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# Advances in the management of dry eye

**Dry eye is the most common presentation to an ophthalmologist, with patients typically complaining of blurred vision, ocular discomfort and a foreign body sensation. Topical lubricants and lid hygiene can give relief. If these simple measures fail, therapies such as topical cyclosporin and autologous serum eye drops can be effective.**

**STEPHANIE L. WATSON**
BSc(Med), MB BS, PhD, FRANZCO

**MINAS T. CORONEO**
MD, MS, MSc, FRACS, FRANZCO

Dr Watson is a Consultant Ophthalmologist, Corneal Unit, Prince of Wales Hospital, Sydney Children's Hospital and Sydney Eye Hospital. She is also an Ophthalmologist in private practice, Bondi Junction, Sydney. Professor Coroneo is a Professor and Head of the Department of Ophthalmology, Prince of Wales Hospital, Randwick, Sydney, NSW.

In patients with dry eye, the tear film is disrupted due to insufficient tear production or excess tear evaporation, resulting in symptoms such as blurred vision and ocular discomfort. Dry eye is also known as 'dysfunctional tear syndrome'. Although dry eye is usually considered a minor complaint, moderate to severe dry eye can have a major impact on quality of life. Despite the use of maximal standard therapy, which can be costly to the patient, many people with dry eye continue to suffer.[1]

An Australian survey of people over 50 years of age reported that 58% of participants had at least one symptom of dry eye and 15% had three or more symptoms.[2] Dry eye is increasingly common in the elderly[3] and is associated with ocular allergy and toxicity.[4] Systemic medications can exacerbate dry eye and cigarette smoke increases the risk of this condition.[5] Night time lagophthalmos (a condition in which the eyelid cannot completely close) can exacerbate it and occurs in 5% of the general population and more in Asian individuals.

In patients with primary Sjögren's syndrome, dry eye is accompanied by a dry mouth. This is a less common cause of dry eye and predominately

**IN SUMMARY**

- **Dry eye is the most common presentation to an ophthalmologist.**
- **Patients with dry eye may complain of a large variety of symptoms, including blurred vision, ocular discomfort, tiring, soreness, pain, burning, photophobia, itch and a sand or gravel sensation.**
- **Moderate to severe dry eye can have a major impact on a sufferer's quality of life.**
- **There is no single gold-standard test for the diagnosis of dry eye; the presence of dry eye symptoms, ocular surface damage and tear film instability are used to diagnose this condition.**
- **A hierarchical approach based on disease severity is used in the management of dry eye.**
- **New agents such as topical cyclosporin represent a significant advance in the management of dry eye.**

## Table 1. Symptoms of dry eye

### Symptoms of ocular discomfort and pain
Foreign body sensation
Pain
General discomfort
Dry eye sensation/dryness
Itchy sensation/itchiness
Burning/stinging
Irritation from smoke
Grittiness
Ocular soreness
Heavy sensation
Hot sensation

### Visual symptoms
Blurred vision
Photophobia
Brightness

### Physical symptoms
Redness
Excess mucus formation/discharge
Stickiness/matted lashes
Epiphora/excess tearing

### Symptoms of ocular dysfunction
Asthenopia (tired eyes)
Difficulty in waking
Ocular fatigue
Inability to function
Difficulty in opening eyes in the morning
Heavy eyelids
Frequent blinking

affects women.[6] In patients with secondary Sjögren's syndrome, dry eye and mouth are associated with an autoimmune connective tissue disease, most commonly rheumatoid arthritis.

## Causes of dry eye

The tear film is composed of aqueous fluid from the lacrimal gland, oil from the meibomian glands and mucous provided by conjunctival goblet cells. Hormonal (androgen levels), neuronal (corneal sensation) and mechanical mechanisms (the eyelids) aid in maintaining a stable tear film. Disruptions of these mechanisms produce an unstable tear film. It is also thought that hyperosmolality of the tear film contributes to dry eye. The end result is inflammation[7-11] and damage (squamous metaplasia) of the ocular surface.[9,12-15] In Sjögren's syndrome, proinflammatory cytokines and lymphocytic infiltration may damage the lacrimal and salivary glands.[16-18]

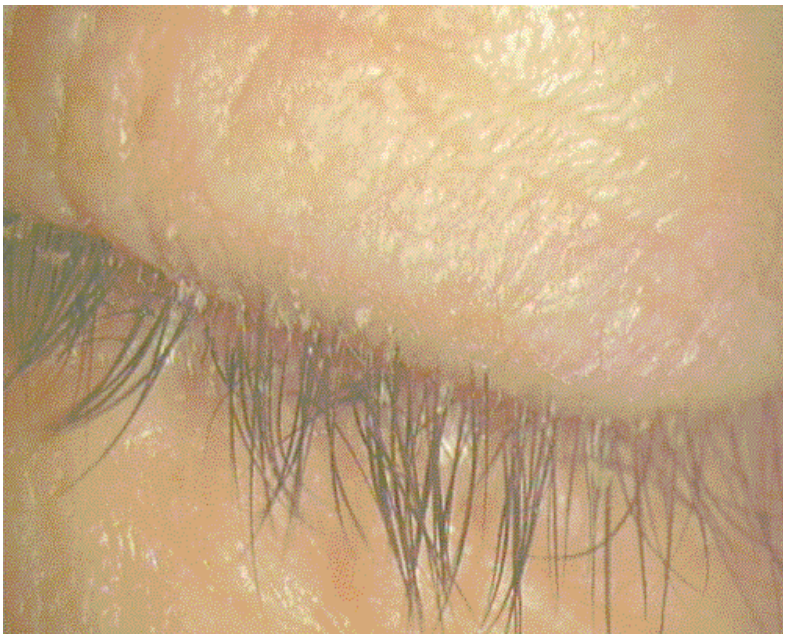

Figure 1. A patient with dry eye and anterior blepharitis; skin scales can be seen on the upper eyelid and collarettes are surrounding the eyelashes.

## How to diagnose dry eye

There is no single gold-standard test for the diagnosis of dry eye.[19] The presence of dry eye symptoms, ocular surface damage and tear film instability are used to diagnose the condition.[19,20] Blepharitis may co-exist and should also be diagnosed (see the box on page 48; Figure 1). To diagnose dry eye a history should be taken to illicit the symptoms. Inquiry should be made about dry mouth, ocular and systemic medications (past and current use), smoking and atopy. Following testing of the visual acuity (with spectacles if worn), the face and eyelids should be inspected, looking for signs of rosacea, eyelid closure, blepharitis and inturned lashes (trichiasis).

### Identify symptoms

A variety of symptoms have been reported by patients with dry eye (Table 1). Symptoms are typically worse in the evening and often relieved by closing the eye or using artificial tears.[13,21]

## A case of dry eye with anterior blepharitis

### History and examination

A 60-year-old woman presented with a two-year history of red and gritty eyes and blurred vision. Preserved artificial tear drops had provided minimal relief. At times her mouth was dry but she could still swallow food without having to drink liquids. She had been taking diuretics for a number of years and she had no significant family ophthalmological history.

Her visual acuity was 6/6 in each eye. Her GP noted that her conjunctiva was injected. With fluorescein and the cobalt blue light from the direct ophthalmoscope, staining was noted on the cornea and conjunctiva in the region between the lids (the palpebral fissure). Anterior eyelid inflammation, grease and skin scales were also noted.

### Diagnosis

A diagnosis of dry eye with anterior blepharitis was made. She was advised that as she had a dry mouth and no history of a connective tissue disorder she may be suffering from primary Sjögren's syndrome (dry eye with dry mouth). The investigations rheumatoid factor, antinuclear antibodies, anti-Sjögren's syndrome (SS) A and anti-SS B antibodies were ordered.

### Management

The patient was commenced on nonpreserved lubricants six times a day and a lubricating ointment at night, and advised to ensure she had an adequate oral fluid intake. To treat the blepharitis, she was encouraged to perform lid hygiene at least twice a day. To control the inflammation, topical fluorometholone was commenced two times a day. A special access scheme application was made for topical cyclosporin (Restasis). She was encouraged to increase her intake of fish and take flaxseed oil daily.

On return to her GP six weeks later, the patient's symptoms had improved; however, she still complained of grittiness and blurring. The investigations for Sjögren's syndrome were negative and her diuretic therapy was exchanged for an alternative antihypertensive medication.

She was referred to an ophthalmologist who confirmed the diagnosis of dry eye. The chronic nature of her condition was reiterated and also the continued need for lubricants, adequate daily fluid intake and daily lid hygiene. Punctal plugs were discussed. The patient was concerned regarding the risk of a watery eye so a temporary plug was placed in the lower canaliculus in one eye. She commenced topical cyclosporin twice a day and the dose of topical fluorometholone was tapered. On review by the ophthalmologist six weeks later, her comfort and redness had improved further. As she had found the temporary plug effective, semi-permanent plugs were placed in the lower canaliculi of both eyes.

Dry eye symptoms, such as a foreign body sensation, burning and the less specific symptoms 'tiring' (ocular fatigue), soreness and pain in the eyes, are also common complaints of patients with conjunctivitis.[13,21] In one study, a sand or gravel sensation was reported by 93% of patients with dry eye.[22] Dry eye can blur vision, often significantly.[21,23-26] Photophobia is common and may be disabling.[22-32] Patients may report that they do not form tears in response to emotional stimuli or chemical irritants.[27] Itch can also occur in patients with dry eye but is more common with allergy.

### Examine ocular surface

A dry eye damages and inflames the ocular surface (cornea and conjunctiva).[9,12,14,15,26,33-35] Clinically, this damage manifests as conjunctival injection and superficial punctate corneal erosions (Figure 2), corneal filaments, coarse mucin plaques, epithelial defects and, in severe cases, melting corneal ulcers.[33,34] Punctuate corneal erosions can be seen after staining with fluorescein (Minims Fluorescein Eye Drops). The stain is instilled in the tear lake and then the cornea is examined using a cobalt blue light on the slit lamp or direct ophthalmoscope. Staining typically occurs in the lower two-thirds of the cornea, whereas the upper third is unstained.[27] This pattern of staining is practically pathognomonic for dry eye.[27] Rose bengal or lissamine green dyes both stain devitalised cells and can be used to demonstrate the degree of ocular surface

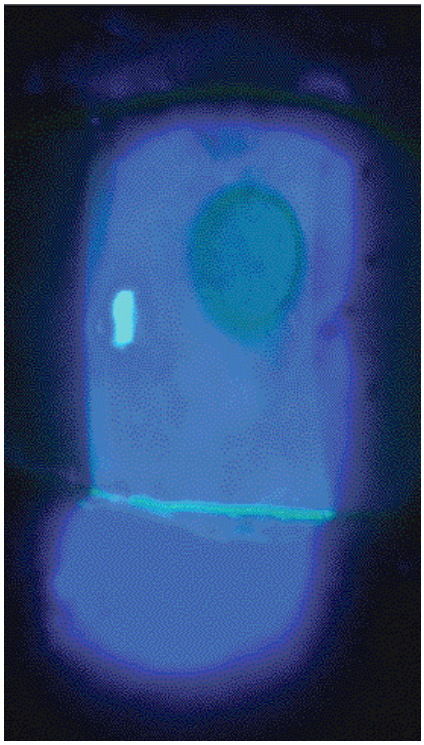

Figure 2. Punctate epithelial erosions on the lower third of the cornea in a patient with dry eye. The erosions have been stained with fluorescein and viewed with light passed through a cobalt blue filter. The marginal tear strip lies along the lower eyelid margin and has also been stained with fluorescein.

damage in patients with dry eye.[19,36-38] However, rose bengal is no longer available in Australia and lissamine green is not yet widely available and may be less sensitive than rose bengal.[36,37]

## Evaluate tear film

Evaluation of the tear film includes the assessment of the marginal tear strip height (the level of tears present on the lower lid; Figure 2). The GP can assess this by magnification and direct illumination. The ophthalmologist may evaluate the tear film further by using the Schirmer's I test and measuring the tear film break-up time.

In the Schirmer's I test, a filter paper strip is placed in the tear film and used to assess aqueous (lacrimal gland) tear production (Figure 3).[19,38] This test is performed without anaesthetic and variable results may be seen as the sensory stimulation for tear production can vary depending on how the test is performed.[39] A Schirmer's I test result of consistently less than 5 mm of wetting after five minutes is considered abnormal and indicates aqueous tear deficiency.[19] Low Schirmer's I values are associated with an increased severity of ocular surface staining (with fluorescein or rose bengal).[6]

Tear film instability can be assessed by measurement of the tear film break-up time.[19,38-40] The break-up time is typically measured using the slit lamp biomicroscope with cobalt blue light, following the instillation of fluorescein into the tear lake. The tear film break-up time is the interval between the last complete blink and the appearance of the first dry spot in the tear film.[6] A value of less than 10 seconds may be abnormal. However, this test may not be reproducible,[41] and the instillation of fluorescein[42] or topical anaesthetic has been reported to reduce tear film stability.[6]

## Consider Sjögren's syndrome

Serological investigations should be ordered if Sjögren's syndrome is suspected. Autoantibodies anti-Sjögren's syndrome (SS) A (also called Ro) and anti-SS B (also called La),[19,43-47] and rheumatoid factor are present in most patients

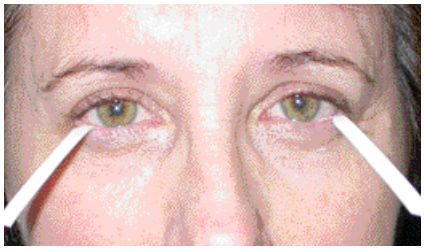

Figure 3. Schirmer's I tear strips may be used by ophthalmologists to assess the aqueous tear production.

with Sjögren's syndrome, and approximately 70% of patients have antinuclear antibodies. The diagnosis can be confirmed by the presence of foci of inflammation on a minor salivary gland biopsy. Patients with Sjögren's syndrome should have a rheumatological evaluation. Sjögren's syndrome can have an impact on the general health of sufferers as there is internal organ and joint involvement in up to half of patients, and lymphoma may develop in around 5% of patients.

## Consider co-existent blepharitis

Lid inflammation (blepharitis) often

**Table 2. Signs and symptoms of dry eye (as defined by the Delphi panel)[49,50]**

| Signs and symptoms | Severity level | | | |
|---|---|---|---|---|
| | Mild (level 1) | Moderate (level 2) | Severe (level 3) | Very severe (level 4) |
| Itch, sandy, gritty, dry | Never to seldom | Sometimes | Frequent | Always |
| Discomfort, stinging, burning, pain | No | Yes | Yes | Yes |
| Vision blurring, interrupted | No | No | Sometimes | Usually |
| Use of artificial tear drops (per day) | <2 | Several | Several | Several |
| Conjunctival staining | Mild | Moderate | Marked | Scarring |
| Corneal staining | Nil | Mild punctate | Marked punctate central | Severe punctate erosions |
| Tear film break-up time* (seconds) | <12 | >2 to <7 | <3 | <3 |
| Schirmer's I test score† (mm) | >10 | >5 to <10 | <5 | <2 |

* Tear film break-up time is the interval between the last complete blink and the appearance of the first dry spot in the tear film.
† Schirmer's I test score is an assessment of aqueous tear production based on the wetting of a filter paper strip that is placed in the tear film.

### Table 3. Treatment algorithm for dry eye (as defined by the Delphi panel)

**Mild***

Education of patients regarding the chronic nature of their condition and the need for compliance with therapy
Environmental modifications
Control systemic medications
Preserved tear supplements
Allergy control
Increased oral water intake

**Moderate***

Unpreserved tear supplements
Gels/ointments at night
Nutritional support – e.g. oral flaxseed and fish oils
Topical cyclosporin
Topical corticosteroids
Secretagogues – e.g. oral pilocarpine

**Severe***

Oral tetracyclines
Punctal plugs (after the control of inflammation)
Autologous serum drops
Therapeutic contact lenses

**Very severe**

Systemic anti-inflammatory therapy (corticosteroids plus cyclosporin)
Acetylcysteine drops
Surgery (punctal cautery)
Moisture goggles

*If there is no improvement then treatment for the next level of severity should be tried.

occurs in patients with dry eye. The signs of anterior blepharitis are lid margin grease, inflammation, skin scales, collarettes (scales around lashes), loss of eyelashes and ulceration. In posterior blepharitis, telangiectasia, notching and inflammation affect the lid margin and there are cheesey secretions, blocked and/or inflamed meibomian gland orifices and at times active chalazia. Blepharitis may be associated with ocular rosacea.[48]

## How to manage mild to moderate dry eye

A hierarchical approach, based on disease severity, is used in the treatment of dry eye. A grading system for the severity of dry eye and a treatment approach have been developed by an international task force of dry eye experts known as the Delphi panel (Tables 2 and 3).[49,50]

Mild to moderate dry eye is often managed by the GP. Management begins with education for patients regarding the chronic nature of their condition and the need for compliance with therapy. All systemic medications associated with dry eye that the patient may be using should be reviewed (Table 4). Marijuana thiabendazole and diphenoxylate hydrochloride have also been associated with dry eye. Environmental modifications such as directing fans away from the eyes and avoiding overheating are advised to reduce tear evaporation. Patients should ensure that they have an adequate oral water intake. Co-existent ocular conditions, such as blepharitis and allergy, should be treated,[51-53] and any ocular therapies that the patient may be using reviewed. Blepharitis should be managed with lid hygiene[54] and preserved agents should be exchanged for nonpreserved agents if possible to avoid corneal toxicity.[4,55,56]

### Tear supplements

Tear supplements are the mainstay of treatment for dry eye.[57] These are available with and without preservatives as eye drops, gels or ointments. They are the most widely prescribed treatment for dry eye.[30,56,58-61] For mild dry eye, preserved artificial tear supplements are given four times a day. If artificial tear supplements are required more than this, a nonpreserved tear supplement should be used, as frequent application of preservatives and calcium chelating agents to a compromised ocular surface may lead to further damage.[59,62] If the patient is still symptomatic and/or has nocturnal lagophthalmos, lubricating ointment should

### Table 4. Systemic medications associated with dry eye

Antihypertensives – e.g. beta-blockers, diuretics
Antidepressants – e.g. tricyclics, monoamine oxidase inhibitors
Antihistamines
Anticholinergics – e.g. benzatropine mesilate
Antiarrhythmics – e.g. amiodarone
Bisphosphonates – e.g. alendronate

be given at night. Gels have a longer ocular retention time than eye drops and for this reason may be preferred by some patients. They can be used instead of, or as a supplement, to eye drops.

A variety of tear supplements are commercially available, including ocular lubricants, which improve tear volume and hydrodynamics but do not replace essential tear components.[63,64] Lubrication increases comfort presumably by reducing the friction between the dried surfaces of the conjunctiva and the cornea.[65] Ocular lubricants contain agents used to increase ocular retention time, including cellulose derivatives such as carboxymethylcellulose and hypromellose (hydroxypropyl methylcellulose 0.3%), polyvinyl derivatives such as polyvinyl alcohol, and chondroitin, sodium hyaluronate and glycerol.[66] Tear supplements are most effective when their electrolyte composition resembles extracellular fluid or tear fluid rather than sodium chloride alone.[33,57,65,67]

A new mucomimetic artificial tear substitute containing a novel gelling agent, hydroxypropyl guar, and two demulcents, polyethylene glycol 400 and propylene glycol (Systane Lubricating Eye Drops) has been shown to protect the intact cornea and epithelial cells in culture from desiccation.[68] Clinically, Systane has been shown to prolong the tear film break-up

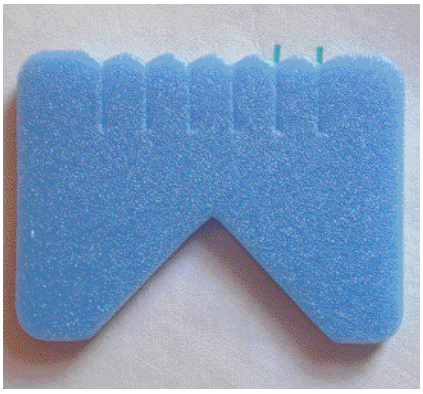

Figure 4. Punctal plugs (coloured blue) can be inserted into the lacrimal cannaliculi to conserve tears in patients with dry eye.

time, and in a noncomparative study it improved the signs and symptoms associated with moderate dry eye.[69,70]

Optive (carboxymethylcellulose with glycerin), a new tear supplement, has been designed to protect ocular surface cells from damage due to hyperosmolality of the tear film. In addition to lubricants and electrolytes, it contains glycerin and other specific compatible solutes, which makes it isotonic. Optive has shown significant improvement in signs and symptoms of dry eye, including Schirmer's I test and the tear film break-up time.

### Anti-inflammatory therapies

Corticosteroids, cyclosporin and nonsteroidal anti-inflammatories can reduce some of the signs and symptoms of dry eye.[71-73] Topical corticosteroids, such as topical fluorometholone (Flucon, FML), can be used in short courses to control the inflammation associated with dry eye. Complications such as cataract, raised intraocular pressure (glaucoma) and the risk of infection, however, limit their long-term use.[74]

Topical cyclosporin 0.05% (Restasis; available in Australia only through the Special Access Scheme) has been approved for clinical use by the TGA and the US Food and Drug Administration for moderate to severe dry eye.

Topical cyclosporin may slow or halt the progression of dry eye. In a phase 3 clinical trial it was shown to increase the production of patients' own tears and increase the density of conjunctival goblet cells.[73] It has been shown to ameliorate symptoms in up to 44% of patients and improve basal tear production (as demonstrated by Schirmer's I test) in up to 59% of patients after six months of treatment.[73] Approximately 15% of patients with dry eye who were treated with topical cyclosporin had a more than a 10 mm increase in Schirmer's I test at six months, 59% had some increase, and there was a 191% increase in goblet cell density.

No serious adverse events have been associated with topical cyclosporin.[73] The most common treatment-related adverse events were burning, stinging and hyperaemia. The main disadvantage of therapy is the cost; in Australia a six-month course of topical cyclosporin twice a day will cost the patient approximately $720.

The onset of effect with topical cyclosporin may take at least six months, such that topical corticosteroids may need to be continued during this time. After 12 months, if the symptoms and signs have completely resolved, some patients may be able to discontinue topical cyclosporin. Patients should then be monitored for at least a year. If recurrence occurs, topical cyclosporin can be recommenced and continued indefinitely, although long-term randomised studies and cost-effectiveness analyses are still needed.

Topical nonsteroidals can improve ocular comfort in dry eye, but should be used with caution as they may promote corneal melting.[75,76] Systemic corticosteroids and systemic cyclosporin have significant potential side effects and their value in dry eye is uncertain.

### Dietary supplements

Recently, essential fatty acid dietary supplements such as flaxseed or fish oils have been suggested as therapy for dry eye.[77-79] A higher dietary intake of omega-3 fatty acids has been associated with a decrease in the symptoms of dry eye.[80] They are thought to stimulate aqueous tear secretion, augment the oil layer of the tear film and have anti-inflammatory properties. Further research is needed to confirm the benefit and safety of fatty acid supplements for dry eye.[79,81]

## How to manage moderate to severe dry eye

Patients with moderate to severe dry eye are usually under the care of an ophthalmologist.

### Punctal occlusion

Punctal occlusion, either permanent or temporary, can conserve tears on the ocular surface and improve the symptoms of dry eye, except in patients with ocular surface inflammation as punctal occlusion may prevent the drainage of tears containing proinflammatory agents.[57]

The puncta may be occluded using punctal plugs (temporary or permanent; Figure 4) or cautery (permanent). Punctal plugs have been shown to reduce dry eye symptoms by at least 70%.[82,85] Complications of punctal plugs include discomfort, epiphora (watering), granulomas, canalicular infection, conjunctival or corneal erosions and subconjunctival haemorrhage.[82,86] Partial or total extrusion of the plug can occur; total extrusion has been reported in up to 60% of cases.[83,84,86]

### Oral tetracyclines

Oral tetracyclines are particularly useful in patients with dry eye and meibomitis and/or rosacea[48] as they improve meibomian gland function and have anti-inflammatory and antimatrix metalloprotinease activities.

### Other agents and surgery

Patients with excessive mucous production may be treated with acetylcysteine drops prepared at a concentration of 5% or

10% by a hospital pharmacy.[87] Therapeutic contact lenses can be used to improve comfort and vision in dry eye but must be used with care due to the risks of ocular infection.[88] In Australia, the most common cause of nontraumatic bacterial keratitis is that associated with improper contact lens wear.

Tear evaporation can be reduced by use of spectacles with occlusive sides ('moisture goggles') and by tarsorrhaphy, a surgical procedure that reduces exposure of the ocular surface by narrowing the width of the palpebral fissure (opening between the eyelids).[89] However, surgery can reduce the visual field and be cosmetically unacceptable.[90]

Agents such as oral pilocarpine can increase or preserve tear production by the main and accessory lacrimal glands. However, systemic side effects may limit its widespread use.[58,91] Lacrimal gland damage may occur in dry eye,[16] (e.g. in patients with Sjögren's syndrome) and this may limit the usefulness of tear stimulation therapies.

Physiological tear supplements, such as autologous serum and salivary 'tears', have been trialled in patients with severe dry eye who have not responded to standard current therapy. The use of autologous serum drops is limited as its preparation is time consuming and inconvenient for the patient, currently impractical on a large scale and problematic for nonautologous use due to the existence of bloodborne infections. Patients may also have a medical contraindication to serum drop therapy, such as anaemia. Providing salivary tears requires a complicated surgical procedure (salivary gland transplantation).[92] Physiological tear supplements may be useful in patients with moderate to severe dry eye.

## Conclusion

Dry eye is a common cause of discomfort and blurred vision. A diagnosis of dry eye is made in a patient by taking a history to illicit dry eye symptoms, examining for signs of ocular surface damage (staining of the cornea and conjunctiva with fluorescein dye) and assessing the tear film. Blepharitis often occurs with dry eye and should be looked for. Mild to moderate dry eye can be managed with simple measures such as tear supplements. For moderate to severe dry eye, newer therapies such as topical cyclosporin and autologous serum drops can provide relief. MT

*A list of references is available on request to the editorial office.*

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**STEPHANIE L. WATSON** Bsc(Med), MB BS, PhD, FRANZCO
**MINAS T. CORONEO** MD, MS, MSc, FRACS, FRANZCO

## References

1. Nelson JD, Helms H, Fiscella R, Southwell Y, Hirsch JD. A new look at dry eye disease and its treatment. Adv Ther 2000; 17: 84-93.
2. Chia EM, Mitchell P, Rochtchina E, Lee AJ, Maroun R, Wang JJ. Prevalence and associations of dry eye syndrome in an older population: the Blue Mountains Eye Study. Clin Experiment Ophthalmol 2003; 31: 229-232.
3. Schein OD, Muñoz B, Tielsch JM, Bandeen-Roche K, West S. Prevalence of dry eye among the elderly. Am J Ophthalmol 1997; 124: 723-728.
4. Wilson FM2. Adverse external ocular effects of topical ophthalmic therapy: an epidemiologic, laboratory, and clinical study. Trans Am Ophthalmol Soc 1983; 81: 854-965.
5. Lee AJ, Lee J, Saw SM, et al. Prevalence and risk factors associated with dry eye symptoms: a population based study in Indonesia. Br J Ophthalmol 2002; 86: 1347-1351.
6. Pflugfelder SC, Tseng SCG, Sanabria O, et al. Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irriation. Cornea 1998; 17: 38-56.
7. Baudouin C. The pathology of dry eye. Surv Ophthalmol 2001; 45: S211-S220.
8. Stern ME, Beuerman RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC. The pathology of dry eye: The interaction between the ocular surface and lacrimal glands. Cornea 1998; 17: 584-589.
9. Pflugfelder SC, Tseng SCG, Yoshino K, Monroy D, Felix C, Reis BL. Correlation of goblet cell density and mucosal epithelial membrane mucin expression with rose Bengal staining in patients with ocular irritation. Ophthalmology 1997; 104: 223-235.
10. Perry HD, Donnenfeld ED. Dry eye diagnosis and management in 2004. Curr Opin Ophthalmol 2004; 15: 299-304.
11. Rolando M, Zierhut M. The ocular surface and tear film and their dysfunction in dry eye disease. Surv Ophthalmol 2001; 45: S203-S210.
12. Nelson JD, Havener VR, Cameron JD. Cellulose acetate impressions of the ocular surface. Dry eye states. Arch Ophthalmol 1983; 101: 1869-1872.
13. Tsubota K, Toda I, Yagi Y, Ogawa Y, Ono M, Yoshino K. Three different types of dry eye syndrome. Cornea 1994; 13: 202-209.
14. Pflugfelder SC, Huang AJW, Feuer WJ, Pereira IC, Tseng SCG. Conjunctival cytologic features of primary Sjögren's syndrome. Ophthalmology 1990; 97: 985-991.
15. Tseng SC. Staging of conjunctival squamous metaplasia by impression cytology. Ophthalmology 1985; 92: 728-733.
16. Tabbara KF, Vera-Cristo CL. Sjögren syndrome. Curr Opin Ophthalmol 2000; 11: 449-454.
17. Pepose JS, Akata RF, Pflugfelder SC, Voigt W. Mononuclear cell phenotypes and immunoglobulin gene rearrangements in lacrimal gland biopsies from patients with Sjögren's syndrome. Ophthalmology 1990; 97: 1599-1605.
18. Tsubota K, Xu KP, Fujihara T, Katagiri S, Takeuchi T. Decreased reflex tearing is associated with lymphocytic infiltration in lacrimal glands. J Rheumatol 1996; 23: 313-320.
19. Lemp MA. Report of the National Eye Institute/Industry Workshop on clinical trials in dry eyes. CLAO J 1995; 21: 221-232.
20. Nichols KK, Begley CG, Caffery B, Jones LA. Symptoms of ocular irritation in patients diagnosed with dry eye. Optom Vis Sci 1999; 76: 838-844.
21. Toda I, Fujishima H, Tsubota K. Ocular fatigue is the major symptom of dry eye. Acta Ophthalmologica (Copenh) 1993; 71: 347-352.
22. Hay EM, Thomas E, Pal B, Hajeer A, Chambers H, Silman AJ. Weak association between subjective symptoms or and objective testing for dry eyes and dry mouth: results from a population based study. Ann Rheum Dis 1998; 57: 20-24.
23. Nelson JD, Gordon JF. Topical fibronectin in the treatment of keratoconjunctivitis sicca. Am J Ophthalmol 1992; 114: 441-447.
24. Shimmura S, Ono M, Shinozaki K, et al. Sodium hyaluronate eyedrops in the treatment of dry eyes. Br J Ophthalmol 1995; 79: 1007-1011.
25. Sullivan LJ, McCurrach F, Lee S, et al. Efficacy and safety of 0.3% carbomer gel compared to placebo in patients with moderate-to-severe dry eye syndrome. Ophthalmology 1997; 104: 1402-1408.
26. Nelson JD, Farris RL. Sodium hyaluronate and polyvinyl alcohol artificial tear preparations. A comparison in patients with keratoconjunctivitis

sicca. Arch Ophthalmol 1988; 106: 484-487.
27. Sjögren H, Bloch KJ. Keratconjunctivitis sicca and the Sjögren syndrome. Surv Ophthalmol 1971; 16: 145-159.
28. Aragona P, Papa V, Micali A, Santocono M, Milazzo G. Long term treatment with sodium hyaluronate-containing artificial tears reduces ocular surface damage in patients with dry eye. Br J Ophthalmol 2002; 86: 181-184.
29. Fox RI, Chan R, Michelson J, Belmont J, Michelson P. Beneficial effect of artificial tears made with autologous serum in patients with keratoconjunctivitis sicca. Arthritis Rheum 1984; 27: 459-461.
30. Grene RB, Lankston P, Mordaunt J, Harrold M, Gwon A, Jones R. Unpreserved carboxymethyl-cellulose artificial tears evaluated in patients with keratoconjunctivitis sicca. Cornea 1992; 11: 294-301.
31. Nelson JD, Drake MM, Brewer JT, Jr., Tuley M. Evaluation of a physiological tear substitute in patients with keratoconjunctivitis sicca. Adv Exp Med Biol 1994; 350: 453-457.
32. Tananuvat N, Daniell M, Sullivan LJ, et al. Controlled study of the use of autologous serum in dry eye patients. Cornea 2001; 20: 802-806.
33. Bernal DL, Ubels JL. Artificial tear composition and promotion of the damaged corneal epithelium. Cornea 1993; 12: 115-120.
34. Lemp MA. Recent developments in dry eye management. Ophthalmology 1987; 94: 1299-1304.
35. Nelson JD, Wright JC. Tear film osmolality determination: an evaluation of potential errors in measurement. Curr Eye Res 1986; 5: 677-681.
36. Kim J. The use of vital dyes in corneal disease. Curr Opin Ophthalmol 2000; 11: 241-247.
37. Manning FJ, Wehrly SR, Foulks GN. Patient tolerance and ocular surface staining characteristics of lissamine green versus rose bengal. Ophthalmology 1995; 102: 1953-1957.
38. Lemp MA. Tear film evaluation. In: Krachmer JH, Mannis MJ, Holland EJ, editors. Cornea. Fundamentals, diagnosis and management. Second ed. Philadelphia: Elsevier Mosby; 2005. p. 225-228.
39. Clinch TE, Benedetto DA, Felberg NT, Laibson PR. Schirmer's test. A closer look. Arch Ophthalmol 1983; 101:1383-1386.
40. Lemp MA. Breakup of the tear film. Int Ophthalmol Clin 1973; 13(1): 97-102.
41. Mengher LS, Bron AJ, Tonge SR. Non-invasive assessment of tear film stability. In: Holly FJ, ed. The preocular tear film in health, disease and contact lens wear. Lubbock, TX: Dry Eye Institute; 1986. p. 64-75.
42. Mengher LS, Bron AJ, Tonge SR, Gilbert DJ. Effect of fluorescein instillation on the pre-corneal tear film stability. Curr Eye Res 1985; 4: 9-12.
43. Fox RI, Robinson CA, Curd JG, Kozin F, Howell FV. Sjögren's syndrome. Proposed criteria for classification. Arthritis Rheum 1986; 29: 577-585.
44. Fox RI, Tornwall J, Michelson P. Current issues in the diagnosis and treatment of Sjögren's syndrome. Curr Opin Rheumatol 1999; 11: 364-371.
45. Vitali C, Moutsopoulos HM, Bombardieri S. The European Community Study Group on diagnostic criteria for Sjögren's syndrome. Sensitivity and specificity of tests for ocular and oral involvement in Sjögren's syndrome. Ann Rheum Dis 1994; 53: 637-647.
46. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002; 61: 554-558.
47. Fox RI, Saito I. Criteria for diagnosis of Sjögren's syndrome. Rheum Dis Clin North Am 1994; 20: 391-407.
48. Watson SL, Coroneo MT. Recognition and management of ocular rosacea. Med Today 2007; 8: 25-31.
49. Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. Cornea 2006; 25: 900-907.
50. McDonnell PJ, Doyle JJ, Stern L, Behrens A. A modified Delphi technique to obtain consensus on the treatment of dysfunctional tear syndrome. Invest Ophthalmol Vis Sci 2004; 45: E abstract 3909.
51. Lee S-H, Tseng SCG. Rose bengal staining and cytologic characteristics associated with lipid tear deficiency. Am J Ophthalmol 1997; 124: 736-750.
52. Raskin EM, Speaker MG, Laibson PR. Blepharitis. Infect Dis Clin North Am 1992; 6: 777-787.
53. McCulley JP, Shine WE. Changing concepts in the diagnosis and management of blepharitis. Cornea 2000; 19: 650-658.
54. Chan DG, Francis IC. Blepharitis: an approach to management. Med Today 2005; 6: 56-59.
55. Dart JKG. Corneal toxicity: the epithelium and stroma in iatrogenic and factitious disease. Eye 2003; 17: 886-892.
56. De Saint Jean M, Brignole F, Bringuier A-F, Bauchet A, Feldmann G, Baudouin C. Effects of benzalkonium chloride on growth and survival of Chang conjunctival cells. Invest Ophthalmol Vis Sci 1999; 40: 619-630.
57. Lemp MA. Evaluation and differential diagnosis of keratoconjunctivitis sicca. J Rheumatol Suppl 2000; 61: 11-14.
58. Sood S, Anthony R, Pease CT. Sjögren's syndrome. Clin Otolaryngol 2000; 25: 350-357.
59. Bernal DL, Ubels JL. Quantitative evaluation of the corneal epithelial barrier: effect of artificial tears and preservatives. Curr Eye Res 1991; 10: 645-656.
60. Geerling G, Daniels JT, Dart JK, Cree IA, Khaw PT. Toxicity of natural tear substitutes in a fully defined culture model of human corneal epithelial cells. Invest Ophthalmol Vis Sci 2001; 42: 948-956.
61. Ubels JL, McCartney MD, Lantz WK, Beaird J, Dayalan A, Edelhauser HF. Effects of preservative-free artificial tear solutions on corneal epithelial structure and function. Arch Ophthalmol 1995; 113: 371-378.
62. Adams J, Wilcox MJ, Trousdale MD, Chien DS, Shimizu RW. Morphologic and physiologic effects of artificial tear formulations on corneal epithelial derived cells. Cornea 1992; 11: 234-241.
63. Tsubota K, Higuchi A. Serum application for the treatment of ocular surface disorders. Int Ophthalmol Clin 2000; 40: 113-122.
64. Holly F, Lemp MA. Tear physiology and dry eye. Surv Ophthalmol 1977; 22: 69-87.
65. Lemp MA. Artificial tear solutions. Int Ophthalmol Clin 1973; 13: 221-229.
66. Djalilian AR, Hamrah P, Pflugfelder SC. Dry eye. In: Krachmer JH, Mannis MJ, Holland EJ, ed. Cornea. Fundamentals, diagnosis and management. Second ed. Philadelphia: Elsevier Mosby; 2005. p. 521-540.
67. Gilbard JP, Rossi SR. An electrolyte-based solution that increases corneal glycogen and conjunctival goblet-cell density in a rabbit model for keratoconjunctivitis sicca. Ophthalmology 1992; 99: 600-604.
68. Ubels JL, Clousing DP, Van Haitsma TA, et al. Pre-clinical investigation of the efficacy of an artificial tear solution containing hydroxypropyl-guar as a gelling agent. Curr Eye Res 2004; 28: 437-444.

69. Hartstein I, Khwarg S, Przydryga J. An open-label evaluation of HP-Guar gellable lubricant eye drops for the improvement of dry eye signs and symptoms in a moderate dry eye adult population. Curr Med Res Opin 2005; 21: 255-260.
70. Guillon M, Chamberlain P, Marks MG, Stein JM. Effect of eye drop compositional characteristics on tear film. Invest Ophthalmol Vis Sci 2004; 45: E abstract 3878.
71. Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. The Cyclosporin A Phase 2 Study Group. Ophthalmology 2000; 107: 967-974.
72. Marsh P, Pflugfelder SC. Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjögren syndrome. Ophthalmology 1999; 106: 811-816.
73. Sall K, Stevenson OD, Mundorf TK, Reis BL, Group CP3S. Two multicentre, randomised studies of the efficacy and safety of cyclosporine ophthalmic emulsion moderate to severe dry eye disease. Ophthalmology 2000; 107: 631-639.
74. Watson SL, Coroneo MT, Steroids and the eye. Med Today 2001; 2(3): 78-85.
75. Avisar R, Robinson A, Appel I, Yassur Y, Weinberger D. Diclofenac sodium, 0.1% (Voltaren Ophtha), versus sodium chloride, 5%, in the treatment of filamentary keratitis. Cornea 2000; 19: 145-147.
76. Aragona P, Stilo A, Ferreri F, Mobrici M. Effects of the topical treatment with NSAIDs on corneal sensitivity and ocular surface of Sjögren's syndrome patients. Eye 2005; 19: 535-539.
77. Trivedi KA, Dana MR, Gilbard JP, Buring JE, Schaumberg DA. Dietary omega-3 fatty acid intake and risk of clinically diagnosed dry eye syndrome in women. Invest Ophthalmol Vis Sci 2003; 44: E abstract 811.
78. Brown NA, Bron AJ, Harding JJ, Dewar HM. Nutrition supplements and the eye. Eye 1998; 12: 127-133.
79. Smith RE. The tear film complex: Pathogenesis and emerging therapies for dry eyes. Cornea 2005; 24: 1-7.
80. Miljanovic B, Trivedi KA, Dana MR, Gilbard JP, Buring JE, Schaumberg DA. Relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women. Am J Clin Nutr 2005; 82: 887-893.
81. Bartlett H, Eperjesi F. Possible contraindications and adverse reactions associated with the use of ocular nutritional supplements. Ophthalmic Physiol Opt 2005; 25: 179-194.
82. Nava-Castaneda AMD, Tovilla-Canales JL, Rodriguez LMD, Pomar JL, Jones CEPh. Effects of lacrimal occlusion with collagen and silicone plugs on patients With conjunctivitis associated with dry eye. Cornea 2003; 22: 10-14.
83. Tai MC, Cosar CB, Cohen EJ, Rapuano CJ, Laibson PR. The clinical efficacy of silicone punctal plug therapy. Cornea 2002; 21: 135-139.
84. Balaram M, Schaumberg DA, Dana MR. Efficacy and tolerability outcomes after punctal occlusion with silicone plugs in dry eye syndrome. Am J Ophthalmol 2001; 131: 30-36.
85. Farrell J, Patel S, Grierson DG, Sturrock RD. A clinical procedure to predict the value of temporary occlusion therapy in keratoconjunctivitis sicca. Ophthalmic Physiol Opt 2003; 23: 1-8.
86. Sakamoto A, Kitagawa K, Tatami A. Efficacy and retention rate of two types of silicone punctal plugs in patients with and without Sjögren Syndrome. Cornea 2004; 23: 249-254.
87. Fraunfelder FT, Wright P, Tripathi RC. Corneal mucus plaques. Am J Ophthalmol 1977; 83: 191-197.
88. Wilson MS, Millis EAW. Contact lenses in ophthalmology. London: Butterworths; 1988.
89. Collin JRO. A manual of systematic eyelid surgery. Second ed. London: Churchill Livingstone; 1995.
90. Kinney SE, Seeley BM, Seeley MZ, Foster JA. Oculoplastic surgical techniques for protection of the eye in facial nerve paralysis. Am J Otol 2000; 21: 275-283.
91. Tsifetaki N, Kitsos G, Paschides CA, Alamanos Y, Eftaxias V, Voulgari PV, et al. Oral pilocarpine for the treatment of ocular symptoms in patients with Sjögren's syndrome: a randomised 12 week controlled study. Ann Rheum Dis 2003; 62: 204-207.
92. Geerling G, Honnicke K, Schröder C, Framme C, Sieg P, Lauer I, et al. Quality of salivary tears following autologous submandibular gland transplantation for severe dry eye. Graefes Arch Clin Exp Ophthalmol 1999; 237: 546-553.