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# Unique New Strategies for the Pharmacologic Treatment of Dry Eye Disease: Focus

**Announcer:**
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**Dr. Wirta:**
Welcome to Unique New Strategies for the Pharmacologic Treatment of Dry Eye Disease: Focus on Neuromodulation presented by Partners for Advancing Clinical Education in partnership with the New England College of Optometry, broadcast on Medlive.com.

My name is Dr. David Wirta. I'm the Medical Director of the Eye Research Foundation Incorporated. I'd now like to introduce my co-presenter, Dr. Selena McGee, a Fellow of the American Academy of Optometry and Founder of Bespoke Vision.

Thank you, Selena, for joining me today.

**Dr. McGee:**
Thanks everybody. Thanks, David, for having me. This is going to be a fun discussion.

**Dr. Wirta:**
I agree.

These are our disclosures.

These are all learning objectives.

Diagnose dry eye disease to prevent potentially serious complications, including eye damage, vision loss and quality of life impairment. Number two, explain underlying pathophysiologies of dry eye disease, including the role of the lacrimal functional unit.

Number three, select pharmacologic agents for treating dry eye disease based on understanding of their mechanisms of action, efficacy and safety, with a focus on neuromodulation and agents targeting the lacrimal functional unit. And lastly, to review mechanisms of actions and clinical trial findings for newer and emerging treatments for dry eye disease, with an emphasis on those targeting components of the lacrimal functional unit.

**Dr. McGee:**
Perfect. OK. So, we are going to dive in, and we're going to start with the diagnosis and pathophysiology of dry eye disease. So, here's Chapter 1, and I'm going to start with a polling question just to see kind of where you guys are in this space. So, here's our first polling question.

How confident are you in your ability to recognize and diagnose dry eye disease? A: Very confident, B: Somewhat confident, C: Neutral, D: Not very confident, E: Not at all confident.

And as we go through this, I'm hoping our goal is to simplify things, make it a little more straightforward, because so many things have changed in the last two decades around diagnosing dry eye disease, and now we have more therapies and more ways to manage dry eye disease. And so, David and I are going to work on simplifying that for us and creating a dialogue that hopefully if you're in the neutral, not very confident, or not at all confident, we can bring you guys up to very confident and somewhat confident.

I'm confident you guys are going to have a great time today. OK. So, let's talk about just the overview and impact on our patient's lives. And this is a multifactorial condition, and when we think about what's really happening at the ocular surface, we lose stability of the tear film. And when that tear film becomes unstable due to many things, medications, walking through the day, doing what you and I are doing right now with screen time, systemic problems, all of those things can cause our loss of homeostasis at the ocular surface. And once we lose homeostasis, we trigger and wind up in that inflammatory cascade and our patients are often going to have symptoms. Many times, they're going to have symptoms that, unless we're really intentional about asking, can easily be overlooked. It is a highly prevalent condition. The most common thing that you and I are going to see in clinic. Women are disproportionately affected once you get over the age of 40, because hormones play a role, and both menopause, as well as pregnancy, can certainly disrupt homeostasis.

But it's interesting, when you look at the data of patients under the of 40, it's pretty equal between men and women. So, don't just pigeonhole your dry eye patients into that one, small category. This can affect anyone at any age, and it's quite detrimental to patients' everyday lives, and it impacts their daily activities, how they move throughout their day. They can experience loss of productivity and just functioning.

And you guys have all had those patients. They're very concerned about what's happening, but they can't always equate what they're experiencing to, I have dry eye disease.

And I think that's what makes it more complex, is there's a multifactorial component and symptoms are often all over the place, unless we're really intentional about identifying that. And then there's the emotional impact. Patients can have depression, anxiety around their symptoms and what they're experiencing, so it's really important for us to diagnose these patients early so that we can intervene early.

When we diagnose and intervene early, I have found that it's less complicated because once you get into the moderate to severe dry eye patient, and you have comorbidities, it can be more difficult to figure out what's really going on in the clinical picture. Often patients are going to have lots of different symptoms, including the ones that you see listed on the screen. Their eyes are irritated, they can water, which you go through that whole paradoxical effect of, wait, you just told me that I have dry disease, Dr. McGee, but my eyes water. And so, you're going to need to explain that to patients. Your eyes can burn, they can sting, discomfort throughout the day, just eye dryness. Grittiness, foreign body sensation, photophobia, itching, blurry vision.

That's the number one reason why patients come in to see me, and it's probably the number one reason why they came to see you, is because they need to see well. And when their vision fluctuates throughout the day, that's going to give you the diagnosis of dry eye disease. And unless we're really intentional about asking when their symptoms occur, do they occur first thing in the morning? Do they occur late in the evening as the day goes? Do they seem to see better at certain different times of the day? Those are all really good questions that will help you elucidate, is this dry eye or is it another component here?

Certainly, contact lens intolerance. And when you look at the contact lens dropout rates over the last 20 years, they have not changed, which is really interesting to me. When we have new modalities, we have new solutions, and yet the dropout rate is still the same. That tells me there's something going on at the ocular surface and that's where we need to start. Redness, mucus discharge, increased frequency of blinking, all of those things our patients experience as they move throughout the day. But typically, at least in my experience, patients aren't going to come in saying, hey, doc, my eyes are dry. So, I think it's really important to be intentional about soliciting these symptoms. And what I think is important, and what I do in my clinic is, I do a speed questionnaire on every single patient, my comprehensive exams, my glaucoma patients, certainly my dry eye consults and my dry eye follow-ups.

That way, that consistency of asking those same questions, I have an objective way to measure, so that the patient's objectively measuring their subjective symptoms. But I have found that that has really allowed me to be more intentional with my time in the exam lane because I already have all that information gathered before the patient gets there.

So, we're going to hear from a patient. This is Jane. She's going to talk about her dry eye symptoms and how they have impacted her life.

**Jane:**
But the symptoms I've been having, that I didn't put down necessarily to dry eye disease, was during the pandemic. I was spending a lot of time on computers because I'm a university lecturer. I started a part-time PhD, so, 12 hours a day on screens. So, my eyes were burning, they were gritty. A lot of that, I thought, was because of the chalazion in my right eye, because that's where I get the most pain.

So, it was grittiness, discomfort, it wouldn't go away. And then, switch to a year later, so April 2021. By that point, with not having any proper treatment, I developed severe pain in the inner corner of my right eye. And so, since I'm a university lecturer, I'm a career coach. I run my own business and a part-time PhD, so there's lots of things. And the advantage of that is that there are things I can drop at any one time and pick up again. So, what I have to do for work, because it was still very much teaching online and working online, coaching sessions online, I had to – I carried on working, but I would need to look away from the screen. I have – where have they gone? – I've got my moisture chamber glasses that I would wear, and various treatments, and the pain continued. But I have to say, if I wasn't working, I would've been focusing on the pain more and I would have become very depressed, so work was almost my salvation.

I had to go on a leave of absence from the PhD because that was very screen-focused at the stage I was at, so I put that on hold for a year and thought carefully about did I want to do that. But my ophthalmologist said that when I was ready, as long as I blinked regularly and used all the treatments, that I could continue.

**Dr. McGee:**
Wow, I mean, this is a person who is trying to work throughout the day, who has put her PhD on hold for a year because she's not sure that her symptoms are going to allow her to have that much screen time. And you guys heard her, she's on her screen typically 12 hours a day. I think that's one of the most important things is asking about screen time and understanding, and letting patients realize that they don't blink as often. They're partial blinks, they're not full blinks. But we can't ask people to not do their jobs.

And then for her, her work was a respite, and you heard her say she was completely focused on work, or she would've been focused on how bad her eyes felt and the pain that she was especially experiencing in that right eye. And so, those symptoms we cannot overlook when you see how it affects patients' everyday lives. And we heard that from her, as she's trying to move throughout her day. And again, I have to wonder, if we could have intervened earlier, would she have had to have waited a whole year and put her PhD on hold?

So, these are things that we should be having these conversations in the clinic and with our patients so that we really fully understand the impact that dry eye disease has on our patient's lives.

**Dr. Wirta:**
Yes, those are excellent points. I would say one thing for a patient like this is, once you hear all the symptoms and you detail perfectly all the symptoms you can associate with dry eye. We're going to delve into some of the treatments, but before that, obviously, the keys are the exam and see what level various aspects of the dry eye examination are at, so we can target some treatments that'll hopefully will be useful for a person like this. Thank you.

**Dr. McGee:**
Yeah. So, let's walk through, just, epidemiology of dry eye disease. And when we look at this, and depending on what study you're looking at, we know that it does increase with age, we know it is more common to women, especially when you get into that perimenopausal/postmenopausal age group. Six-point-eight percent have been diagnosed with dry eye disease. And when you look at autoimmune disorders, this is a special segment of patients with dry eye disease. Certainly, we're all familiar with Sjogren's, but patients that have TED, that's one of the most common reasons they come in because their eyes are dry. And certainly, it's partly because of exposure keratopathy, that can be one reason. But the disease itself actually effects the lacrimal gland, and so the lacrimal gland will decrease how many tears it's producing. A patient with lupus, a patient with rheumatoid arthritis. And then, remember, typically autoimmune diseases are an umbrella, and so patients can have rheumatoid arthritis and associated Sjogren's syndrome. They can have Sjogren's syndrome and an associated lupus. And so, it's not just one of these many times. They may have multiple. And so, dry eye disease is its own autoimmune disease that's happening at the ocular surface.

When we look at what's really happening in the pathophysiology, and we think about what's happening with aqueous deficient, and in that patient population where we have a decrease in the amount of tears made, that's what we typically think of. Based on the limp study, 14% of people will have aqueous deficient disease.

And when we look at evaporative dry eye, and what's happening as people move throughout their day, it really is a supply and demand issue. We might make enough tears, but we can't keep up with the demands of our day. And like Jane, 12 hours of screen time, we may not make enough tears to sustain that throughout the day. And clinically, I look at this as, they certainly coexist. I do put in my chart that this has a highly evaporative component or an aqueous deficient component, but I don't really lean and just silo things very specifically because honestly, they overlap so often in clinic.

But this slide looks really complicated, so I'm just going to kind of zoom out for a minute and walk us through this. And when we think about what's happening at the ocular surface, we have desiccating stress and desiccating stress can be lots of different things, ocular surgery, a contact lens, a new cosmetic, staring at a computer screen, environment, autoimmune disorders, a systemic medication. Those are all things that cause desiccating stress. Once you have desiccating stress and the ocular surface structures cannot sustain

what's happening, then you have tear film instability.

Tear film instability leads to hyperosmolarity, and all that means is we're evaporating too quickly. So, hyperosmolarity is when we have a higher salt content in the tears because we have not enough water component of what's happening with the tears. And once you have hyperosmolarity and that salt content, which we can measure – and for me, I measure that on every single patient that has symptoms. Once you have hyperosmolarity, remember, the epithelial cells cannot survive in that, so you're going to start to have cell apoptosis and cell death, and you're going to see that clinically with corneal staining.

And so, once we have that, then you're going to start to get inflammation. And you get cytokine release, and you have T cells that are activated that are going to recruit more of their friends. You get more inflammation and now you have more tear film instability, and we get into that whole vicious cycle. That's really what this diagram is telling us, so hopefully that gives you a 30,000-foot view of this slide and what we're thinking about when we look at the ocular surface.

The role of tear evaporation and inflammation in dry eye disease can certainly go hand in hand, but it really does begin with how quickly those tears are evaporating and that supply and demand issue. And our tears are made up of 2,000 different components. There's nothing we can artificially do to recreate that. And that tear film stability is inherent and it's the first refractive part of the whole entire system. So, if we don't have a good tear film in place, the patient's not going to see well, right? And then, we're going to wind up with nerve problems and we may eventually wind up with a neurotrophic patient because we've down-regulated their nerves on – There're 7,000 nerves on the front surface. We're going to talk a little bit more about that.

But tear evaporation is certainly a component of this, and then we walked through how we get into that whole inflammatory cascade.

When we talk about the lacrimal functional unit, remember that this whole component is a system. So, the cornea has 7,000 different nerve endings, they are constantly surveying and telling the brain what to do. The brain is turning around and giving these signals to the lacrimal functional unit, and remember, it's made up of all the components. It's the lacrimal gland and the accessory glands, it's your meibomian glands, and it's also your goblet cells that are making the mucin that everything sticks to. So, that LFU is central to maintaining ocular health and central to making sure that the front surface stays healthy and that our patients see well.

So, when they look at these afferent neural signals that are travelling from the lacrimal functional unit to the CNS, again, we've got all these nerve endings on the front surface and that is how the front surface maintains that integrity by telling the brain here's what's happening, I need you to do this. And so, it's surveying the system at all times. And then, the brain turns around with its efferent signals, travelling from the CNS to the LFU, and like we just discussed, then it stimulates the meibomian glands, the goblet cells, as well as the lacrimal gland and the accessory glands. And when you stimulate the LFU, there's no way to just do pieces of that. You're doing the entire system. And so, understanding that at this level is super important for the discussion that we're going to continue to have today when we think about stimulating the lacrimal functional unit and what that really means. And so, what I want you to take away from this is LFU equals every part of the tear film, meibomian glands, lacrimal gland and the accessory glands, as well as the goblet cells that are producing mucin onto the front surface. Super important as we move through.

We talked about detecting things early, and there are several components to a dry eye exam. And this is not difficult, this is not meant to make your clinic life more cumbersome. Start with the lids, have the patient look down. Identify does the patient have any kind of blepharitis. Do they have an issue with their lid length? Pull and push on those lids so that we know what is happening with the lids first, because that's often where problems arise before we ever get to the front surface.

So, start with the lids, and then look at your cornea. Utilize fluorescein so that we can see compromised epithelium. I like to use a little retin filter, the same one that I use to identify and assess GP lenses and scleral lenses on the front surface. I use that same filter to look at corneal fluorescein staining. You can see much easier and you can also see conjunctival staining.

And then, make sure that you're identifying gland function. So, push on those glands. There's multiple ways to do that. I personally just use my clean digits; I always have those attached to me. But you have to know the functionality of what's happening with those glands. It's not enough to just look at structure. And so, looking at the gland is super important.

And then, one of my favorite tests is tear film assessment, as far as tear meniscus height. And I'm doing that alongside my staining. So, you know what's normal, what's abnormal, if it's too much, if it's too low. When you look at enough that are normal, you're just going to know. You can certainly measure it in more sophisticated ways, but for me I just utilize my fluorescein and if I have too much, OK, well, maybe we have a drainage problem and we have conjunctival achalasia. There's another disease mechanism that is not allowing things to drain versus someone that's aqueous deficient, they don't have a tear layer. Then, that's going to lead me down a path of, OK, what else is going on here systemically with the patient.

The bottom line is, dry eye disease is certainly underdiagnosed and often undertreated, and if we treat these patients and diagnose

them earlier, it's much, in my opinion, more easy to manage. And it's critical to get ahead of this because we don't want our patients to end up like Jane, who basically takes a year off of her life because she wasn't diagnosed early enough in this scenario.

So, we heard from Jane about her symptoms. Let's go back to Jane and let's hear her tell her journey of how she was diagnosed. And then, David and I will talk a little bit more about Jane.

**Jane:**
It was back in 1999 when I couldn't wear contact lenses any longer that the optometrist said, you've got dry eyes because I looked like I was crying all the time when I wore contact lenses. But nobody ever explained that it was a disease or it could get worse, they just said your eyes are dry so that was it. And it wasn't until February 2020, and I developed a chalazion in my right eye. Went to the doctor's, and he said just use hot compresses. Still no mention of dry eye. And then we had the pandemic, so it took through until about September 2020, when I still had eye pain, the chalazion was still there, and the optometrist suggested I needed to speak to an ophthalmologist because of my chalazion and dry eye disease.

I wish somebody had taken dry eye seriously and had alerted me to it. I listen to the adverts now on the radio here for opticians, and they are saying, we do these tests, a dry eye test, and thought, well, about time. And that's great for everybody else. I really wish that existed 10 years ago, or they'd mentioned that as a problem. And I'm now working with people who are in their 20s, 30s, 40s with dry eye disease, and it seems to be something that's unfortunately, increasing and I just think early intervention could have stopped me, I think, getting to the point where I'm at, where I'm taking the nerve pain medication and cyclosporin and everything. I wish I had done more research into it earlier as well.

**Dr. McGee:**
So, I mean, basically what we heard Jane say is, tell the patient they have dry eye disease and explain this is a chronic condition that you're going to manage with the patient. It doesn't have to be over complicated, right? David, how do you talk to patients? What's your – How do you walk through patients like this?

**Dr. Wirta:**
Well, I think the first component is to learn directly from the patient what their concerns are. So, she would have come at a visit, my eye hurts, I'm having trouble at work seeing the screen, it's blurry. Whatever her primary complaints are should direct your exam. I mean, clearly everyone in the eye business has their routine that they like to do on every patient, so they don't miss anything that we're supposed to catch. But obviously, when you pick up elements of the history, that will then direct you to embellish and enhance portions of your examination. You may or may not spend as much time on the fluoresceine exam with someone with no complaints, whereas someone such as her who has complaints that enlighten you to dry eye, you certainly focus in more tear volume, like you said, tear break-up time, staining, obviously. So, listen to the patient. That's been my motto, always, as a physician.

**Dr. McGee:**
Love it.

OK. So, this basically sums up everything that we've talked about. And presenting with the patient, are they symptomatic, asymptomatic? I like these kinds of decision trees. They can be very helpful just to organize where you are in the exam and how you're going to approach the patient. So, certainly this is a reference that you can utilize to do that. And then, triaging questions. You've heard me say a couple of times, I like to always ask how they feel in the morning? If they start off the day dry, then we have a lid seal problem. I'm going to manage that a little bit differently than I would someone that has an evaporative issue that's staring at a screen 12 or 14 hours a day.

So, these triaging questions can be, again, very helpful. I like a questionnaire, but something that you can do consistently, that is really the key to elucidating symptoms that patients may not just show up in our clinics presenting with. We sometimes have to put on like a little sleuthing hat and consistently ask these questions.

So, I am going to, at this point, turn it over to David and walk you guys through what standard of care looks like and newly-approved treatments for dry eye disease.

**Dr. Wirta:**
Thank you very much, Selena. I very much enjoy hearing your expertise on the subject of dry eye. Very impressive, thank you very much. I'm now going to go over some of the standard of care and certainly, focus in on some newly approved treatments for dry eye disease.

Chapter 2. The plot thickens. So, we'll start out like we love to do at the beginning of the chapter with a polling question. This one is: How confident are you in your ability to effectively manage dry eye disease? A: Very confident, B: Somewhat confident, C: Neutral, D:

Not very confident, and E: Not confident at all.

So, certainly, you're here listening to this video CME presentation, and we're hoping to bump your score up on this by the end. But certainly, you and I, we can't help but feel like there's been a sort of a deluge of new treatments, new ideas, and it can be overwhelming at times. And certainly, you've heard of something, but you haven't tried it, and so you don't really know how it works in your hands. So, certainly there's trial and error. We're going to be presenting you with some research facts and you can draw from those somewhat. But certainly, there'll be an element where you'll have to learn about something, try it, and see for yourself on your own patients how it works.

This is a general guideline of stage management for dry eye disease. Certainly, these types of things don't need to be rigorously followed. But certainly, if you're looking to expand your portfolio of treatments and you want to know where certain things fit in, these guys can certainly be helpful. So, the Step 1 treatment, so this is someone who doesn't know they have dry eye before and you've diagnosed it. You've helped them come up with their symptoms and describe them in more detail. Certainly, education. So, I find in my practice, education is key. Whether it's from you or one of your ancillary staff, you need to explain dry eye, what it can do, and the problems it causes, but also put things in perspective for the patient that for the majority of patients it's really a symptomatic condition. Right? We see things on exam, maybe there's some blurred vision, but mostly the patient is really uncomfortable or marginally uncomfortable.

Certainly, we can talk about local environment, where they work, how their eyes are affected. We give them education about dietary modifications, which seem possibly to affect but the science hasn't necessarily proven them to make changes, but certainly reasonable to try. We can also look at different medications they take. This is definitely in the range of things that would help if patients are on a medication that causes drying, such as antihistamines that they can taper off of or stop safely. And then we move into some more specific, actual treatments. First thing, over-the-counter ocular lubrication. There's various consistencies from liquid, liquid gel. Patients can decide which one they like. I always tell people, when you're picking an artificial tear, it should be comfortable when it goes in your eyes and you should, basically, have no adverse reaction to it such as stinging or any kind of discomfort.

And if it feels good, gives them benefit, then that's a good one for them. And they can go based on price or whatever after that for their initial choice.

And certainly, Selena mentioned the eyelid. The eyelid and the eye surface, they're one. So essentially, if you see any eyelid pathology, particularly some form of blepharitis, some sort of eyelid hygiene or warm compass can be profoundly successful at Step 1 anywhere along the way, actually.

Step 2. If they have – The more sort of failure of Step 1 or need more. They got some improvement, but they're not quite where they want to be as far as symptoms and you're not happy necessarily maybe with the eye surface exam, you can move on to non-preserved ocular lubricants. Certainly, the cut-off is 4 to 6 times a day. If someone's using something literally in their eyes to lubricate more than 6 times a day, they must, I would say, must be on preservative-free treatments. That's just a heavy load of preservatives. So, that's one cut-off that I use. You could definitely, moving forward on the eyelid spectrum, if they have what you see as demodex situation, collarets around the eyelashes, you may pursue a specific treatment to a demodex, which I always have prescription for that now. You can also, and I move in my practice fairly quickly to punctal occlusion tear conservation. So, I like to use a temporary punctal plug. It gives my patients a chance to try it out, and they're very well-tolerated. I don't use a collagen plug, I use one that's made to last at least a month so they can have a real trial of it's efficacy. Also, moisture goggles. Particularly if they have some sort of gap when they're sleeping or, like Selena mentioned, early morning bad dry eye symptoms, the moisture goggles. I haven't had great success with this, but certainly something on the list to try. You can then more in, also, to more of an ointment, which generally doesn't tolerate well during the day, but at nighttime is nice. If they really need heavy hydration, we can go with an ointment.

There's also now a plethora of in-office treatments, mostly around physical heating and expression of the oil glands. And there's thermal pulsation devices. LipiFlow, for instance. If you have one, you know already that they can provide benefit, and they can be relatively long-lasting depending on the patient.

And then in Step 2 we have a whole host of the prescription drugs. They're anything from like, some we've had forever like a corticosteroid, which are anti-inflammatory. We can also have things like we've had for a moderate amount of time, like the cyclosporine and now there's newer versions which are much better tolerated in the anti-inflammatory space. As well as LFA antagonists. But also, there is the water-free artificial tear from No Blink, which is fantastic. And now, we also have now some neuromodulators, which we'll talk more a little bit in a few slides, such as nasal sprays, and there are also antibiotics and such, particularly if they have an eyelid component.

Step 3. These will be a small group of patients where you might go outside and do like plasma tears or therapeutic contact lenses.

These – Most likely, you're going to – I mean, I would maybe send to a cornea specialist if I really can't handle them at Step 1 and Step 2. So, you certainly shouldn't feel bad if you want to get a second opinion. I would be – I'm fine doing that myself, so.

And certainly, Step 4. Hopefully you don't see many patients in this group, but then you're looking at an amniotic membrane graph, maybe tarsorrhaphy, something like that. I wouldn't surgical punctual occlusion down at this level because cautery of the punctum is quite effective. It is reversible if done right. So, that might be moved up with the rest. If the punctal plugs fail, you could go right to the surgical cauterization of the punctum.

OK. I think I went over much of these, but just in a quick summary, thoroughly assessing the eyeball surface and eyelids is critical. First, symptoms of the patient, then these, are the cornerstone of choosing your treatments. We talked about preservative-free treatments, particularly if increase in the multiple times a day of the treatment. You want – Obviously, if it's not working, first make sure they're using it properly. That's critical with any treatment, really with dry eye treatment. And what I found is that you tell a patient to do something – this is true of anything, but with dry eye they might do it for a while and they get better, and then they stop doing it. So, I tell them a lot of times, these are tools. Use your tools, you'll get better. If you fall off the wagon and your eyes bother you again, you don't necessarily have to call me again. Pick up the tools again and start using the tools to see if you improve.

Although artificial tears are probably the most common, and a mainstay of dry eye treatment, they're not as good as the natural tears. Natural tears are not just water, as we all know. They contain anti-inflammatories, lipids, antibodies, growth factors, peptides, mucins, metabolites. So, it's really what is best for the eye and artificial tears are a substitute and that's it. Not a perfect substitute.

Another newer treatment is the eye drop perfluorohexyloctane, which is an interesting water-free solution, so by nature it's also preservative-free. This is a picture of its chemical structure showing its lipophilic and aerophilic sections. And it works as a coating over the surface of the eye in the tear film, and its aim is to reduce the evaporative effects of dry eye.

Also, trehalose and hyaluronic acid. I don't have a lot of experience with this, but it's another product that's up and coming that I think has a place. I'm not sure mainstream but, has a place.

We're moving on. Chapter 3: Treatments targeting neuromodulation and key clinical trials.

We talked – Well, we didn't, but Selena talked quite a bit about the LFU and its pathways to the central nervous system, which is what these products really rely on.

The first is, we're going to discuss just very briefly, is a sonic external device applied to the side of the nose. This device stimulates the trigeminal nerve, which in effect stimulates the lacrimal function unit to produce tears. And essentially, they've studied it via Shirmer testing, which would make the most sense because its endpoint is increasing tear production. Also, they looked at OSDI, which is a measure of symptoms for dry eye, and they also found that it improved symptoms over time. Very safe to use. Minimal, if no significant adverse events, and particularly, no damage to the skin at the location it was used.

Next up, varenicline spray. This product is a nasal spray. It's preservative-free. It stimulates the parasympathetic nervous system by targeting the nicotinic acetylcholine receptors on the trigeminal nerve inside the nose. These activated nerves then stimulate the LFU, and they produce tears. The safety and efficacy were demonstrated in multiple trials, including ONSET-1 and ONSET-2, and the MYSTIC trial, which is a long-term trial.

ONSET-2 was the Phase 3 study. Essentially, patients were diagnosed with dry eye disease based on OSDI, which is the symptom score, and Schirmer's testing, which is tear production score less than 10. They were randomized to receive the treatment versus placebo. The treatment was broken to two different concentrations of the nasal spray.

This shows the results. The primary endpoint were the percentage of patients achieving a greater than 10 millimeter increase in Schirmer's testing scores at Week 4. And you can see, compared with vehicle, both concentrations that were tested showed statistically – quite statistically significant improvements in the number of patients making more than 10 over baseline Schirmer's.

Secondary endpoints included some symptom scores, such as the eye dryness scale, which is EDS, and as with many symptom scores, they're more variable, they're less objective by nature, and so there was statistical significance shown in the EDS in the clinic, it looks like at Week 4.

As far as safety, the number one side effect of the spray is sneezing or some kind of like coughing, something from the actual application and stimulation of the nerves inside the nose, and it's high as you can see. The symptoms of sneezing or other sort of irritation was almost all the patients to some extent.

Now, we're moving on to another target for neuromodulation in dry eye, and that's the TRPM8 receptor. This is a cold-sensitive thermal receptor found on the branches of the trigeminal nerve innervating the cornea and the eyelids. It's associated with detection of ocular

surface dryness, either through evaporative cooling or other sort of stimulation on eyelid or cornea. And when this nerve is triggered, it results in tear production, so an obvious target for dry eye treatment.

The molecule that's been tested at this receptor is acoltremon. It is a TRPM8 agonist. This molecule was studied in two pivotal Phase 3 trials, the COMET-2 and COMET-3 trials. And you can see they involved 1 to 1 randomization between acoltremon and vehicle eye drops given twice a day for a period of 90-days. The primary endpoint for this study, which was similar to the varenicline study, was a proportion of patients showing a greater than 10 millimeter increase in Schirmer's scores compared to baseline. And we can see in both trials, the COMET-2 and the COMET-3 trials, both trials were essentially identical sister trials. We see that the acoltremon-treated patients showed a resounding improvement in patients showing this much improvement in Schirmer's scores compared to the placebo group, and both were very statistically significant. So, it met the primary endpoint for Schirmer's.

The key secondary endpoint was change in baseline in the SANDE score. The SANDE score is a score of dry eye symptoms. And we can see that in COMET-3, the decrease in dry eye symptoms with treatment was statistically significant and it approached significance in COMET-2 study but did not quite meet it. But definitely showed the trend towards increasing improvement in symptoms for the treatment group.

We also looked in the study at the change in total corneal staining from baseline to the treatment and we can see that over time, the acoltremon-treated subjects showed more improvement in total corneal staining throughout the study than those on the placebo treatment. So, this was also important information gleaned from the study.

The safety profile. The safety profile is excellent. There is one side effect that did show up, which is the incidence of burning or stinging. You can see in the middle of the table, that is approximately 50% in both studies compared to the placebo or vehicle group, which didn't have significant burning or staining. What's important to note is that this is likely a function of the action of the molecule on these sensory nerve endings. So, we'd expect some sort of sensation from an active product. In addition, what's important is the percent discontinuing due to the treatment adverse event, which is the third line and it's very low in the treatment group. So, essentially, 1 to 2% of patients exited due to any kind of treatment side effect. And if you specifically asked, did you stop the study the 3-month study because of stinging? No patient in COMET-2 stopped the study medication because of sting, and in COMET-3 only two subjects, and the total number of subjects was 450.

So, this is not a major stinging, but it is something you would certainly want to know about if you're thinking about this potential treatment.

Our conclusion. Significant increase in patients showing a significant improvement in Schirmer's score or tear production. There's a rapid, sustained increase in tear production in a large proportion of the patients. We also saw improvements in dry eye disease symptoms, including the global SANDE score. And it was well-tolerated as I just mentioned.

Well, this was sort of a rapid-fire exposure to a very complicated subject, and I hope everyone learned a bit, and we'll have some key takeaways from today's events.

**Dr. McGee:**
Perfect. Thanks, David. Thanks for going through all the clinical data.

Just a quick note, because it was a lot of data in a short amount of time, I think one of the most impactful things about this is if you can make the body make its own tears, ultimately that's our goal, right, with any kind of therapeutic. And so, it's very exciting and interesting to me that we can do that in different ways, and now we will hopefully have a drop that's going to do that for us as well. So, I think it's a really exciting time to be in the dry eye space. So, thank you for walking us through that data. That was awesome.

**Dr. Wirta:**
Thank you, Selena, for the great discussion. You've made amazing points, and your knowledge is exceptional in this matter. I really was impressed. I would also like to thank Alcon Vision LLC for their sponsorship, and please remember to complete the post-test at the end of the session to secure your CME credits. Please visit MedLive.com to view today's session, along with other sessions On Demand.

My name is Dr. David Wirta. Thank you for joining us.

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