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Review article

Rationale for 24-hour management of dry eye disease: A review

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ABSTRACT

The symptom severity of patients with dry eye disease (DED) varies over a 24-hour period. It is typically worse upon waking than later in the morning and deteriorates towards the evening. Substantial differences in the characteristics and physical properties of the tear film, such as levels of inflammation, pH, osmolarity, volume and stability, also exist between night (sleeping) and day (waking), and over the course of the day itself. Data on diurnal variation in symptom severity and tear film characteristics have been reviewed to recommend a management strategy that supports the various needs of patients with DED over a full 24-hour period.

Treatment strategies for DED must be matched to the variations in the severity of DED and to the environments that eyes are subjected to over a 24-hour period. While artificial tears are used to moisturise the ocular surface and reduce damage to the corneal epithelium during the day, gels are used at night-time; they are more viscous and have a longer ocular surface retention time than artificial tears. Several combinations of these products are currently available in tandem to support the 24-hour variation in tear film characteristics. The present review of published literature provides evidence that the approach of the daytime use of artificial tears to protect the eye from aggravating environmental factors in combination with the night-time use of gels to relieve more severe symptomatology. This, in turn, should provide optimal 'around-the-clock' DED management.

1. Introduction

'Dry eye disease (DED) is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles' [1]. DED is a chronic disease that affects substantially more women than men [2]. It is differentiated from other ocular surface diseases (symptomatic disease without signs of DED and asymptomatic disease with signs of DED), as outlined below, and subcategorised into aqueous-deficient and evaporative DED [1]. Aqueous-deficient DED results from reduced lacrimal secretion in the presence of a normal rate of tear evaporation, while evaporative DED results from excessive water loss through evaporation from the tear film in the presence of normal lacrimal function [3]. Meibomian gland dysfunction (MGD) causes low delivery of meibum to the ocular surface [4] and leads to a defective lipid layer of the tear film, making it a common cause of evaporative DED [3]. Aqueous-deficient and evaporative DED subtypes are not mutually exclusive [1]; a mixed phenotype has been observed in 1/3 of patients [5]. Patients with a mixed phenotype may exhibit more severe DED; patients may start with DED with either an evaporative or aqueous component that evolves to acquire both forms [6]. Sjögren's syndrome (SS), an autoimmune disease that attacks the lacrimal glands and reduces tear production, represents a particularly severe case of mixed-phenotype DED [3].

Symptomatic ocular surface disease without signs of DED and asymptomatic disease with signs of DED represent two entities distinct from DED [1]. Symptomatic patients without signs are categorised into patients with neuropathic pain and those with a preclinical DED state [1]. Asymptomatic patients with signs are divided into patients with reduced corneal sensitivity and those with a predisposition to developing DED, for example following ophthalmic surgery [1].

Patients with DED experience diurnal variation in the severity of their symptoms, which can range from mild to severe [7]. Symptoms and visual function are typically better in the morning and decline towards the evening [8–10]. Depending on the type of DED, symptoms may also be worse upon waking than over the following few hours [11–13]. Tear film composition and physical properties vary over a 24-hour period, with differences between night (sleeping) and day

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(waking) [14–21] and also over the course of the day itself (see next section) [22–25].

The majority of available data on the 24-hour variation in DED severity come from patients studied during waking hours, generally comparing morning with evening or focusing on the first few hours of waking. By contrast, there is a paucity of data collected from sleeping patients. In this review article, the available clinical and pathophysiological data on diurnal and (where available) nocturnal variation in DED severity will be reviewed. These data will then be used to suggest a management strategy that addresses the varying needs of patients with DED over a full 24-hour period, including during the under-researched night-time period. DED may be affected by contact lens use [2], so here, only studies of non-contact lens wearers will be considered.

2. Methods

In order to collect data on diurnal and nocturnal variation in DED severity, a literature search was performed. This literature search was conducted using PubMed, clinicaltrials.gov and Google as primary sources to investigate published and relevant data on the relief and treatment of DED over 24 h, supplemented by the review of abstracts presented at selected congresses (American Academy of Ophthalmology, Tear Film & Ocular Surface Society, European Society of Ophthalmology, Association for Research in Vision and Ophthalmology) from January 2007 to May 2017. Search terms were 'dry eye' with 'night', 'nocturnal', diurnal' or 'sleep'. Information was extracted by manual screening based on the inclusion of data on non-contact-lens-wearing patients with DED. Studies not identified by the formal searches were included at the discretion of the authors as appropriate.

3. Diurnal variation in DED symptomatology

Key studies that investigated changes in symptom severity over the course of the day ranged in size from small, exploratory investigations (n = 21) [8] to studies in larger cohorts (n = 259) [10]. Patient populations included in the different studies had a history of DED [8], with some studies including patients with symptoms of ocular discomfort [10] and others including patients with SS [9]. DED symptomatology and its changes in response to treatment may be assessed by objective ophthalmic measures, including best-corrected visual acuity (BCVA), and also by patient-reported measures, such as visual analog scales (VASs) [8–10,26]. VAS is a psychometric measuring instrument that is used to document subjective symptom severity in individual patients; patients report their experiences based on comparison with a visual rating scale, often a simple horizontal line with patients marking their severity from 0 (very poor) to 100 (excellent) and precise scores derived from measuring the position of the mark on the line [26]. Symptomatology affects quality of life [2] and is, therefore, an important assessment for patients with DED [27]. However, overall there is a poor correlation between subjective patient symptoms and objective clinical signs, such as those revealed by fluorescein-based tear break-up time (TBUT) and the Schirmer test [27]. Patients with DED commonly experience symptoms such as burning and stinging, soreness and irritation, foreign body sensation and blurry vision [28]. All studies described in this review had similar observations, with patients experiencing reduced visual function and more severe symptoms in the evening compared with the day; summarised in Table 1 [8–11,13].

3.1. Daytime vs evening

Objective evidence for differences in DED over the course of a day comes from a study of 21 patients with DED who underwent ophthalmic examinations and reported symptom severity using a VAS at two visits on the same day (one in the morning and another in the evening) [8]. Patients were found to maintain their BCVA for a significantly shorter

Table 1
Variation in DED symptoms over a 24-hour period.

Author	Study population	Observations	Key findings	Conclusion
Walker et al [8]	Patients with DED (n = 21)	Ophthalmic exam and VAS-reported symptoms, morning and evening	• Increased keratitis and conjunctival redness in the evening vs morning • Poorer self-reported function in the evening vs morning • Increase in irritation and decrease in comfort, evening compared with morning, more pronounced in DED patients	*DED symptoms are worse in the evening compared with daytime*
Dumbleton et al [10]	Patients with mild, moderate or severe DED (n = 145), asymptomatic controls (n = 114), assessed by OSDI questionnaire	VAS-reported symptoms daytime and evening		
Begley et al [9]	Patients with SS (n = 21), patients with non-SS KCS (n = 73) healthy controls (n = 28)	DEQ 2001 questionnaire ratings for within 2 hours of waking, and in the evening	• Most SS and non-SS-KCS patients reported moderate/severe symptoms in the evening but not in the morning • Controls reported few symptoms	
Bitton et al [11]	Patients with DED (scoring ≥ 14 on McMonnies questionnaire;n = 15), asymptomatic controls (n = 15)	Evaluation at 10 pm, 7 am, 8 am, 9 am, 10 am including VAS ratings (comfort, dryness, clarity of vision and grittiness)	• In patients with DED, VAS ratings were significantly poorer at 7 am vs 10 pm, improving between 8 am and 9 am; controls had higher scores than patients at all timepoints • More viscous tear film (elevated TMH) immediately upon waking in both groups • TBUT was low at 10 pm and 7 pm in patients with DED, higher and less variable in controls	*DED symptoms are worse on waking compared with later in the day*
Maissa et al [13]	Patients with DED (mean OSDI 17.7; n = 131, 48% were symptomatic)	VAS-reported comfort on waking, in the daytime, and in the evening	• Mean comfort VAS was highest in the daytime	

DEQ, Dry Eye Questionnaire; non-SS KCS, non-Sjögren's keratoconjunctivitis sicca; MGD, Meibomian gland dysfunction; OSDI, Ocular Surface Disease Index; SS, Sjögren's syndrome; TBUT, tear break up time; TMH, tear meniscus height.

period of time between blinks and take significantly longer to read from a list of words, coinciding with reporting greater limitations in visual function related to their DED symptoms (such as blurred or poor vision while reading) in the evening compared with the morning [8]. This was accompanied by a significant increase in keratitis and conjunctival redness from morning to evening [8]. In another study, among the 145 symptomatic participants and 114 asymptomatic participants (not considered to have DED at a screening visit) who did not wear contact lenses, VAS ratings of comfort and vision were lower in the evening compared with the day, while ratings of dryness, grittiness, stinging and irritation were higher in the evening compared with the day [10]. With respect to each symptom, irritation demonstrated the greatest amount of diurnal variation, with asymptomatic and symptomatic patients reporting respective daytime VAS scores of 10.3 ± 17.1 and 32.6 ± 25.6, and evening VAS scores of 12.1 ± 20.6 and 41.9 ± 26.8 [10]. Moreover, symptomatic patients started with a lower VAS comfort score than asymptomatic patients in the day (60.2 ± 24.4 vs 85.5 ± 16.1) and demonstrated a greater diurnal loss in comfort VAS score than the asymptomatic patients by the evening (−8.4 vs −3.8) [10]. In a study that compared patients with SS ($n = 21$) with non-Sjögren's keratoconjunctivitis sicca (non-SS KCS) patients ($n = 73$) and healthy controls ($n = 28$), both patient groups showed an increase in the number of patients who reported symptoms of moderate to severe intensity at the end of the day vs within 2 h of getting up in the morning; in comparison, the vast majority of controls did not show such symptoms during either period [9]. The morning-to-evening worsening of observed or patient-reported DED symptoms may potentially be explained by elements of the diurnal environment, such as air-conditioned offices and computer use [8]. Indeed, computer use has been associated with a significant decrease in blink rate and amplitude compared with silent primary gaze conditions in healthy individuals ($n = 25$), which could potentially lead to a worsening in symptomatology [29]. Blink rate is dependent on visual task [30]; the nature of tasks could be expected to vary over the course of the day and therefore impact blink rate (of note, blink rate increases in the evening [31], which could potentially alleviate some evening DED symptomology). Furthermore, one study found that the risk of DED was increased in young and middle-aged office workers who use a computer for an excess of 4 h per day ($n = 4393$) [32].

3.2. king and morning

Studies that investigated DED symptom changes following waking have generally included small patient populations ($n \leq 40$). These studies have used patient-reported measures to assess variation in symptoms and have been conducted in patient populations that were identified as having DED using symptom assessment questionnaires [11,13] or in a specific population of patients classified as having MGD [12]. Together, these studies present a general picture of symptoms that are worst first thing in the morning but subsequently improve over the next few hours in patients with DED (described below) [11–13]. Bitton *et al.* found that in patients with DED, comfort, dryness, clarity of vision and grittiness were significantly poorer upon waking at 07.00 than in the evening at 22.00; however, significant improvements were observed at 08.00 and 09.00 compared with 07.00 [11]. Measurements taken at 08.00 and 09.00 were similar to those taken at 22.00 [11]. In a second study that included 40 patients with at least mild DED symptoms (Ocular Surface Disease Index [OSDI] ≥ 13) who presented with mild to moderate anterior blepharitis or MGD, 80% reported that their 'eyelids were stuck together in the morning' upon waking [33]. In a further study of 11 patients with DED with mild or moderate MGD (OSDI ≥ 13), mean comfort VAS scores were 40.6 ± 16.6 within the first 30 min of waking, increased during the day to a peak of 58.6 ± 22.9, and then decreased between 18.00 and sleep to 45.6 ± 19.5 (no statistical comparisons were performed between different time points) [12]. These results are confirmed by a larger study of patients with DED (non-contact lens users; $n = 131$) that found a comparable pattern of change in comfort VAS scores [13]. To summarise the conclusions from these studies collectively, symptoms in those patients diagnosed with DED tend to be worse upon waking than later in the morning, with a subsequent deterioration towards the evening; poor comfort at waking is particularly prominent in MGD-associated DED [12].

3.3. During sleep

As mentioned, DED has not been characterised in the closed eye (during sleep); however, up to 5% of the general population may experience lagophthalmos (incomplete eyelid closure), [34] and this includes patients with DED. Lagophthalmos often leads to disruption of the corneal epithelium located between the eyelids; this could potentially contribute to patients' DED symptoms, which are typically then prominent upon waking [34].

4. 24-hour variation in the tear film

Composition of the tear film varies over a 24-hour period: changes in the level of inflammatory mediators, osmolarity and pH, as well as changes in tear volume and tear film stability, have all been demonstrated [14–21]. Along with the environmental factors mentioned previously, these may contribute to the worsened symptoms of DED in the evening compared with the morning.

4.1. Tear film composition

The composition of the tear film is substantially different during the day compared with the night [14–17,20,21]. Tears recovered from eyes that have been closed all night contain a significantly greater concentration of inflammatory mediators, including secretory immunoglobulin A (sIgA), albumin and complement components, compared with tears that have been recovered from open eyes during the day [14–17]. Overnight eye closure has also been associated with complement activation (a molecular immune response that causes the death of bacteria both directly, through lysing them, and indirectly, through recruiting immune cells to engulf and clear them [35]) and an increase in the recruitment of circulating neutrophils (protective immune cells [35]) from the bloodstream into the ocular film [15]. In addition to the marked increase in inflammatory components, tear osmolarity is significantly reduced and tear pH is more acidic in samples recovered after overnight eye closure compared with samples recovered from open eyes [20,21]. The differences in the composition of the tear film upon waking and throughout the day suggest that the composition changes during the night [11], with the increase in inflammatory mediators potentially serving to protect the closed-eye environment from pathogens [14], such as the gram-positive bacteria that accumulate overnight in the presence of reduced tear production and flow, and associated with the closed eye phase [18,36].

In a tear film study of 10 healthy individuals where tear samples were obtained at two different times of the day, tear film levels of sIgA significantly decreased ($p = 0.035$) from a mean of 2.7 mg/mL in the morning (09.00–10.00) to 2.5 mg/mL in the early evening (17.00–18.00) [22]. This decrease in the inflammatory mediator may potentially indicate that the accumulated proteins are stabilised throughout the day, following their production by plasma cells overnight [22]. It remains to be seen whether similar patterns of immunoglobulin accumulation are seen in patients with DED; the vast majority of studies into tear film composition have been conducted in healthy individuals, so there is a need for studies in patients with DED to confirm whether the 24-hour variation seen in healthy individuals is maintained or disrupted in DED.

Table 2
Available treatments for the management of DED over a 24-hour period: paired day and night options.

Manufacturer	Product	Marketed for		Ingredients (% w/v)												
		Day	Night	Carbo-mer	CMC	Emollient					Glycerine	HA	HPG	Retinol palmitate	Propylene glycol	TSP	Trehalose
						Light mineral oil	Liquid paraffin	Mineral oil	White petrolatum	White soft paraffin							
Alcon (Camberley, UK)	Systane® Balance [59]	✓	–					✓ Not specified					✓ Not specified		0.6		
	Systane® Nighttime Eye Ointment [60]	–	✓					3	94								
Allergan (Marlow, UK)	Optive Fusion™ [61]	✓	–	–	0.5						0.9	0.1					–
	Optive® Gel Drops [62]	–	✓	–	1						0.9	–					–
Bausch and Lomb (Kingston upon Thames, UK)	Artelac® Rebalance® [63]	✓	–	–	–							0.15					–
	Artelac® Nighttime Gel [64]	–	✓	0.2	–							–					–
	Soothe XP-Xtra Protection Emollient (Lubricant) Eye Drops [65]	✓	–			1.0		4.5									
	Soothe Night Time Lubricant Eye Ointment [66]	–	✓					20	80								
Farmigea (Teddington, UK)	HydraMed [67]	✓	–									0.2				0.2	
	HydraMed Night [68]	–	✓				✓ Not specified			✓ Not specified				250 (IU/g)			
Optrex (Slough, UK)	Rehydrating Eye Drops [69]	✓	–	–	–							✓ Not specified					–
	Night Restore Gel Drops [70]	–	✓	–	–							0.4					–
Thea Pharma-ceuticals (Keele, UK)	Thealoz Duo® [71]	✓	–	–	–							0.15					3
	Thealoz Duo® Gel [72]	–	✓	0.25	–							0.15					3

CMC, carboxymethylcellulose; HA, hyaluronic acid; HPG, hydroxypropyl guar; IU, international unit; TSP, tamarind seed polysaccharide.

4.2. Tear volume

Work has shown that in the healthy eye, tear volume is reduced immediately upon waking compared with later in the day, suggesting that (in the healthy eye) aqueous tear secretion is reduced in the night compared with the day [18]. Given that the rate of tear flow under normal physiological conditions in animals and humans is reduced by anaesthesia, Baum suggested that reduced night-time tear production results from a reduction in the cortical stimulation of the lacrimal gland when the eyes are closed at night compared with when they are open during the day [18]. In contrast to these results on tear film volume upon waking, Bitton *et al.* measured tear meniscus height (TMH) upon waking and at four other time points and found that TMH was greatest immediately upon waking, with few differences being observed between the other measurements taken at 08.00, 09.00 and 22.00 [11]. Bitton *et al.* suggested that upon eye opening, neuronal stimulation at the ocular surface by environmental factors such as ambient air temperature, humidity, drafts, air debris and other irritants could increase the stimulation of the lacrimal gland and, in turn, increase tear production [11]. In addition to being affected by changes in the production of tears by the lacrimal gland [11,18], open-eye tear volume is affected by water lost through evaporation [37]; ocular surface desiccation results from a defect in one or both of these processes (lacrimal gland tear production and/or evaporation) [3].

4.3. Tear film stability

Most studies have been conducted in healthy subjects, and when analysing the diurnal variation in these individuals, it is important to remember that they have longer TBUTs and consequently greater team film stability than patients with DED [38,39]. The stability of the tear film varies diurnally, with stability being reduced later in the day compared with in the morning [24]. Tear film stability can be measured both invasively and non-invasively; patterns of change in TBUT are consistent across the two methods [24].

Tear film stability appears to be low early in the morning; when non-invasive TBUT was measured every 2 h from 08.00 to 20.00 in healthy individuals, values were lowest at 08.00 and tended to plateau between 10.00 and 12.00 [25]. The authors suggested that the lowered stability of the tear film at 08.00 may have been due to the direct pressure of the eyelids on the corneal epithelium during sleep, with stability rising later in the morning following the gradual removal of the contaminants that were acquired during sleep [25].

Bitton *et al.* compared tear film stability and tear ferning in asymptomatic controls (considered not to have DED, $n = 15$), sleeping patients with DED ($n = 15$) and patients with DED following waking ($n = 15$). Tear film measurements were obtained before sleep at 22.00 and immediately upon eye opening in the morning at 07.00, 08.00, 09.00 and 10.00 [11]. In both DED groups, the tear film was found to be more viscous (elevated TMH) immediately upon waking compared with all other time points, with viscosity falling approximately 1 h later. A highly viscous tear film upon waking may account for why some patients find their eyelids are 'stuck together' upon waking [33] and supports observations of the tear film containing an accumulation of overnight-produced proteins rather than being predominantly aqueous [14–17]. In patients with DED, non-invasive TBUT was lowest at 22.00, with a mean ± standard deviation TBUT of 5.7 ± 2.9 s, remained low at 07.00 the following morning (6.9 ± 2.9 s) and increased at 08.00 (9.9 ± 5.0 s) ($p = 0.004$, 08.00 vs 22.00) [11]. In controls, TBUT was higher and showed less variation than in patients with DED. Furthermore, a degraded tear ferning pattern (indicative of an aberrant tear film) was observed in patients with DED and in controls at 07.00; this recovered towards pre-sleep values within an hour of waking [11]. Given that the majority of patients only had moderate symptoms of DED, the authors suggested that this may have accounted for the similarity of the results between the patients and controls. The results of this study suggest that the properties of the tear film undergo a change during extended periods of eye closure; these changes are reversed within an hour of eye opening.

5. Available treatments for the management of DED over a 24-hour period

Treatment strategies for DED must be tailored to individual patients and matched to the variations in the severity of DED, the challenges associated with activities undertaken (e.g. computer use) and in the environments that eyes are subjected to over a 24-hour period [8–13].

Several products are currently available in the market to provide 'around-the-clock' relief from DED. Even though the various treatments available are based upon different active and inert ingredients, they are typically a combination of an artificial tear for daytime and a drop with gel consistency for night-time use (Table 2) [40].

5.1. Daytime treatment: artificial tears

Artificial tears represent a daytime treatment option with minimal side effects and are recommended as first-line therapy to manage symptoms that are mild in severity (additional products may be added to the treatment regimen when symptoms are not adequately controlled) [28,40,41]. Artificial tears are used to moisturise the ocular surface and reduce damage to the corneal epithelium [41]. The human studies discussed in the subsequent paragraphs have not stated that they are daytime specific, but they have been carried out in awake subjects.

Hyaluronic acid (HA) is commonly found within artificial tears (Table 2). It is a naturally occurring lubricant found within the eye [42] that has been shown to remain bound to the ocular surface for up to an hour [43] and to protect ocular cells from dehydration [44,45]. HA has non-Newtonian shear-thinning properties, which mean that viscosity is increased between blinks and reduced during blinks [46]; HA also stabilises the ocular surface epithelial cell barrier and has been shown to increase tear film thickness [47,48].

Carboxymethylcellulose (CMC) is another ingredient found in some artificial tears, either alone or in combination with HA (Table 2). CMC has mucoadhesive properties that enable it to remain bound to human corneal epithelial cells for up to 2 h [49]. While Baudouin *et al.* found that artificial tears containing CMC were non-inferior to those containing HA in terms of efficacy and safety [50], evidence suggests that combining CMC and HA in treatments is beneficial [51,52]. She *et al.* observed significantly improved corneal fluorescein staining and goblet cell retention (goblet cell loss is indicative of chronic ocular inflammation and cell hyperosmolarity) in mice treated for 28 days with eye drops that contained CMC + HA compared with mice treated with eye drops containing HA or CMC alone [52]. Furthermore, Simmons *et al.* showed that a formulation containing both HA and CMC led to significantly greater improvements in a patient-reported score for DED symptoms after 90 days of use compared with a CMC-only formulation [51].

Hydroxypropyl-guar (HPG) is a non-ionic polymeric thickener [40] added to some drops, including in combination with propylene glycol (PPG) in a lipid-based artificial tear (Table 2). The high molecular weight (1000–5000 kDa) of HPG serves to prolong the retention of the PPG on the ocular surface [53]. Other aqueous-based artificial tears exist that contain HPG in combination with both PPG and polyethylene glycol (PEG) [53]; the therapeutic benefits in patients with DED have been shown in a number of studies. For example, artificial tears that contain HPG, PEG and PPG have been associated with a 47.1% improvement from baseline in corneal staining over 42 days [54]. In another study, TBUT was significantly improved in patients treated with HPG, PEG and PPG-containing tears compared with CMC-containing tears, suggesting that the former combination may be superior in terms of improvements to the stability of the tear film [55]. Improvements in

ocular irritation scores have also been noted following treatment with HPG-, PEG- and PPG- containing artificial tears in an open trial of patients who complained of dry feeling eyes [56].

Tamarind seed polysaccharide (TSP) has been added to some artificial tears to improve the uniformity of the tear film [57]. TSP has a similar structure to the conjunctival transmembrane mucin (MUC1); MUC1 is thought to convert the corneal epithelium from a hydrophobic to a hydrophilic surface, thereby enabling the distribution of the tear film over the cornea [57]. In a study that compared artificial tears containing TSP with those containing HA, both formulations demonstrated optimal tolerability, while statistically significantly greater improvements from baseline were noted for symptom scores related to trouble blinking, ocular burning and foreign body sensation for TSP-containing tears [57]. HA and TSP combination tears have also been studied; these have been shown to be as effective as CMC-containing tears at improving TBUT and OSDI measurements [58].

Osmoprotectants such as trehalose or glycerol may be added to artificial tears to protect the eye from hyperosmolarity and, in turn, reduce inflammation and associated cell damage [73]. Glycerol is a polyol that has been shown to have osmoprotective effects in corneal cells *in vitro* [74]. Trehalose stabilises cell membranes by reducing the amount of water on the surface of a protein, which, in turn, protects corneal epithelial cells from dehydration and death by desiccation [75]. Wozniak *et al.*showed that the tear film thickness was significantly greater in 60 patients with moderate to severe DED following treatment with a combination of trehalose and HA than with HA alone, suggesting that the two ingredients may act synergistically [76]. In a mouse model of DED, trehalose has been shown to stabilise the tear film through downregulating proteins that destabilise the mucin layer of the tear film [77].

In addition to aqueous artificial tears, given that DED is commonly caused by the excessive evaporation of water in response to MGD and a defective lipid layer of the tear film, lipids such as phospholipids, fatty acids and triglycerides have been added to many artificial tears in recent years; the benefits of lipid-based artificial tears has been observed in patients with DED [3,4,40]. Lipid-containing drops are formulated as emulsions [40]. Various studies have demonstrated that lipid-based artificial tears can improve the signs and symptoms of DED. For example, Korb *et al.*compared the effects of two different lipid-containing artificial tears and observed a significant increase in lipid layer thickness from a baseline of ~60 nm up to almost double after a single drop application [78]. In a study conducted by Simmons *etal.*, significant improvements in OSDI symptom scores and TBUT were noted in patients who were treated with both lipid-containing artificial tears and aqueous artificial tears, with no significant differences reported between the two [79]. Additionally, in a study that compared a CMC-containing drop and added lipid with a glycerine drop and added lipid, evaporation and OSDI score were significantly reduced and improved, respectively, in patients who received the added-lipid formulations compared with the CMC-only drop [80].

5.2. Overnight treatment: gels and ointments

As shown in Table 2, gels and ointments are often marketed as the 'night-time' portion of a 24-hour treatment strategy [40]. Gels are more viscous than artificial tears, which provides the advantage of longer retention time on the ocular surface, and are thereby recommended for night-time use [81]. Gels may cause blurring of vision, which is not a problem when they are instilled just before sleep for night-time treatment [82]; however, one potential drawback is their negative effect on the viscosity of the tear film upon waking. Night-time gels must be compatible with the overnight osmolarity of tears [21]. Overall, fewer studies have been conducted on eye gels than on artificial tears.

Night-time gels and ointments have similar active ingredients to their daytime counterparts (Table 2), with adjustments to the formulations to increase viscosity (for example, increased CMC in Optive® Gel Drops vs Optive Fusion™ [Allergan, Marlow, UK] and increased mineral oil in Soothe XP-Xtra Protection Emollient [Lubricant Eye Drops] vs Soothe Night Time Lubricant Eye Ointment [Bausch and Lomb, Kingston upon Thames, UK]). As with daytime treatments, night-time-targeted gels contain multiple active ingredients to improve treatment response. For example, a gel containing CMC 1%/glycerine 0.9% was compared with a CMC 1%-only gel in 188 patients with moderate to severe DED. Patients treated with CMC 1%/glycerine 0.9% demonstrated improvements from baseline in symptom score, corneal staining and TBUT earlier (at Day 7) than patients treated with CMC 1% gel (at Day 30) [83].

Carbomers may also be used in eye drops/gels to increase viscosity and have been shown to improve TBUT and subjective symptoms compared with baseline in patients with DED [84,85]. However, there is a suggestion that HA may be preferable to carbomer. In a canine model of DED, switching from a carbomer-containing tear replacement to an HA-containing tear replacement resulted in significant improvements in ocular surface health and discomfort [86]. In terms of safety, local allergic reactions were observed in a minority of patients following treatment with carbomer-containing gel [85]. These were not seen in trials of a CMC-containing gel, in which the most common adverse event was a transient blur in vision [83].

Although no clinical data are available for night-time use of any of the gel formulations described above, it is possible to suggest that using a product with a more viscous composition than 'daytime' artificial tears may provide longer lasting lubrication and help to relieve the signs and symptoms of DED overnight and upon waking. While various combinations of active ingredients have been compared, it is important to note that there have been no head-to-head studies of the formulations in Table 2, so choice of product may be guided by the eye care practitioner, patient preference, and tolerability. In addition, there have been no formal studies of 24-hour management strategies (artificial tears followed by gel drops at night) compared with daytime or night-time treatment only, and such studies would be extremely valuable in identifying the best treatment options for patients, and quantifying their benefits.

For patients with lagophthalmos, a 24-hour management strategy is also recommended, using artificial tears during the day and ointment at night [34]. An improved and more rapid response to the ointment may occur if the ointment is used in combination with techniques such as taping the eyelids or applying external lid weights to hold the eyes closed during sleep [34]. Covering the ocular surface should, in turn, help reduce the likelihood of developing symptoms of DED [34].

6. Recommendations for 24-hour management of DED

Over a 24-hour period, the fluctuating severity of symptoms of DED may be addressed via the use of paired treatments. During the day when DED symptoms may be less severe than later in the evening/night, an artificial tear treatment can be used. This review has shown that symptoms are worst, tear production and film stability are reduced and inflammation is increased in the eye in the evening and upon waking [8–25]. Therefore, a more viscous gel treatment, which will stay on the eye for longer, may be warranted for night-time use to improve ocular surface protection in the absence of aqueous tear production during sleep [18] and provide the maximum amount of symptom relief and protection against desiccation at a time when it is not possible to re-apply treatment as often as during the day [40]. Based upon the authors' personal experience supported by the findings of the current review, the following approach for 24-hour management of DED is recommended:

- Artificial tears should be used early, upon the onset of symptoms
- CMC- or HA-only artificial tears should be considered as a first line of treatment or for mild DED. If symptoms are not resolved by this, a CMC-HA combination artificial tear, or a CMC- or HA-based tear

incorporating a thickener, osmoprotectant, or added lipid, may be used [40]
- Artificial tear application should be customised and used on waking, in the evening, and prior to exposure to factors that aggravate symptoms, such as being in a dry environment or using a computer for long periods of time
- Gels should be used to provide overnight symptom relief and applied just before going to bed
- More severe cases of DED require more intense management of symptoms, for example, patients with very severe DED may require systemic anti-inflammatory agents or surgery [40]

7. Conclusion

To manage the symptoms and clinical signs of DED over a 24-hour period, an artificial tear should be used during the daytime in conjunction with a gel at night to best protect the ocular surface. This combination of treatments is compatible with the distinct differences in the characteristics of the tear film between the night-time and daytime and should, therefore, provide optimal management of DED 'around the clock'. Further research into the variation in symptomatology and tear film characteristics between the day and night, and environmental influences on these, may generate better insight into how DED should be best managed over the course of a 24-hour period.

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