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DED Origin Story: Understanding the Role of MGD

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[Chapter 1]

Dr. Epitropoulos:
Good evening, everyone, and thank you so much for joining us for the Dry Eye Disease Origin Story: Understanding the Role of MGD. My name is Alice Epitropoulos, and I am joined today by my esteemed colleagues, doctors Michael Greenwood and Dr. Sheppard. So again, I'm Alice Epitropoulos. I'm a Cataract and Refractive Surgeon in Columbus, Ohio. I'm on faculty at Ohio State. We have a Dry Eye Center of Excellence. Dr. Michael Greenwood is quite the overachiever. He is fellowship trained in cornea and glaucoma. He performs advanced techniques in corneal transplants, refractive surgery, MIGS procedures. He does it all at Vance Thompson Vision in Fargo, North Dakota. And John Sheppard really needs no introduction. He is the rock star of ophthalmology, literally. He is an amazing musician. I asked him to do a rap on that, but he also practices ophthalmology. He is President at Virginia Eye Consultants and Professor of Ophthalmology, Microbiology, Molecular Biology at Eastern Virginia Medical School.

And with that, Michael is going to start us off and tell us a little bit more about the prevalence and diagnosing our patients with dry eye disease and MGD.

Dr. Greenwood:
Thank you so much. Thanks for having me. Oh, yeah, I probably need this. Just real quick, in the audience, raise your hand if you're a doctor. And raise your hand if you're a staff member, technician, anything else? And if you don't have any arms, raise your hand. Did I miss anybody? Is there somebody that I missed? Okay. So for those online, the majority of people here are doctors, but we've got some other people as well.

So dry eye is a big problem. It's the number one most undertreated and underdiagnosed disease in eye care. And when you think about it, we've got trouble with the eyelid, trouble with the eye lashes, poor position of the eyelids and eyelashes, conjunctival problems, all three layers of the tear film, ocular inflammation, all that stuff. And so there's no wonder why it's a huge problem in eye care. And there's about 30 million people that have dry eye disease in the U.S., but only 16 million of them are diagnosed. So half of the people are walking around undiagnosed with dry eye. And it's a huge, huge problem that, you know, we feel like we've been kind of banging the drum on this for a while, but it still is a big problem that's underrecognized.

And the one thing that really sticks out and that maybe isn't known is that the majority of dry eye disease is actually evaporative dry eye disease. So when we first, you know, we'll get into this a little bit more in the treatment side. But in the beginning, you know, we were just doing anything we could to produce more tears. But the problem is, the major cause or the major pathology is in the evaporative part, you know, where you can see here, you know, up to 86% of people have the evaporative dry eye part, which starts with meibomian gland dysfunction. And if you're sitting in the audience being like, I don't see it that much, well, it's out there; 63% of cataract patients, 80% of glaucoma patients, you can see the numbers with contact lens wearers. And just in general, like I mentioned before, 86% have – have dry eye. So patients that are walking into your clinic every single day have meibomian gland dysfunction. We just

need to find it and look for it.

And so how do we do that? Well, we can ask patients for symptoms. And there's a bazillion different symptoms. I've listed quite a few here, but not everyone's going to come in and complain about that. Or they might, you know, patients for sure don't make the correlation on it. They're like, 'Hey, my vision, you know, sometimes it's good, sometimes it's not. I think I need new glasses.' And I was like, No, you probably have dry eye. And, but a lot of times patients are asymptomatic too, and they just don't notice it. Maybe they've got other ocular conditions or systemic conditions where they just can't feel it. And so up to 60% of patients are asymptomatic, but 50% of those patients had central staining and it can present, you know, in up to 80% of patients again.

So why does it matter to the people in the room here? Well, one, you're talking to these patients a lot, trying to get them to understand it. Again, they're in your clinic, but more importantly, it can affect your topography, biometry, keratometry high order aberrations, which ultimately impacts your cataract refractive decision-making and your measurements. And so if a patient has dry eye and you don't treat it, they're going to end up with a poor outcome from their cataract surgery. So they're going to be unhappy, and that's going to make me unhappy. So it really is something that we need to address.

And there's all sorts of challenges. Again, there's all sorts. There's different signs - or sorry, different symptoms. Sometimes you get different signs that are conflicting. The symptoms aren't alone diagnostic, and so we need different ways to do it. So we'll kind of talk a little bit about some of the diagnostic testing.

And so the first one I'll kind of talk about is osmolarity. And does anybody out in the audience, do you guys use osmolarity? A couple. All right. And so the - I want to get all my pictures up here. So there's different ways to do it, but basically it comes on a little chip. You just take a little sample of the tear. And then from this small little sample taken, you know, usually by the technician, you go and place the device back on the stand and it gives you a reading. And it gives you a number. And in this case, low is good. Anything under 310 is considered normal. Anything above 310 is considered abnormal. And if you have a difference between 10 between the two eyes, that's also abnormal. And so why does that matter? The difference, even if they're both under 310, but the difference between the two is 10 or greater, it's because you've got tear film instability. There's just mixtures that are going up and down. And at Cinco de Mayo, we talked about this a little bit, but if you have a high number or high osmolarity, it's like having a little bit too much tequila in your margarita. You're going to take a sip and it's going to be a little bit - a little bit spicy for you. And so the goal here is we want really dilute tears because dilute tears are better for the surface. If you've got high osmolarity or high concentration of your tears, it's just more concentration of stuff that's going to be sitting on your eye, leading to inflammation, and starting this cascade of dryness. And I didn't look, but I think you guys use this in the clinic? Do you do it on every patient? People that have complaints? Where do you guys use osmolarity?

Dr. Sheppard:
Well there's two ways to approach this. One is a business approach, and one is a clinical approach. If you try to do every dry eye test on every new dry eye patient or cataract patient who walks in the office, the patient will be there for 3 hours and you'll have a plethora of information you can't interpret. There's no diagnostic panel like cholesterol, and you can't do more than one thing at a time for a dry eye diagnosis. So if you do an osmolarity and then you put in a plug, you only get paid for the highest code. In reality, it's our job to look at the patient and try to figure out what the most important problem is. And as a screening tool, osmolarity is great because it will tell you if they have dry eye or if their litany of complaints is due to another problem, like allergy, meibomian gland disease, or lid dysfunction, or toxicity, or environmental problems. So it's a good differentiator. It's a good initial binary pathway determination of whether or not they really have dry eye. So it's very useful and it's very subject to user error. If your technicians don't know how to collect this, if they don't get to the machine in time, and if patient's been taking their drops, I never let them have any drops whatsoever before they have this test. You may even have to bring them back on another visit to get an accurate test, but it's very useful under controlled circumstances.

Dr. Epitropoulos:
Well, you know, I think it's important, especially in our preoperative patients that are undergoing cataract surgery, to really, you know, try to assess this, identify dry eye disease. Before, you know, we published a paper in 2015 showing that patients that were hyperosmolar had greater variability in their K readings than IOL power calculations compared to normal osmolar patients. So it really kind of helps to identify those patients that are at high risk of refractive surprises.

Dr. Sheppard:
Who published that study?

Dr. Epitropoulos:
Dr. Epitropoulos, Dr. Matossian, there were several authors on that paper.

Dr. Greenwood:
Very nice. Thank you very much.

So moving on, another diagnostic test that you can use as sort of another screening test is inflammatory marker or looking for MMP-9 in tears. It's a nonspecific inflammatory marker with a, you know, pretty wide normal range, and it's a little bit more sensitive diagnostic marker than the clinical signs. But it does have good correlation with the clinical exam findings. And so the way this works is similar to, you know, we showed with the tear sample collection, but it's a, basically a not preloaded but ready to go device with a small little absorbent sponge on the end. You have the patient look up, you soak up some of the tears, and then you assemble the test. You wait a little bit and then it gives you, you know, one line, two line, and it tells you if it's positive or negative. Similar to, you know, we used to always reference like a pregnancy test, nowadays it's a COVID test. And so you can see how that kind of works. And so same question real briefly, do you - how many people in the audience use this test on a routine or use it in general? So not as many as the previous. And then do you guys use this, yes or no?

Dr. Epitropoulos:
I have it in our office. You know, I think that, you know, like Dr. Sheppard said, you know, we have our technicians doing so many things and, you know, so we you know, we use it in preoperative patients but not consistently on, yeah.

Dr. Greenwood:
And we're kind of the same with both of those.

Dr. Sheppard:
It's another binary differentiator. If you're convinced they have inflammation, you go down the anti-inflammatory pathway, it's semi-quantitative. You have like the light, the normal and the super pink. That gives you about 40, 80 and 120 ng/mL. And you can actually follow these as a response indicator for a given anti-inflammatory topical agent. Question, sir?

Audience Member:
Bill Trattler published a paper on preoperative cataracts. He found that 50% had lid margin disease. I don't know if you saw that paper.

Dr. Sheppard:
That's the PHACO study from Bill Trattler, yes.

Dr. Greenwood:
Can you repeat - can you repeat the question for the online people?

Audience Member:
Oh, yeah. Oh, yeah. Bill Trattler from South Florida published a paper. I'm sure, Alice, you're familiar with this. He found that almost 50% had lid margin disease pre-op, which is an astounding number.

Dr. Greenwood:
I haven't seen that paper, but just to comment, I mean, to go back to one of the original slides, you're correct. Like it is an astounding number. And we're just not recognizing it or maybe taking advantage of some of the, you know, not the diagnostic part, but the therapeutic part where we want to address it ahead of time. Because again, if they've got, you know, signs, symptoms, it's interfering with their biometer and stuff like that, you're not going to get the result you want and the patient isn't going to get it either. And now with some emerging treatments, now we have the opportunity to address that a little bit better than we did in the past.

Dr. Sheppard:
That's the often quoted PHACO study. He looked at pre-op cataract patients, 78% had dry eye, 3/4 didn't know it and complained of symptoms. And so about 2/3 of those dry eye patients had MGD. That's kind of the same as Mike Lim's study from over a decade ago when he saw that 86% of dry-eyed patients had MGD.

Dr. Epitropoulos:
And Preeya Gupta came up with very similar findings showing the high prevalence of patients with dry eye disease presenting for cataract surgery.

Dr. Greenwood:
So those are kind of like the, you know, quote unquote, invasive procedures because you have to physically, you know, touch the patient. This is an example of something that's, you know, noninvasive or imaging kind of based. And so there's ocular surface interferometers and they can look at lipid layer and see how, you know, thick or thin it is. And again, you know, more is better in this case because you want to have a nice lipid layer that's sitting on top of your tear film, so it sticks around longer, it spreads it out nice and neat. And then you can also take a look at the blink ratio, like how often are patients blinking all the way because that mechanical action of the eyelids touching, you know, coming together, and blinking, that helps decrease inflammation, keep the meibomian glands open, you know, so that the wine bottle isn't getting corked up, so to speak. I don't know why all my references are alcohol based in this

moment, but I tell patients you want your meibomian glands to be nice and open. You don't want them corked up like that. You don't want it to come out like thick toothpaste. You want it to come out, you know, with the consistency of oil. But so there's ways to measure that. And I forgot to poll the audience. But does anybody use this in your practice on a routine basis? So yeah, again, so fewer. We use this one quite a bit. And the other thing that comes along with this is the meibomian gland structure. And so I like to compare this, you know, for the people that don't treat, you know, dry eye or meibomian gland dysfunction on a routine basis. But you're - everyone's used to looking at optic nerves. And so it's sort of like comparing it to glaucoma status where you've got a nice healthy nerve or you've got a nice healthy meibomian gland structure. But as soon as you start to see some changes now you want to take intervention before it's at end stage and it's too late because once you lose these meibomian glands, you can't really get them back. And so you want to keep what you have. So we use this a fair amount. And when I first got it, I was like, I don't really need this. Like, I can see meibomian gland dysfunction or blocked up glands, you know, very easily at the slit lamp. But this is a great tool for educating patients. It's another, you know, reference is like an x-ray to them and patients want to see it. They want to know like, why do I have dry? What's causing it? And so you can show them like, 'Hey, here's your meibomian gland structure, here's what normal is.' And they're like, 'Oh my gosh, I - I got to do something about this. Like, I'm worried that I'm losing something.'

And again, you know, if you don't want to get any of the tools or the diagnostics or the things we talk about, we've always got our clinical exam. And this is just another example showing what kind of normal function is. Again, when you press on these lids, you want it to come out like a nice oil, you know, very easy to come out, spreads very nicely. When it gets a little bit more thick, you know, and kind of clumpy, you can push on it gently and you can see it kind of come out kind of, you know, like unmixed peanut butter maybe. And then it gets into like the toothpaste stuff. And you just don't want it to be that way. And you can describe it to patients that way. They understand those references very well. And so if, you know, you don't need these tests, but you've got to do a good clinical exam because if you don't look for it, you're going to miss it. But we know that it's out there and it's very easy to do. You have the patient look up, you have the patient look down. You can press gently on the exterior of their lid margin and you can see what the consistency and the number of their glands is going to be. So that's, you know, the diagnostics in a nutshell.

Dr. Epitropoulos:
That was a great summary. I wanted to ask, do you do a dry eye questionnaire in the office?

Dr. Greenwood:
Yeah, we do. And we use kind of like a variation of the speed test. And so we use it, but we don't look at it all the time, which is, you know, a sin on our end. But we do use it because it can help tease things out a little bit or it provides like a prompt for the technicians to, you know, when they get it, they can look at it and they can start asking the patients a little bit deeper on the questions like, 'Hey, I see that you checked off a couple of these boxes, you know, fluctuating vision or whatever, you know, can you tell me more?' And that helps us dive a little bit deeper. So we do use it because it helps kind of stimulate conversation.

Dr. Epitropoulos:
How about you, John?

Dr. Sheppard:
It's a nice system to have. You know, I like to have a standardized symptom inventory. My favorite ocular surface disease inventory is do you have dryness, itching, or burning? That's all I want to know. But we also do a speed test and a great way to do that because it's qualitative and frequency oriented is you use phreesia, which is an inventory intake, iPad-like device, and you give it to the patients. They put all their data in there, they put their complaints in, they can fill out a questionnaire. Then you get a number, and you can see a somewhat objectively they're improving. So if you haven't looked at phreesia, it saves you about two FTEs at the front desk.

Dr. Epitropoulos:
And we use the speed questionnaire also. And, you know, my technicians actually, you know, use that in order to kind of take it to the next step. If they're symptomatic, then they'll go ahead and get point-of-care testing. If they're asymptomatic, then they don't. And again, a lot of that is billing. But don't be fooled because there's a lot of asymptomatic, dry-eye patients out there.

[Chapter 2]

Dr. Epitropoulos:
Good evening, everyone, and thank you so much for joining us for the Dry Eye Disease Origin Story: Understanding the Role of MGD. My name is Alice Epitropoulos, and I am joined today by my esteemed colleagues, doctors Michael Greenwood and Dr. Sheppard. So again, I'm Alice Epitropoulos. I'm a Cataract and Refractive Surgeon in Columbus, Ohio. I'm on faculty at Ohio State. We have a Dry Eye Center of Excellence. Dr. Michael Greenberg is quite the overachiever. He is fellowship trained in cornea and glaucoma. He performs advanced techniques in corneal transplants, refractive surgery, MIGS procedures. He does it all at Vance Thompson Vision in Fargo, North Dakota. And John Sheppard really needs no introduction. He is the rock star of ophthalmology, literally. He is an amazing

musician. I asked him to do a rap on that, but he also practices ophthalmology. He is president at Virginia Eye Consultants and Professor of Ophthalmology, Microbiology Molecular Biology at Eastern Virginia Medical School.

So once we identify dry eye disease, then we can customize treatment based on the type and the severity of the disease. And a lot of this, you know, you know, the ASCRS algorithm uses, you know, whether it's visually significant or not. We can also use this to determine the most appropriate implants to use for patients considering cataract surgery.

One, you know, one of the first-line therapies for dry eye disease are omega-3's. That has been shown to help with signs and symptoms of dry eye. And, you know, especially, again, you know, those patients that are thinking about premium lenses. And, you know, again, patients that have signs of inflammation, if they have reduced tear production, then I think it's, you know, I think it's, you know, very appropriate to use an immunomodulator.

And both cyclosporin and lifitegrast have been shown to improve lipid layer parameters in several clinical trials to date. And topical steroids have been used for years off label to treat dry eye disease. And now we have an FDA approved, you know, it's a nanosuspension of loteprednol etabonate 0.25%. And it's FDA approved to treat both signs and symptoms of dry eye disease up to 2 weeks. And despite the potency of loteprednol, it is an ester steroid which is considered safer with lower side effects.

The use of topical antibiotics with or without steroids can also be very helpful for those patients that have chronic lid disease and MGD. And I love the fact that azithromycin is back in our armamentarium, and I think it's specifically advantageous for its anti-inflammatory effects, distinct from its antibiotic properties. It penetrates into the ocular tissues and has a very long duration of action. So a lot of my patients, just for maintenance therapy, I have them using azithromycin once a week. Some studies have shown that azithromycin is as effective or even more effective than oral doxycycline. Do either one of you use azithromycin?

Dr. Greenwood:
No, but as you were talking about it - I use it, but not in the same way you do. But as you were mentioning that, I was like, oh, that's like a really good idea. So it's probably something that I'm going to actually start doing more of.

Dr. Epitropoulos:
Yeah.

Dr. Sheppard:
I use it orally as well, and it's a lot cheaper than a Z-pack. I prescribe Z-packs almost every day for people who have pulmonary symptoms, it achieves wonderful blood levels and you can use it systemically, but topically it's a very viscous preparation and the bottle only has about 12 drops in it, so it's a bit of a nuisance. In Europe, tobramycin has a BID preparation that's a little bit easier to apply and more plentiful. But the anti-inflammatory and anti-collagenase and MMP-9 activity as well as the broad-spectrum antimicrobial activity make it a great choice topically and a lot of my patients will use it at night 1 week out of the month and that seems to be a good maintenance therapy and affordable under the current circumstances.

Dr. Epitropoulos:
And then also antibiotic steroid combinations, you know, with tobramycin have also been very beneficial for patients with lid margin disease. It contains the xantham gum, which is the vehicle, and that allows the, you know, kind of maximum surface - maximum ocular surface penetration. So you can actually have a lower concentration of a steroid, which, you know, is equivalent to higher dose. And then also, you know, it is also a very effective for methicillin resistant staph and strep. So it's a great option that we often forget about.

And then also patients that don't respond to topical antibiotics or physical therapy, then, you know, we often resort to oral, you know, antibiotics, like John said, in especially those patients that have inflammation, rosacea that are a little bit more resistant. And tetracycline and its derivatives, such as doxycycline and minocycline, have also, you know - they've been used and found to be very effective in these patients with chronic lid disease. And again, research supports low doses of doxycycline. So when I prescribe this to my patients, I usually give them 20 mg twice a day. And that has been shown to be as effective as higher doses.

So I like to look at treating, you know, treating this as a 3-step approach. There are several in-office procedures that we can perform. So again, lid margin hygiene, removal of obstruction, and reduction or elimination of inflammation. And you know, these 3 mechanisms work synergistically but are most effective when treated earlier before atrophy or there's permanent damage to those glands.

Microblepharoexfoliation uses a medical-grade micro sponge to exfoliate the lids and the lashes, reducing bacteria and demodex that contributes to inflammation and obstruction of the glands. And the biofilm is analogous to the plaque that builds up around the gums and the teeth that causes that chronic gum disease.

Thermal pulsation or LipiFlow, it uses a combination of heat and vectored pulsation and it is applied to the anterior and posterior lid margins to unclog those obstructed glands. It's been around the longest. It was FDA approved in 2011. It's a 12-minute procedure, and

1 treatment has been shown to last up to 3 years.

And then there is the iLux, which is a hand-held thermal device. And it - what makes this unique is it allows that direct visualization of the glands through a magnifier. And you can actually customize this by kind of going back to maybe address glands that look a little bit more clogged or a little bit more inflamed. And again, it applies focal heat through a light source to those obstructed glands.

And, you know, this was a study that Joe Tauber did and colleagues, and he showed a comparison of objective and subjective effects. And it went out to 4 weeks with iLux compared to LipiFlow; iLux was noninferior to LipiFlow. Both treatments produced significant improvements in symptoms and in meibomian gland dysfunction testing. There was no statistically significant differences between the 2 treatments. And again, I think it's important to keep in mind that this goes out to 4 weeks. It'll be interesting to see if we come out with data that 1 year or 3 years.

Then there is the TearCare, which is a - uses a localized heat therapy. It's applied to the external lids for about 15 minutes. Patients can still blink throughout the procedure, and it's recommended that is followed by manual expression.

And again, this was another study that was published by Preeya Gupta and John Hovanesian. It was published in *Cornea* looking at TearCare compared to again, LipiFlow. And you'll see in the black bars is TearCare treatment, and in the gray is the LipiFlow. And results again were equivalent for the improvement in dry eye signs. Tear breakup time, meibomian gland scores, conjunctival corneal staining, and meibomian gland health. And again, this is out to 4 weeks.

And then MiboFlow is another in-office procedure. It delivers heat up to 108 degrees to the tarsal conjunctiva. It is non-disposable and you can adjust the treatment settings.

And then there's the hands-free goggle system. There's Thermal 1-Touch and eyeXpress that provides a uniform regulated heat to the external surface of the external lids.

And manual meibomian gland expression. Sorry to have to do this while you guys are eating dinner.

Dr. Greenwood:
Champagne?

Dr. Sheppard:
That's a good one.

Dr. Epitropoulos:
Cheers.

Dr. Greenwood:
Yeah, that is incredible.

Dr. Epitropoulos:
So I have this patient actually come into my office about every 3 months to get this. And it's actually pretty humorous because my staff lines up to watch it.

Dr. Greenwood:
But how old is that patient roughly?

Dr. Epitropoulos:
She is about 45.

Dr. Greenwood:
Yeah, I was going to say she looks young. Yeah. That’s tough.

Dr. Epitropoulos:
Yeah, yeah. But, you know, it's therapeutic. She feels better after it’s expressed.

Dr. Greenwood:
So, yeah, you went through all the – you’ve got one more slide, maybe I'll wait till you're done.

Dr. Epitropoulos:
Yeah, go ahead if you want to comment, yeah.

Dr. Greenwood:

Yeah. So. So I've had all of the - except for the goggles, I've had all of those thermal things done to me. I think they're all great.

Dr. Epitropoulos:
Have you had this?

Dr. Greenwood:
No. No. And I have, like, mild MGD. I'm pale guy, I'm prone to it. And - but I think they're great. And patients like different ones for different reasons. Some like to have their eyes open and they like to see what's going on. I personally like the thermal pulsation where I can't see anything because we put them on, we turn it up, we turn on some spa music, we dim the lights, and I just like relax.

Dr. Epitropoulos:
It's a dry eye spa.

Dr. Greenwood:
And yeah, it is a dry eye spa. So it feels good. And like they work very well for me. Billing and stuff like that has been a little bit more challenging. But all of them are great and patients love them for different reasons.

Dr. Epitropoulos:
Yes, I agree.

And then intraductal probing using a microcannula also helps to relieve obstructed meibomian glands. And it should be done under local anesthesia because it can be pretty uncomfortable.

And IPL, actually, it was originally developed for dermatology but has been adopted more recently with rosacea and MGD. And it again targets those abnormal inflammatory telangiectatic vessels that contributes to inflammation. And it was just recently approved for treating signs of dry eye disease due to MGD.

So again, incorporating various therapies and advanced office-based treatments will allow for greater success in management of this disease and improving long-term outcomes.

[Chapter 3]

Dr. Epitropoulos:
Good evening, everyone, and thank you so much for joining us for the Dry Eye Disease Origin Story: Understanding the Role of MGD. My name is Alice Epitropoulos, and I am joined today by my esteemed colleagues, doctors Michael Greenwood and Dr. Sheppard. So again, I'm Alice Epitropoulos. I'm a Cataract and Refractive Surgeon in Columbus, Ohio. I'm on faculty at Ohio State. We have a Dry Eye Center of Excellence. Dr. Michael Greenwood is quite the overachiever. He is fellowship trained in cornea and glaucoma. He performs advanced techniques in corneal transplants, refractive surgery, MIGS procedures. He does it all at Vance Thompson Vision in Fargo, North Dakota. And John Sheppard really needs no introduction. He is the rock star of ophthalmology, literally. He is an amazing musician. I asked him to do a rap on that, but he also practices ophthalmology. He is President at Virginia Eye Consultants and Professor of Ophthalmology, Microbiology, Molecular Biology at Eastern Virginia Medical School.

Dr. Sheppard:
There's a lot of excitement in this field. First of all, the sight science allows the doctor to come in and do something, not just the technician. I think that's very powerful. Similarly, with thermal pulsation, the doctor places the interfaces and then leaves the room. So there's an MD/OD touch for the patient. The mask and probe is very effective in people who don't experience much pain. If they have a low threshold, beware. And there's another new treatment out, it's a radiofrequency mask that can be used in the office or at home, or both with a digital interface developed by Eyedetec and Barry Linder sitting over there, which is the future of ocular surface analysis and intervention for meibomian gland disease with a wide variety of patient presentations.

But the pharmacologic future is truly exciting. We existed for nearly 20 years with one drug for dry eye, the infamous Restasis, which still sells more than anybody else at about a half a billion dollars, despite generics in the marketplace. But the future has a number of great candidates ahead of us. Azura and Novaliq and Aldeyra and Tarsus have exciting products that will be in your prescription pads within the next 2 to 3 years.

Marc Gleeson's Australia company, Azura, has developed an adaptation of a very popular skin medication that works upon the meibomian glands, yielding liquid secretions, opening the glands in phase 2 clinical trials with remarkable sign and symptom results. It works upon disulfide bonds. It's an agent that removes various forms of concretions and keratinization on the lid margin, just as it does for dermatologic patients. And about 50% of patients became asymptomatic and the meibomian gland quality returned to normal for at least 3 months. And you see a reduction of clogging saponification. And the delightful spaghetti produced in Dr. Epitropoulos's Ohio

office, must be the Columbus Diet. So the phase 2b studies truly showed significant improvements. They used the speed scores as their primary endpoint and they found visual analog scale improvements in discomfort and ocular itching as well. There were adverse events, but they were mild and transient, similar to non-treated subjects, and discontinuation was only about 2%.

So NOV03 was developed by Novaliq in Heidelberg, Germany, and they have partnered with Bausch and Lomb. There are two confirmatory registration phase 3 trials the GOBI and the MOJAVE, and they showed primary efficacy in signs and symptoms in both trials. The sign, of course, was central corneal fluorescein staining, and the symptom was visual analog scale dryness. And you will see here at the very beginning of the trial, even within 2 weeks, that both the signs and symptoms improved with a very narrow standard deviation. The control, the placebo was sustained balance, a drop of over-the-counter similar viscosity to the active agent. And you can see here that in both trials, the corneal fluorescein staining dropped very quickly and remained low consistently in both trials, whereas the analog dryness scale decreased and continued to decrease all the way up until the secondary end point at 57 days. The primary endpoint, of course, was at 29 days. So this shows rapid onset of action with statistical significance not seen in other clinical trials. The safety was remarkable. The side effects, the complaints were the same as the vehicle. We found that in some of the analyses, even in responders, that only about 0.2% of patients had significant installation site discomfort. That again, is unprecedented in other clinical trials. The reason that NOV03 is so effective is it's not really a drug; it's just physical chemistry in action. It's a coating agent. It spreads on the surface of the eye immediately. It's a semi fluorinated alkane. It's water free, therefore no preservatives. The drop size is only 10 microliters, and it coats the eye. It prevents evaporation. So when you had to take physical chemistry as an undergraduate in pre-med, you might have actually developed a product like this. It is not really a pharmaceutical. And it's different, a different mode of action. You can put in active agents to put this in afterwards, in my opinion, and use conjunctive/adjunctive therapy. So this has a PDUFA date in June. I believe that it will be approved.

Reproxalap is from Todd Brady's company in Boston, Aldeyra. This is a RASP inhibitor. Who's heard of reactive aldehyde species in medical school? Nobody. You know, nobody's heard of a number of parallel important anti-inflammatory targets that have heretofore not been addressed. We all know about steroids and lipoxygenase and cyclooxygenase. Well, these reactive aldehyde species are causing mischief throughout our body, especially on the ocular surface. And if you look at the phase 2 and 3 studies, the TRANQUILITY trials, which have been duplicated, you see an immediate drop in both the ocular dryness score as well as the dry eye chamber score. There's a CAE, a controlled adverse environment, where you stick someone in a box with 18% humidity and make them stare upwards for an hour and a half at a TV with a fan blowing in their face. And that's meant to accelerate the development of dry eye signs and symptoms, and facilitate the analysis of rapid recovery with a given pharmaceutical agent. It's worked well in phase 2 and earlier trials. It hasn't worked really well in phase 3 trials, but it's a great torture test.

The Schirmer test was also shown to improve and show sustained improvement, and the responder analysis showed remarkable duration and patient satisfaction. This particular agent is also submitting data for the treatment of allergic disease.

This is a steroid efficacy-like drug without steroid side effects. And to have a dual indication for allergy and dry eye meets a huge unmet need. There's probably about 2/3 of the 30 million dry eye sufferers in this country who also suffer from ocular allergy. Ocular allergies are the most common form of allergy in this country.

So over 12 weeks, the reproxalap treatment was superior to the vehicle in both signs and symptoms in both trials. And the symptoms improve within 1 to 3 minutes, as shown in the trial. And one of the adjunctive secondary endpoints was ocular redness, which also improved in the conjunctiva. So the duration in the trials was up to 12 weeks. This is preservative free. It's well tolerated. And the lack of adverse events and excellent tolerability also give us great promise.

The reactive aldehyde species metabolite malondialdehyde can be measured in tears. It's higher in dry eye patients. When you give the drug, malondialdehyde decreases concomitant and in conjunction with the signs and symptoms. So this is actually a verified biomarker for improvement in a disease with an integrated inflammation target that corresponds to that metabolite. So the FDA may actually recognize this biomarker in approving the drug.

Lotilaner is from Tarsus Pharmaceutical. Liz Yeu, my partner, is the CMO of this company, and they have a whole litany of trials all the way up to phase 3 that shows that this drug, which is a specific antiparasitic drug, decreases collarettes. It's not hard to diagnose this. You don't need expensive machines and really good technicians. You just tell the patient to look down and you look for collarettes. If you're really obsessive-compulsive, you can yank out the lash and look under the microscope at the living, breathing, crawling, demodex and gross everybody out, including the patient. It's even more motivational than a meibography. But they saw that there was a rapid progression to elimination of the collarettes at the primary endpoint at day 43, and that clinically meaningful collarette cure, but not complete elimination, was also highly statistically significant and this activity persists in the patient. So this is actually a treatment that treats the disease. We've had a lot of interventions for demodex blepharitis like hypochlorous acid and tea tree oil and a wide variety of commercial products, but they're just sterilizing antiseptic agents. This is a drug that kills parasites and it's relevant to a number of

systemic third-world infections as well. So you can see that the TAEs were minimal and they were similar to vehicle and the drop discomfort was quite satisfactory or very satisfactory in about 3/4 of the patients. So we believe the compliance will be good and that patients will have continued relief. About 80% of people over the age of 80 have demodex. So raise your hand if you don't have demodex. Thank you. Exciting stuff on the horizon for all of us.

Dr. Greenwood:
It's cool because again, like we're - you're addressing multiple different mechanisms of action with these things, stuff that doesn't exist yet. So it's more, you know, tools in our toolbox that we can use to, you know, address all the variety of causes.

Dr. Sheppard:
It's like being an internist, you know, you really have a very nice way to distinguish different forms of ocular surface disease. My late mentor, Dick Thoft, was the first to identify the ocular surface. There's 8 components, there's the conjunctiva, there's the corneal epithelium, there's the nasal lacrimal drainage system, and the lids, and adnexa, and there's the lacrimal functional unit, that unit that produces tears, the meibomian glands, the goblet cells, and the aqueous producers, and the lacrimal glands major and minor, and then, of course, there's the 5th and 7th cranial nerve and the tear film. So there's a number of direct interventions that can be applied to each of those individual components. And the ocular surface only functions as well as its weakest member. Just like an orchestra with 7 virtuosos and 1 squeaky violin, they sound lousy.

Dr. Epitropoulos:
Very good. I'm very excited for the future for these drugs.

Dr. Greenwood:
We usually don't. Yeah, usually you're not talking about like, hey, dry eye is like super awesome. I can't wait for a patient to come in and talk about their dry eye, but I think we're getting to that point now.

Dr. Epitropoulos:
Well, I'd like to just take a couple of minutes and entertain any questions before we go into our case presentation. Anybody have any questions? Or online any questions?

Dr. Sheppard:
We have one question from Dr. Ranade. How much emphasis on correct blinking quality and pace do you emphasize to your patients? Are there drugs and procedures that have effects that don't last when compared to ocular exercises and perhaps direct lid environmental control?

Dr. Greenwood:
So I'll take a stab at it. I mean, I mention it to patients quite a bit, like even when we're doing like a YAG or anything like that, you can see that they just aren't blinking, there's staining and stuff there. And so I just mentioned to them like, 'Hey, your eyes are pretty dry, like you just don't blink very much.' And they'll kind of, they'll look at me and say, 'What?' And I'm like, 'Well, blink.' And I'll say, like, 'you can't tell, but your eyes aren't going all the way down. So every once in a while when you remember, just blink real hard and that'll help things out.' And then so I don't know any data on it, but I do know that it's helpful, you know. And then there is some stuff in the pipeline for people that have like paralysis that will, you know, trigger them to start blinking and do that so they don't have to worry about exposure keratopathy and things.

Dr. Epitropoulos:
You know, there was a study – and the normal blink rate is about 20 blinks per minute. And when we're looking at our digital device, our phone or computer, that blink rate drops down to 4 to 6 blinks per minute. Pretty dramatic. And with the digital era that we're living in today, I think that explains, you know, some of the increase in prevalence that we've, you know, seen with MGD along with the average American diet too, you know, in Columbus, Ohio. So I think that, you know, I implement the 20/20/20 rule, every 20 minutes, look, you know, look 20 feet across the room, blink several times, maybe put some lipid-containing tears and then resume your tasks.

Dr. Sheppard:
Yeah. This is where cranial nerve 5 and 7 come in. If there's a 7 problem, they don't blink well. If there's a 5 problem, they don't feel any irritation, so they don't blink. And then clearly younger people are getting dry eye disease. We have worldwide epidemics of ocular surface disease because of digital devices and of myopia because of digital devices and the continued use. So there's going to be a job for all of us for the foreseeable future, thanks to my cell phone.

[Chapter 4]

Dr. Epitropoulos:

Good evening, everyone, and thank you so much for joining us for the Dry Eye Disease Origin Story: Understanding the Role of MGD. My name is Alice Epitropoulos, and I am joined today by my esteemed colleagues, doctors Michael Greenwood and Dr. Sheppard. So again, I'm Alice Epitropoulos. I'm a Cataract and Refractive Surgeon in Columbus, Ohio. I'm on faculty at Ohio State. We have a Dry Eye Center of Excellence. Dr. Michael Greenwood is quite the overachiever. He is fellowship trained in cornea and glaucoma. He performs advanced techniques in corneal transplants, refractive surgery, MIGS procedures. He does it all at Vance Thompson Vision in Fargo, North Dakota. And John Sheppard really needs no introduction. He is the rock star of ophthalmology, literally. He is an amazing musician. I asked him to do a rap on that, but he also practices ophthalmology. He is President at Virginia Eye Consultants and Professor of Ophthalmology, Microbiology, Molecular Biology at Eastern Virginia Medical School.

So this is a 66-year-old physician, surgeon, that comes in for cataract evaluation. He's complaining of glare, halos, starbursts at nighttime. He also complains of intermittent blurring, especially when he's using his, you know, EMR system or computer. And, you know, his speed score is 5. So he's not real symptomatic. And again, no really other past ocular history other than contact lens wear. But he says he really doesn't feel comfortable driving at night anymore. Again, he's experiencing difficulty reading, using the computer. And again, you know, I think it's pretty significant the symptom of vision coming and going. That's, you know, that's probably one of the most significant symptoms that patients have that, you know, they might not realize that they have dry eye disease, that along with tearing. So many people come in and say, 'Well, I'm tearing, how can I have dry eye disease?'

Alright. So here's his exam. He's got collarettes. So he's got some demodex going on. He's got significant staining on the cornea and conjunctiva. Flomax history. So he really only dilates to 5. He's got 3+ NS and his best corrected vision is 20/40. So I'd like to hear from my panel experts to see how you would treat this nice physician that wants his cataracts taken out.

Dr. Greenwood:
I'll start. We'll go - yeah.

Dr. Epitropoulos:
Would you treat him? Or would you go straight to cataract surgery?

Dr. Greenwood:
Yeah. No, I would not go straight to cataract surgery. I was like, as you're reading this note, I was like, oh my, this guy has everything, right? And so I used to, you know, so you kind of have two approaches to this of like, well, do I just do a kind of a little bit and kind of do a stepwise approach? But when you do that, it's kind of like, hey, your house is on fire, so you throw a bucket of water at it. So he's got so much going on and he, you know, he's a busy person. He probably doesn't have time to do a lot of stuff, but he also doesn't have time to waste, you know, with poor vision. He probably wants to have surgery and get moving. So I would hit this guy hard with as much stuff as I can. And depending on your clinic or whatever, you know, you have available. But, you know, he's got the collarette, so you want to address that with something that's, you know, commercially available. In the future, we've got something coming down the pipe which will be, you know, probably more convenient. And then, you know, he's got meibomian gland problems. And so you start working on that and get him going as fast as he can. So I'm probably doing, you know - he doesn't have any plugs, so I'm doing, you know, plugs. I'm doing some sort of meibomian gland treatment. Yeah, you got the pictures there, so he's got severe dropout, and so you want to address that, you know, as quick as you can.

Dr. Epitropoulos:
John, would you?

Dr. Sheppard:
I get 3 types of dry eye patients. One, the patient who's seen 5 other doctors and has 17 complaints and 50 articles with them when they come to the office. They're very complicated, so you only change one intervention at a time so you know what's going on and they think you're paying attention. The second is a complex patient with other ocular diseases, especially glaucoma, because they're putting poison in their eye every day and destroying stem cells. The third type is like this. It's a surgical candidate. So you throw out the scientific method. You try to find something wrong with every system in the ocular surface and treat it directly. So I don't care if they get better on plugs and doxycycline and steroids and some type of a super tear and meibomian gland excretion, the whole works; just get the job done as quickly as you can so you normalize the biometry. And if 3 of the interventions work and 3 of them don't, you don't care, they have a normal surface, they have a nice low HOA assessment on their topography, and they're ready to go with their premium lens, understanding that their dry eye will come back if they don't keep taking their medicines. And they'll be really mad if you put in a trifocal.

Dr. Epitropoulos:
So to your earlier point, obviously MGD is extremely prevalent in patients coming in for, you know, cataract surgery. In a study that Dr. Kushner did, 180 patients, 56% showed some level of MGD, and half of those were asymptomatic. So again, you have to look for this

disease. You're not going to always get patients telling you that they have dry eye disease. And if you miss the diagnosis, there's going to be some consequences. Your biometry is going to be off, patients are going to come to you afterwards saying, 'My eyes are so uncomfortable now that you took my cataracts out. They weren't uncomfortable before and it's your fault.'

So, you know, again, you know, looking at literature that we talked about before, you know, that the prevalence of dry eye disease is extremely common, 8 out of 10 patients coming in for cataract surgery have signs and/or symptoms of dry eye disease. So again, this patient I treated with hot compresses, omega-3's, LipiFlow treatment, put them on a topical anti-inflammatory drop, and also lipid-containing artificial tears. Brought them back about 4 weeks later for biometry. And you can see that the biometry, the rings look more symmetrical, more normal. And he was happy to go ahead and proceed with cataract surgery with better biometry.

Dr. Sheppard:
So given how common dry eye disease and MGD are, should we be proactively asking patients probing questions about fluctuating vision, tired eyes, and other symptoms of MGD? Or should we wait until they complain?

Dr. Greenwood:
I think we need to be proactive on it, and it sort of depends on what they're coming for. Like, you know, you referenced the 3 types of patients that you see. You know, if someone's coming in for surgery, for sure you've got to be asking about it. And because you just can't start chasing your tail by doing surgery and then chasing everything down and saying, you know, 'Oh, well, you had this before, but I didn't address it. So we did surgery and blah, blah, blah, blah, blah.' So I think you need to be proactive about it. You need to look for it. It is part of our eye exam, right? You start with the lids, lashes, and work your way back. It's part of, you know, patient care. And so I think being proactive is only beneficial for you and your patient.

Dr. Sheppard:
Thank you, Mike. Finally, Alice, if a patient doesn't want any procedures, and we know most of them are cash based, what's your go-to treatment?

Dr. Epitropoulos:
Well, you know, unfortunately, dry eye disease is a very expensive disease. There's a lot of insurance companies - you know, insurance doesn't cover a lot of the treatments that we have to offer. But again, I think that educating our patients is key. You know, showing them that their tear osmolarity is abnormal. And, you know, to your point earlier, showing them their meibography, what it normally should look like compared to what their glands look like, and then patients get it. And, you know, if they realize that it's going to - potentially could affect their outcomes, their surgical outcomes, they're more likely to want to make an investment in their eyes. But, you know, again, if they don't want an in-office procedure, again, I document that. I'll try to see if I can get an immunomodulator, you know, approved by, you know, their insurance, you know, try to get them started on omegaan3, and then using lubricating drops and maybe even a topical steroid to accelerate that.

Dr. Sheppard:
Steroids. Yeah.

Dr. Greenwood:
And the more you can explain to the patient, like what the true pathology is, the more willing they are to do something about it. You know, you referenced demodex and the mites. And if you tell a patient, 'Hey, you just got some crud on your eye, but take this drop twice a day, it'll make you feel better.' They'll be like, 'I don't know.' If you said like, 'Hey, you have a mite on your eye and this drop will, you know, get rid of it,' that they're more likely to take it because they want to get rid of the pathology.

Dr. Epitropoulos:
We have another question.

Audience Member:
Hi. Thank you very much for the talk. It's been very interesting. One question is on the case of the physician that had cataract, on the treatment that you put on, you didn't start on any demodex treatment, even though he had collarettes. How often do you usually start doing the demodex treatment when you find collarettes?

Dr. Epitropoulos:
Well, you know, that's a great point. So we don't have anything FDA approved right now for demodex. But what I do is, you know, oftentimes I will - when I do a LipiFlow treatment, I will automatically do BlephEx. And BlephEx is pretty effective against demodex. And then I have a protocol for my post LipiFlow patients, lid scrubs, warm compresses, and for those patients that have collarettes, I'll use tea tree oil, Cliradex or some kind of tea tree oil lid scrub. IPL is also pretty effective against demodex too. But I'm again very excited about the Tarsus product that is in our near future.

Dr. Greenwood:
Same.

Audience Member:
Thank you.

Announcer:
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