A Pragmatic Approach to the Management of Dry Eye Disease: Evidence into Practice

Laura E. Downie* and Peter R. Keller†

ABSTRACT
Dry eye disease (DED) is a highly prevalent chronic ocular disorder that can lead to significant discomfort and visual disturbance. It is a potentially debilitating condition that can have significant negative impact on quality of life. A diverse range of management options exists for DED, including tear supplement products, anti-inflammatory agents, immunomodulators, punctal occlusive devices, and environmental modifiers. Although the availability of a variety of treatment approaches provides clinical flexibility and can enable individualized care, it can also complicate clinical management decisions and lead to variability in the nature of the clinical care provided to patients. By considering two dry eye case scenarios, this review evaluates the currently available evidence relating to DED therapy to describe a pragmatic clinical approach to best-practice management of dry eye patients.

Key Words: dry eye, treatment, evidence-based practice, tear film, tear supplement, punctal occlusion, meibomian gland, meibomian gland dysfunction, aqueous deficiency, lacrimal function unit, artificial tear, ocular lubricant, cyclosporine, corticosteroid, lacrimal.

Dry eye disease (DED) is a highly prevalent chronic ocular condition that can lead to significant discomfort and visual disturbance. Epidemiological studies indicate that DED currently affects up to one in five adults, or about 25 million people, in the United States. Although historically there has been criticism that DED has been relatively trivialized by the medical community, it is becoming increasingly recognized that DED can be a debilitating condition that significantly impairs quality of life. The effect of moderate to severe DED on quality of life is comparable to the burden of renal dialysis or moderate angina. Dry eye disease is highly correlated with anxiety and depression. As such, the potential negative impact of DED is not to be underestimated.

A diverse range of management options exists for DED. In 2007, the committees of the international Dry Eye WorkShop (DEWS) published a number of comprehensive reviews relating to the core clinical aspects of DED. The report of the DEWS Management and Therapy Subcommittee both summarized the available management and therapeutic options for treating DED and described the level of evidence from the literature to support these interventions. Since then, a number of new treatment modalities has emerged. Many other potential approaches have been patented, indicating the possibility of new therapies becoming available in the future.

Optometrists play a major role in providing ongoing care to DED patients, particularly those with mild to moderate disease, where therapy is well within the scope of primary eye care practitioners. Although the availability of a variety of treatment approaches potentially provides clinical flexibility and can enable individualized care, it can also complicate clinical management decisions. Eye care practitioners have identified difficulties with treating moderate to severe DED. Furthermore, significant variability in the clinical care provided to dry eye patients has been described in a self-reported clinical practice survey of Australian optometrists.

The purpose of this article is to provide a pragmatic approach to best-practice management of DED. Using a similar method to a previous article focusing on evidence-based optometric care, this review is structured around two case scenarios to evaluate the currently available evidence relating to DED therapy.

MANAGEMENT OF MILD TO MODERATE DRY EYE DISEASE

Consistent with contemporary optometric training, a key recommendation of the DEWS Management and Therapy Subcommittee was for dry eye treatment to be stratified according to disease severity, with an additive approach to the number of interventions.
for more advanced disease. Although there is currently no gold standard approach for diagnosing DED severity, the DEWS Definition and Classification Subcommittee published a classification system (summarized in Table 1), separating DED into four categories (grades 1 to 4) based on the frequency and intensity of clinical symptoms and signs. Based on available epidemiological data, most DED patients under optometric care would be expected to present with grade 2 to 3 disease, which for the purpose of this review is considered moderate DED. Although the prevalence of grade 4 disease, herein termed severe DED, is not known, it likely represents less than 5% of optometric presentations.

Two DED scenarios demonstrate a practical clinical approach (summarized in Table 2) to the delivery of evidence-based management. As the focus of this review is on the optometric management of DED, surgical interventions are not discussed in detail; a structured approach to the surgical management of DED is available elsewhere.

Clinical Case Scenario 1

History and Diagnostic Findings

A 58-year-old female school teacher presents for an eye examination with regard to 6-month onset intermittently burning, irritated, and watery eyes; she has not noticed any visual disturbance. She has been taking hormone replacement therapy (HRT) for treatment of postmenopausal symptoms for the past 9 months. Prior ocular history is negative for injury, infection, or surgery. She has never worn contact lenses.

The key findings from a dry eye diagnostic clinical workup are:

- Symptoms:
  - Ocular Surface Disease Index score: 24
  - Visual acuities (VAs): OD 20/20, OS 20/20
  - Tear stability:
    - Tear Break-up Time (TBUT), using a 1-μL volume of sodium fluorescein (NaFL): OD 8 s, OS 6 s
  - Ocular surface assessment:
    - Corneal NaFL staining (Oxford Scale): OD grade 1.1, OS grade 1.8
    - Conjunctival lissamine green staining (Oxford Scale): OU grade 1.0 (nasal and temporal conjunctiva)
    - Lissamine green staining highlights mild irregularity in the position of Marx’s line (OU)

- Tear volume:
  - Tear meniscus height (measured using slit lamp photography): OD 0.25 mm, OS 0.21 mm
  - Schirmer test (without anesthesia): OD 13 mm, OS 12 mm in 5 min

- Eyelid assessment; key findings:
  - Meibomian gland morphology (grades 0 to 3): OU grade 1 (a few capped glands along each eyelid)
  - Meibomian gland expressibility (grades 0 to 3): OU grade 2.0 (cloudy, slightly particulate meibum expressed with moderate pressure)

In this diagnostic protocol, the Schirmer test was performed without anesthesia to provide an estimate of the patient’s potential for aqueous tear production (i.e., both reflex and basal tears), as part of assessing for potential aqueous deficiency. This patient is given an etiology-based diagnosis of moderate meibomian gland dysfunction (MGD), with tear film instability secondary to reduced meibum quality. Whether there is an aqueous deficiency component is equivocal; the meniscometry values are below those expected for a normal lacrimal lake (being ≥0.35 mm); however, Schirmer I values are within normative ranges (at ≥5 mm in each eye).

It is worthwhile considering how this etiology-based diagnosis relates to the DEWS classification for DED severity (Table 1). The categorization of severity can be confounded by apparently conflicting grades when using different clinical sign and/or symptom criteria. For instance, this patient may be considered to have mild and/or episodic symptoms (grade 1), however, the TBUT with fluorescein and eyelid findings approach grade 2 severity. Although clinically practical, categorical division of severity has limitations. Other approaches to grading DED severity have been proposed, including an independent component analysis with a composite scale based on the commonly performed diagnostics tests.

### TABLE 1.

Grading scheme for the severity of dry eye disease

<table>
<thead>
<tr>
<th>Severity level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular discomfort</td>
<td>Mild and/or episodic</td>
<td>Moderate episodic or chronic</td>
<td>Severe frequent or constant without environmental stress</td>
<td>Severe and/or disabling and constant</td>
</tr>
<tr>
<td>Effect(s) on vision</td>
<td>None or episodic mild</td>
<td>Annoying and/or episodically activity limiting</td>
<td>Annoying, chronic and/or constant, limiting activity</td>
<td>Constant and/or possibly disabling</td>
</tr>
<tr>
<td>TBUT with fluorescein, s</td>
<td>Variable</td>
<td>≤10</td>
<td>≤5</td>
<td>Immediate</td>
</tr>
<tr>
<td>Corneal staining</td>
<td>None to mild</td>
<td>Variable</td>
<td>Marked central</td>
<td>Severe punctate erosions</td>
</tr>
<tr>
<td>Conjunctival staining</td>
<td>None to mild</td>
<td>Variable</td>
<td>Moderate to marked</td>
<td>Marked</td>
</tr>
<tr>
<td>Eyelids</td>
<td>Healthy to mild</td>
<td>MGD (variable)</td>
<td>Frequent MGD</td>
<td>Trichiasis, keratinization, symblepharon</td>
</tr>
<tr>
<td>Schirmer test, mm/5 min</td>
<td>Variable</td>
<td>≤10</td>
<td>≤5</td>
<td>≤2</td>
</tr>
</tbody>
</table>

Table adapted from the report of the Definition and Classification Subcommittee, International Dry Eye Workshop, 2007.
informative for diagnosing dry eye severity; however, other studies have questioned its clinical utility. Importantly, low symptom severity should be considered in the context of objective signs, in which failure to institute early intervention may result in advancement of the disease, leading to more pronounced ocular surface damage.

Modification to Environmental and Exogenous Factors

The symptomatology of DED is often multifactorial. Patient counseling in relation to environmental influences for DED can be valuable. However, this aspect of management is often not incorporated into care plans by eye care practitioners. Although it may seem obvious, recommendations related to perturbing environmental factors should involve the avoidance, as is practically feasible, of conditions that promote reduced tear secretion and/or increased tear evaporation. This includes minimizing exposure to low humidity environments and airconditioning or forced hot-air systems. Other modifications that may be of benefit when performing computer tasks include ensuring periodic breaks with eyelid closure and consciously increasing blinking frequency. Exposure to smoke, which compromises tear lipid layer integrity, is an additional exacerbating factor that should be avoided. Recent studies show scope for improved patient counseling by optometrists regarding the ocular benefits of smoking cessation.

Antihistamine, antidepressant, and antianxiety medications are also associated with DED. The Women’s Health Study, involving more than 25,000 postmenopausal women, showed that HRT, and in particular estrogen-only medications, conferred a significantly higher risk of DED. Indeed, the onset of dry eye symptoms within months of commencing HRT in clinical case scenario 1 is consistent with this association. The Women’s Health Study also demonstrated that a higher dietary intake of omega-3 essential fatty acids was associated with a reduced incidence of DED in women. This association between diet and ocular health emphasizes the need for

### TABLE 2.

<table>
<thead>
<tr>
<th>Dry eye severity</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modification to environmental and exogenous factors</strong></td>
<td>• minimize exposure to low-humidity environments and airconditioning/forced hot-air systems¹²,⁴⁴</td>
<td>• maintain relatively humidified indoor environment³</td>
<td>• visual display terminals: lower computer screen to below eye level⁷ and have periodic rest breaks²⁵; avoid smoke⁶</td>
<td>• as practicable, minimize intake of exacerbating medications: antihistamines, antidepressants, anxiolytics, estrogen-containing hormone replacement therapy²⁹; increase dietary intake of omega-3 essential fatty acids¹²</td>
</tr>
<tr>
<td><strong>Tear supplementation (also see Table 3)</strong></td>
<td>Low viscosity, typically qid (may contain preservative); consider lipid replacement products for patients with evidence of MGD</td>
<td>Low and/or moderate viscosity, typically qid to q2h (nonpreserved)</td>
<td>Typically moderate to high viscosity, qid to q2h (nonpreserved)</td>
<td>As per grade 3 plus ointment(s) noite</td>
</tr>
<tr>
<td><strong>Eyelid therapy (for patients with evidence of evaporative DED)</strong></td>
<td>Eyelid hygiene (including warming, massage, and expression) bid</td>
<td>As per grade 1 plus consider oral tetracycline derivatives and/or topical azithromycin*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-inflammatory agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tear volume–enhancing measures</strong></td>
<td>Punctal occlusion*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biological tear substitutes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other nonsurgical approaches</strong></td>
<td>Moisture chamber spectacles†</td>
<td>Mini-scleral and scleral contact lenses†</td>
<td>As per grade 3, plus systemic anti-inflammatory agents*</td>
<td></td>
</tr>
<tr>
<td><strong>Surgical interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table adapted from the report of the Management and Therapy Subcommittee, International Dry Eye WorkShop⁷ and the report of the Management and Treatment Subcommittee, International Workshop on Meibomian Gland Dysfunction.³⁹

*Limited high-quality evidence is currently available.
†No high-quality evidence is currently available.
bid, two times daily; MGD, meibomian gland dysfunction; qid, four times daily; noite, nightly; q2h, two hourly.
eye care professionals to question and counsel their patients about their general dietary habits. A detailed review of the potential benefits of diet, and nutraceutical consumption, for the tear film has recently been published. In terms of topical preparations, the preservative benzalkonium chloride has been identified as a contributor to ocular surface toxicity and can exacerbate DED. The extent of ocular damage relates to the preservative concentration, the frequency of instillation, and the severity of any underlying ocular surface disease. Nonpreserved preparations are preferable for patients with more severe disease.

Tear Supplementation

Tear supplement products are the mainstay of DED therapy. The mechanism(s) underlying symptomatic improvement with tear supplements in DED is not well understood but may relate to factors that include increasing tear film volume, tear stabilization, providing a smoother refractive surface, replacement of deficient tear constituents, reducing tear hyperosmolarity, dilution of tear inflammatory cytokines, and/or reducing the friction between the corneal epithelium and palpebral conjunctiva. The composition of individual tear supplements can differ significantly, leading to variations in the viscosity, osmolarity, and pH of formulations. Broadly, these agents consist of hypotonic or isotonic buffered solutions that contain electrolytes, surface-active agents, and viscosity-enhancing components, with or without preservatives. At present, there is insufficient evidence from randomized controlled clinical trials (RCTs) as to the relative superiority of particular products for subtypes or severities of DED. There is a paucity of head-to-head studies comparing one product directly with another, making it difficult for practitioners to apply an evidence-based approach when recommending specific products. Furthermore, that these products are available on an over-the-counter (OTC) basis lends toward pharmacists and their professional staff being positioned to also provide advice to patients about DED. A need to improve the ophthalmic training of pharmacists and associated staff about the diagnosis and treatment of DED has been recently reported in the United Kingdom.

In recognition of these challenges, Tong and colleagues, in a recent publication, summarized the product profiles of a range of common OTC tear supplement products. This information is integrated with the DEWS DED Severity Staging Scale to formulate a tear supplementation summary chart (Table 3). Although not exhaustive, it covers a range of tear supplement products and includes details relating to the key constituents, preservative components, pH, osmolarity, and viscosity. Details are also included regarding whether the product is designed primarily for an aqueous-deficient and/or evaporative dry eye.

For mild DED, most products consist of low-viscosity formulations with preservatives; although, as detailed in Table 3, some of these products are also available in preservative-free formulations. Four times daily dosing is generally considered necessary for symptomatic improvement. Notably, there is a wide variation in the pH of different tear supplements. A relative disparity in tear and eye drop pH will likely result in a stinging sensation on instillation. Although tear pH is not routinely measured clinically, a physiological range between 6.9 and 7.5 has been reported, and this does not differ significantly in DED. Knowledge of the pH of tear supplement products is therefore potentially of value for guiding changes to product usage based on patient-reported feedback of any discomfort.

Higher-viscosity products are appropriate for increasingly severe DED as a means of improving ocular retention time, but with the trade-off of transient visual disturbance. Differences in the osmolarity of formulations are also worth noting; some products are specifically formulated to be relatively hypo-osmolar to assist with restoring tear electrolyte balance, which is perturbed in DED. Table 3 also provides information about a range of paraffin- and oil-based ointments; these products are reserved for severe DED and should be applied just before sleep because of their considerable degrading effects on vision.

Eyelid Therapy

As illustrated in case scenario 1, many patients with DED can show concomitant, and sometimes conflicting, signs of evaporative and aqueous-deficient dry eye. In such cases, treatment of any potential contributory meibomian gland pathology should be instituted. Many optometrists favor eyelid hygiene (i.e., eyelid scrubs, mechanical gland expression, and/or eyelid cleansing) in their dry eye treatment procedures.

In 2011, the International Workshop on Meibomian Gland Dysfunction committee published a detailed treatment algorithm, describing the specific steps for treating the spectrum of MGD. In brief, eyelid hygiene (including warming for a minimum of 4 min once or twice daily, followed by moderate to firm massage of the meibomian glands with expression) is regarded as first-line therapy. Although a range of eyelid warming devices are available, there is currently a lack of standardization with regard to the ideal treatment protocol(s) for these procedures. As most practicing optometrists recognize, unfortunately, self-administered eye warming therapy may not be effective for all patients; this could be caused by various factors, including poor adherence and/or variability with regard to how the procedure is performed.

In this regard, the automated LipiFlow thermal pulsation system (TearScience, Morrisville, NC), an in-office treatment that delivers controlled heating and pressure to the superior and inferior palpebral conjunctiva, has been proposed as a potentially useful alternative. In an observer-masked RCT comparing a single LipiFlow treatment with combined twice-daily eyelid warming and lid massage for 3 months, LipiFlow was found to be at least as effective as the traditional therapy. There is currently, however, still a need for further studies to more rigorously evaluate this system.

Clinical Case Scenario 1

Optometric Management

The management of this patient with mild DED is relatively straightforward. As per Table 2, informing this patient about modifiable risk factors and the potential contributory effect of environmental factors is warranted. Inquiry into the patient’s diet and whether she routinely consumes food rich in omega-3 EFAs are indicated. Consideration with regard to the possible contribution of the estrogen-containing HRT would also be of value.

Given the concomitant signs of tear instability and mildly reduced tear production, it is worthwhile adopting management strategies that can potentially improve both the aqueous and lipid tear deficiency components. One approach would be to institute

---

Copyright © American Academy of Optometry. Unauthorized reproduction of this article is prohibited.
daily eyelid hygiene and to commence a trial of tear supplements; a low- to moderate-viscosity tear replacement product, four times daily (qid), would be appropriate. Given the MGD overlay, a lipid-containing lubricant would be justified.43

Although there are no gold standard guidelines for review periods in managing DED, we consider that clinical reevaluation within 4 to 6 weeks would be reasonable for this patient. The chronic nature of the condition, and the importance of maintaining therapy, which is noncurative, should be emphasized.

**TABLE 3.** Summary chart of common tear supplement products, with their indication stratified for dry eye disease severity, with details relating to key constituent(s), preservative, pH, osmolarity, viscosity, and the manufacturer-defined mechanism of action

<table>
<thead>
<tr>
<th>Grade of DED*</th>
<th>Product name (manufacturer)</th>
<th>Key constituent(s)</th>
<th>Preservative</th>
<th>pH§</th>
<th>Osmolarity, mmol/kg</th>
<th>Viscosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or more</td>
<td>• Blink Tears (AMO)</td>
<td>PEG 400 0.25% + HA</td>
<td>Ocupure†</td>
<td>n/a</td>
<td>n/a</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>• GenTeal (Novartis)</td>
<td>HPMC 0.3%</td>
<td>Sodium perborate</td>
<td>6.53</td>
<td>196</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>• Liquifilm Tears (Allergan)</td>
<td>PVA 1.4%</td>
<td>Benzalkonium chloride 0.0005%</td>
<td>6.10</td>
<td>206</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>• Refresh Optive (Allergan)</td>
<td>CMC 0.5% + glycerin 0.9%</td>
<td>Purite</td>
<td>n/a</td>
<td>n/a</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>• Systane Ultra (Alcon)</td>
<td>PEG 400 0.4% + PG 0.3% + HP-Guar</td>
<td>Polyquad-1†</td>
<td>7.07</td>
<td>255</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>• Refresh Optive Advanced (Allergan)</td>
<td>CMC 0.5% + glycerin 1.0% + polysorbate 80 (0.5%)</td>
<td>Purite†</td>
<td>n/a</td>
<td>n/a</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>• Soothe XP-Xtra Protection (Bausch + Lomb)</td>
<td>Light mineral oil (1.0%) + mineral oil (4.5%)</td>
<td>Polysquad-1</td>
<td>n/a</td>
<td>n/a</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>• Systane Balance (Alcon)</td>
<td>PEG 400 0.6% + oil micro-emulsion (Lipitech)</td>
<td>Polyquad-1</td>
<td>7.00</td>
<td>n/a</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>• Optrex spray (Reckitt Benckiser)</td>
<td>Hamamelis virginiana</td>
<td>Benzalkonium chloride 0.0005%</td>
<td>7.22</td>
<td>283</td>
<td>Low†</td>
</tr>
<tr>
<td>2 or more</td>
<td>• Bion Tears (Advanced Vision Research)</td>
<td>HPMC 0.3% + Dextran 70 0.1%</td>
<td>None</td>
<td>7.53</td>
<td>246</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>• Hylo-fresh (AFT Pharm)</td>
<td>HA 0.1%</td>
<td>None</td>
<td>n/a</td>
<td>n/a</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>• Refresh (Allergan)</td>
<td>PVA 1.4% + Povidine 0.6%</td>
<td>None</td>
<td>5.64</td>
<td>246</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>• Refresh Plus (Allergan)</td>
<td>CMC 0.5%</td>
<td>None</td>
<td>6.52</td>
<td>276</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>• Tears Naturale Free (Alcon)</td>
<td>HPMC 0.3% + Dextran 70 0.1%</td>
<td>None</td>
<td>7.68</td>
<td>287</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>• Thera Tears (Akorn)</td>
<td>CMC 0.5%</td>
<td>None</td>
<td>8.95</td>
<td>145</td>
<td>Low</td>
</tr>
<tr>
<td>3 or more</td>
<td>• Celluvisc (Allergan)</td>
<td>CMC 1.0%</td>
<td>None</td>
<td>6.94</td>
<td>293</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>• Hylo-forte (AFT Pharm)</td>
<td>HA 0.2%</td>
<td>None</td>
<td>n/a</td>
<td>n/a</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>• Retaine MGD (Ocusoft)</td>
<td>Light mineral oil 0.5% + mineral oil 0.5%</td>
<td>None</td>
<td>6.50</td>
<td>n/a</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>• Duratears lubricating eye ointment (Alcon)</td>
<td>Liquid paraffin + white soft paraffin + wool fat</td>
<td>None</td>
<td>n/a</td>
<td>n/a</td>
<td>Ointment</td>
</tr>
<tr>
<td></td>
<td>• Polyvisc (Alcon)</td>
<td>Liquid paraffin + white soft paraffin + wool fat</td>
<td>None</td>
<td>n/a</td>
<td>n/a</td>
<td>Ointment</td>
</tr>
<tr>
<td></td>
<td>• GenTeal PM (Novartis)</td>
<td>Mineral oil (0.15%) + Petrolatum (0.85%)</td>
<td>None</td>
<td>n/a</td>
<td>n/a</td>
<td>Ointment</td>
</tr>
</tbody>
</table>

**Bold** text indicates that the manufacturer primarily markets the product for aqueous-deficient DED.

**Italics** text indicates that the manufacturer primarily markets the product for tear lipid deficiency associated with MGD.

**Bold italics** text indicates eye ointments rather than tear supplement products per se.

*Grade of DED, as categorized according to the DEWS Definition and Classification Subcommittee¹ (see Table 1).
†The tear supplement product is also available in a preservative-free formulation.
‡The product is sprayed onto the surface of the closed eyelid rather than instilled as an eye drop.
§pH values are quoted as from Tong and colleagues36 and/or the manufacturers’ product information.

CMC, carboxymethylcellulose; DED, dry eye disease; HA, hyaluronic acid; HP-Guar, hydroxypropyl-guar; HPMC, hydroxymethylcellulose; MGD, meibomian gland dysfunction; n/a, data are not available; PEG, polyethylene glycol; PG, propylene glycol; PVA, polyvinyl alcohol.

**MANAGEMENT OF SEVERE DRY EYE DISEASE**

Severe DED is commonly associated with systemic conditions, such as Sjögren syndrome and rheumatoid arthritis.13 Because of the extent of ocular surface damage, and the symptomaticity experienced by patients, the management of severe DED usually requires multiple interventions to target different components of the disease pathophysiology. Importantly, the management protocol is additive (Table 2), with first-line therapies (such as environmental modification, tear supplements, and eyelid...
Evidence for RCTs supports the utility of topical corticosteroids, such as fluorometholone acetate 0.1%, for reducing dry eye signs and symptoms; however, their well-documented potential long-term side effects (including the risk of intraocular pressure elevation, cataract formation, and increased susceptibility to ocular infection) limit their use to the control of acute inflammatory exacerbations. In this regard, so-called soft corticosteroids, such as lotoprednol 0.5%, show an improved safety profile and may be considered as a therapeutic alternative in DED.

The role of nonsteroidal anti-inflammatory drugs (NSAIDs) in managing DED is unclear. Topical NSAIDs are theoretically attractive because they are not associated with the same adverse ocular effects of corticosteroids; the most common side effects are conjunctival injection and stinging upon instillation. However, in the late 1990s, concern was raised with regard to an apparent association between a specific topical NSAID, diclofenac sodium, and corneal ulceration and melting. Although these agents are commonly used for symptomatic relief of postoperative ocular inflammation, there is limited literature to suggest whether their application is beneficial, or otherwise, in DED.

Topical cyclosporine-A has also emerged as a potential alternative anti-inflammatory therapy for DED. Cyclosporine-A is a lipophilic fungal antimitabolite that inhibits interleukin-2–induced activation of lymphocytes. The immunomodulatory effects of cyclosporine-A can be beneficial in a range of systemic inflammatory conditions, including psoriasis, rheumatoid arthritis, and ulcerative colitis.

For DED, cyclosporine-A is proposed to control anterior eye inflammation and improve tear function. In January 2015, the European Medicines Agencies published clearance for a cationic suspension of 0.1% cyclosporine-A for once daily use. Two recent systematic reviews have reported on the efficacy and safety of a range of different topical cyclosporine-A formulations for dry eye management. These reports suggest that cyclosporine-A is relatively safe for treating DED; however, there is still a need for larger RCTs, which use standardized dry eye diagnostic criteria, to clarify its clinical efficacy.

Tetracyclines are another family of pharmaceutical agents that are potentially beneficial for treating moderate to severe DED. Oral tetracyclines, such as doxycycline and minocycline, are bacteriostatic antibiotics that primarily imparts anti-inflammatory and antiangiogenic effects at the doses commonly used for treating ocular inflammation. Specifically, these drugs reduce the activity of collagenases, phospholipase-A2, and a number of matrix metalloproteinases.

Doxycycline has been shown to attenuate the production of inflammatory mediators interleukin-1 and tumor necrosis factor-α in the corneal epithelium. The most common medical application of tetracyclines is in the treatment of rosacea, including its ocular manifestations; a dose of 40 mg/d of doxycycline is generally considered optimal, in terms of its anti-inflammatory effects, for this application.
Also of potential benefit for managing MGD is the semisynthetic macrolide antibiotic azithromycin. In addition to its antibacterial functions, azithromycin has potent anti-inflammatory properties, which are proposed to be beneficial for treating MGD. Topical azithromycin can improve meibum secretion quality\(^{(58)}\) and reduce meibomian gland plugging.\(^{(59)}\) Oral azithromycin has a long half-life and therefore requires a relatively short duration of administration. Five-day pulse therapy with azithromycin, consisting of 500 mg on the first day and 250 mg for 4 days, has been recently reported to be as effective for reducing MGD symptoms as oral doxycycline dosed 200 mg/d for 1 month.\(^{(60)}\) Although oral azithromycin is generally well tolerated, consultation with a patient’s primary care physician is indicated before its prescription.

Omega-3 EFA supplementation represents another avenue for modifying the inflammatory status of the body.\(^{(61)}\) The balance of omega-3 to omega-6 EFA intake has changed in modern times, thereby altering the balance of inflammatory cytokines.\(^{(62)}\) Long-chain omega-3 EFAs bias prostaglandin metabolism toward the production of anti-inflammatory eicosanoids. A number of relatively small RCTs have been undertaken to assess whether omega-3 EFA supplementation is beneficial in DED. A recent meta-analysis of these studies concluded that improvements in clinical parameters of tear stability and tear secretion (i.e., TBUT and Schirmer test) were evident in DED patients taking omega-3 EFA supplements.\(^{(63)}\) However, there is still a need for clarification with regard to the optimal dosage for therapeutic benefit, the ideal form of omega-3 EFA, and/or whether concurrent omega-6 supplementation is beneficial. Furthermore, the potential antiinflammatory effects of oral omega-3 EFAs need to be considered in the context of the patient’s general health and concomitant medications before proceeding with this course of management.

### Punctal Occlusion

Physical blockage of the lacrimal puncta can be considered for moderate to severe DED. Punctal plugs are an option for patients with symptomatic DED, a Schirmer test with anesthesia of less than 5 mm in 5 min and ocular surface staining.\(^{(64)}\) A range of different punctal plugs exist; however, the relative superiority of designs is unclear. A Cochrane systematic review, published in 2010, reported that there was a relative paucity of RCTs assessing the safety and/or efficacy of punctal occlusion in DED.\(^{(65)}\) It was concluded that silicone plugs could provide symptomatic relief in severe DED, and collagen plugs appeared to be equally effective on a short-term basis.\(^{(65)}\)

Potential complications are however not insignificant and include the risk of extrusion, migration into the lacrimal drainage system, punctal and canalicular stenosis, and canalicularitis;\(^{(66)}\) long-term risks are unclear. Although serious complications are infrequent, they can necessitate surgical intervention. Furthermore, punctal plugs may be inappropriate for patients with uncontrolled ocular surface inflammation because their insertion may attenuate the outflow of proinflammatory cytokines.\(^{(67)}\) Pretreatment with anti-inflammatory therapy is recommended before punctal occlusion.

Permanent occlusion, involving thermal or laser cauterization of the puncta, can also be performed for severe cases of aqueous tear deficiency. This level of intervention is typically reserved for severe DED patients who have experienced recurrent plug extrusion and/or complications; the approach serves to primarily assist with improving ocular surface wetting.\(^{(67)}\)

### Biological Tear Substitutes

Biological fluids can be applied to the anterior ocular surface as tear replacement products. Autologous serum, derived from a patient’s own blood, is considered a potentially advantageous therapy for DED because of its capacity to act as a tear substitute containing many biochemical elements that are similar to the natural tear film.\(^{(7)}\) Standards for the preparation, storage, and administration of autologous serum drops have been published.\(^{(68)}\) A 20% concentration is most common, although higher concentrations (50% to 100%) have also been investigated.\(^{(69)}\) Recently, a Cochrane review was undertaken to compare the efficacy and safety of autologous serum eye drops compared with tear supplements in the management of DED; four eligible RCTs were included.\(^{(70)}\) The authors concluded that there was inconsistency in the findings related to the potential benefits of autologous serum eye drops and that multicenter high-quality RCTs were warranted to more clearly define the potential benefit(s) of this intervention.

### Mini-Scleral and Scleral Contact Lenses

The first report of the potential utility of scleral contact lenses in the management of DED was published more than 40 years ago.\(^{(70)}\) Since this time, advances in contact lens technology, primarily relating to the availability of gas-permeable materials and the manufacture of mini-sclerals, have encouraged renewed clinical interest in this modality. The use of mini-scleral and scleral lens designs for DED is premised on the rationale of the lens vaulting the cornea, thereby allowing the postlens tear reservoir to protect and hydrate the ocular surface. Currently, the available evidence regarding the safety and efficacy of mini-scleral and scleral lenses for DED derives from a prospective interventional case series,\(^{(71)}\) retrospective analysis,\(^{(72)}\) and case studies.\(^{(73)}\) Further work is required to more clearly define the role of these contact lenses in the management of DED.

### Clinical Case Scenario 2

#### Optometric Management

A stepwise approach to management begins with considering potential environmental and personal modifiable risk factors. Specific recommendations regarding appropriate tear supplements and the frequency of instillation are indicated. In particular, this patient could use nonpreserved low- and/or moderate-viscosity tear supplements regularly during the day (e.g., q2h) and an ointment before sleep. In addition to improving comfort, enhancing the volume and consistency of the tear film would assist with reducing the friction-related ocular surface signs (such as LWE and LIPCOF). The presence of significant anterior eye inflammation, including marked bilateral ocular surface staining and reduced visual acuities, necessitates topical anti-inflammatory therapy. An option would be for a short-course (e.g., 2-week period) of a topical ketone corticosteroid, such as fluorometholone acetate 0.1% q2h to qid, to acutely downregulate the ocular inflammatory response. Alternatively, as a longer-term therapy, topical cyclosporine emulsion 0.05% bid may be considered. The need to allow a 15-min interval...
between instilling tear supplements and topical anti-inflammatory medications should be advised. Although this patient primarily has clinical signs of aqueous deficiency, consistent with the associated Sjögren syndrome, there are some coexistent signs of tear film instability; in this regard, simple measures to improve meibomian gland secretions in the form of twice daily eyelid hygiene could be instituted.

To assess the patient’s response to therapy, an initial review within approximately a 2-week period would be reasonable; this allows for the monitoring of change(s) to the extent of ocular damage, the adjustment of treatment (if required), and/or provision of patient reassurance. Intraocular pressure measurement should be undertaken on patients prescribed corticosteroids.

Depending on the response to initial treatment, additional interventions such as punctal occlusion and autologous serum eye drops may be required. Consideration with regard to the relative benefits versus risks of such treatments is indicated, particularly before proceeding with relatively more invasive strategies, such as punctal plugs.

The ongoing frequency of follow-up appointments is dependent on the patient’s response to the prescribed interventions, the level of continuing therapeutics, and whether improvement in the level of disease control is observed. Severe DED that is recalcitrant to the spectrum of nonsurgical treatment options may require referral for possible surgical intervention.

CONCLUSIONS: FUTURE THERAPIES FOR DRY EYE DISEASE

This review provides a pragmatic approach to the clinical management of DED. A major challenge of managing this condition is that there is currently no cure for DED. There is also no singularly effective management strategy. The current mainstays of therapy are palliative rather than therapeutic, and many patients remain symptomatic despite adherence to treatment. As the global population ages, the prevalence and socioeconomic impact of DED are projected to increase dramatically. A strong need therefore exists for systematic, pragmatic, rather than ad hoc therapy to enhance DED treatment and improve patient outcomes.

A range of new therapies is presently in development and/or undergoing preclinical and clinical investigations. For example, in Japan, phase II and III clinical trials of topical mucin secretagogues, which enhance ocular mucin production to support tear film adhesion, have had positive findings with improvements demonstrated in both subjective symptoms and objective dry eye signs. A lubricating mucin-like glycoprotein, proteoglycan-4 (or lubricin), which has been recently discovered to exist at the ocular surface, may also be of value as a topical treatment for DED.

For MGD, early findings relating to the benefits of intense pulsed light therapy are promising. Indeed, we predict ongoing improvement in the available treatment options and the efficacy of novel interventions for DED in the future.

ACKNOWLEDGMENTS

This work is partially funded by a University of Melbourne Early Career Researcher Grant (2014, LED) and a Kaye Merlin Brutton Bequest (2014, LED). LED is an investigator for industry-sponsored clinical trials (Allergan Pty, Ltd.) and a recipient of an unrestricted research grant (CooperVision Pty, Ltd.).

REFERENCES


Laura E. Downie
Lecturer and NHMRC TRIP Fellow
Department of Optometry and Vision Sciences
University of Melbourne
Parkville, VIC 3010
Australia
e-mail: ldownie@unimelb.edu.au

Optometry and Vision Science, Vol. 92, No. 9, September 2015
Copyright © American Academy of Optometry. Unauthorized reproduction of this article is prohibited.