**Introduction**

Part 1 of this article reviewed the techniques available to the clinician for evaluating the dry eye. Using a combination of tests, the aetiology of the dry eye can be best established and the optimal management strategy selected. In managing dry eye patients, the aim is to improve ocular comfort and quality of life and, if possible, to facilitate the return of the tear film and ocular surface to their normal, homeostatic states. A wide variety of treatments exist for dry eye. Depending on the cause and severity, management may be as simple as educating the patient about environmental modifications which could improve ocular comfort, or as complex as salivary gland transplantation surgery to preserve vision. This article describes a number of contemporary strategies available for managing dry eye.

Review of the scientific literature and extensive discussion with dry eye experts led the DEWS Management and Therapy Subcommittee in 2007 to recommend that clinician base dry eye treatment selection on disease severity. Depending on the outcome of the dry eye evaluation, a dry eye will fall into one of four disease severity levels. The features of these levels, 1 to 4, are described in Table 1, together with guidelines for treatment, also tailored to severity. The various treatment recommendations are described in more detail below, and described in relation to specific tear film deficiencies in Table 2.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Features</th>
<th>Treatment recommendations</th>
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<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td>Mild or episodic discomfort, often in response to environmental triggers, with or without visual symptoms. Mild (if any) signs of conjunctival hyperaemia, ocular surface staining, lid disease. Tear film stability and production are variably affected.</td>
<td>Educate about environmental or dietary modifications. Modify deleterious systemic medications. Use of artificial tear supplements, gels and/or ointments. Eyelid therapy.</td>
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<tr>
<td><strong>Level 2</strong></td>
<td>Moderate discomfort and intermittent visual symptoms with or without exposure to provocative stimuli, more frequently exhibit corneal or conjunctival staining. Lid disease may feature, and tear film stability and production are usually affected.</td>
<td>If Level 1 treatments insufficient, add: Topical anti-inflammatory treatment Tetracyclines (lid disease and rosacea) Punctal plugs Secretagogues (if available) Goggles / moisture chamber spectacles</td>
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<tr>
<td><strong>Level 3</strong></td>
<td>Frequent or constant symptoms without provocation, and visual symptoms, which may be activity limiting. Moderate to marked ocular surface staining, possibly with filamentary keratitis, tear debris and mucus clumping. Lid disease is common and tear film stability and production are often markedly reduced.</td>
<td>If Level 2 treatments insufficient, add: Autologous serum Bandage contact lenses Permanent punctal occlusion (e.g. cautery)</td>
</tr>
<tr>
<td><strong>Level 4</strong></td>
<td>Signs and symptoms exhibited. Symptoms often severe, constant and disabling. Marked conjunctival hyperaemia and ocular surface staining with filamentary keratitis, mucus clumping, marked tear film debris and possibly even ulceration. Marked lid disease often present, associated with trichiasis, symblepharon and keratinisation. Tear film break up is immediate and production rates are minimal.</td>
<td>If Level 3 treatments insufficient, add: Systemic anti-inflammatory agents / immunosuppressives Surgery: lid surgery / tarsoorrhaphy mucus membrane, amniotic membrane or salivary gland transplantation.</td>
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Table 1. Typical signs and symptoms associated with increasing levels of dry eye severity (level 1 = least severe, level 4 = most severe, together with suggested treatment strategies at each level.)
Lifestyle Advice

Patients symptomatic of dry eye can often become more comfortable with minor modifications to their lifestyle and/or diet. Use of a number of systemic medications, particularly anticholinergics such as antihistamines and antidepressants can exacerbate dry eye and should be minimised or eliminated if possible. Similarly desiccating environmental conditions caused by air-conditioning or central heating should be avoided. Lowering computer monitor height, in order to minimise the exposed interpalpebral aperture and thereby decrease the evaporative surface area, can reduce the effects of VDU use. (Figures 1(a) and (b)) Full and regular blinking should also be encouraged. Wearing goggles or closely fitting, wrap-around style, spectacles increases the periocular humidity. However, if considered cosmetically unacceptable by affected individuals, other strategies, such as the placement of a humidifier, or bowls of water, close to work areas, may help to reduce symptoms.

While individual patients may claim benefit from a number of different foodstuffs, based on scientific evidence, the only dietary components consistently shown to improve dry eye signs and symptoms are the essential fatty acids. Essential fatty acids are required by the body but cannot be synthesised therefore they must be consumed either within dietary sources or in the form of nutraceuticals. The average Western diet contains over twenty times more potentially detrimental Omega 6 than beneficial Omega 3. Such Omega 6 fatty acids act as precursors for proinflammatory mediators, while Omega 3 fatty acids function to inhibit the synthesis of these mediators. Good sources of Omega 3 fatty acids are cold fish (e.g. mackerel, salmon and sardines), and flaxseed, walnut and canola oil. A carefully designed study, conducted in the US, evaluated the diets of over 32,000 post-menopausal women and, controlling for demographic factors, hormone therapy, and total fat intake, they found that a higher ratio of Omega 6 to Omega 3 fatty acid consumption was associated with a significantly increased risk of self-reported dry eye syndrome. Conversely, tuna consumption was inversely associated with dry eye syndrome such that those eating between 5 and 6 servings of tuna per week were significantly less likely to report dry eye symptoms than those eating 1 or fewer servings per week. The results were therefore able to suggest that a higher dietary intake of Omega 3 fatty acids is associated with a decreased incidence of dry eye syndrome in women, which is consistent with anecdotal clinical observations and proposed biological mechanisms.
Periocular humidity increases can be achieved with the aid of moisture chamber spectacles with side-shields. They may or may not include a moist insert. This increased humidity has been shown to increase the thickness of the lipid layer and lengthen the inter-blink interval. Although contact lenses are a recognised dry eye stimulus, in severe dry eye, a bandage contact lens may be helpful in protecting and hydrating the cornea. (Figure 2) Highly oxygen permeable materials can enable overnight wear in some circumstances, and enhancements in visual acuity and comfort, together with improvements in ocular surface quality have been documented.

Tear supplementation

Despite the range of management strategies for dry eye, artificial tear supplements or lubricants remain the mainstay treatment for dry eye. (Figure 3) A huge range of products exists, varying in tonicity and in the electrolytes, surfactants and viscosity agents that they contain. Most products are isotonic, or are hypotonic in an attempt to counteract the pro-inflammatory hyperosmolarity of the dry eye tear film. Compatible solutes such as glycerine and levocarnitine have recently been incorporated in some products. They are believed to play a role in osmoprotection, by forming a protective barrier between the hyperosmolar tears and the epithelial cells at risk of damage. In terms of electrolytes, potassium and bicarbonate have been shown to be most beneficial. Potassium has an important role in maintaining corneal thickness while bicarbonate promotes wound-healing and helps to maintain normal epithelial ultrastructure. Based on its importance in maintaining the protective mucin gel in the stomach, bicarbonate is also believed to benefit the gel-forming ocular surface mucins.

Viscosity agents in artificial tear products increase retention time, and therefore effect, on the ocular surface. For best patient compliance, viscosity should be matched as closely as possible to severity of symptoms. Patients with mild-moderate dry eye are unlikely to tolerate the blurring of vision on instillation and residue on eyelashes experienced with highly viscous solutions that the moderate to severe dry eye patient will accept for the benefit of an increased period of comfort. Gels containing high molecular weight carbomers offer superior retention times to most lubricant drops and are generally better tolerated than petroleum-based ointments due to reduced blurring effects. Sodium hyaluronate (SH) is a naturally occurring extracellular matrix glycosaminoglycan (GAG). As a tear supplement it has a number of useful features. Its viscoelastic (non-Newtonian) rheological properties allow it to shear during eyelid movement (i.e. during blinking), but to remain viscous between blinks, mimicking the natural tear film. The mucoadhesive properties promote prolonged retention on the ocular surface and its excellent capacity to bind and retain a significant quantity of water aids in corneal hydration. SH also has a vital role in cellular
development, in controlling inflammation, and in promoting wound-healing. CD44 is a cell surface adhesion molecule for which SH is the ligand. Trauma and inflammation are associated with an increase in the expression of CD44. Recent research has shown in in vitro studies of human epithelial cells, that the main role of SH appears to be in promoting epithelial cell migration rather than either cell proliferation or expression of CD44. The benefit of SH as a topical therapy is believed to lie in the adhesion between CD44 on the cells and SH, which coats the exposed cornea, facilitating rapid epithelial cell migration and subsequent wound closure. Of note to practising clinicians is that, in April 2008, the hyaluronic acid category was approved for inclusion on the NHS Drug Tariff, enabling reimbursement.

SH has been shown to have beneficial effects in clinical trials. Johnson et al (2006) compared 0.1% and 0.3% SH to saline in moderate dry eye subjects and found that SH increased tear film stability and reduced irritation symptoms in comparison to saline. In a more recent study, the same research group established that, although drops containing 0.18% SH and 0.3% carbomer 934 were both effective therapies for moderate dry eye, the SH-containing formulation was marginally more effective therapeutically, and also less likely to cause blurring on instillation. Other researchers have evaluated SH in the treatment of moderate dry eye with superficial keratitis. In a comparison of 1% carboxymethylcellulose (CMC) and 0.18% SH, again both treatments showed therapeutic benefit, but CD44 expression was decreased only with the SH and subjects reported improved comfort levels with SH compared with CMC.

Other formulations incorporate oil, in the form of castor or mineral oil, in an attempt to supplement the tear film lipid layer. Also directed towards improving the lipid layer, is the recently developed liposomal spray containing phospholipids in a stable form. The spray is applied to the closed eye, and the liposomes spread onto the preocular tear film surface, restoring the lipid layer. (Figure 4) In a recent randomised, double-masked study, the liposomal spray was compared to saline. Results of this study showed that the liposomal spray, applied to the closed eye, significantly increased the thickness of the lipid layer and significantly improved tear film stability, measured non-invasively, for up to 90 minutes post-application.

Preservatives, particularly benzalkonium chloride (BAK) and the chelating agent EDTA, exacerbate ocular inflammation associated with dry eye. Therefore non-preserved preparations are preferable, especially for moderate-to-severe dry eye patients with increased levels of inflammation and repeated drop instillation. Preference for the convenience and reduced cost of multi-dose preparations, however, has driven manufacturers to develop products with less toxic preservatives, such as polyquad, sodium chlorite and sodium perborate. The latter preservatives ‘disappear’ on instillation, converting to non-harmful by-products, although care must be taken in severe dry eye patients in whom tear volumes are extremely low, as total degradation of the preservative may not occur.

Studies in the literature suggest that while most topical lubricants provide some relief, they do not entirely resolve dry eye signs and symptoms. There is also little evidence to show that there is one product significantly better than another. Most patients will state a preference for a particular product therefore it may be necessary to try several products before achieving maximal patient satisfaction.
Retention of tears

Punctal Occlusion
While permanent punctal occlusion may be attempted surgically (canalicular ligature, canaliculectomy, punctal tarsorraphy, ligature, and patching) or thermally (cauterity, diathermy and argon laser), the majority of punctal occlusion is temporary, using dissolvable or non-dissolvable punctal or intracanalicular plugs.

Short-term occlusion
Until recently, collagen plugs provided the practitioner with the ideal means of conducting a trial of punctal plugs. These temporary plugs, made of bovine collagen, are approximately 2mm in length and range from 0.2 to 0.6mm in diameter. (Figure 5) Once inserted into the canaliculus, and in contact with the tear fluid, the plug swells and blocks tear outflow. They are maximally effective over a period of approximately 3 – 5 days, dissolving completely within 7 – 10 days.

These collagen plugs composed of animal tissue, are still available for use in the US and some other countries, but in early 2005, were withdrawn from the UK market due to the unresolved concerns of the MHRA (Medicines and Healthcare Products Regulatory Agency – An Executive Agency of the Department of Health, UK) over Bovine Spongiform Encephalopathy (BSE). The resulting loss of CE mark on this product now prevents the distribution of all brands of collagen plugs in participating EU countries, including the UK. Manufacturers state that work is currently underway to develop a directly comparable synthetic replacement for collagen with a short duration of action but no such products are available at the current time. Unfortunately, practitioners must therefore rely upon the synthetic absorbable plugs as their temporary plug for trial purposes. The disadvantage with regard to use for trial is the extended duration of effect of these dissolvable plugs, which ranges between 2 and 6 months, as well as the increased cost.

Medium term occlusion
With their effect lasting for several months, synthetic absorbable intracanalicular plugs have applications in post-LASIK dry eye, which, for the majority of affected individuals, is a temporary phenomenon. The plugs are available in a range of diameters. (Figure 6)

Long term occlusion
Non absorbable punctal or intracanalicular plugs are designed to remain in place indefinitely, although they can be removed (with variable degrees of success) if deemed necessary. Most silicone punctal plugs are based on the design of Freeman, with a flange that sits exterior to the punctum, a narrower neck sitting within the punctal opening and a wider base that serves to occlude the canaliculus. (Figure 7) The flange allows the clinician to confirm that the plug is in place.
and enables straightforward removal if the need arises. A sizing gauge must be used to select the most appropriate size of punctal plug, as too large a plug risks extrusion and too narrow a plug risks insertion below the punctal ring. (Figure 8) Some patients are aware of mild irritation from the flange of these plugs when in place, and may prefer an intracanalicular style of plug. Silicone intracanalicular plugs (Herrick plugs, Lacrimedics Inc.) resemble golf tees in appearance, and on insertion sit at the narrowed portion of the canaliculus. (Figure 9) Removal, if necessary, is by irrigation only, but this is difficult to confirm and it has been reported that such plugs can become lodged and infected within the lacrimal sac, necessitating complex nasolacrimal duct surgery for removal. More recently developed materials for long-term occlusion include a hydrogel polymer (Form Fit™, Oasis Medical Inc., CA, USA), which is inserted as a rigid rod into the canaliculus where it rapidly absorbs fluid and takes up the shape of the canaliculus, occluding tear flow. Similarly, the SmartPlug (Medenium Inc., CA, USA) is supplied as a long narrow rod, for insertion into the canaliculus. This thermodynamic hydrophilic acrylic material then shortens in length and increases in diameter at body temperature, occluding the canaliculus.

Improvement in dry eye symptoms has been documented in up to 86% of patients fitted with punctal plugs. Signs of dry eye have also been reduced, including improved tear film stability, reduced corneal staining and decreased osmolarity. The risk of infection with properly fitted punctal plugs is small, but patients should be aware of relevant signs, and understand the importance of seeking advice should redness or pain occur. Before fitting, fully informed consent should be obtained for this relatively invasive procedure.

Care must be taken to select patients appropriately. Lid disease is a contraindication to punctal plugging, significantly increasing the risk of infection, therefore any concurrent blepharitis, for example, must be well controlled prior to considering this treatment modality. Punctal plugging is indicated for patients with a demonstrable aqueous deficiency. Those with poor tear quality leading to an evaporative dry eye, rather than a reduced quantity of tears, seldom experience relief with punctal plugging, and may even suffer epiphora.

Tear stimulation

Topically applied secretagogues, including diquafosol (which stimulates both aqueous and mucin secretion) and 15-S-HETE (a mucin stimulant) are currently under investigation by pharmaceutical companies, and may provide benefit to dry eye patients in the future. Currently available in the US, the systemically administered cholinergic agonists, pilocarpine and cevimeline, have been shown to improve signs and symptoms of dry eye, but the drug-induced side effects, particularly of pilocarpine, limit the popularity of these agents.
Anti-inflammatory Therapy

Inflammation is recognised to be a key component in the pathogenesis of dry eye. Anti-inflammatory treatments thus have enormous potential in the management of ocular surface disease.

Corticosteroids
Corticosteroids are potent anti-inflammatory agents, which directly regulate gene expression through traditional glucocorticoid receptor-mediated pathways, and interfere with transcriptional regulation of pro-inflammatory genes through non-receptor pathways. They have the ability to inhibit inflammatory cytokine and chemokine production, decrease synthesis of MMPs and cell adhesion molecules, and stimulate lymphocyte apoptosis. Clinical studies have reported improvement in dry eye signs and symptoms following corticosteroid therapy, without steroid-related complications, at least in the short-term. However, the significant risk of toxicity in the longer term, limits the usefulness of corticosteroids for the treatment of chronic dry eye.

Cyclosporin
The fungal-derived peptide, cyclosporin A (CsA), is a potent immunomodulatory agent, which inhibits T-cell activation and inflammatory cytokine production, through interference with cytoplasmic transcription, and also inhibits apoptosis. Clinically, CsA has been shown to reduce conjunctival rose Bengal staining and superficial punctate keratitis and to improve symptoms in moderate-severe keratoconjunctivitis sicca. Combined, the results of two independent Phase III clinical trials showed that, relative to the vehicle, 0.05% or 0.1% CsA significantly improved corneal fluorescein staining and the Schirmer test score with anaesthesia, both regarded as objective signs of dry eye disease. In the patients treated with CsA, 59% demonstrated increased Schirmer wetting with 15% exhibiting an increase of 10mm or more. In comparison, only 4% of the subjects treated with the vehicle showed this magnitude of improvement. However, while there appears to be a valuable role for CsA in the more severe forms of aqueous-deficient dry eye, the role in mild-moderate dry eye is less convincing. The commercial product, Restasis (Allergan Inc), was FDA approved in 2002.

Natural tear substitutes
The healthy tear film contains a number of components, which are critical in the maintenance of corneal and conjunctival integrity but, have yet to be successfully replicated or incorporated in a stable form, in synthetic ophthalmic products. Autologous serum, the product of whole blood that remains after clotting, contains components such as epidermal growth factor (EGF), vitamin A, transforming growth factor-β (TGF-β), fibronectin, substance P, insulin-like growth factor 1 (IGF-1), nerve growth factor (NGF), and other cytokines necessary for the proliferation, differentiation, and maturation of the normal ocular surface epithelium. Autologous serum eye drops have been shown in a number of studies to successfully treat severe dry eye across a range of ocular surface disorders. These include Sjögren's syndrome, graft-versus-host disease (GVHD), superior limbus keratitis, Stevens-Johnson syndrome, cicatricial pemphigoid, LASIK, neurotrophic keratopathy and persistent epithelial defects.
The production of autologous serum eye drops is labour-intensive and strict protocols must be followed in the selection of patients and in the preparation and storage of the drops.\textsuperscript{23} As a result, serum eye drops can be a relatively expensive option, with the cost per day being equated to that of a bottle of preserved lubricant.\textsuperscript{24} However, recent research, suggests that for those patients unable to obtain relief from maximal lubricant therapy and/or punctal plugging, autologous serum treatment is a management option worthy of consideration.

In individuals with end stage dry eye disease and no aqueous tear production, salivary submandibular gland transplantation may be considered. Following the combined maxillofacial and ophthalmic surgery, patients might expect comfort to be improved, and dependence on tear supplements to be reduced, but often no improvement in vision is observed.\textsuperscript{25}

**Tetracyclines**

Oral tetracyclines and their derivatives (e.g. doxycycline) are recognised both for their antimicrobial and anti-inflammatory properties. Decreased levels of toxic meibomian gland breakdown products are the result of the antimicrobial activity, which is believed to take effect through inhibition of staphylococcal lipase and lipolytic exoenzyme production.\textsuperscript{26} Administered in lower concentrations, the anti-inflammatory properties of the tetracyclines make them suitable for treatment of chronic inflammatory eyelid disease (meibomianitis), particularly that associated with ocular rosacea. Tetracyclines decrease the production of interleukin-1 (IL-1) and tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)), and decrease the activity of collagenase, phospholipase A\(_2\) and a number of matrix metalloproteinases.

**Eyelid therapy**

**Lid hygiene**

The use of lid scrubs is recommended for patients with blepharitis (seborrhoeic or staphylococcal) to reduce the inflammatory load. A number of sterile, single-use, lid scrub products are available. Also available is a hypoallergenic foaming lid cleanser (TheraTears SteriLid, Advanced Vision Research, MA, USA), which also contains tea-tree oil, to help control Demodex infestation.\textsuperscript{27} If a significant Demodex infestation is identified by cylindrical collarettes around the eyelash bases, a once weekly lid scrub using a 50% solution of tea-tree oil is recommended in addition to this daily lid clean. Patients must be reminded that lid hygiene is an ongoing therapy, which must be performed regularly, in order to maintain reduced symptoms. Once control is achieved in mild cases, it may be possible to reduce the frequency of treatment, but not cease treatment altogether.
Warming the meibomian secretions facilitates outflow in patients with meibomian gland dysfunction. Warm compresses can be fashioned in a number of ways, from a hot, damp washcloth to a warmed, muslin-covered river stone. An alternative is the commercially-produced MGDRx EyeBag (EyeBag Company, Halifax, UK). (Figure 10(a)) This is a pouch filled with flaxseeds which is heated in the microwave for 30 seconds and placed over the closed eyes for 5 minutes, prior to gentle eyelid massage to encourage flow of the meibomian oils onto the surface of the tear film. (Figure 10(b)) The use of warm compresses has demonstrated significant improvements in tear film stability and lipid layer thickness and a decrease in tear film evaporation rate. Other heat treatments include latent heat goggles, and a warm moist air device, both of which have been shown to improve tear film characteristics in dry eye patients.

**Topical antibiotics**

A mild topical antibiotic, such as fusidic acid 1% (Fucithalmic), may be indicated to help decrease staphylococcal infection. It will not eradicate bacterial infection, and while it may help to break the cycle of inflammation and reduce symptoms, it is a short-term solution and not a substitute for good eyelid hygiene.

**Tailor the therapy to the dry eye aetiology wherever possible:**

<table>
<thead>
<tr>
<th>Lid disease / lipid deficiency</th>
<th>Aqueous deficiency</th>
<th>Mucin deficiency</th>
<th>Ocular surface inflammation</th>
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</thead>
<tbody>
<tr>
<td>Blinking exercises</td>
<td>Tear supplements / hyaluronic acid</td>
<td>Mucomimetic drops / HP Guar</td>
<td>Autologous serum</td>
</tr>
<tr>
<td>Lid hygiene / warm compresses</td>
<td>Punctal occlusion</td>
<td>Secretagogues</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Tea tree oil (Demodex)</td>
<td>Cyclosporin A (US)</td>
<td>Mucomimetic gels / ointments</td>
<td>Tetracyclines (eyelid)</td>
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<td>Secretagogues</td>
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<tr>
<td>Lipid drops / sprays</td>
<td>Moisture retaining goggles/spectacles</td>
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<td>Tetracyclines</td>
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**Table 2:** Suggested treatments for specific tear film or ocular surface deficiencies or inflammation

There have been significant advances in the treatment and management of dry eye in recent years. A number of management strategies exist and these should be considered either alone, or in combination, as indicated from the results of careful tear film and ocular surface testing. As the pathophysiology of dry eye has become better understood, treatments are evolving from substances that simply hydrate the ocular surface to therapies that inhibit inflammation, stimulate natural production of tear constituents, and maintain ocular surface health and function. It is anticipated that as new therapies become available and are introduced to clinical practice, the quality of life for individuals affected by dry eye disease will continue to be improved.
Figure Legends

Figure 1: Exposed ocular surface area can be reduced significantly, (b) compared with (a), by lowering computer monitor height.

Figure 2: Bandage contact lenses may provide relief for some dry eye patients.

Figure 3: A typical range of artificial tear products on the Pharmacy shelf.

Figure 4: Liposomal spray, designed to enhance the tear film lipid layer, applied to the closed eye.

Figure 5: Collagen plugs, providing up to a week of intracanalicular occlusion, can no longer be used in the UK.

Figure 6: Synthetic absorbable intracanalicular plug (blue) immediately prior to insertion into the lower punctum. Occlusion with these plugs typically lasts between 2 and 6 months.

Figure 7: Silicone (Freeman style) punctal plugs provide permanent (although reversible) occlusion.

Figure 8: Gauging tool used to estimate the size of the punctum, prior to selection of the appropriate punctal plug.

Figure 9: Herrick plug (Lacrimedics Inc., USA) for intracanalicular occlusion.

Figure 10: Treatment for meibomian gland dysfunction. The warm compress (MGDRx EyeBag) is placed over the eyelids for several minutes (a) prior to gentle digital manipulation to enhance expression of meibomian fluid (b).
References


