Deciphering Dry Eye Syndrome and Ocular Allergy: Accurate Diagnosis and Appropriate Treatment

PeerView inReview

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What’s Inside

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11 New Frontiers in the Treatment of Dry Eye Syndrome
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Activity Information

Activity Description and Educational Objectives
In this activity, a prominent expert in ocular surface disorders discusses the accurate diagnosis of dry eye syndrome and ocular allergy, and explores individualized evidence-based treatment strategies for patients with these conditions.

Upon completion of this activity, participants should be better able to:
- Apply approaches to accurately diagnose patients with dry eye syndrome and/or ocular allergy
- Discuss current and emerging treatments for dry eye syndrome and ocular allergy in terms of mechanism of action, efficacy, and safety
- Employ individualized evidence-based strategies to treat patients with dry eye syndrome and/or ocular allergy

Target Audience
This activity has been designed to meet the educational needs of ophthalmologists, internists, family practice/general practice physicians, and other clinicians involved in the management of patients with dry eye syndrome and/or ocular allergy.

Requirements for Successful Completion
In order to receive credit, participants must view the activity and complete the post-test and evaluation form. A score of 70% or higher is needed to obtain CME credit. There are no pre-requisites and there is no fee to participate in this activity or to receive CME credit. Statements of Credit are awarded upon successful completion of the post-test and evaluation form.

Media: Enduring Material
Release and Expiration Dates: November 09, 2016 - November 08, 2017
Time to Complete: 45 minutes

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Deciphering Dry Eye Syndrome and Ocular Allergy:
Accurate Diagnosis and Appropriate Treatment

Advances in Strategies to Diagnose Dry Eye Syndrome

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Both are increasing in prevalence, both impact quality of life, and both conditions have similar symptoms, but they can be differentiated to determine the appropriate treatment, because the appropriate treatment is often very different.

So, let's get started with the diagnosis of dry eye syndrome and ocular allergy.

First of all, both are very common and responsible for a large number of patient visits. As a matter of fact, these two conditions combined are the single most common reason why patients come in to a doctor's office for evaluation. And that's true for not only ophthalmology, but optometry as well.

Deciphering Dry Eye Syndrome and Ocular Allergy: Accurate Diagnosis and Appropriate Treatment


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First of all—and I think this might be one of the most important concepts—the symptoms of dry eye are extraordinarily variable, and that’s one of the reasons why it’s very difficult sometimes to make the diagnosis, because every patient will have a different symptom.

Let’s talk about the dry eye syndrome symptoms and risk factors. Some patients complain of dryness. Some patients complain of tearing. Some patients complain of itching/burning. They can have foreign body sensation, excess tearing, redness, and pain. Sometimes, they get photophobia. But my best symptom is changes in visual acuity—vision that changes during the course of the day or changes between blinks.

It changes between morning and night. It changes after 5 minutes on the computer. When you have changing visual acuity, that’s almost always dry eye disease, until proven otherwise.

I mentioned the risk factors earlier. They include increasing age; female; hormonal imbalances; abnormal corneal innervation, which can sometimes occur after surgery; and medications such as antihistamines and steroids. Some diuretics also cause dry eye. Contact lens wear always makes dry eye worse. Vitamin deficiency is seen in third-world countries most commonly. After radiation; environmental stress.

Certain infections will cause dry eye, particularly herpetic disease. Allergies can cause dry eye. Autoimmune arthritis is very commonly associated with dry eye, and that also includes thyroid disease. Finally, smoking can also cause dry eye disease.

Diagnosis of DES: Signs

- Evaluate dry eye status
- Conventional studies
  - Lissamine green/rose bengal conjunctival stains
  - Fluorescein corneal staining
  - Schirmer test
  - Tear meniscus and debris
  - Tear break-up time
  - Corneal sensation

This brings us to “How do you diagnose dry eye?” Well, you listen to the symptoms, and then you look for the signs. Conventional signs are studies that include lissamine green or rose bengal—and I like both of these very much. In the top slide, you see a classic lissamine green conjunctival stain in the interpalpebral fissure. This is pathognomonic of dry eye, when it presents this way. But this is usually a later finding of dry eye.

Diagnostic Tests for Dry Eye Syndrome

- Fluorescein: stains cornea more than conjunctiva
- Rose bengal: stains conjunctiva more intensely than cornea; more sensitive for mild DES vs fluorescein
- Lissamine green: less pain, discomfort, toxicity vs rose bengal; somewhat less sensitive and more transient

Schirmer Test

- Quantitatively measures the tear production by the lacrimal gland during a fixed time period
- Thin strip of filter paper is placed in the inferior cul-de-sac

TBUT

- Quantitative test for measuring tear film stability
- Time required for tear film to break up following a blink
- A fluorescein strip is moistened with saline and applied to the inferior cul-de-sac
- After several blinks, the tear film is examined using the broad beam of a slit lamp with a blue filter for the appearance of the first dry spots on the cornea

Other tests: tear-meniscus height, corneal sensation


Fluorescein corneal staining occurs in even more advanced disease. Schirmer testing has been around since Otto Schirmer invented it over 100 years ago—and to be truthful, I don’t use it very much because it doesn’t give me that much information. I do like to look at tear meniscus and tear break-up time. And corneal sensation can be helpful as well. The problem is that many of these signs are very nonspecific.
### Deciphering Dry Eye Syndrome and Ocular Allergy: Accurate Diagnosis and Appropriate Treatment

**Why Use Advanced Diagnostic Testing in DES?**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive Predictive Value (PPV), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schirmer I &lt; 10 mm¹</td>
<td>83</td>
<td>68</td>
<td>31</td>
</tr>
<tr>
<td>TBUT &lt; 10 sec¹</td>
<td>72</td>
<td>62</td>
<td>25</td>
</tr>
<tr>
<td>Staining, rose bengal¹</td>
<td>25</td>
<td>90</td>
<td>31</td>
</tr>
<tr>
<td>Tear meniscus height ≤ 0.35 mm¹</td>
<td>93</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td>Osmolarity &gt; 308 mOsms/L²,³</td>
<td>75-95</td>
<td>88</td>
<td>87</td>
</tr>
<tr>
<td>MMP-9 ≥ 40 ng/mL⁴</td>
<td>85</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>Conventional Sjögren biomarkers⁵</td>
<td>40-60</td>
<td>40-60</td>
<td>Not available</td>
</tr>
<tr>
<td>Lipid-layer thickness ≤ 60 nm⁶</td>
<td>48</td>
<td>90</td>
<td>Not available</td>
</tr>
<tr>
<td>New Sjögren markers⁷</td>
<td>&gt; 95</td>
<td>&gt; 95</td>
<td>Not available</td>
</tr>
</tbody>
</table>


There is some advanced diagnostic testing, however, which I think is very important, and is the wave of the future. I want to practice smarter, not practice harder. And to do this, I use point-of-service testing that adds significant sensitivity and specificity to the diagnosis of dry eye.

You can see here that Schirmer testing, tear break-up time, staining, and tear meniscus all have very low predictive value, while osmolarity and MMP-9 levels are very highly predictive of dry eye disease. So, I very much rely upon these tests in diagnosing dry eye. It makes the diagnosis faster and easier, and lets me spend more time with my patients talking about therapy.

I’m looking at the meibomian gland. Looking at the lipid layer thickness can be helpful. And there are some new Sjögren markers, as well.

**Point of Service Testing in DES**

1. Patient presents with DES complaints
2. Symptom questionnaire (eg, OSDI, DEQ, Schein questionnaire)
3. Technician confirms symptoms are present
4. Noninvasive advanced tear film testing
   - Osmolarity levels/MMP-9
   - Meibomian gland imaging
5. Slit lamp examination and invasive follow-up testing to confirm diagnosis

In our office, patients come in for an ophthalmic examination, and we do point-of-service testing. The patient will make a complaint of dry eye. We have a questionnaire that includes testing such as the OSDI, the DEQ, and the Schein questionnaire. If a patient answers three questions positively, that empowers our technician to confirm that the symptoms are present and then do testing.

We do osmolarity testing with tear lab and MMP-9 testing. And we also do meibomian gland imaging. With this testing, I have the information in front of me when I see the patients, and I can do my slit lamp exam and follow-up testing to confirm the diagnosis.

**Two Numbers Crucial to Understanding Osmolarity**

MAXIMUM of the two eyes: 314 mOsms/L
- Tears higher than 300 mOsms/L demonstrate loss of homeostasis and likely become pathogenic
- >308 mOsms/L

DIFFERENCE between the two eyes: 24 mOsms/L
- This tells you how stable the tear film is.
- Normal tears are stable and near 300 mOsms/L bilaterally. A difference of >8 mOsms/L is a hallmark of tear film instability.

If you’re doing tear osmolarity, you have to understand some very important ideas. If the tear osmolarity is higher than 308 mOsms/L, most likely the patient has dry eye disease. But also very commonly, the patients have lost their natural homeostasis, and they lose their ability to control osmolarity, and because of that, there can be a difference between the two eyes of greater than 8 mOsms/L. If the difference is greater than 8 mOsms/L, this is also pathognomonic of dry eye disease.
Here you see, on the bottom of the slide, a patient who has an osmolarity of 290 mOsms/L in one eye and 314 mOsms/L in the other eye. The 314 mOsms/L is clearly abnormal, but the difference of 24 mOsms/L between the two eyes, in this case, is also abnormal.

When you're examining patients with dry eye disease, don't forget to look at the eyelids—now, you can look at the eyelids yourself at the slit lamp, but we have much better technology available today. This is interferometry with DMI, and you can actually see the meibomian glands. You can see them lighting up, and you can see loss of meibomian glands in patients who have meibomian gland disease.

This allows the doctor to show the patient exactly where the glands are blocked and why the patient is significantly symptomatic. This test has really changed the way I diagnose dry eye and has allowed me to become a better clinician by educating my patients about the importance of managing their meibomian gland disease.

MMP-9 is an inflammatory marker. [An in-office tear analysis] tests for the presence of matrix metalloproteinase-9, and you get a positive result in 10 minutes. When you see a red and blue line, this tells you that the patient has high levels, that there's an inflammatory ocular surface, and that this patient most likely has dry eye. It's very sensitive and specific to dry eye disease.

**DES: Determining Disease Severity**

<table>
<thead>
<tr>
<th>Dry Eye Severity Level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discomfort, severity, and frequency</td>
<td>Mild and/or episodic; occurs under environmental stress</td>
<td>Moderate episodic or chronic, stress or no stress</td>
<td>Severe frequent or constant without stress</td>
<td>Severe and/or disabling and constant</td>
</tr>
<tr>
<td>Visual symptoms</td>
<td>None or episodic mild fatigue</td>
<td>Annoying and/or activity-limiting, episodic</td>
<td>Annoying, chronic, and/or constant, limiting activity</td>
<td>Constant and/or possibly disabling</td>
</tr>
<tr>
<td>Conjunctival injection</td>
<td>None to mild</td>
<td>None to mild</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Conjunctival staining</td>
<td>None to mild</td>
<td>Variable</td>
<td>Moderate to marked</td>
<td>Marked</td>
</tr>
<tr>
<td>Corneal staining (severity/location)</td>
<td>None to mild</td>
<td>Variable</td>
<td>Marked central</td>
<td>Severe punctate erosions</td>
</tr>
</tbody>
</table>

*M Must have signs and symptoms.


Now that we have diagnosed dry eye disease, we have to determine how severe the disease is. This is a guideline for the different levels of dry eye, ranging from level 1, which is mild, up to level 4, which is severe and disabling. Thankfully, we don't see level 4 too often.
**DES: Determining Disease Severity (Cont'd)**

<table>
<thead>
<tr>
<th>Dry Eye Severity Level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal/tear signs</td>
<td>None to mild</td>
<td>Mild debris, ↓ meniscus</td>
<td>Filamentary keratitis, mucus clumping, ↑ tear debris</td>
<td>Filamentary keratitis, mucus clumping, ↑ tear debris, ulceration</td>
</tr>
<tr>
<td>Lid/meibomian glands</td>
<td>MGD variably present</td>
<td>MGD variably present</td>
<td>Frequent</td>
<td>Trichiasis, keratinization, symblepharon</td>
</tr>
<tr>
<td>TFBUT, sec</td>
<td>Variable</td>
<td>≤10</td>
<td>≤5</td>
<td>Immediate</td>
</tr>
<tr>
<td>Schirmer score, mm/5 min</td>
<td>Variable</td>
<td>≤10</td>
<td>≤5</td>
<td>≤2</td>
</tr>
</tbody>
</table>

*Must have signs and symptoms.


And the important part about this nomogram is that when you diagnose the severity of dry eye, it also helps you develop a treatment strategy based on the severity of the disease.
Approaches to Differentiate Among Ocular Allergy, Dry Eye Syndrome, and Ocular Infection

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Ocular Allergy: Types

AC

VKC

GPC

AKC

4. Courtesy of Dr. Donnenfeld.

Dr. Donnenfeld: Let’s move on to ocular allergy now. Ocular allergy is extremely common, especially if you live in an area that’s warm and moist.

Here you see allergic conjunctivitis in the upper left. On the upper right, you see vernal keratoconjunctivitis. Lower left is giant papillary conjunctivitis, most likely from contact lens wear. GPC and VKC are best diagnosed by flipping the lid and looking at the bottom of the lid, where you can actually make the diagnosis.

Bottom right, you see atopic keratoconjunctivitis. And in this disease, you see that there’s also skin damage and damage to the lid margin, with lichenification and thickening of the lid margin as well.

Ocular Allergy: Symptoms, Signs, and Risk Factors

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itching</td>
<td>Hyperemia of the conjunctiva and eyelids</td>
<td>Personal or family history of allergic disease</td>
</tr>
<tr>
<td>Tearing</td>
<td>Conjunctival chemosis and papillae</td>
<td>Environment</td>
</tr>
<tr>
<td>Burning</td>
<td>Eyelid edema</td>
<td>Younger age</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>Clear, watery, or stringy discharge</td>
<td>Male sex</td>
</tr>
<tr>
<td>Ocular dryness</td>
<td></td>
<td>Hygiene (hypothetical)</td>
</tr>
</tbody>
</table>


So, let’s talk about the symptoms of ocular allergy, the signs, and the risk factors. Symptoms begin with itching. Itching, itching, itching. So, patients who have itching have allergy until proven otherwise. Now, you can have dry eye and have itching, but again, itching, 99% of the time, is going to be allergy. And that’s the most important symptom we have to diagnose this disease.

Patients can also complain of tearing, burning, foreign body sensation, and ocular dryness. The signs are hyperemia of the conjunctiva and eyelid. They can have chemosis—or swelling of the conjunctiva—and papillary changes, if you flip the upper lid. They will have eyelid edema. They’ll have swelling. They’ll have clear, watery, or stringy discharge—a stringy mucous discharge is really very pathognomonic of allergy.

Risk factors include a personal or family history of allergic disease. Many times, these patients have environmental allergies as well. It can be dander. It can be cat hair. It’s usually more common in younger patients. It’s actually common in males and in females, but a little bit more common in males. Hygiene may hypothetically play a role.

A lot of risk factors are environmental, and getting patients into the right environment and getting rid of plush rugs and pillows can be very helpful.
Deciphering Dry Eye Syndrome and Ocular Allergy: Accurate Diagnosis and Appropriate Treatment

Point-of-Care Allergy Testing

**Skin Test**
- Can identify patients with atopic and allergic conditions, such as conjunctivitis
- Does not specifically determine the etiology of conjunctivitis
- Other findings needed to corroborate test
- Must have access to epinephrine in case of anaphylaxis


We do a lot of allergy testing in our practice—doing skin testing, identifying patients who have allergy. We very commonly can find the cause of their allergies by doing skin testing, and this allows us to do a more specific treatment protocol that includes staying away from environments in which they are at risk.

You have to have epinephrine in case of anaphylaxis if you’re doing allergy testing, but I find it very helpful. Or you can work with an allergist, who can help you with this, as well.

**DES Versus Ocular Allergy**

<table>
<thead>
<tr>
<th>More likely allergy if:</th>
<th>More likely DES if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Itching is predominant symptom</td>
<td>• Burning or foreign body sensation is more predominant than itching</td>
</tr>
<tr>
<td>• Itching occurs seasonally</td>
<td>• Burning and itching worsen when concentrating on visual tasks (eg, reading, computer work)</td>
</tr>
<tr>
<td>• Patient has history of allergic phenotypes</td>
<td>• Presence of itchy eyelids accompanied by eyelid crusting</td>
</tr>
</tbody>
</table>

But it’s dry eye if they complain of foreign body sensation, burning, scratching, visual fluctuation, or they have itchy eyelids that are accompanied by eyelid crusting, which is a sign of meibomian gland disease.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Discharge</th>
<th>Eye Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES</td>
<td>Stringy</td>
<td>Typically bilateral (can be unilateral)</td>
</tr>
<tr>
<td>Allergic conjunctivitis</td>
<td>Watery or stringy</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Viral conjunctivitis</td>
<td>Watery</td>
<td>Unilateral initially, but can lead to infection of other eye</td>
</tr>
<tr>
<td>Bacterial conjunctivitis</td>
<td>Mucopurulent or purulent, often associated with morning crusting and difficulty opening the eyelids</td>
<td>Unilateral initially, but can lead to infection of other eye</td>
</tr>
</tbody>
</table>


Remember, with dry eye, you’ll have a stringy discharge, and it can be bilateral or unilateral, but it’s usually both eyes. Whereas with allergy, it tends to be more watery, and the stringing is much longer and much more redundant. It’s always bilateral disease.

In viral disease, which can also cause a red eye, it’s a watery discharge, usually unilateral, but then it goes on to the second eye very commonly. And finally, bacterial conjunctivitis has a mucopurulent discharge with white discharge, and the eyelids are very commonly stuck together in the morning when they wake up.

**Differential Diagnosis of the Red Eye**

When you look at dry eye versus ocular allergy, if it’s itching, think allergy. Patients who have family history of allergy, including diseases such as asthma, also very commonly have ocular allergy.


So, here you see a nomogram for the differential diagnosis of red eye. The differential starts with pain. Patients who have pain very commonly have more serious disease. Blurred vision is also a symptom more highly associated with more significant disease. So, when patients have pain or blurred vision, they require an ophthalmic examination as soon as is reasonable.

If they don’t have pain and they don’t have blurred vision, then most likely, it’s a less significant problem. But you, again, can look for signs of allergy, with itching or discharge being purulent or watery. That goes on to the diagnosis of allergic, bacterial, or viral conjunctivitis.
New Frontiers in the Treatment of Dry Eye Syndrome

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Goals of DES Therapy

- Maximize clarity and quality of tears
- Target patient’s specific DES (e.g., aqueous deficient, evaporative, or both)
- Prevent progression of disease


Dr. Donnenfeld: So, let’s talk about new frontiers now in the treatment of dry eye. This is one of the most exciting areas in ophthalmology and optometry today: the new treatments of dry eye syndrome.

The goals of dry eye are to maximize the clarity and the quality of the tears; to be target specific, to treat the cause of the dry eye, whether it be aqueous deficiency, evaporative, or both; and also to prevent progression of the disease. So it’s very nice to treat the symptoms of dry eye, but as a clinician, I’m most interested in trying to stop the progression of disease.


The first-line therapy for most [dry-eye patients] is artificial tears. This is a lubrication. It replaces tear film components, but artificial tears are never as good as a patient’s own natural tears. Using tears can decrease tear osmolarity by lubricating the eye, and that makes the patients feel better.

They generally work for a half an hour to an hour. There are a couple of good products that are out there that are hypo-osmolar that work very nicely. And there are some now that have increased viscosity, as well. They increase the retention time. And these new, more modern tears stay on the ocular surface longer and give a more prolonged relief. But again, remember, they treat the symptoms, not the cause of the disease.

When treating patients with dry eye, remember that preservatives can be very damaging to the ocular surface. So, I never use a preserved tear more than every 4 hours. If I go more than 4 hours, I like to use a nonpreserved tear.

There are also different types of tears. There are tears that have the preservative benzalkonium chloride, and those that have a transient preservative, such as a stabilized oxychloro complex—these denigrate with exposure to air or to light, and they don’t have as much of an effect, and don’t cause as much ocular damage.

Benzalkonium chloride can be a little bit more toxic to the ocular surface. So again, if I use a tear that has benzalkonium chloride, I don’t want to use it more than every 4 hours.

Nonpreserved tears work great. They’re a little bit more expensive, but for patients with more significant dry eye, I find they make a very nice improvement in the patient’s ocular surface disease.

Theoretically, act as a lacrimal substitute to provide lubrication and contain other biochemical components mimicking natural tears more closely

Used in severe DES

Analyses of studies revealed inconsistency in the possible benefits in improving patient-reported symptoms and TBUT, and lack of effect based on other objective clinical measures

More studies are needed


Serum tears are taken from the patient’s own serum, and this can be a panacea for some patients. The plasma of a patient has about 100 to 200 different proteins—things like lactoferrin, immunoglobulins, and growth factors—that work very well on the ocular surface.

We spin down the patient’s blood. We then take off the red blood cells and leave the supernatant, which is clear. And this tends to be very helpful for patients with more significant dry eye disease.

Nutritional supplements, for me, are one of the mainstays of therapy for dry eye disease. Nutritional supplements made up of omega-3s decrease inflammation. They improve the oily layer of the tear film. They improve the aqueous consistency, as well.

There are a number of good products that are available today. I strongly believe in the use of omega-3 fatty acids, and there are a couple of omega-3s that are re-esterified that are even better.

The problem with some of the omega-3s out in the market today is that they have alcohol added to them to remove the toxins, such as mercury, and in doing that, it converts the natural triglyceride omega-3 into an ethyl ester not found in nature, which the body can’t absorb.

Some of these new omega-3s give much higher tissue levels and can really improve the quality of tear film not only in meibomian gland disease but also in aqueous deficiency dry eye.

Let’s now talk about medical therapy with topical treatments for dry eye. The first drug was topical cyclosporine, which was approved over a decade ago. And until recently, it was the only drug FDA approved for dry eye. This was really a landmark therapy for treating dry eye disease. The mechanism of action is to prevent T-cell activation in the lacrimal gland and the ocular surface. A number of studies were done that I was actually part of that showed a significant improvement in several parameters, including Schirmer scores, in patients who received cyclosporine. There have been some long-term studies that have shown that it definitely helps to improve the ocular surface, improve tear quality and quantity, and improve patient comfort. Most common adverse events include burning, stinging, and hyperemia.

Topical corticosteroids have been around for a long time. They are not approved for use in dry eye, but we find them very helpful. I like to use loteprednol most commonly. It has a very high therapeutic index with a very low toxicity. It does not cause cataractogenesis or glaucoma very commonly. But everyone has to realize that if you use steroids, you will get a very good effect very quickly. But the problem with these drops is they cannot be used for long periods. They can only be used for 2 to 4 weeks.

I use them on patients who are on medical therapy and who get flare-ups. That is, when they go to higher altitudes or to dry environments. But again, short-term use limits their utility, but when they are used, they can be very, very helpful.

Another good treatment for dry eye syndrome is mucolytic agents. These are topical. They break the disulfide bridges. I don’t usually use them that often. They can be helpful for filamentary keratitis, and they may be as effective as a steroid–antibiotic combination. But they do sting, and they have a very odorous smell to them, as well. Refrigeration is recommended.
Topical azithromycin has been found to be very helpful for meibomian gland disease. It helps with dryness and meibomian gland scores. We rub the azithromycin into the patient’s lid once a day, and we do that for about a month, and then we stop for a month, and we alternate—so [the patients are treated] a month on, and a month off.

Topical azithromycin in Patients With DES Associated With MGD\(^1\),\(^a\)

![Graph showing grades of ocular symptoms before and after treatment with azithromycin.](image)

**Most common AE**: eye irritation (1% to 2% of patients)\(^2\)

\(^{a}\) Off-label use.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Itch</th>
<th>FBS</th>
<th>Dryness</th>
<th>Burning</th>
<th>Stiffness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>


There are no randomized trials for doxycycline or minocycline, but I use them very commonly. The results have been around for a long time. The most common mistake that people make is they use too much. Doxycycline can be started at 50 mg twice a day for a month and then go down to 50 mg once a day after that.

### Treatment of DES: Secretagogues\(^1\),\(^a\)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Topical</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocarpine</td>
<td>☑️</td>
<td>☑️</td>
</tr>
<tr>
<td>Cevimeline</td>
<td>☑️</td>
<td>☑️</td>
</tr>
</tbody>
</table>

**MOA**
- Stimulate aqueous tear mucin secretion
- FDA approved for use in severe dry mouth related to Sjögren syndrome

**Efficacy**
- Mainly improve dry mouth symptoms but also have benefit in DES
- Reserved for patients with severe DES

**Adverse Events**
- Diarrhea, sweating, and bradycardia are common; limit widespread use

\(^{a}\) Off-label use.


There are some systemic secretagogues, as well, including pilocarpine and cevimeline. They have a lot of side effects, however—diarrhea, sweating, and bradycardia—and this limits their use. But for patients who have significant dry eye, as well as dry mouth with Sjögren syndrome, they can be very helpful for a limited number of patients. The patients who use them who find them helpful can find them to be extremely helpful.

I don’t use them very much, except for patients who usually have a systemic rheumatoid disease, such as Sjögren syndrome.

### New Treatment Option for DES: Lifitegrast

- Inhibits the integrin LFA-1 from binding to ICAM-1, interrupting the T-cell–mediated inflammatory cycle
- Approved in July 2016 for the treatment of signs and symptoms of DES

**Conjunctiva**
- New tissue
- New vessels
- Tissue with inflammatory cells


Oral tetracyclines are also helpful for dry eye. They’re primarily used for patients who have meibomian gland disease and are very helpful for ocular rosacea. They have an anti-inflammatory, as well as an antibacterial, effect and a decrease in inflammatory markers.

**Treatment of DES: Oral Tetracyclines\(^a\)**

- Used primarily for DES associated with ocular rosacea
- Used primarily for anti-inflammatory properties vs antibacterial effects
  - Decreased proinflammatory markers (eg, MMP, IL-1, TNFα)
- Studies primarily performed with oxytetracycline\(^a\) and tetracycline in ocular rosacea patients\(^1\)\(^2\)\(^3\)
  - No randomized trials with doxycycline or minocycline

\(^{a}\) Off-label use. \(^{b}\) Unavailable in the United States.

The newest option for dry eye disease is lifitegrast. This was approved by the FDA in July 2016, and this is the first FDA-approved medication in over a decade. It’s also the first medication that improves the signs and symptoms of dry eye disease. And it works by inhibiting LFA—which is lymphocyte function–associated antigen—from binding to ICAM, which is intracellular adhesion molecule.

And it does this by preventing adhesion, which has a very rapid effect on inflammation by preventing migration, recruitment, and diapedesis of T cells, and the release of cytokines.

The FDA studies were very impressive, with the phase 3 studies showing $P$ values of less than .0001 in patient symptomatology. The SONATA phase 3 safety study showed that lifitegrast was safe and well tolerated. This was a study that I was an author on. It gave a 1-year follow up on patients who had dry eye disease.

Other treatments for dry eye disease are punctal occlusion. I love punctal occlusion, but I always like to start the patient on immunotherapy before I use punctal occlusion, because I don’t want to trap a toxic tear film against the ocular surface. So, I start with cyclosporine or I start with lifitegrast or steroid, and then a couple weeks later, I’ll add punctal occlusion.

Moisture chamber goggles or sun shields are useful in very windy environments, especially outdoors. And contact lenses can help in very severe dry eye disease.

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**Lifitegrast: Phase 3 Studies**

- Lifitegrast improved ICSS and EDS

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment Effect (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement from BL EDS at d 84 vs PBO</td>
<td>7.16 (3.04-11.28)</td>
<td>.0007</td>
</tr>
<tr>
<td>Mean change from BL EDS at d 42 vs PBO</td>
<td>9.32 (5.44-13.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean change from BL EDS at d 14 vs PBO</td>
<td>7.85 (4.33-11.37)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

- SONATA phase 3 safety study: lifitegrast was safe and well tolerated

- Most common (>5%) TEAEs occurring in either treatment group were instillation-site irritation (burning), instillation-site reaction, reduced visual acuity, dry eye, and dysgeusia
- Drop comfort improved within 3 minutes of instillation

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**Other DES Treatments**

**Punctal Occlusion**

- Commonly used to reduce drainage of tears through the lacrimal ducts, increase lubrication on the ocular surface, and prolong the effect of tear supplements
- Can be permanent with punctal cautery
- Limited evidence suggests symptomatic relief in severe DES
- Complications include extrusion, internal migration, biofilm formation, and infection

**Moisture Chambers, Eyeglasses With Sun Shields**

- Noninvasive, palliative treatments that may be useful
- May help protect and hydrate the corneal surface in severe DES
- Small risk of corneal vascularization and corneal infection

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**Moisture Chambers, Eyeglasses With Sun Shields**

- Commonly used to reduce drainage of tears through the lacrimal ducts, increase lubrication on the ocular surface, and prolong the effect of tear supplements

**Hydroxypropyl Cellulose Ophthalmic Insert**

- Slow-release prescription lubricant placed in inferior cul-de-sac of eye
- Improves discomfort, burning, dryness, grittiness, stinginess, and light sensitivity, as well ability to perform activities of daily living and in QOL

**Thermal Pulsation**

- For evaporative DES
- Heat and massaging used to evacuate the blockages from the glands, allowing the glands to resume oil production

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There are some other technologies, such as hydroxypropyl cellulose inserts. They sit in the inferior cul-de-sac and are sometimes tolerated, but very commonly, patients find them irritating. But for the patients who like them, they really get significant relief. And then, thermal pulsation to treat evaporative dry eye can be very helpful in opening the blocked oil glands and allowing the glands to resume oil production.


<table>
<thead>
<tr>
<th>Severity Level</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>- Education and environmental/dietary modifications</td>
</tr>
<tr>
<td></td>
<td>- Discontinuation of exacerbating medications</td>
</tr>
<tr>
<td></td>
<td>- Artificial tear substitutes, gels/ointments</td>
</tr>
<tr>
<td></td>
<td>- Eyelid therapy</td>
</tr>
<tr>
<td></td>
<td>If treatments above inadequate, add:</td>
</tr>
<tr>
<td></td>
<td>- Anti-inflammatory agents</td>
</tr>
<tr>
<td></td>
<td>- Tetracyclines (for meibomianitis, rosacea)</td>
</tr>
<tr>
<td></td>
<td>- Punctal plugs</td>
</tr>
<tr>
<td></td>
<td>- Secretagogues</td>
</tr>
<tr>
<td></td>
<td>- Moisture-chamber spectacles</td>
</tr>
<tr>
<td>2</td>
<td>- Serum</td>
</tr>
<tr>
<td></td>
<td>- Contact lenses</td>
</tr>
<tr>
<td></td>
<td>- Permanent punctal occlusion</td>
</tr>
<tr>
<td>3</td>
<td>- Systemic anti-inflammatory agents</td>
</tr>
<tr>
<td></td>
<td>- Surgery (lid surgery, larsonophathy; mucous-membrane, salivary-gland, amniotic-membrane transplantation)</td>
</tr>
<tr>
<td>4</td>
<td>- Serum</td>
</tr>
<tr>
<td></td>
<td>- Contact lenses</td>
</tr>
<tr>
<td></td>
<td>- Permanent punctal occlusion</td>
</tr>
</tbody>
</table>


The dry eye syndrome treatment guidelines reported by the International Dry Eye Workshop in 2007 break down dry eye into mild, moderate, and severe, and make these recommendations about how to start therapy. I do believe that patients should have informed consent—that if they even have mild disease, it’s worth having a conversation with them about anti-inflammatory agents that can treat the cause of the dry eye, rather than treating the symptoms.

### DES: Emerging Therapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MOA</th>
<th>Mode of Delivery</th>
<th>Development Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tavilermide¹</td>
<td>TrkA agonist</td>
<td>Topical</td>
<td>3</td>
</tr>
<tr>
<td>Thymosin β4 (RGN-259)²</td>
<td>Regulator of actin polymerization</td>
<td>Topical</td>
<td>3</td>
</tr>
<tr>
<td>LME636³</td>
<td>TNF inhibitor</td>
<td>Topical</td>
<td>2</td>
</tr>
<tr>
<td>Tear neurostimulator⁴</td>
<td>Increases tear production upon stimulation</td>
<td>Intranasal device</td>
<td>Under FDA review</td>
</tr>
<tr>
<td>KPI-121⁵</td>
<td>Nanoparticle formulation of loteprednol</td>
<td>Topical; mucus-penetrating particle technology</td>
<td>3</td>
</tr>
<tr>
<td>New cyclosporine formulations⁶</td>
<td>Calcineurin inhibitor</td>
<td>New formulations and technologies</td>
<td>3</td>
</tr>
<tr>
<td>New cyclosporine formulations⁶</td>
<td>Calcineurin inhibitor</td>
<td>New formulations and technologies</td>
<td>3</td>
</tr>
</tbody>
</table>

1. Multidose cyclosporine was FDA approved in November 2016.


Emerging therapies include tavilermide—which is in phase 3—which is a secretagogue. There are a variety of other medications that are also coming that are very exciting. Tear neurostimulator is the first device for improving tear production and looks very interesting.

A nanoparticle formulation of loteprednol is looking to penetrate mucus and improve dry eye. And there are new cyclosporine formulations, including a multidose cyclosporine, coming in the next few months.
Updates in Treatment Options for Patients With Ocular Allergy

Goals of Ocular Allergy Therapy

1. Minimize and control signs and symptoms
2. Improve QOL
3. Reduce risk of adverse effects

Dr. Donnenfeld: Now that we've talked about dry eye, let's just talk about the treatment options for patients with ocular allergy. The goal of ocular allergy therapy is to minimize and control symptoms, improve quality of life without overtreating, and reduce the risk of the side effects of allergy, which include damage to the cornea from the allergy, and cataract and glaucoma from corticosteroid therapy.

Dr. Donnenfeld: Now that we've talked about dry eye, let's just talk about the treatment options for patients with ocular allergy. The goal of ocular allergy therapy is to minimize and control symptoms, improve quality of life without overtreating, and reduce the risk of the side effects of allergy, which include damage to the cornea from the allergy, and cataract and glaucoma from corticosteroid therapy.

Ocular Allergy Treatments: Allergen Avoidance

1. Stay indoors when allergens are high
2. Keep windows closed
3. Wear wrap-around sunglasses
4. Clean filters and ducts
5. Replace allergen-harboring items, such as pillows and carpets
6. Wash hair before going to sleep

Allergen avoidance is the primary behavioral modification but is often the most challenging for patients.

Ocular Allergy Treatments: Palliative

Artificial Tear Substitutes
- Provide a barrier and help improve first-line defense at the level of conjunctival mucosa
- Help dilute various allergens and inflammatory mediators that may be present on the ocular surface and help flush the ocular surface of these agents
- Refrigerating may provide more immediate relief
- Preservative-free formulations preferred for ocular allergy

Cool Compresses
- Provide palliative relief
- Should be recommended along with artificial tears to minimize eye rubbing, which leads to further histamine release and worsening symptoms


The first rule of allergy is to avoid it. Stay indoors when allergens are high. Keep the windows closed. Clean the filters and ducts. Replace allergen-harboring items. Avoid shag carpets and rugs—hardwood floors do just great. You do not want to use feather pillows. And wash hair before going to sleep to remove mites that might contribute to allergy. This is a crucial aspect in managing allergy.
Artificial tears lubricate the ocular surface and flush out the allergens. They can be very helpful, as are cool compresses. But most importantly, remember that every time you rub your eyes, you take mast cells, and they break them down and secrete inflammatory mediators. So at all costs, avoid eye rubbing, which only makes allergy worse.

Topical Pharmacologic Treatment: Antihistamines and Mast Cell Stabilizers

Antihistamines
- Examples: emedastine, levocabastine
- More effective for acute treatment
- Provide rapid relief of redness and itching
- Limited duration of action (up to 4 x/d dosing)

Mast Cell Stabilizers
- Examples: pemirolast, nedocromil, lodoxamide, cromolyn
- More effective in decreasing or eliminating symptoms of an attack when taken in advance
- Can be prescribed weeks or months in advance of a patient’s peak symptoms

Overall, topical antihistamines and mast cell stabilizers appear to be safe and well tolerated.

Therapies include antihistamines. They provide rapid relief. They work very nicely. And they have to be dosed two to four times a day.

There are also some mast cell stabilizers that can prevent the degranulation of mast cells, and they can be prescribed weeks to months ahead of the allergy season to make sure the eye is maximally controlled at the time that the allergens are present. Overall, antihistamines and mast cell stabilizers are safe and well tolerated.


There’s a group of combination antihistamines and mast cell stabilizers, and you see them listed here. They all work very well, and some of them now are down to one drop once a day, providing 24-hour relief and giving patients good control of their allergies through a combination effect of antihistamine and mast cell stabilization.

The most recent additions include bepotastine, alcaftadine, and olopatadine, all of which provide excellent relief for patients who have allergic disease.
Alcaftadine 0.25% was FDA approved in 2010 and, again, showed a marked improvement at 3 minutes versus placebo for seasonal and perennial allergens and is very well tolerated by most patients.

The most recent approval was olopatadine 0.7%, which is the first drug that is approved for 24-hour relief and is very well tolerated, again, showing a significant improvement at 24 hours after initiation of therapy.


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**Combination Antihistamine/Mast Cell Stabilizers: Alcaftadine 0.25%**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Time of Itching</th>
<th>Placebo Mean Score</th>
<th>BBOS 1.5% Mean Score</th>
<th>Difference in Mean Itching Score, Placebo - BBOS 1.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vis 5: 15-min onset of action</td>
<td>3</td>
<td>1.9 (70)</td>
<td>0.4 (70)</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>2.1 (70)</td>
<td>0.9 (70)</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1.9 (70)</td>
<td>0.5 (70)</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Vis 4: 6-h persistence of action</td>
<td>3</td>
<td>2.1 (67)</td>
<td>0.5 (64)</td>
<td>1.4</td>
</tr>
<tr>
<td>5</td>
<td>2.3 (67)</td>
<td>0.8 (64)</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2.1 (67)</td>
<td>0.8 (64)</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Vis 3B: 16-h persistence of action</td>
<td>3</td>
<td>2.0 (70)</td>
<td>1.2 (68)</td>
<td>0.8</td>
</tr>
<tr>
<td>5</td>
<td>2.3 (70)</td>
<td>1.3 (67)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2.1 (69)</td>
<td>1.2 (68)</td>
<td>0.9</td>
<td></td>
</tr>
</tbody>
</table>

- FDA approved in 2010 for once-daily dosing for the prevention of ocular itching associated with allergic conjunctivitis in patients aged ≥ 62 y
- Phase 3 studies: significant rapid reduction in ocular itching vs placebo, with ≥ 8-h duration of effectiveness
- Improvements in hyperemia, tearing, and eyelid swelling also observed
- Most common AE (<25% of patients): mild taste following instillation
- Other AEs (2% to 5% of patients): eye irritation, headache, nasopharyngitis

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Let’s look at the comparison of treatments. In patients with seasonal conjunctivitis, olopatadine, ketotifen, epinastine, and emedastine were more efficacious than FML in preventing itching. They all gave the same results in terms of reducing tearing. And the ocular surface finding by impression cytology improves with all of these drugs.

### Ocular Allergy Treatments: Anti-Inflammatories

<table>
<thead>
<tr>
<th>Topical Steroids (eg, Loteprednol, Fluorometholone, Prednisolone, Difluprednate, Dexamethasone, Rimexolone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Exert action early, often most effective in controlling inflammation associated with ocular allergy</td>
</tr>
<tr>
<td>• Typically used in patients nonresponsive to conventional therapy or in cases of acute, pronounced allergic response</td>
</tr>
<tr>
<td>• Loteprednol, fluorometholone, or prednisolone acetate 0.125% typically used because of propensity for effective control of inflammation and low side-effect profile</td>
</tr>
<tr>
<td>• More potent steroids (eg, prednisolone 1%, difluprednate, dexamethasone) may be considered in advanced and nonresponsive cases</td>
</tr>
<tr>
<td>• AEs: Risk of intraocular pressure elevation and cataracts</td>
</tr>
<tr>
<td>• Should not be used long term</td>
</tr>
</tbody>
</table>


Anti-inflammatory therapies work wonderfully, and we all know that steroids are the most efficacious therapy for managing disease. For patients with profound ocular allergy, I very regularly will use corticosteroids on a regular basis with very low-dose steroids, such as loteprednol, FML, or prednisolone acetate 0.125%, providing very good relief.

And again, it’s a risk:reward ratio—knowing that these steroids should be used for limited times. But when patients are very symptomatic, there’s nothing that provides relief like a corticosteroid.

### Cyclosporine and Tacrolimus

- Cyclosporine and tacrolimus are effective alternatives to steroids for patients with severe or chronic forms (eg, AKC, VKC)
- Tacrolimus and pimecrolimus may be safe alternative to steroids for allergic inflammation of eyelid skin due to eczema
- Act more slowly than steroids


Cyclosporine and tacrolimus are also effective and are good long-term therapies for the advanced form of chronic disease allergies, such as AKC and VKC. They appear to be safe and effective. But they do act more slowly than steroids, so they have to be on board for long periods of time.

### Ocular Allergy Treatments: Other Options

<table>
<thead>
<tr>
<th>Combining Decongestant (eg, Oxymetazoline Tetrahydrozoline, Naphazoline) With Antihistamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Traditionally, cornerstone of allergy therapy</td>
</tr>
<tr>
<td>• Use is decreasing</td>
</tr>
<tr>
<td>• AEs (eg, mydriasis, rebound hyperemia) and contraindication in patients with narrow angle glaucoma</td>
</tr>
<tr>
<td>• Availability of safer and more effective agents</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NSAIDs (eg, Ketorolac, Bromfenac, Nepafenac)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Relieve pain associated with inflammation</td>
</tr>
<tr>
<td>• Do not block histamine, only inhibit part of the inflammatory cascade</td>
</tr>
<tr>
<td>• Use in allergic conjunctivitis has decreased</td>
</tr>
</tbody>
</table>

Other therapies include decongestants. NSAIDs are very rarely used today. They originally were approved for allergy, but they don’t really play a significant role any longer.

Systemic therapy is used for severe refractory allergic conjunctivitis, including systemic [immunosuppressive therapy] and allergen immunotherapy. I very commonly will consult an allergist when I want to include systemic therapies for my patients with severe allergic disease.

Considerations in Selecting Treatment: Comorbidities

Considerations in patients with ocular allergy and DES
- Systemic antihistamines may worsen ocular dryness
- Punctal plugs for DES hold allergens on the ocular surface
- Crossover therapies: artificial tears, avoidance of inciting agents, cyclosporine, and steroids

Considerations in patients with ocular allergy and glaucoma or cataract
- Steroids increase risk

Comorbidities may be what underlies much of the therapeutic failure of allergy treatment

Here we have an ocular allergy treatment algorithm looking at different therapies, including prescription and over-the-counter medications for mild, moderate, and severe ocular allergy.

Considerations in selecting treatments are the comorbidities. Realize that ocular allergy very often will make dry eye worse. So, systemic antihistamines may make it much worse. Punctal plugs will hold the allergens in place. And there’s a crossover with certain therapies, including artificial tears, avoidance of inciting agents, cyclosporine, and steroids in helping both dry eye and allergy together. Comorbidities may be what underlies much of the therapeutic failure of allergy treatments.

New emerging therapies are listed above, including NS2, hydrocortisone ointments, and sustained-release dexamethasone. These are exciting. They are in phase 2, and the dexamethasone is in phase 3 FDA trials.
Conclusions

- DES and ocular allergy significantly impact patients, and their prevalence is increasing.
- Physicians must differentiate between these disorders to appropriately select therapy.
- Treatment options for both DES and ocular allergy have recently expanded and continue to grow.
- A variety of factors influence treatment selection, including disease severity and the presence of other conditions.

In conclusion, dry eye disease and ocular allergy significantly impact patients’ quality of life and quality of vision. Their prevalence is increasing. Physicians must differentiate between these disorders in order to treat appropriately. Treatment options for both dry eye syndrome and ocular allergy have recently expanded and continue to grow. A variety of factors influence treatment selection, including disease severity and the presence of other conditions.

Dry eye disease and ocular allergy are among the most common reasons why patients come to the eye doctor’s office, and developing a good treatment protocol for managing these common diseases is one of the most important things we can do in our offices to improve the quality of care we provide to our patients. Thank you very much.