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DRY EYE DISEASE
DIAGNOSIS AND MANAGEMENT

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Published
November 2017

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Background

Dry eye disease (DED) is a distinct clinical entity with a grouping of clinical signs and symptoms. According to TFOS DEWS II the following definition encapsulates our current understanding of DED: Dry eye 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 (DEWS II).

A central mechanism that has become cemented with the pathophysiology of DED is that evaporation results in tear hyperosmolarity which drives the cycle of inflammation forward *(Figure 1) (1)*.

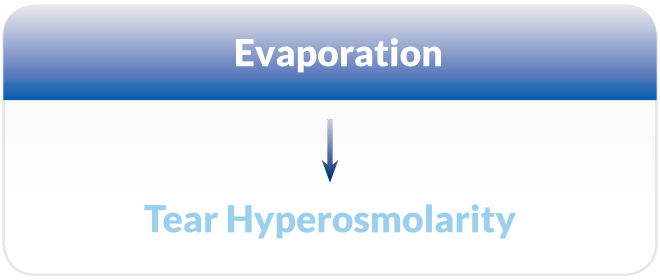

Figure 1. Evaporation and tear hyperosmolarity relationship (DEWS II) (1)

The classification of DED previously into two separate categories has evolved whereby aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE) exist on a continuum *(Figure 2)*.

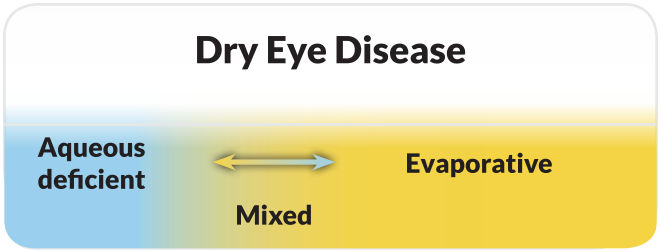

Figure 2. Continuum of DED from Aqueous deficient to Evaporative (2)

Patients suspected of having DED can be grouped into 2 categories; symptomatic and asymptomatic *(Figure 3)*. Each of the two groups can further be divided into subgroups by the presence or absence of clinical signs. Those with clinical signs are broken down into 4 main categories: Pre-disposed DED state, neurotrophic conditions (dysfunctional sensation), other ocular surface disease (OSD), or DED.

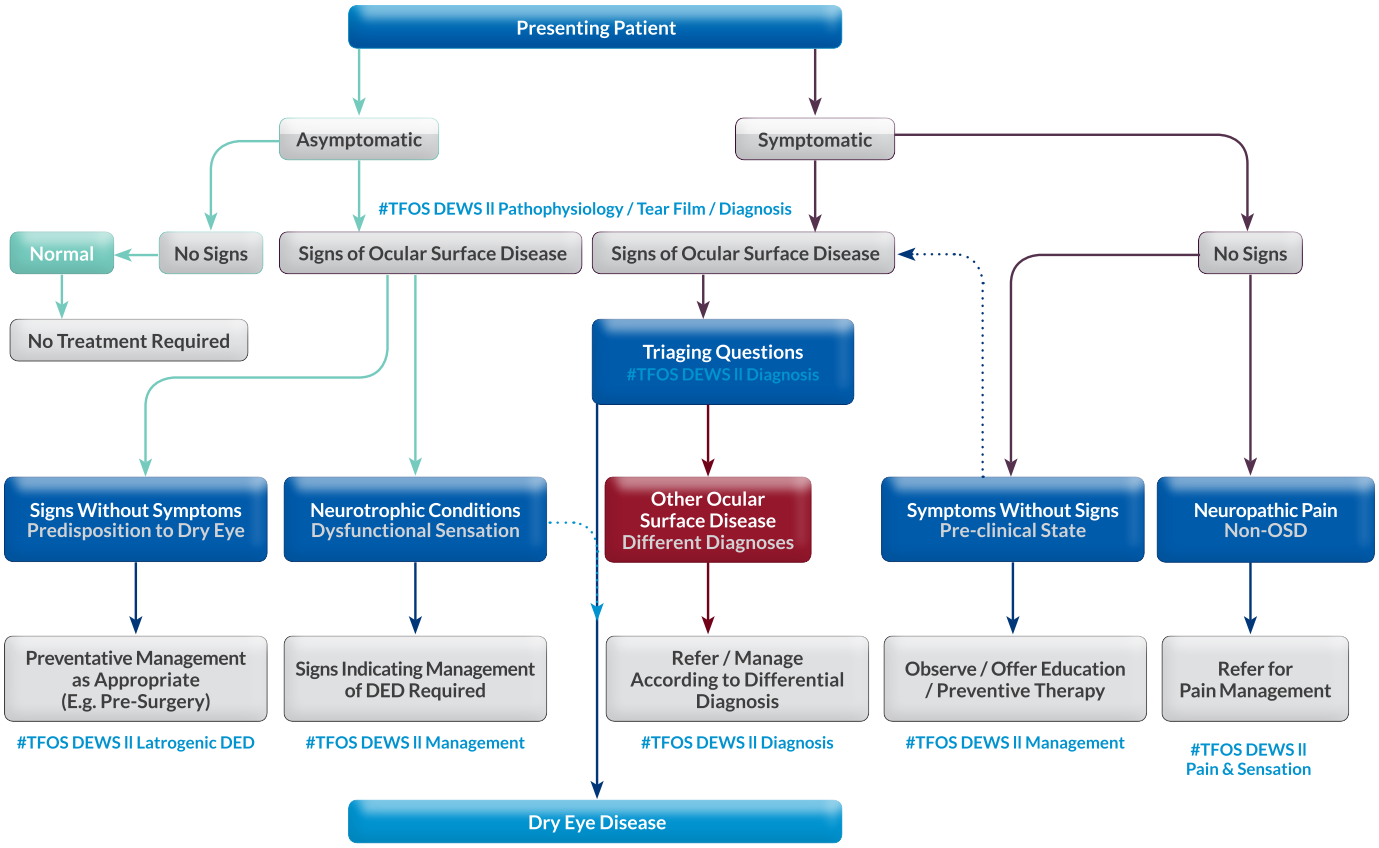

Figure 3. DEWS II classification flowchart (2)

DED, as noted on the previous page is the continuum between ADDE and EDE. Clinicians can use this algorithm to also identify symptomatic patients without signs; neuropathic (non-OSD) and pre-clinical symptomatic patients. These two subgroups are separate and distinct from what we would classically define as DED and have a different management pathway from DED.

Both defining DED and classifying patients appropriately gives way to more effective and specific clinical management. DED is indeed a condition that ultimately affects vision and all aspects of visual care should include an efficient process to identifying those patients at risk. Refractive (surgical and ophthalmic), contact lens, glaucoma are but a few segments of eye care that are impacted by a suboptimal ocular surface. The purpose of this reference guide is to allow the clinician to have a proper DED diagnostic and management pathway which will result in improved patient visual health.

Diagnosis

Diagnostic testing for DED is extensive and may not be readily available to all clinicians, so it is recommended that should the available testing not be definitive, an appropriate referral be made to complete the assessment. A simplified approach to the DED diagnostic protocol as adapted from DEWS II can be broken down into *triaging questions, validated symptom questionnaire, homeostasis markers and subcategory specific testing* (2).

Triaging Questions

Exclusion of masqueraders of DED is part of the intake process and can be analyzed through the questions listed in *Figure 4*. Severe symptoms in the absence of signs may suggest a neuropathic component.

How severe is the eye discomfort?	Unless severe, dry eye presents with signs of irritation such as dryness and grittiness rather than 'pain'. If pain is present, investigate for signs of trauma / infection / ulceration.
Do you have any mouth dryness or enlarged glands?	*Trigger for Sjögren's syndrome investigation.*
How long have your symptoms lasted and was there any triggering event?	Dry eye is a chronic condition, present from morning to evening but generally worse at the end of the day, so if sudden onset or linked with an event, examine for trauma / infection / ulceration.
Is your vision affected and does it clear on blinking?	Vision is generally impaired with prolonged staring, but should largely recover after blinking; a reduction in vision which does not improve with blinking, particularly with sudden onset, requires an urgent ophthalmic examination.
Are the symptoms or any redness much worse in one eye than the others?	Dry eye is generally a bilateral condition, so if symptoms or redness are much greater in one eye than the other, detailed eye examination is required to exclude trauma & infection.
Do the eyes itch, are they swollen, crusty or have they given off any discharge?	Itching is usually associated with allergies while a mucopurulent discharge is associated with ocular infection.
Do you wear contact lenses?	Contact lenses can induce dry eye signs and symptoms and appropriate management strategies should be employed by the contact lens prescriber.
Have you been diagnosed with any general health conditions (including recent respiratory infections) or are you taking any medications?	Patients should be advised to mention their symptoms to the health professionals managing their condition, as modified treatment may minimize or alleviate their dry eye.

Figure 4. Triaging questions to identify DED masquerading factors (2)

Risk Factors

Personal and iatrogenic factors may include but are not limited to the following (2) (3):

- Pharmaceutical use (antidepressants, anticholinergics, antipsychotics, antispasmotics and antihistamines, chemotherapeutics, antihypertensive, anti-arrhythmics, antithyroid agents, opioid analgesics, accutane)
- Smoking
- Chronic preservative exposure (glaucoma medications, cosmetic and aesthetic compounds)
- Ocular surgery
- Ocular surface injury
- Androgen insufficiency, depletion
- GVHD

Validated Symptom Questionnaires

The two most widely accepted and validated questionnaires for DED severity are Ocular Surface Disease Index (OSDI) and Dry Eye Questionnaire 5 (DEQ-5) *(Appendix 1 and 2) (2) (4)*. When triaging questions and risk factors have been addressed, OSDI ≥ 13 or DEQ-5 ≥ 6 signals the need for homeostasis marker testing which is detailed below.

Homeostasis Markers

A positive symptom questionnaire plus at least one of the following homeostatic markers will yield a diagnosis of DED.

Tear Break-up Time ≤10s (NIBUT vs. FBUT)

Non-invasive BUT is the preferred method where available which can be measured subjectively with any commercial placido-disk pattern topography or keratometer as the time required to notice the first break in the pattern at any position on the disk. Alternatively, commercial systems such as the *Oculus Keratograph 5M* as well as some others use an auto-detection method to acquire this metric. A consistent method of NIBUT measurement should be used in any given clinical setting. Alternatively fluorescein BUT (FBUT) can be used however because this can affect other homeostasis marker testing, FBUT should follow tear osmolarity testing *(2)*.

Ocular Surface Staining

Fluorescein staining strip should be shaken of excess saline and applied to the inferior temporal aspect of the palpebral conjunctiva while allowing > 2 minutes to follow. Corneal staining of > 5 spots is considered a positive test. Conjunctival and Lid Wiper staining can be observed using Lissamine Green or Rose Benga, where available, and is best visualized 3-6 minutes after applying the vital dye. A similar technique should always be used when applying staining. Conjunctival staining of 9 or more spots and or Lid Wiper Epitheliopathy > 2mm in length and > 25% width is considered a positive test result (2).

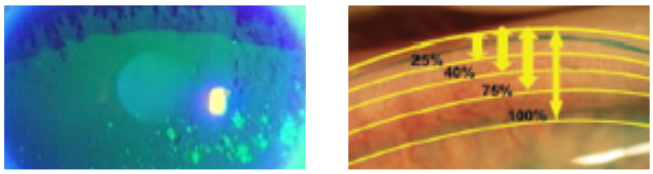

Figure 5. >5 spots of corneal staining (left), Lid wiper staining and grading (right) (6)

Tear Osmolarity ≥ 310 mOsm/L in either eye or inter-eye difference > 8 mOsm/L

Both In Vivo and *Ex Vivo* options for tear film osmolarity testing can be used and have been shown to be equivocal *(5)*. This sequence of this testing should follow NIBUT or precede FBUT testing.

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I-PEN®, by I-MED PHARMA Inc., is the world's first, hand-held, point-of-care, solid state electronic diagnostic device to detect and indirectly measure the elevated tear film osmolarity levels associated with mild, moderate and severe Dry Eye Disease.

Normal	Marginal	Mild	Moderate	Severe
< 290	290-310	310-330	330-350	> 350

275	290	305	320	335	350	365	380

Dry Eye Workflow

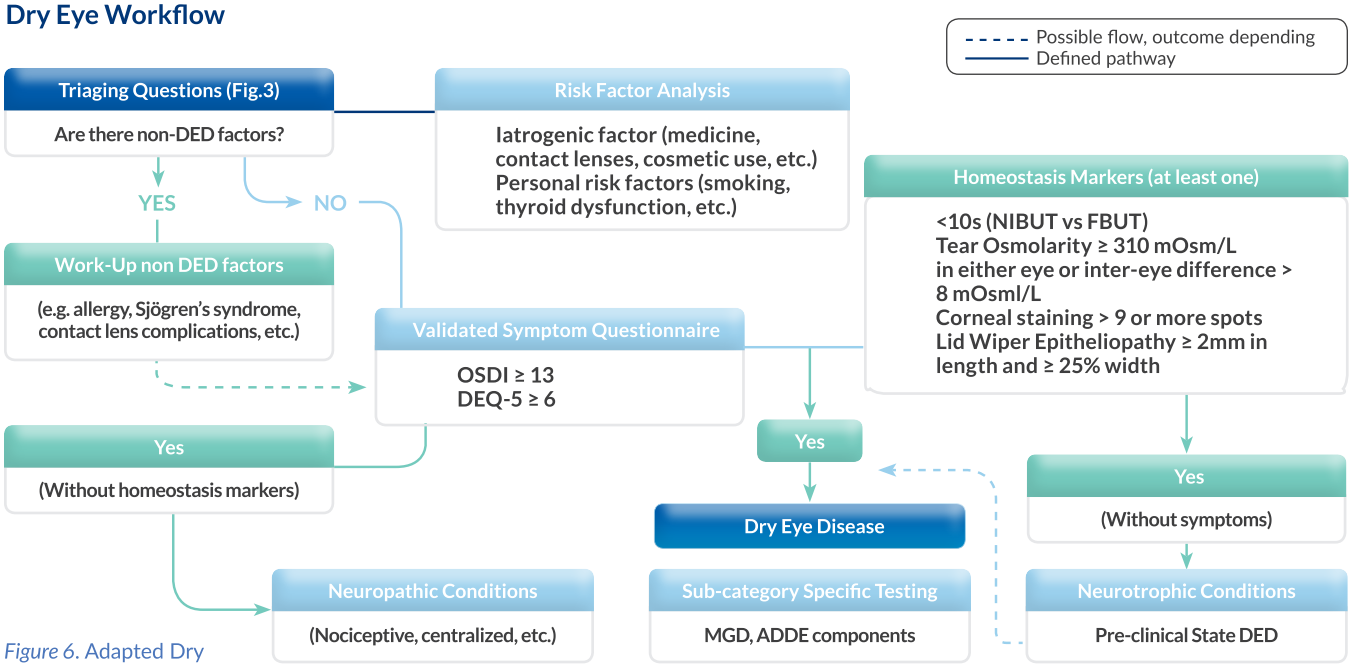

Figure 6. Adapted Dry Eye Workflow for Clinical Assessment

Based on the *Figure 6*, a clinical rule can be implemented which is described as:

OSDI/DEQ-5 (≥13/≥6) + 1 (or more) Homeostasis Markers = Positive DED

Sub-Category Diagnostic Testing

Once a diagnosis of DED is reached, there are a multitude of diagnostic tests available in the current market. The goal of the sub-category testing is to determine the etiology of DED.

- Evaporative Dry Eye related to Meibomian Gland Dysfunction (MGD)
- Aqueous Deficient Dry Eye
  - A) Sjögren's Syndrome
  - B) Non-Sjögren's Dry Eye (NSDE)
- Mixed etiology Dry Eye

The following list, although not exhaustive, represents diagnostic testing supported by current scientific literature for subcategory differentiation:

MGD Specific Testing

- Meibography
- Diagnostic gland expression (eg. Meibomian Gland Evaluator)
- Lipid Layer Thickness
- Blink analysis
- Lid closure (microlagophthlamos)
- Thermography
- Evaporimetry

Ocular Surface Testing

- Biomarker testing (MMP-9)
- Osmolarity Testing (I-PEN®)
- LIPCOF (Lid Parallel Conjunctival Folds)
- Eyelash evaluation (Demodex)
- *In vivo* Confocal Microscopy
- Corneal esthesiometry
- Conjunctival Redness

Aqueous Testing

- Schirmer
- Phenol red thread
- Meniscometry (SMTube®)
- OCT meniscometry

Osmolarity Testing
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The world's first, hand-held in-vivo device measuring tear osmolarity rapidly and reliably.

Meniscometry
SMTube®

The latest quantitative tear function test: rapid, reliable and non-invasive.

Management

According to the DEWS II management and therapy report, the aim of clinical management of DED is to restore homeostasis to the ocular surface. Given the multifactorial etiology of this disease, it is not entirely possible to develop a unifying approach to treating this condition. Depending on the diagnostic findings using the workflow, the patient may require multiple therapies. As such a stepped approach to choosing the appropriate therapy is recommended, while keeping in mind that crossover between steps of therapy may be required *(Figure 7)*.

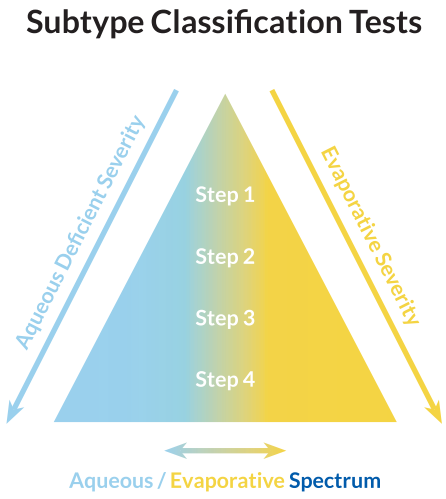

Figure 7. DEWS II Step-wise approach to sub-category based management *(7)*

Step 1

Education regarding the condition, its management, treatment and prognosis
Modification of local environment
Education regarding potential dietary modifications (including oral essential fatty acid supplementation - I-VU® OMEGA-3 PLUS)
Identification and potential modification/elimination of offending systemic and topical medications
Ocular lubricants of various types (I-DROP® PUR and I-DROP® PUR GEL) (if MGD is present, then consider lipid-containing supplements)
Lid hygiene (I-LID'N LASH®) and warm compresses/ heat therapy masks of various types (I-RELIEF®)

Step 2

If above options are inadequate consider:

Non-preserved ocular lubricants to minimize preservative-induced toxicity (I-DROP® PUR and I-DROP® PUR GEL)
Tea tree oil treatment for Demodex (if present) (I-LID 'N LASH® PLUS and I-LID 'N LASH® PRO)
Tear conservation
- o Punctal occlusion (I-PLUG®)
- o Moisture chamber spectacles/goggles

Overnight treatments (such as ointment or moisture chamber devices)
In-office, physical heating and expression of the meibomian glands (including device-assisted therapies)
In-office intense pulsed light therapy for MGD
Prescription drugs to manage DED
- o Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
- o Topical corticosteroid (limited-duration)
- o Topical secretagogues
- o Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
- o Topical LFA-1 antagonist drugs (such as lifitegrast)
- o Oral macrolide or tetracycline antibiotics

Step 3

If above options are inadequate consider:

Oral secretagogues
Autologous/allogeneic serum eye drops
Therapeutic contact lens options
- o Soft bandage lenses
- o Rigid scleral lenses

Step 4

If above options are inadequate consider:

Topical corticosteroid for longer duration
Amniotic membrane grafts
Surgical punctal occlusion
Other surgical approaches (e.g. tarsorrhaphy, salivary gland transplantation)

Dietary Modifications
I-VU® OMEGA-3 PLUS

Pharmaceutical grade Omega-3 fish oil with EPA, DHA and DPA.

Preservative free Ocular Lubricants
I-DROP® PUR and PUR GEL

The only viscoadaptive, preservative-free artificial tear to continually refresh and stabilize the tear film.

Lid Hygiene
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Unique formulation gently removes ocular debris and hydrates skin without stinging, burning or irritation.

Heat Therapy Mask
I-RELIEF®

Soft, reusable, eye mask with exclusive ThermaBeads™, provides moist heat therapy for the relief of dry eye symptoms.

Tea Tree Oil Treatment
I-LID 'N LASH® PLUS AND PRO

Enhanced formulation with Tea Tree Oil works to disinfect while cleansing bioburden and hydrating eyelids.

Punctal Occlusion
I-PLUG®

Designed for patient comfort and proper retention, available individually packaged, preloaded on sterile disposable inserter.

Discussion

Within the steps of management, clinicians invariably need to customize the treatment plan to cater to the particular case. Knowledge of all options available will enhance patient outcomes. Below are some therapeutic options to consider within the stages.

Tear Replacement Approaches

After lifestyle changes, the least invasive approach to restoring homeostasis is artificial tear substitutes. Within this category, viscosity enhancing agents can enhance the stability of the tear film by increasing residence time on the eye:

- Carbomer 940 (polyacrylic acid)
- Carboxymethyl cellulose (CMC)
- Dextran
- Hyaluronic acid (HA)
- HP-guar
- Hydroxypropyl methylcellulose (HPMC)
- Polyvinyl alcohol (PVA)
- Polyvinylpyrrolidone (PVP)
- Polyethylene glycol
- Glycerol

Lipid enhancing tear replacements come in three different emulsion categories, macroemulsion (100+ nm drop size), nanoemulsion (10-100 nm drop size) and microemulsion (<10 nm drop size). These can be helpful in low lipid tear films due to MGD.

MGD and Anterior Blepharitis

MGD and blepharitis management has evolved and the acceptance of lid hygiene as a mainstream maintenance strategy is widely accepted (8). Topical, oral and in-office clinical options can give the clinician a wide selection of options depending on presentation.

Blepharitis

- Topical Azithromycin
- Tea tree oil cleansers and 4-Terpineol (5-50% concentrations have shown Demodex count reduction)
- Ivermectin
- Microblepharoexfoliation

MGD

- Warm compresses (45°C for >5 min)
- Omega 3/Essential Fatty Acid supplementation
- Meibomian gland expression (in-office)
- Lid debridement or scaling
- Thermal Pulsation
- Intense Pulsed Light
- Intraductal gland probing

Other Therapeutic Options

For the purpose of this summary, the treatment options listed are not exhaustive; however clinicians can employ the therapies mentioned to build a menu of non-pharmacological treatment options.

Corneal Exposure Options

- Contact lenses (therapeutic bandage)
- Scleral contact lenses
- Moisture chamber goggles
- Punctal occlusion (temporary or permanent)

Pharmacological and Doctor Initiated Options

- Topical glucocorticoids agents
- Topical Immunomodulator agents (non-glucocorticoid)
  - o Cyclosporine A
  - o Tacrolimus
- Topical Non-steroidal anti-inflammatory agents
- Topical LFA-1 antagonist
  - o Lifitegrast
- Oral tetracyclines (doxycycline, minocycline)
- Macrolide (oral and topical azithromycin)
- Oral secretagogues (pilocarpine)
- N-Acetylcysteine
- Nasal neurostimulation
- Amniotic membrane transfer (cryopreserved and dehydrated)
- Topical autologous serum
- Topical platelet-rich plasma (PRP)

Interventions such as tarsorraphy and conjunctival resection for conjunctivalchalasis are a few examples when surgery is indicated for managing aspects of DED. All efforts to minimize the need for surgical intervention should be taken however. Non-surgical options like IPL and radiofrequency (RF) heat can result in collagen remodeling and improvement of the lid anatomy in cases of poor lid elasticity, which can be an effective treatment option (9) (10).

Conclusion

This DED Diagnosis and Management Reference Guide is largely an evidence-based adaptation of the TFOS DEWS II work. Managing DED is a rapidly changing subject and with increasing options and levels of evidence, our framework will shift. The booklet is meant to guide clinicians to the fundamental markers in diagnosing this condition accurately and consistently. Only then can management efficacy be compared in a meaningful way. Taking an objective repeatable approach can bring much needed light to this multifactorial disease, and in that light our clinical pathway will become clearer.

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"You treat a disease: You win, you lose. You treat a person, I guarantee you win – no matter the outcome."

- Dr. Hunter Doherty "Patch" Adams

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Ocular Surface Disease Index©

Please answer the following question by checking the box that best represents your answer.

Have you experience any of the following during **the last week:**

		All of the Time	Most of the Time	Half of the Time	Some of the Time	None of the Time
1.	Eyes that are sensitive to light?					
2.	Eyes that feel gritty?					
3.	Painful or sore eyes?					
4.	Blurred vision?					
5.	Poor vision?					

Have problems with your eyes limited you in performing any of the following during **the last week:**

		All of the Time	Most of the Time	Half of the Time	Some of the Time	None of the Time
6.	Reading?					
7.	Driving at night?					
8.	Working with a computer or bank machine (ATM)?					
9.	Watching TV?					

Have your eyes felt uncomfortable in any of the following situations during **the last week:**

		All of the Time	Most of the Time	Half of the Time	Some of the Time	None of the Time
10.	Windy conditions?					
11.	Places or areas with low humidity (very dry)?					
12.	Areas that are air conditioned?					

Scoring Instructions

Item Scoring

The total OSDI score is calculated based on the following formula:

$$\text{OSDI} = \frac{(\text{sum of severity for all questions answered}) \times (100)}{(\text{total \# of questions answered}) \times (4)}$$

where the severity was graded on a scale of

0 = none of the time,
1 = some of the time,
2 = half of the time,
3 = most of the time,
4 = all of the time.

Interpretation

A score of 100 corresponds to complete disability (a response of "all of the time" to all questions answered), while a score of 0 corresponds to no disability (a response of "none of the time" to all questions answered). Therefore, change from baseline of -12.5 corresponds to an improvement by at least one category in half of the questions answered.

Subscale Scoring

Subscales scores are computed similarly with only the questions from each subscale used to generate its own score. Therefore, any substance analyzed separately would also have a maximum possible score of 100.

The three subscales (vision-related function, ocular symptoms and environmental triggers) are broken out as follows:

Subscale	Questions
Vision-Related Function	4, 5, 6, 7, 8, 9
Ocular Symptoms	1, 2, 3
Environmental Triggers	10, 11, 12

DEQ 5

1. Questions about **EYE DISCOMFORT:**

A) During a typical day in the past month, **how often** did your eyes feel discomfort?

0 Never
1 Rarely
2 Sometimes
3 Frequently
4 Constantly

B) When your eyes felt discomfort, **how intense was this feeling of discomfort** at the end of the day, within two hours of going to bed?

Never have it 0 | Not at all intense 1 2 3 4 5 Very intense

2. Questions about **EYE DRYNESS:**

A) During a typical day in the past month, **how often** did your eyes look or feel dry?

0 Never
1 Rarely
2 Sometimes
3 Frequently
4 Constantly

B) When your eyes felt dry, **how intense was this feeling of dryness** at the end of the day, withing two hours of going n to bed?

Never have it 0 | Not at all intense 1 2 3 4 5 Very intense

3. Questions about **WATERY EYES:**

A) During a typical day in the past month, **how often** did your eyes look or feel **excessively watery?**

0 Never
1 Rarely
2 Sometimes
3 Frequently
4 Constantly

Score: ____ + ____ + ____ + ____ + ____ = ____

1a + 1b + 2a + 2b + 3 = Total