

Definition and Diagnostic Criteria of Dry Eye Disease: Historical Overview and Future Directions

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The definition and diagnostic criteria of dry eye disease (DED) proposed by the Japan Dry Eye Society and other countries are reviewed. The first definition and criteria of DED in Japan were proposed in 1995. In that report, DED was considered a disease of tears, which subsequently damaged ocular epithelia. The presence of subjective symptoms was not included in the criteria. In 2006, a new definition proposed that interactions between the tear film and ocular surface epithelia play important roles in DED. The presence of subjective symptoms, including visual disturbances, changes in tears, and epithelial damage were proposed to be major components of DED, and eyes positive for all three components were diagnosed as “definitive dry eye.” A third version was proposed in 2016, which emphasized unstable tear films as a core finding in DED. Following this guideline, eyes with an abnormally low tear film breakup time and the presence of subjective symptoms are considered to have DED. The current definition and criteria are different from those proposed in other countries. For example, the recently published DED definition by the Dry Eye Workshop II (DEWS II) of the Tear Film and Ocular Surface Society (TFOS) focuses more on the underlying pathogenesis of DED, including inflammation, hyperosmolarity of tears, and neurosensory abnormalities, as well as unstable tear films.

Keywords: dry eyes, diagnostic criteria, definition

HISTORICAL OVERVIEW OF DEFINITION AND DIAGNOSTIC CRITERIA OF DED

The first comprehensive definition of DED was published in 1995 on the basis of consensus from the National Eye Institute (NEI) Industry Working Group on Clinical Trials in DED.¹ In the report, DED is defined as follows:

“Dry eye is a disorder of the tear film due to tear deficiency or excessive evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort.”

The definition clearly states that changes in the tear film are the cause of DED, which subsequently cause irritating symptoms and epithelial abnormalities. It also suggests that tear deficiency and excessive evaporation are the major causes of DED. This concept was reflected in the classification in this publication. DED was divided into two major categories involving tear deficient and evaporative, and then was further subclassified into a range of intrinsic and extrinsic causes. It is important that the definition uses the term “disorder” and not “disease.” This definition and classification scheme have influenced subsequent DED studies and clinical approaches, including the Preferred Practice Pattern reported by the American Academy of Ophthalmology in 2013² and others.³⁻⁷

The second major progress was made in the early 2000s, and the results were published in the report of the International DEWS of the TFOS in 2007.³ This report states:

“Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.”

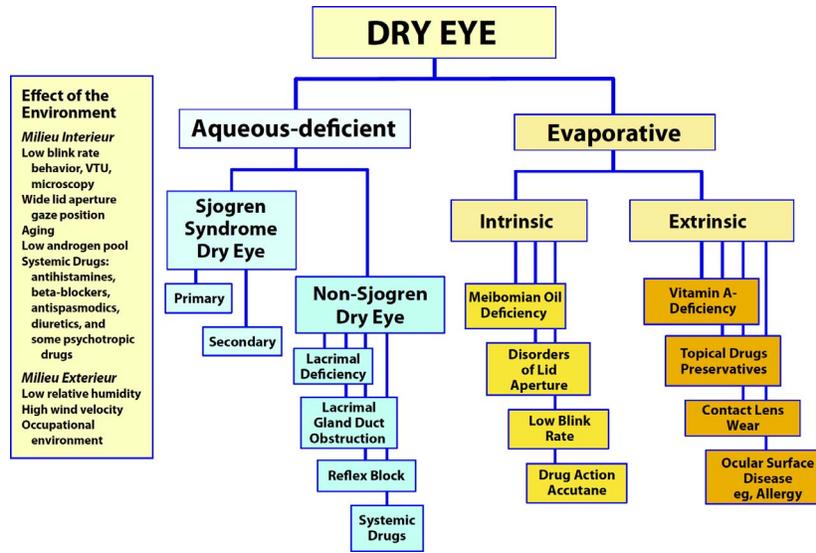
This definition proposes several differences from the previous NEI report. First, DED was considered to be a disease caused by abnormalities in either tears or the ocular surface. Tears were not considered to be the sole cause of DED, and changes in the epithelium could cause abnormalities in tears. In this regard, DED was considered to be a dysfunction of the integrated functional unit comprising the lacrimal glands, ocular surface, eyelids, and sensory and motor nerves.⁸ Second, DED might cause visual disturbances.⁹⁻¹¹ Third, increased osmolarity and ocular surface inflammation were included in the DED definition.¹²⁻¹⁴ Inclusion of these pathogenic factors in the definition of DED was new and contrasted with previous NEI reports. The definition caused controversy among researchers regarding whether the inflammation and hyperosmolarity had a casual or causal relationship with DED. The classification system of the DEWS report basically revised the 1995 NEI report, with aqueous-deficient DED and evaporative dry eye as the major two subtypes (Fig. 1). Aqueous-deficient was further classified into Sjögren and non-Sjögren categories. Evaporative dry eye was subclassified into intrinsic and extrinsic categories, and they were further classified as resulting from a range of causes.

In a recent revision, published in 2017, dealing with the DED definition and classification in the DEWS II report, the following definition of DED is provided:

“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.”⁴

This definition is basically a minor revision of DEWS, which used the term “homeostasis of the tear film” to suggest that a



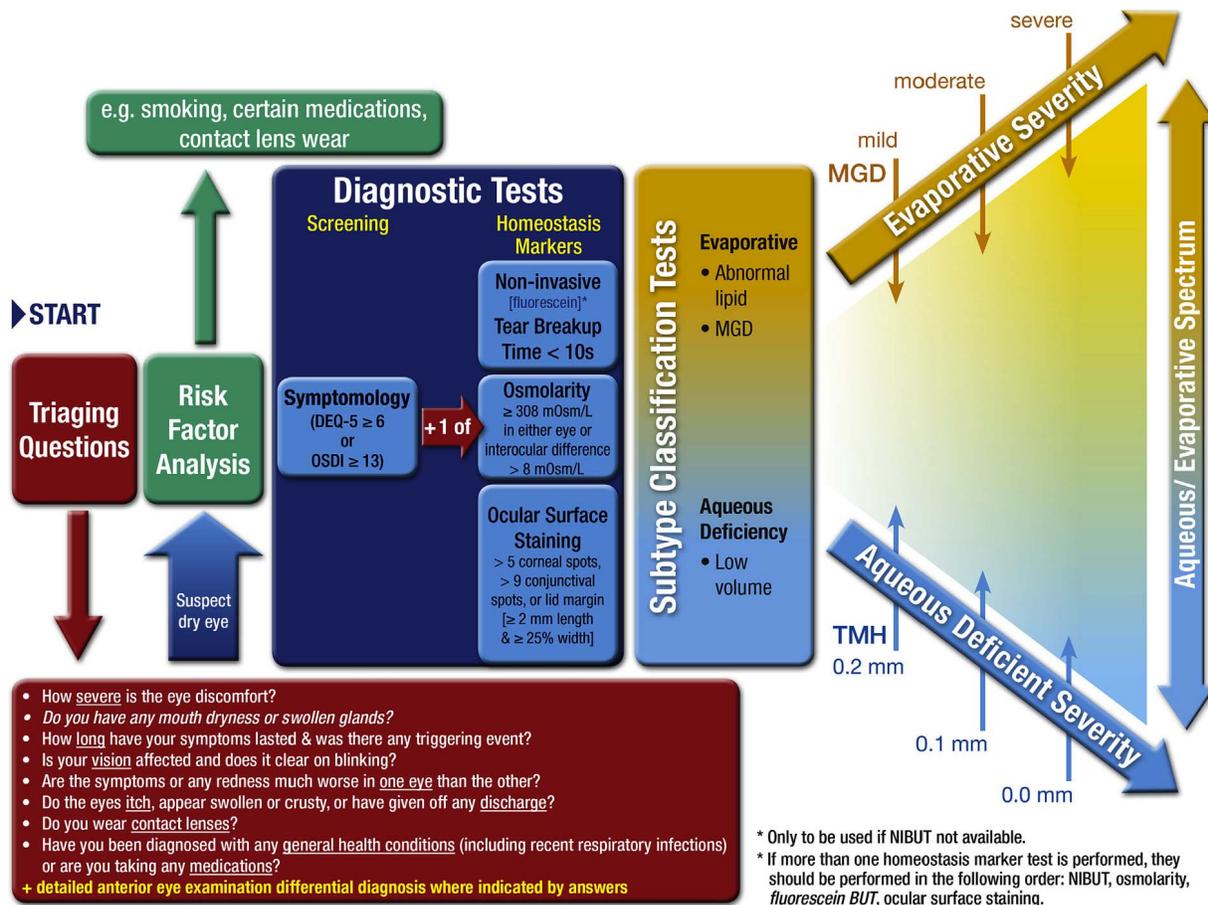


Effect of the Environment

Milieu Interieur
 Low blink rate behavior, VTU, microscopy
 Wide lid aperture gaze position
 Aging
 Low androgen pool
 Systemic Drugs: antihistamines, beta-blockers, antispasmodics, diuretics, and some psychotropic drugs

Milieu Exterior
 Low relative humidity
 High wind velocity
 Occupational environment

FIGURE 1. Major etiological causes of DED proposed by the DEWS of the TFOS 2006. The left box illustrates the influence of the environment on risk of an individual developing DED. Note that aqueous-deficient dry eye has two major subtypes: Sjögren and non-Sjögren syndrome DED. Evaporative dry eye is subdivided into intrinsic and extrinsic causes, and can be further classified into subgroups. Reprinted with permission from Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. *Ocul Surf.* 2017;15:276–283. © 2017 Elsevier Inc.



- How severe is the eye discomfort?
 - Do you have any mouth dryness or swollen glands?
 - How long have your symptoms lasted & was there any triggering event?
 - Is your vision affected and does it clear on blinking?
 - Are the symptoms or any redness much worse in one eye than the other?
 - Do the eyes itch, appear swollen or crusty, or have given off any discharge?
 - Do you wear contact lenses?
 - Have you been diagnosed with any general health conditions (including recent respiratory infections) or are you taking any medications?
- + detailed anterior eye examination differential diagnosis where indicated by answers

* Only to be used if NIBUT not available.
 * If more than one homeostasis marker test is performed, they should be performed in the following order: NIBUT, osmolarity, fluorescein BUT, ocular surface staining.

FIGURE 2. Tests to diagnose and monitor DED proposed by DEWS II of the TFOS.¹⁶ The test starts with screening questions for DED, followed by a series of examinations, such as slit-lamp biomicroscopy, osmolarity, BUT measurement, and staining tests. Then, further tests for subtype classification, including meibomian gland/lid margin changes and tear volume examinations, are performed. Reprinted with permission from Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II Diagnostic Methodology report. *Ocul Surf.* 2017;15:539–574. © 2017 Elsevier Inc.

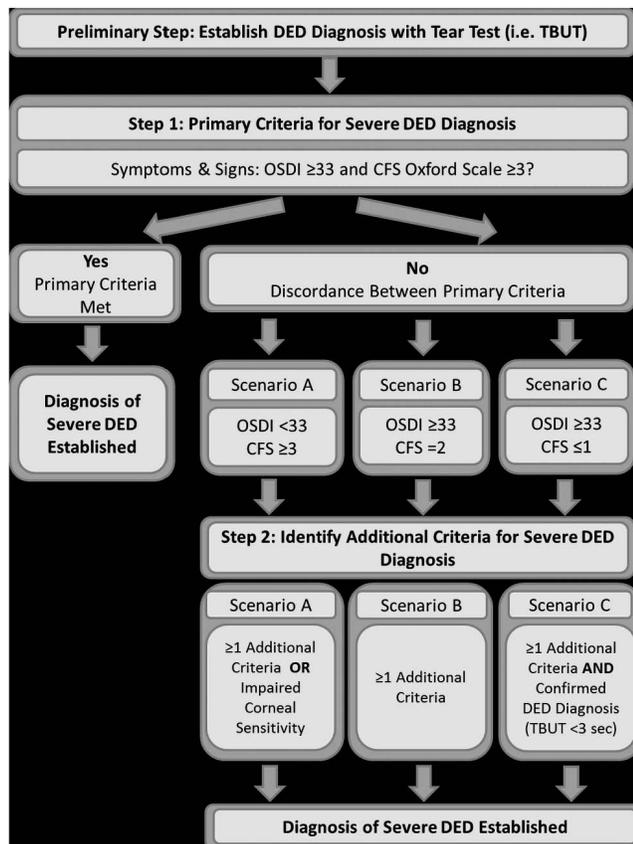


FIGURE 3. Diagnostic criteria and scoring algorithm for DED proposed by the Ocular Dryness Disease Severity (ODISSEY) European Consensus Group of dry eye specialists.¹⁹ The algorithm addresses the challenges associated with symptom and sign discordance in some cases of severe DED, and describes specific criteria relevant to evaluating DED severity in three different patient scenarios. Reprinted with permission from Baudouin C, Aragona P, Van Setten G, et al. Diagnosing the severity of dry eye: a clear and practical algorithm. *Br J Ophthalmol*. 2014;98:1168–1176. This is an Open Access article distributed in accordance with the Creative Commons Attribution Non-Commercial (CC BY-NC 3.0) license.

variety of factors could influence the homeostasis. The definition followed the previous one by describing factors that were important in the pathogenesis of DED, which included tear film instability, hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities. Neurosensory abnormalities were included in the definition for the first time, reflecting recent interest in the importance of alterations in pain and sensations in DED.¹⁵ The classification system succeeded the recent DEWS II reports with several modifications.⁴ The newly proposed classification scheme considered cases in which patients exhibited DED symptoms without obvious DED signs, or presented with symptoms that were not characteristic of DED. The former were cases with either a preclinical state of DED or neuropathic pain in which the somatosensory system was affected. The latter was considered to be related to reduced corneal sensitivity (a neurotrophic condition). Eyes with both signs and symptoms were classified as either aqueous-deficient or evaporative dry eye. Although this part of the classification was basically the same as previous classifications, there was a slight modification to clarify that there was a significant number of eyes that had both aqueous-deficient and evaporative components, so that these two subcategories were not exclusive.

In the diagnosis report, DEWS II listed a variety of diagnostic tests, which included questionnaires, tear film tests, epithelial abnormalities, and others.¹⁶ Although the report did not propose specific diagnostic criteria, it indicated the most appropriate (efficacious) tests to diagnose and monitor DED (Fig. 2).

There are other groups that proposed definitions and/or diagnostic criteria. In 2006, a panel of international DED specialists established a consensus using the Delphi approach. In this report, the use of “dysfunctional tear syndrome (DTS)” instead of DED was proposed.¹⁷ The report concluded that treatment strategies should rely on symptoms and signs rather than tests. The panel defined clinical signs to be considered in assessing the severity of DTS, which were used to develop a severity-based treatment algorithm. A major aim of the report was to establish a treatment algorithm; no specific definition or diagnostic criteria were suggested.

The Korean Corneal Study Group suggested a DED definition and treatment algorithm in 2014. In the report, they define DED as “a disease of the ocular surface that is associated with tear film abnormalities.”¹⁸ They proposed diagnostic criteria involving one or more symptoms (either irritating or visual symptoms), plus at least one objective sign including either ocular surface staining or tear film instability.

A European group also proposed diagnostic criteria for severe DED. In this report, Baudouin and associates¹⁹ proposed that patients with a high ocular surface disease index (OSDI; >33) and increased corneal fluorescein score (≥3) were considered to have severe DED, whereas an OSDI <33 with a fluorescein score ≥3, OSDI ≥33 with a fluorescein score = 2, or an OSDI ≥33 with a fluorescein score <2 were considered as severe DED if there were different DED findings, such as impaired corneal sensitivity, a breakup time (BUT) <5 seconds, and additional criteria (Fig. 3).

RECENT PROGRESS REGARDING THE CONCEPT OF DED IN JAPAN

The first definition and diagnostic criteria of DED were proposed by the Japan Dry Eye Society (JDES) in 1995, the same year that the NEI report was published. In this report, DED is defined as “Ocular surface epithelial damage caused by qualitative or quantitative abnormalities of tears.”²⁰ Diagnostic criteria were also proposed (Table 1). The definition and criteria had some similarities to those proposed by the NEI report; however, there were two distinct differences. First, the Japanese definition did not include the presence of subjective symptoms, based on the observation that end-stage DED patients with keratinized ocular surfaces seldom complained of irritating symptoms. Second, the Japanese dry eye guideline proposed cutoff values involving alterations in tears (Schirmer’s I test value ≤5 mm, cotton thread test ≤10 mm, or a BUT ≤5 seconds) as well as epithelial damage (fluorescein score ≥1 point [maximum = 3] or Rose Bengal staining scores ≥3 points [maximum = 9]).

The second version of the Japanese dry eye definition and criteria was published in 2006. In the report, dry eye is defined as follows: “Dry eye is the chronic disease in tears and corneal/conjunctival epithelia caused by various factors. It may accompany irritating symptoms and/or visual disturbances.” This definition differs from the previous version in that abnormalities in tears and ocular surface epithelia were considered to be reciprocal, forming a vicious cycle. It also suggests that multiple intrinsic or extrinsic factors contribute to the development of DED, including decreased tear secretion, Meibomian gland dysfunction, and wearing of contact lenses. The Japanese 2006 report included diagnostic

TABLE 1. Diagnostic Criteria of the JDES, 1995 Version

<p>Category 1. Abnormalities of Tear:</p> <ol style="list-style-type: none"> Schirmer's test I ≤ 5 mm Cotton thread test ≤ 10 mm Breakup time ≤ 5 seconds <p>Considered to be positive when any one of the tests is positive.</p> <p>Category 2. Ocular Surface Epithelial Damage:</p> <ol style="list-style-type: none"> Fluorescein score ≥ 1 point (maximum of 3 points) Rose Bengal score ≥ 3 points (maximum 9 points) <p>Considered to be positive when any one of the tests is positive.</p> <p>Diagnosis of DED:</p> <ol style="list-style-type: none"> Definite dry eye if both category 1 and 2 are present Probably dry eye if category 1 or 2 is present

criteria of DED (Fig. 4),^{21,22} which included three categories of subjective symptoms, abnormalities of tears, and epithelial damage. The abnormalities of tears included a decreased BUT or Schirmer's value, and the epithelial damage included positive staining scores (≥ 3 of 9 points) in either fluorescein, Rose Bengal, or Lissamine Green staining tests. One of the characteristics of the criteria was that there were two categories for DED diagnosis, involving definite dry eye and probable dry eye. These criteria were based on the assumption that all of the above-mentioned tests were sensitive enough to diagnose DED. Positive results for all three categories were sufficient to make a diagnosis of DED. However, eyes could have DED, even if only two of the three categories were positive, because the diagnostic tests may not be sufficiently accurate. It was suggested that the addition of other newly developed tests would increase the accuracy of the criteria; however, the committee decided to include only tests widely performed in general practice. Since the announcement of the JDES definition/criteria in 2006, it has been widely used by Japanese DED researchers, and has contributed to the promotion of DED studies.

AWARENESS OF "SHORT BUT-TYPE DRY EYE"

Since the development of the second version of the dry eye definition and criteria, many Japanese DED specialists have recognized the importance of the so-called "short BUT-type dry eye" (sBUT dry eye). This type of DED is characterized by positive symptoms and decreased BUT (≤ 5 seconds) without notable epithelial damage. It was reported that 441 of 561 office workers (78.6%) showed decreased BUT, and approximately 50% were categorized as having sBUT dry eye.^{23,24} Previous studies reported that the severity of symptoms, as well as visual performance and mucin expression, of sBUT dry eye were comparable to those of typical aqueous-deficient dry eye.²⁵⁻²⁷ Although sBUT dry eye was considered to be a "probable dry eye" by 2006 criteria, these findings indicated that sBUT dry eye should be managed in a similar manner as "definite dry eye." The importance of sBUT dry eye is further discussed by Tsubota.²⁸

THE DEVELOPMENT OF A 2016 DRY EYE DEFINITION

The awareness of the importance of tear film instability in DED has led to a revision of the DED definition/criteria, with a new version proposed by the JDES in 2016. The importance of tear film instability has also been shared with other Asian ophthalmologists. Since the establishment of the Asia Dry Eye Society (ADES) in 2012, Asian dry eye specialists, including those in China, Korea, and Japan, have discussed the development of an ADES dry eye definition and criteria. The consensus was published in *Ocular Surface* in early 2017,²⁹ and was basically the same as the report by the JDES. In the report, the DED definition is, "Dry eye is a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage." This definition clearly states that the unstable tear film is the central component of DED. In addition, although the presence of subjective symptoms, including visual disturbance, was also important, the presence of epithelial damage was no longer essential. The new criteria

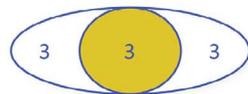
2006 Japanese Diagnostic Criteria for Dry Eye

- 1. Subjective Symptoms**
- 2. Tear Functions**
 - 1) Schirmer test I ≤ 5 mm (5 minutes)
 - 2) Tear film break up time (BUT) ≤ 5 seconds

* Subject who meets either criteria 1 or 2 is considered to fulfill that criteria.
- 3. Vital Staining**

Lissamine green, Rose Bengal, fluorescein staining *

* A staining score of more than 3 points out of 9 is considered to be positive.



1. Subjective Symptoms	○	×	○	○
2. Tear Function Abnormalities	○	○	×	○
3. Vital Staining	○	○	○	×
Diagnosis of Dry Eye	Definite dry eye		Probable dry eye	

FIGURE 4. Diagnostic criteria of DED proposed by the JDES (2006 version).^{21,22} The criteria consist of three components: subjective symptoms, tear function, and vital staining test. Patients positive for all three components are regarded as "definite dry eye," whereas those positive for two of three components are regarded as "probable dry eye."

TABLE 2. Comparison of Dry Eye Definition and Diagnostic Criteria Between JDES/ADES and DEWS II

	JDES/ADES	DEWS II
Definition	A multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage.	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.
Criteria	Presence of subjective symptom plus BUT <5 seconds	Positive symptomatology (Dry Eye Questionnaire-5 >5 or OSDI >13), plus noninvasive BUT <10 seconds, or Osmolarity >308 mOsm/L or interocular difference >8 mOsm/L, or Ocular surface staining (>5 corneal spots, >9 conjunctival spots, or lid margin)

were also published along with the ADES/JDES definition. According to the criteria, patients were considered to have DED when they had DED symptoms and decreased BUT (≤ 5 seconds). Neither Schirmer's value nor the presence of epithelial damage was a part of the criteria.

As the new dry eye definitions/criteria of the ADES/JDES report are highly dependent on BUT measurements, training in the proper use of this test is of key importance. BUT measurements can sometimes be unreliable if an excessive amount of fluorescein solution is used, or a solution that may alter the tear film quality. Assessment of the appropriate cutoff value of the BUT may also be required. The JDES/ADES report proposed a cutoff value of ≥ 5 seconds, whereas the DEWS II report proposed a cutoff value of >10 seconds.

COMPARISON OF THE CURRENT DEFINITION/CRITERIA BETWEEN DEWS II AND ADES/JDES

The dry eye definitions proposed by the DEWS II and ADES/JDES have both similarities and differences (Table 2). Both definitions share the similar concept that tears and ocular surface epithelia form a communal environment, and disruption of the environment results in the development of DED; however, the core concepts of DED differ. The DEWS II definition included multiple potential pathogenesis in DED, including hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities as well as tear film instability. The DEWS II report emphasized the pathophysiology of DED, whereas the ADES/JDES report emphasized the diagnostic value of the physician's observations. The ADES/JDES report therefore placed the emphasis on "visible changes," whereas the DEWS II report placed the emphasis on "invisible changes." The differences could have been the result of the differences in committee members. The DEWS II committee was composed of both clinicians and researchers, whereas the ADES/JDES committee was composed exclusively of clinicians.

FUTURE DIRECTIONS

There has been rapid progress in basic and clinical research on DED over the past several decades, which has been reflected in changes in the definition and diagnostic criteria of DED. It should be noted, however, that all of the previous reports were generated based on expert consensus. Although some used

systematic methods for decision making, such as voting or Delphi methods, they are regarded as "authority-based" rather than "evidence-based." In addition, some of the reports had financial support from pharmaceutical companies, which may have influenced the direction of the discussion. Further progress in dry eye research would generate more comprehensive and clinically relevant dry eye definitions and criteria.

The JDES recently proposed the concept of "tear film-oriented diagnosis (TFOD)" and "tear film-oriented treatment (TFOT)" (see a later chapter). In this concept, it is important to distinguish which tear film components (lipid, aqueous tear, and mucins) are compromised, and subsequent treatments should be used to compensate for the corresponding abnormal components. Observation of the tear film breakup pattern may provide important insight into identify abnormal components.³⁰ This concept is discussed in detail by Yokoi and Georgiev.³¹

Poor correlations between signs and symptoms in DED have been a challenging issue in DED research. Many recent studies have emphasized the importance of neurosensory abnormalities in DED, as indicated in the DEWS II report; however, no clinically useful method for assessing this component is currently available. The goal of DED treatment is to alleviate the patient's discomfort, so future research should be directed toward developing diagnostic measures that correlate with the patient's symptoms. The current definitions and criteria of DED should then be revised in accordance with the progress of such studies.

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