionally, the effects of leading pharmaceutical regimens for DED, such as topical cyclosporine, in the different DED subgroups remain unclear even in a meta-analysis of published clinical trials.[17]

Artificial Tear Solutions

Artificial tears are formulations that contain one or more lubricants or emollients in combination with electrolytes, surfactants, and viscosity-enhancing agents. Over-the-counter artificial tear drops, gels, ointments, or lubricants are widely used as first-line therapy for managing dry eye and sustaining ocular comfort during contact lens wear.[18] The majority of these products contain a lubricant or demulcent. Some common ones include propylene glycol, polyethylene glycol, dextran, cellulose-based derivatives and glycerin. These products supplement the aqueous tear layer and lubricate the ocular surface. Other categories of OTC eye drops include emollients and emulsions. Emulsions are lipid-based formulations that contain a mixture of the lubricant in aqueous form and lipid ingredients such as phospholipid and mineral oil as inactive ingredients that enhance the delivery of the lubricant. These ingredients help replace the tear lipid layer and reduce evaporation.

It is key to understand how the Food and Drug Administration (FDA) regulates artificial tear products. Following an OTC monograph is a common way to introduce non-prescription products such as lubricants, analgesics, fever reducers and NSAIDs that are safe and effective when consumers follow the directions on the label or as directed by the health care professional.[19] The above features for a product are summarized in the OTC monograph that lists different categories of medicines with their respective indications. The active ingredient(s) in the monograph and the product's primary function determines this category.[19]

Manufacturers often improve the efficacy of OTC products with inactive ingredients such as gelling agents and lipids to enhance delivery of the active ingredient. These inactive ingredients can enhance the efficacy of a given formulation and often times differentiate the branded/proprietary artificial tear formulations from other private label formulations.[20] The "compared to" statements on generic/private label products are not claims of equivalence. They are merely invitations to compare. It is important for practitioners to recommend the most appropriate option that is best aligned with the clinical presentation,[21] and to help patients understand that not all claims of equivalence are supported by clinical evidence.

HP-Guar Based Lubricant Eye Drops – Technology Overview

The SYSTANE® family of lubricants in the U.S. include SYSTANE® ULTRA, SYSTANE® BALANCE and most recently SYSTANE® COMPLETE lubricant eye drops, in addition to the SYSTANE® Gel and ointment formulations. SYSTANE® ULTRA lubricant eye drops are developed with two lubricants, PEG 400 (0.4%) and PG (0.3%,) and an advanced delivery system with Hydroxypropyl guar (HP-guar/HPG). HP-guar, an inactive ingredient serves as a viscosity-enhancing gelling agent that creates a unique

and intelligent delivery system on the ocular surface to provide symptomatic relief of dry eye. Upon instillation in the eye, HP-guar enhances the visco-elasticity of the tear film via cross-linking with borate. This facilitates the development of a viscoelastic, gel-matrix with shear thinning and bio-adhesive properties. The gel-matrix promotes retention of the active demulcents for tear film stability, lubrication, and extended protection of the ocular surface.[22]

Multiple studies have reported excellent efficacy of PEG/PG lubricant eye drops in providing symptomatic relief, immediate and sustained increase in tear film thickness, reduced ocular surface staining, reduced tear osmolarity, ocular surface inflammation and improved visual function.[23-28]

Lipid-Enhanced Artificial Tears

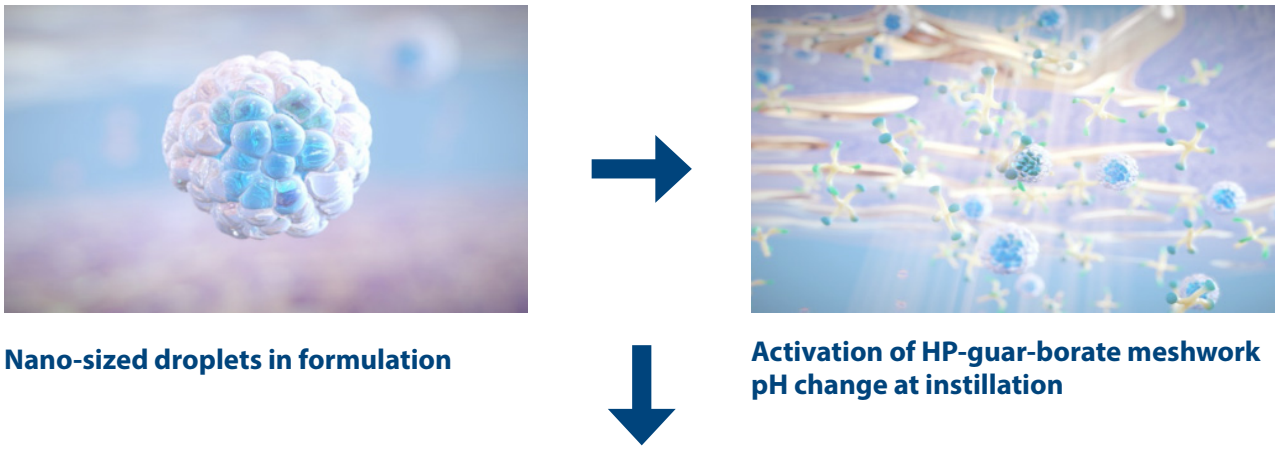
Lipid-enhanced artificial tears are used widely for the management of MGD and EDE.[13] Studies have shown that polar lipids in the tear film such as anionic phospholipids can provide a stable interface between nonpolar lipids at the surface of the tear film and the muco-aqueous layer, and can enhance tear lipid thickness and stability.[29] SYSTANE® BALANCE is an oil-based microemulsion containing propylene glycol as the lubricant, a polar phospholipid (dimyristoyl phosphatidylglycerol (DMPG) and mineral oil. The efficacy of SYSTANE® BALANCE has been established in multiple clinical studies and its use was shown to produce significant improvements in symptoms and signs of dry eye.[30-32] SYSTANE® BALANCE is particularly useful in DED with underlying MGD, with studies showing improved meibomian gland functionality as early as 4 weeks after its use.[31-33] This formulation with a polar phospholipid and mineral oil components resulted in increased and sustained lipid layer thickness in normal subjects and those with EDE.[30]

Formulation of Emulsions Using Nano-Technology and Associated Benefits

Emulsions may be classified based on the size of the constituent lipid droplets, with large droplet sizes (> 400 nm) called macroemulsions which are partially opaque and white (with clear oil phase). A limitation of these emulsions is the potential loss of optical transparency on application.[13] Nanoemulsions are an advanced delivery system, with small-sized droplets (10-100nm droplet diameter) and are homogenous, transparent dispersions of oil and water that offer several potential benefits including enhanced long-term stability, high optical clarity and increased bioavailability.[34] Emulsions also have high encapsulation rates and reduced droplet size with nanoemulsions serve as a better delivery vehicle for lipids to the ocular surface to help protect from evaporation of the tear film.[35]

Figure 2: Comparison of surface area between non-nano and nano-sized materials[36]

SYSTANE® COMPLETE lubricant eye drops is the latest SYSTANE® artificial tear solution and is a nanoemulsion containing propylene glycol 0.6% as the lubricant and nanoparticles of anionic phospholipid/mineral oil complex and a 3-fold higher amount of HP-guar than SYSTANE® BALANCE to improve the viscoelastic properties of the formulation.[37] The nano size of the lipid phase is made possible with proprietary manufacturing technology. The reduced droplet size with the nanoemulsion also optimizes the coverage area of phospholipid delivered to the tear film.[22] SYSTANE® COMPLETE is thus formulated to provide better ocular surface coverage (compared to SYSTANE® BALANCE), promote tear film stabilization, prolong retention of the lubricant propylene glycol, and enhance the moisture retention of the tear film with the unique HPG/borate visco-elastic meshwork. [22]



Nano-sized droplets in formulation

Activation of HP-guar-borate meshwork pH change at instillation

The viscoelastic HP-guar meshwork continues to cross-link, maintain the protective barrier and serve as a depot for slow release of the lubricant

Figure 3: Systane® Complete - Mechanism of Action

Pre-clinical evaluations of SYSTANE® COMPLETE were conducted using desiccation experiments on immortalized human corneal epithelial cells in comparison to the vehicle (nanoemulsion minus HPG). The PG/HPG-nanoemulsion demonstrated greater hydration protection against desiccation and significant improvement in cell barrier protection following exposure to benzalkonium chloride (BAK).[22] This was also demonstrated with reduced corneal staining in animal models of dry eye. Surface lubrication assessed with coefficient of friction measures showed greater lubricity in pericardial tissues compared with vehicle.[22] SYSTANE® COMPLETE formulation also demonstrated significantly better moisture retention, protection, elastic filament strength and cell barrier function compared to SYSTANE® BALANCE in preclinical studies.[22]

Conclusion

In summary, treating dry eye disease is a significant and important opportunity to enhance the ocular wellbeing of patients. Careful selection of artificial tears best suited to address all causes and aspects of dry eye subtype(s) is paramount in optimal management of dry eye. Technologically advanced formulations with visco-elastic delivery systems and nanoemulsions offer a simplified approach and significant advantages in addition to providing safe and effective relief. ECPs have an increased opportunity to better serve at-risk subpopulations by proactively treating them.

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