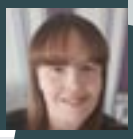

COMPETENCIES COVERED

DISPENSING OPTICIANS
Communication, Standards of Practice, Ocular Examination, Ocular Abnormalities

CONTACT LENS OPTICIANS
Communication, Standards of Practice, Ocular Examination

OPTOMETRISTS
Communication, Standards of Practice, Ocular Examination, Ocular Disease

This CET has been approved for 1 point by the GOC. It is open to all FBDO members, and associate member optometrists. The multiple-choice questions (MCQs) for this month's CET are available **online only**, to comply with the GOC's Good Practice Guidance for this type of CET. Insert your answers to the six MCQs online at www.abdo.org.uk. After member login, go into the secure membership portal and CET Online will be found on the L menu. **Questions will be presented in random order**. Please ensure that your email address and GOC number are up-to-date. The pass mark is 60 per cent. The answers will appear in the January 2021 issue of *Dispensing Optics*. The closing date is 9 December 2020.

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Dry eye

Recent evidence surrounding the lack of correlation between **signs and symptoms**

By Clare Hayes FBDO CL SFHEA

Eyecare practitioners (ECP) see patients with varying degrees of minor to moderate dry eye in practice daily. Whatever the level of experience a practitioner has, we will all have experienced the common scenario where we see a patient who has intense symptoms leading to distress, but little in the way of signs that would support the severity reported. We may also see the opposite of this: patients presenting with multiple signs but few or no symptoms. These situations can be very difficult for the practitioner to manage.

Dry eye disease (DED) affects a large portion of the population and although it is difficult to ascertain exact numbers, the Dry Eye Workshop II 2017 (DEWS II)[1] reports global prevalence as between five and 50 per cent – and as high as 75 per cent if based on signs alone. We know that DED can be unique to the individual but, as practitioners, we rely on the signs to indicate the basis for the dry eye. Fundamentally, is the DED aqueous deficient dry eye (ADDE) caused by an aqueous deficiency, leading to an unstable tear film that may arise from a number of causes including age or poor lacrimal production[2,3] – or evaporative dry eye (EDE) possibly due to an insufficient lipid layer[4]? Determing the classification enables us to target management solutions.

The DEWS II study was published in 2017 and represents a watershed moment in our understanding of DED. Many questions have been answered and clarity found. However, as DEWS II acknowledges, there is still no definitive sign that is present in all patients, and there is no agreed explanation as to why there is sometimes a lack of correlation between signs and symptoms.

This article will explore the post DEWS II evidence base to see whether further understanding in this area has been gained, and how this relates to ECP's routine practice.

WHAT IS DRY EYE?

The most recent definition of DED comes from DEWS II[1]: *"Dry eye is a multifactorial*

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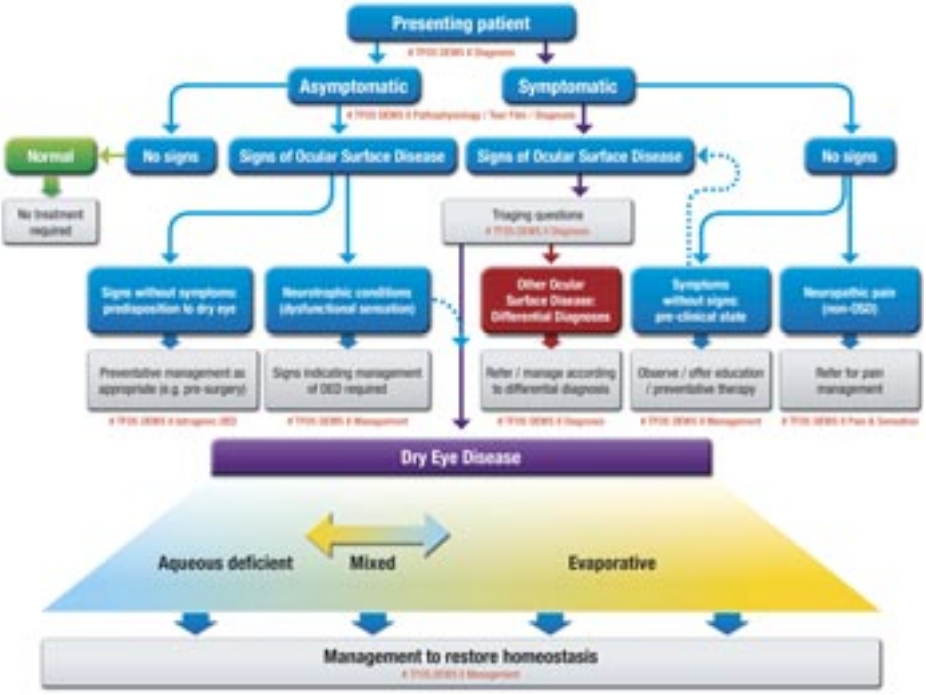

Figure 1. Dry eye disease classification taken from the TFSO DEWS II definition and classification report 2017 (courtesy of Professor James Wolffsohn)

disease of the ocular surface characterised 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."

Fundamentally, DED is generally considered to be a symptomatic disease resulting from poor tear stability and hyperosmolarity of the tear film leading to ocular inflammation[1,2]. DEWS II uses clinical signs to make the distinction between a patient having DED and the lack of signs as the patient being in a pre-clinical state, or the discomfort being of neuropathic origin.

It is important that a practitioner is aware of the type of DED their patient may have in order to inform the management of the condition[5,6]. DEWS II provides a table to aid in the classification (**Figure 1**). However, DEWS II also reports that the classifications of DED are not mutually exclusive, and exist on a continuum with the patient possibly moving between classifications and having overlap.

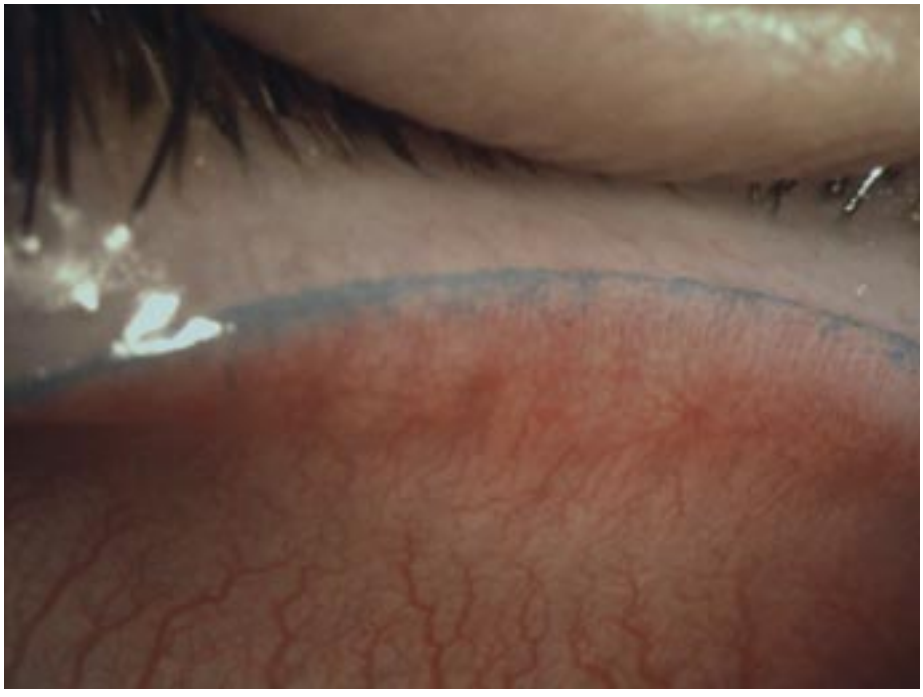

Figure 2. Lid wiper epitheliopathy (courtesy of Brian Tompkins)

Dry eye symptoms include mild irritation, gritty, watery eyes, redness, discomfort, pain and sometimes, blurred vision[7,8]. Moderate to severe cases may lead to difficulties in performing everyday tasks[9], poor general health and depression[1] leading to a detrimental effect on a person's quality of life[10]. This condition also has a financial burden on the patient and society[1].

Generally accepted clinical signs include reduced tear break-up time (TBUT), blocked meibomian glands, poor quality meibum, corneal and/or conjunctival staining, lid wiper epitheliopathy, reduced visual acuity, reduced contrast sensitivity and poor tear osmolarity[4,9].

There are many objective tests used to indicate DED and its severity. Although there is currently no gold standard test[8], TBUT is considered to be a reliable indicator of the presence of DED[11], as is corneal and conjunctival staining[12]. Both TBUT and corneal and conjunctival staining are indicators of desiccation, which is believed to correlate closely with DED[2]. Both of these tests are routinely done within the practice setting, and are often the first tool a practitioner uses to diagnose DED. An examination of the meibomian glands for blockages is also required. Blockages of the meibomian glands can lead to an interruption in the lipid layer, exacerbating evaporation.

DEWS II has recognised the potential role of tear osmolarity in DED. Hyperosmolarity is an indicator of interrupted homeostasis and is considered a key and potentially defining feature of DED[1]. This can be measured by collecting a sample of tears and using an analyser to give a reading. Whilst it is recognised that this is a useful test, it is not routinely done in practice as it can be cost prohibitive outside of a research or specialist arena[1].

Lid wiper epitheliopathy (LWE) (**Figure 2**) has also been highlighted as a sign of DED[14]. The lid wiper is responsible for spreading the tears across the ocular surface[15]. LWE is believed to arise from friction between the lid in contact with

the ocular surface due to a lack of lubrication[16]. It has been shown that LWE is present in up to 88 per cent of symptomatic DED patients[17] – and has been demonstrated to correlate with dry eye questionnaire scores and non-invasive tear break up time[18].

Whilst further research is needed into the role LWE plays in DED, Efron *et al* (2016)[16] postulate that LWE could be the basis of the symptoms of DED – and could go as far as to account for the lack of other commonly associated signs in symptomatic patients.

Patient-reported symptoms generally have equal or greater weight than signs alone in the practitioner's decision to diagnose and manage the patient as having DED[19]. In order to assess symptoms in a clinical manner, a patient questionnaire may be used. There are many in use currently, but perhaps the most commonly used in practice is the Ocular Surface Disease Index (OSDI)[19,20]. The questionnaire uses 12 questions that focus on vision and asks the patient to score each statement from 'None of the time '(1) to 'All of the time' (4) and then uses a formula to generate an overall mark from 0 to 100. Normal is considered to be 0 to 12, mild 13 to 22, moderate 23 to 32 and severe 33 to 100[21].

POST DEWS II EVIDENCE

It has been three years since the seminal study DEWS II was published. From this study, ECPs gained greater insight into DED and led to many changing areas of our practice and some ECPs to specialise in dry eye.

A search of literature published between 2017 to 2020 was conducted to determine what new information has been published on the subject of the discordance between signs and symptoms that confounds the practitioner so. Only a handful of studies have been published during or since 2017 so there is not much new information available, but what can be found is very enlightening.

In September 2018, Ngo *et al*[22] published results of a small sample study of 20 symptomatic and 20 non-symptomatic women. The study recruited female participants between the ages of 46 to 73. This choice meant that the results they found related to two of the groups considered most at risk of DED – females and older patients – although the groups were not broken down into age categories meaning a deeper consideration of the results and age were not possible.

The participants completed the OSDI and were then assessed for TBUT (non-invasive), corneal staining, LWE and Marx line placement. The participants also underwent an eyelid margin assessment and meibography. A Schirmer test was conducted and each participant had their visual acuity recorded.

It was found that the symptomatic group showed higher amounts of corneal staining, had more blocked meibomian glands, poorer meibum quality and lower TBUT than the non-symptomatic group – but the differences did not meet a statistically significant threshold. It was also found that, whilst LWE is believed to play a part in dry eye[14], this was not supported in the findings.

The study found no statistically significant linear correlation between any of the clinical tests with the reported symptoms, but did show there was an association between corneal staining and meibum quality – and noted that the symptomatic group generally did exhibit a higher number of clinical signs than the non-symptomatic group.

A recently completed study in Ghana focused on 212 first-year university students, ranging in age from 17 to 35 years, with a view to investigating the association between subjective DED tests and patient reported symptoms in the younger population[23].

The participants were asked to complete the OSDI then undergo visual acuity measurement, a contrast sensitivity test, assessment of TBUT with fluorescein, a corneal staining check, and an examination of the meibomian glands to determine expressibility and quality of oil expressed.

They found that all participants had an OSDI score suggesting mild or above dry eye. However, only blink rate and contrast sensitivity showed any significant correlation between the results and the OSDI score. The authors theorised that the contrast sensitivity reduction was in part due to the corneal staining seen in most participants[23]. These findings support previous results linking blink rate to dry eye[4]. The study found, unsurprisingly, that as the blink rate increased, the OSDI scores improved. They found no significant correlation with any other tests.

The Ghana study adds to the existing body of knowledge in several ways. It is one of the few studies to date looking at a sample of younger patients in Africa[23]. Although this was not the goal, by taking increased age out of the study, it has allowed further consideration of the results without this recognised risk factor for the condition[1].

However, the study limited itself by focusing solely on students. This may be relevant as it is conceivable that the lifestyle and visual demands on a student, particularly computer screen use, do not accurately reflect the population as a whole. This would give an unintended bias to the results, as it has previously been reported that there is an increased risk of DED with sustained reading and electronic devices[24].

Notably, given the dates of these two studies and the current awareness of the role of hyperosmolarity in dry eye[1], no osmolarity tests were conducted thus missing an opportunity – as it has been reported that tear osmolarity is the best measurement of DED and correlates with disease severity[25,26]. However, it should be recognised that this correlation is disputed by some[27]. Further, the Ghanaian study did not consider the role of the lid wiper and did not assess for LWE.

The contrast sensitivity findings of the Ghanaian study are typically one of the least reported signs in the literature. These findings may indirectly link to the findings of Bakkar *et al* (2016)[28] in a cross-sectional study of 1,039 subjects in Jordan asked to complete the OSDI.

Fifty-nine percent of participants reported scores of 20 or above and were classified as having DED. Of those participants, 70 per cent reported light sensitivity. Whilst these are different symptoms, the possibility exists that both are related to the dry dusty conditions, perhaps influencing corneal staining leading to these visual symptoms, and the climate of the regions in which the studies were conducted.

The study only used the OSDI and not any objective signs, therefore, aside from this being one of few DED studies in the region, it adds little valuable evidence to the subject other than to highlight that local environmental factors may play a role.

Whilst there is an almost universal agreement that there is often a lack of correlation, there is little research recent research into the reasons for the discordance between signs and symptoms in dry eye patients.

In the first study of its type, Vehof *et al* (2017)[29] looked at 648 participants in an eye clinic who scored 13 or above on the OSDI and had been diagnosed as having dry eye by an ophthalmologist.

The participants were given a questionnaire in a bid to determine comorbidities between health conditions and dry eye. The questions covered lifestyle factors such as computer use, contact lens and spectacle wear. The participants had to answer in-depth health questions on the questionnaire, and were asked to qualify their health from a range of 'bad' to 'excellent'. An ocular exam was also conducted to assess clinical signs.

The findings showed that subjects with Sjörgen's disease, graft versus host disease (GVHD) and those of increased age showed lower subjective OSDI scores than the signs would suggest. Those subjects with conditions resulting in chronic pain, irritable bowel syndrome, atopic patients and those with depression resulted in higher symptom scores than the signs would seem to support. In particular, those with chronic pain and those with atopic disorders showed a 30 and 20 per cent increase respectively.

Vehof *et al* suggest that the increased OSDI scores for atopic subjects could be due to these patients having a more highly sensitised cornea, thereby reporting symptoms at an earlier point than someone without. There is no independent evidence as yet to support this theory, however, a study in 2018 also theorised that some patients have a hypersensitive cornea and linked this to a general hypersensitivity to pain[30].

There is evidence to suggest that dry eye symptoms of pain and discomfort may indicate neuropathic ocular pain due to damage of the somosensory pathways[5,31,32]. This may account for the discordance observed in subjects with chronic pain conditions. It is suggested that the increase in DED symptoms compared to signs could be likened to those processes in neuropathic pain – and even that DED itself may be for some people, another form of neuropathic pain[32].

Vehof [et al] (2017)29 did not link their results to previous findings showing that the severity of DED reduces corneal sensation following repeated corneal disturbance[24] – thus leading to the logical conclusion that the signs of these conditions would be more severe than the symptoms indicate as the condition becomes more severe. GVHD is also shown to have an impact upon the lacrimal gland and conjunctiva[33].

In a further study looking at dry eye amongst military veterans, a link was found between increased symptoms and post-traumatic stress disorder[31], which could go towards supporting findings that depression was linked to increased symptoms. However, as patients with chronic pain may suffer from depression also[33] it is not possible to reliably separate these two factors in any of the studies.

A separate study that Vehof *et al* published in 2018 sought to determine if the clinical evidence supports the concept that females are more prone to dry eye and increased symptoms, and the possible reasons why[34]. It was found that in some cases, women reported up to 40 per cent greater symptoms compared to signs, particularly those induced by the environment such as wind and air-conditioning, along with increased light sensitivity.

This study demonstrated that females have a higher sensitivity and a lower threshold for pain, and that the female cornea is more sensitive, linking this to female hormone production. These findings are supported by studies that show females are more at risk of chronic and neuropathic pain[28]. Some studies do support the idea that the female cornea is more sensitive compared to males, although this is by no means universally accepted.

Recent research seems to indicate that the corneal surface de-sensitises with age thus leading to greater signs than symptoms would indicated should be expected[29,30]. From an ECP point of view, this is useful knowledge.

Knowing the cause of dry eye (or classification) aids the clinician in advising on the best management option[5,6,13]. A study in 2018 looking at dry eye drops chosen based on clinical indications noted that whilst some drops had a greater impact on signs, they had less impact on symptoms – and often they were not necessarily the participant's preferred choice[6].

This study shows that if the clinician is aware of the key ingredients of the drops or gel they recommend, they have a greater chance of relieving the symptoms the patient experiences along with the signs when and if they correlate. It was also shown that, sometimes, the clinically preferred management may not be the one that gives the best subjective outcome for the patient.

This research also highlights that not only is there a difference between reported symptoms and observed dry eye signs as supported by the literature, the patient factor cannot be discounted. This means that the management offered to the patient must offer tangible benefits in order to be worthwhile.

SO, WHAT HAVE WE LEARNED SINCE DEWS II?

Neither DEWS II, nor any of the research since, has been able to provide a definitive clinical sign of dry eye that correlates with patient reported symptoms. The explanations offered for the disparity by Vehof *et al*[30] go some way towards explaining why they exist, but do not offer any solutions.

An awareness of the link between heightened symptoms and chronic pain conditions, depression and the potential female/pain sensitivity outcomes, can aid the ECP – if only to remind them that perhaps the best tool currently at their disposable is a reliable questionnaire, such as the OSDI, followed up by targeted questions to gather more information on what has been highlighted.

The literature pre-DEWS II, and DEWS II itself, would seem to indicate that tear osmolarity[25] and the lid wiper[16] are the most reliable indicators of dry eye and may provide the missing piece to link signs and symptoms. However, the research is by no means conclusive. Sadly, recent research has not considered both of these indicators together.

Perhaps from a clinical perspective, it could be argued that all of this is secondary when presented with a patient who is experiencing symptoms, and who requires management regardless of clinical signs. From a pragmatic standpoint, clinical signs may only be of use to the clinician in

order to categorise the type of DED in order to determine management.

Some studies[8,24,25] advocate the value of an approach that considers all of the signs and symptoms a patient may exhibit and feel; each is relevant and should not be disregarded if the rest of the information is contradictory. They suggest a composite score system whereby each sign and symptom is considered and given a score; this totals up to a final number that gives an overview of the patient as a whole. This concept accounts for the fact that one sign may be directly influenced by another[8].

Another argument suggests that the severity of DED exists on a continuum, and perhaps it is the patient's place within that continuum, based on both signs and symptoms, that should define the severity rather than a fixed distinction[25].

Patients seen in practice are not research participants, they are not chosen to fit an inclusion criterion specific to a research study, and as such they cannot truly be expected to fit into any one category. Given the differences that patients experience, the contradictory nature of the signs observed should be expected as each new sign offers new information[35]. Indeed, the varying nature of the clinical signs observed is in itself a sign and we could perhaps offer this as a defining feature of DED.

Research informs evidence-based practice, but it is difficult to account for the variable that is the human being. The evidence base as yet offers no resolution to the contradictions between signs and symptoms – although a deeper, holistic understanding of the patient as an individual, and a recognition of the role of the lid wiper and tear osmolarity, offer a glimpse of a potential way forward.

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Take away points

- *There is the potential that more than 7 out of 10 patients seen in everyday practice could have some form of dry eye disease.*
- *Not all patients will have both signs and symptoms.*
- *Dry eye disease often does not exist in a vacuum. The patient may have other, systemic conditions also.*
- *Patients with chronic conditions that cause pain, such as Rheumatoid arthritis, Crohn's disease etc, or those with allergies, may be more prone to DED or exacerbated symptoms.*
- *Patients suffering from depression, anxiety or PTSD may suffer more than signs would suggest.*
- *The more the ECP knows about the type and possible cause of the DED the patient suffers from, the greater the chance of choosing correct management options.*
- *Question, question and question. The use of a DED questionnaire is useful in identifying patients who have symptoms. It is then important that the ECP follows up anything the questionnaire has highlighted. The more information the ECP has, the greater the chance of managing the condition.*
- *Every patient is unique.*
- *If you have reached the limits of what you can do for your patient, refer them on to a dry eye specialist. We have a duty of care to our patients and a requirement to work within our competence. By referring, you are fulfilling those obligations and showing your patient you take their well-being seriously.*

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