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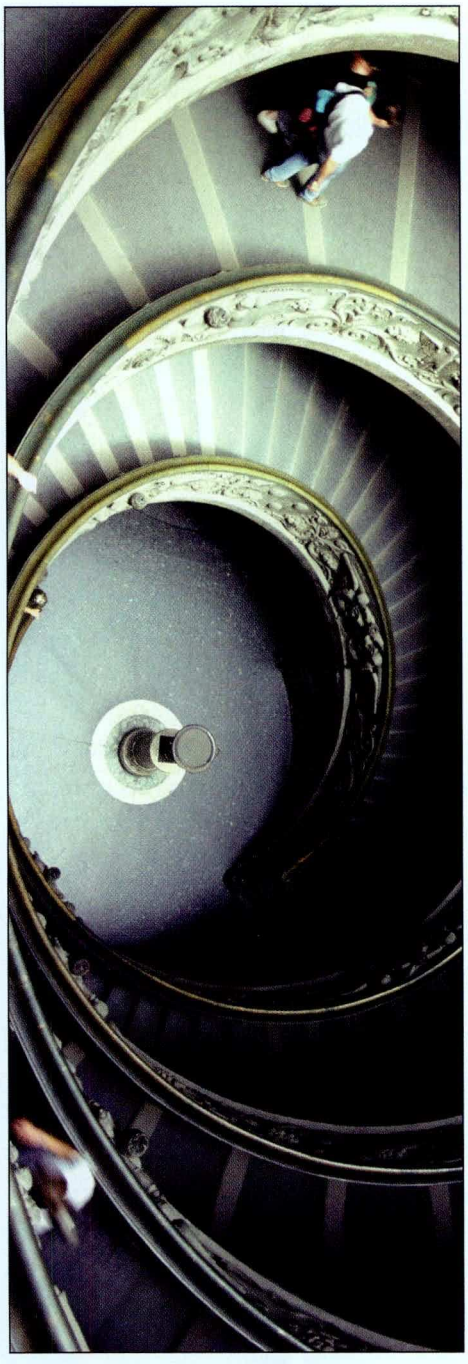
A Roundtable Discussion on Dry Eye



INTRODUCTION

Dry Eye is a pervasive and ubiquitous disease or condition. Dry Eye syndrome affects more than 10 million people in the United States and is one of the leading reasons for patients to consult eye care practitioners. This number probably grossly underestimates the number suffering from the condition because it does not include the estimated 50% of symptomatic contact lens wearers and there are currently approximately 35 million contact lens wearers in North America. While most of these patients do not suffer from severe dry eye, the condition can be debilitating and affect vision of many sufferers. This discussion is also timely because of environmental changes that presumably affect eye health and dry eye has been identified as a very important area of research.

Desmond Fonn *(moderator).*
I would like to thank you all for attending. The purpose of this forum is to discuss the diagnosis and management of Dry Eye. We are here at the kind invitation of Alcon Canada and I would specifically like to thank Brian Beatty and David Bard for sponsoring this Roundtable discussion. I hope that the next two hours will be fruitfully spent discussing important clinical issues. Brian and I selected the topics for discussion knowing full well that the time restraints would be a serious limitation. I will attempt to control the discussion as moderator and with that let me begin by asking the first question.

Q *Dr Desmond Fonn:* Dr Caffery the current definition of dry eye is: "Dry eye is a disorder of the tear film due to tear deficiency or excessive

ATTENDEES:
Dr Desmond Fonn, Professor, School of Optometry & Director of the Centre for Contact Lens Research, University of Waterloo (UW);

Dr Kerby Kelly, practice in Regina, (UW 1986);

DR. TREFFORD SIMPSON: Professor, School of Optometry & Associate Director of the Centre for Contact Lens Research, UW;

Dr Etty Bitton, Associate Professor, School of Optometry, University of Montreal (UW 1988);

DR. NISH RAJANI: practice in Toronto (UW 1995);

Dr Lyndon Jones, Professor, School of Optometry & Associate Director of the Centre for Contact Lens Research, UW;

Dr Lucie Berthiaume - Lesault, practice in Ottawa (UW 1988);

Dr Trevor Miranda, practice on Vancouver Island (UW 1995);

Dr Barbara Caffery, practice in Toronto (New England College of Optometry 1977);

Dr Dagmar Lutzi, private practice in Kitchener-Waterloo (UW 1978);

Dr Fadi Maroun, practice in Montreal (New England College of Optometry 1994);

Dr Gerald Leinweber, practice in Red Deer (UW 1980).

tear evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of discomfort". Does this definition still suffice and if not how should it be altered?

Dr. Barbara. Caffery: Since the definition was published 10 years ago much has been learned about dry eye and the ocular surface. In 2005, the Dry Eye Workshop (DEWS) was established to review the definition and determine whether it should be altered. Deliberations on this subject are continuing.

The first point that I want to make is that in health care there is more at work than a definition. A definition of a disease is important but so are the criteria for diagnosis and the classification criteria. It is important not to confuse these terms.

Let's start by determining what a definition is. The Oxford dictionary states that a definition is "an exact description of the nature, scope or meaning of something". It may be useful to look at the definitions of other diseases to help us get a feel for how the term is used in health care. For example rheumatoid arthritis is defined as "a chronic and destructive form of joint inflammation caused by the body's own immune system attacking the tissues". Sjogren's syndrome is "an autoimmune disorder in which immune cells attack and destroy the glands that produce tears and saliva". Diabetes is "a metabolic disorder resulting from the body's inability to make enough or properly use insulin". Definitions then seem short and precise. Our present definition of dry eye disease seems rather long by comparison but perhaps that is necessary given the vagaries of dry eye disease.

Dr. F. Maroun: I think that the issue of inflammation requires our attention. Newer studies have come out that link the cornea, conjunctiva, lacrimal gland and lids as an integrated unit. There are hormonal and sensory issues that also apply to the breakdown in dry eye disease. Finally the idea of inflammation should be added to the definition because of the studies that show the use of low dose steroids can improve the condition.

Dr. T. Simpson: The problem I have with the current definition of dry eye is it states the disease is a tear disorder. I believe there can be clinical dry eye without a tear film disorder, for example in contact lens wear. Another example is dry eye following laser surgery. I think calling the disease an ocular surface disease may be more inclusive.

Dr. D. Lutzi: I have a problem with the latter part of the present definition in that it includes symptoms of ocular discomfort. I have many patients who dont have symptoms and have signs of dry eyes.

Dr. L. Jones: On the other hand, there are a large number of patients who have symptoms but no signs. It would be wrong to leave out those patients just because our clinical testing is not sufficient to describe their condition. However, I would like the definition to be as short as possible.

Dr. G. Leinweber: I think that the definition needs to be short followed by a description with the details. The definition can be broad but the categories should be clearly described to make it easier for diagnosis.

Q *Dr Desmond Fonn:* Should contact lens induced dry eye be placed in the same category as general dry eye and if not how does it differ?

Dr Trefford Simpson's: A flippant response would be they are the same but unfortunately this is not supported by direct and indirect data from a number of directions.

The first bit of evidence is epidemiological. There is a large body of information that has emerged over the last decade that suggests that the prevalence of dryness is approximately 20%. Table 1 provides examples from a variety of countries illustrating this. However, we and others have shown that the prevalence is as much as 2-4 times higher in contact lens wearers[1;2].

The tear film in lens wearers and non-wearers is also fundamentally different. This was recently illustrated by Nichols et al [3] who showed differences in the thinning rates of prelens and precorneal tear films. So, if tear film thinning and drying are related to symptoms, again we have a difference depending on whether a lens is or is not on the eye.

Another physiological difference stems from a current theory that there is an "integrated loop" containing the structural, sensory and secretory components of the ocular surface that all operate in concert to generate a wet comfortable, healthy ocular surface[4]. This is

COUNTRY	PREV-ALENCE	SAMPLE SIZE	METHODS
Sweden (Jacobson et al.)	15%	705	Questionnaire Clinical tests
Japan (Hikichi et al.) (Shimmura et al.)	17% 33%	2,127 2,500	Questionnaire Clinical Tests Questionnaire
USA (Maryland: Schein et al.) (Beaver Dam Study:Moss)	14.5% 14.4%	2,520 3,722	Questionnaire Clinical tests Questionnaire
Scotland (Doughty et al.)	29%	292	Questionnaire
Canada (CANDEES)	28.7%	13,517	Questionnaire
Australia (McCarty et al.)	10.8%-16.3%	926	Questionnaire Clinical Tests
Denmark (Bjerrum)	24%	504	Questionnaire Clinical Tests
USA and Canada (Begley et al.)	22%	1,054	Questionnaire

disrupted in a variety of ways during contact lens wear (including the altering the tear film, the structure of the ocular surface [5-7] and the sensory channels [8]) that suggests that it is unlikely that symptoms in those wearing and not wearing lenses would be similar.

Finally, the treatment of dry eye in lens wearers is so fundamentally different than that in non-lens wearers that it renders any argument about the similarity or dissimilarity irrelevant. In those patients whose symptoms of dryness are extreme, if they are lens wearers, simply removing the lenses is the basic treatment. This is done by millions of contact lens wearers each year and is one of the direct causes of contact lens discontinuation [9]. Obviously non-lens related dry eye does not have as easily identifiable an etiology and therefore the therapy and prognosis is much more unclear.

So in closing, there are a number of converging lines of evidence that lens-related and non-lens related symptoms of dryness are not the same. Perhaps, however, because the basic treatment of each of these is so fundamentally different, any question about similarity is moot in any case.

Dr Dagmar Lutzi: You're looking at it from a sensory point of view. Maybe this is too simplified, but I think that the dry eye contact lens condition is different in that you're putting a soft lens on the eye which needs hydration and it's absorbing the tears. Someone who has borderline lacrymal deficiency is going to be fine without lenses; with the lenses on they're not okay because the little tears that they have are being absorbed by the lens material. So the cause of that dry eye or the symptoms are totally associated with the contact lens; once you remove the contact lens it's not there. So I think the mechanical aspect is often the cause of the problem.

Dr Trefford Simpson: I don't disagree, except we have shown a number of years ago that physical loss of water is not necessarily what drives the symptoms. In symptomatic patients the physical loss of water looks like it is related to discomfort, but it's not the only thing. We used lenses that lost water at different rates and it didn't matter because the discomfort increased regardless of the rate of water loss was. So if it's a retention of water in the bulk or around the surface it's probably not as straightforward. Then we looked at asymptomatic patients and their lenses were losing water at the same rate and their discomfort wasn't increasing at the same rate as the symptomatic people. So it might be something related to the lens itself, but it's not as straightforward as we were hoping. We were hoping materials that lost water the least would be most effective at treating patients who had symptoms. That was not the case.

Q *Dr Desmond Fonn:* Should ocular inflammation be included as part of the global definition of dry eye?

Dr Lyndon Jones: As far as the definition is concerned, the current definition was already long enough, but inflammation is obviously involved in many cases of dry eye. Inflammation should be included in the discussion, but that it may be better served by being included within the description of the disease and in the diagnostic tests performed.

Interestingly, it was pointed out that during the 1994 workshop paper on dry eye diagnosis and management, that there was almost no mention of inflammation, reflecting the changing view of the role of inflammation in dry eye. This is felt to be due to a number of reasons, the major one being that at that point in time the laboratory techniques available to investigate inflammatory biomarkers were poorly developed. A recent Medline literature search looking at the relationship between inflammation and dry eye reveals that over a hundred

peer-reviewed papers have been published on this topic. However, the first of these did not appear until late 1997 to early 1998, reflecting the relatively recent development of this area of research.

Historically, a big problem with analyzing tear samples is that most analytical techniques require large volumes of fluid for the analysis to be undertaken. This obviously poses a problem in tear film analysis of dry-eyed patients, who simply do not have large volumes of tears. The recent development of laboratory-based techniques such as flow cytometry and many other related technologies have allowed researchers to take very small samples of tear fluid (sometimes <1 microlitre) and provide a wealth of information on the biomarkers contained within this fluid sample.

While we acknowledge that dry eye and inflammation are linked, we do not know if the inflammation produces the dry eye state, or whether the dry eye problems result in an inflammatory cascade. It would appear that there is good evidence to support either model and both processes may occur, depending upon the type of dry eye that is present and the severity.

Dr Barbara Caffery: The body's response to many forms of primary disease is an inflammatory reaction response to the primary anomaly. If you break your leg, the inflammation at that level is very high, but we don't talk about the disease as an inflammatory disease. It's a disease of broken bones that needs to be fixed. The inflammation itself may need to be treated, of course.

Dr Lyndon Jones: The management of inflammation and dry eye currently involves the use of a number of agents. One simple method involves the regular use of artificial tears to flush the toxic biomolecules, such as pro-inflammatory cytokines, from the ocular surface, thereby preventing them damaging the ocular surface. However, recently there has been a growth in the number of therapeutic agents specifically targeted towards reducing the inflammatory cascade. These include the release of agents aimed at reducing cytokine release and build-up (such as Allergan's Restatis), along with other anti-inflammatory agents such as steroids.

Dr Nish Rajani: With the availability of Restasis and other agents such as Lotemax and Alrex - which are site-specific, non-penetrating, very safe-to-use steroids - dry eye is being treated more and more as an inflammatory disease, and with great results".

Q *Dr Desmond Fonn:* Can symptoms alone be diagnostic of dry eye?

Dr. Lucie Berthiaume: I have always taken the approach of concluding my examination by summarizing my findings with the patient and making sure to refer to their chief complaint. The chief complaint is most often identified during the patient's history, but other complaints or symptoms, can also come up during the course of the exam. Many patients will present with statements such as "My eyes are dry"- easy enough. If your eyes are dry, then they must be dry, regardless of the clinical findings: no corneal or conjunctival staining, no poor tear meniscus and even no reduced BUT.

In a busy practice there are in my opinion, only a certain number of tests you can do to identify dry eye signs. If these tests are negative as they are in some cases, this does not exclude dry eye diagnosis. We can certainly spend more time with more in depth evaluation of patients presenting specifically with dry eye but I would question whether a Shirmer test should be performed on every patient who has symptoms of dry eye.

Other patients will report symptoms of dry eye but say such things as "My eyes burn", " My eyes feel gritty", "I need to blink more at times". In these cases these patient do not think their eyes are dry, and it's a surprise to tell them that what they are feeling and experiencing may be due to dry eye.

Dr. Leinweber: In our office we have a "Welcome Back" or "Welcome to Our Practice" questionnaire that asks about symptoms such as whether or not your eyes burn, do they water, do you get tearing you're reading, do you find you have to blink a lot when you're reading because your vision gets blurred? If we get a positive response to some of those questions, then a more detailed investigation will follow. Symptoms are so important in the diagnosis and treatment options.

Dr. Bitton: I think dry eye is significantly under diagnosed because most people do not present with their chief complaint being that their eyes are dry. Many patients are there for their annual exam, and it's usually

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a secondary complaint, or when prodded by questions that the dry eye symptoms will come out. I think at least one single question would be something like "Do you think you have dry eye".

Dr. Caffery: When a patient comes in with symptoms and you see evidence of dry eye, I always make a point of explaining to the patient that dry eye is chronic and the need for treatment, will need to be ongoing. Often those patients return and won't have followed up with the treatment plan. We therefore first need a product that makes it easy for the patients to comply.

Dr Desmond Fonn: Which tests are essential in the diagnosis of dry eye?

Dr Dagmar Lutzi: I think the major test that is essential in the diagnosis of dry eye is a thorough biomicroscopy, including instillation of fluorescein. This will actually encompass a series of other tests. Biomicroscopy should include an investigation for lid disease; specifically, one should look for blepharitis and meibomian gland dysfunction. Although technically not diagnostic of dry eye, these conditions certainly exacerbate it.

Corneal integrity can be evaluated by fluorescein staining which is typically found in the lower third of the cornea in dry eye. One must be careful not to instill excess amounts of flourescein, as this may mask subtle staining that may be associated with this disease. Excessive conjunctival staining can also be an indication of dry eye. Rose bengal stain can be used to detect degenerated and dead cells on the anterior surface of the eye that will not stain with fluorescein. Lisamine green works similarly and is reported to be less irritating to the patient than rose bengal.

Tear breakup time can be performed during biomicroscopy to assess tear quality. A low tear breakup time may represent a deficiency in the mucin layer of the tear film, a contributing factor in dry eye. Fluorescein aids in the evaluation of the height of the tear meniscus. The tear meniscus should also be examined for the presence of excess debris or mucous that might be indicative of dry eye. Schirmer tear test is is used to measure tear quantity, however, it is time-consuming and its interpretation may be influenced by the instillation of a topical anaesthetic prior to performing the test.

Dr Gerry Leinweber: Are there any tests that our staff are capable of doing?

Dr Barbara Caffery: My staff does Schirmer test. There's a huge amount of literature on Schirmers testing and I consider it a very important part of diagnosing dry eye.

Dr Fadi Maroun: One test that hasn't been brought up is collagen plugs. I'm not too sure why optometry has not been more proactive about using collagen plugs as a temporary plug. We are always keen on adding products to the eye, which again is changing the chemistry on the ocular surface, versus keeping that which is there and seeing if you can solve the problem. This test is not time-consuming and it can bring the patient back to the office ten days later.

Dr Lucie Berthiaume: Another way you can deal with this, if there are no clinical signs, there are just symptoms, is to send them home with artificial tears, make sure they will comply and have them back maybe two or three weeks later to reassess their symptoms.

Dr Desmond Fonn: Tear break-up time (TBUT) is considered to be a useful test of tear film stability. Is this statement true and what is the best method of measuring tear break-up time?

Dr Etty Bitton: Tear break-up time has had a long clinical and controversial history. The TBUT is considered a clinically reliable test of tear film stability, with some pitfalls. The TBUT has shown a great amount of variability in the literature, and certainly we see it in practice with our patients. Most of the variability has been attributed to the methodology: How much fluorescein is instilled? How is the TBUT being measured? Are the lids being held open? What size beam is being used to observe the cornea? All these factors contribute to the variability observed between visits. Furthermore, the magical 10-second cut-off has been challenged by work from Cho[10,11] where ethnic differences were noted. Consequently care should be taken in applying the 10 sec cut-off to all of our patients since lid structure, environmental factors can contribute to a lower acceptable norm for those individuals. To limit the variability of the TBUT even further, Korb[12] proposed a smaller fluorescein strip, called the Dry Eye Test (DET), which limits the amount of fluorescein instilled in the eye. Unfortunately the DET is no longer commercially available.

How should TBUT be measured? The fluorescein strip should be moistened using non-preserved saline, with the excess shaken off. The strip should then be applied gently to the inferior palpebral conjunctiva. Allow the patient to blink 2-3 times to spread the fluorescein evenly prior to assessment. To maximize viewing, the Cobalt filter should be in place along with the use of a yellow barrier filter (Wratten #12), now an integrated part of most modern slit lamps.

To properly observe the cornea during the TBUT, Cho [10] suggested using a wide illumination beam. This may cause photophobia in some patients, hence lowering the intensity of light may render the patient more comfortable. To further enhance the reliability of the TBUT, Nichols [13] suggests doing the test twice and taking an average. In conclusion, the TBUT is an easy test to perform and remains clinically useful if attention to methodology is taken.

Dr. Lyndon Jones: I think if people are taught how to perform the test, it will certainly increase the reliability. Do something simple, like --cut the fluorescein strip in half and use as little non-preserved saline as possible. The difference that you observe when you use the Wratten 12 filter is phenomenal.

Dr. Kerby Kelly: What about the non-invasive tear break-up time (NIBUT) test?

Dr. Trefford Simpson: There are several ways of measuring TBUT without the use of fluorescein, hence NIBUT. We use a corneal topographical device which creates placido ring images on the cornea which seems to work well.

Dr. Barbara Caffery: My impression is that if I have a soft lens wearer take their lens off and the TBUT is going to be much lower than without having worn their lens. So how reliable do you think a lens-removed TBUT is?

Dr. Lucie Berthiaume: I think that's an excellent question. It's definitely been shown that the TBUT in CL wearers is shorter, and so, again, I'd advocate that it could be used as a good screening.

Dr. Lyndon Jones: People have actually looked at how long it takes you to re-establish a tear film after removing your soft lens, and it's a minimum of 20 minutes.

Dr. Barbara Caffery: A quick comment. I think we have to use Lissamine green or Rose Bengal to evaluate staining of the conjunctiva.

Dr. Desmond Fonn: Do you think you've seen more staining with these 2 dyes than fluorescein and is that telling you something more about the condition?

Dr. Barbara Caffery: Yes, I think I see more disturbed cellular walls, or whatever it is that causes this dye to penetrate.

Q *Dr Desmond Fonn: What are the traditional methods of treating mild and moderate dry eye?*

Dr Nish Rajani: Treating mild to moderate ocular surface disease is relatively straight forward; patient compliance of our treatment regimens, well that's a different story. I think that the greatest obstacle in treating dry eye syndrome successfully is proper patient education so that they will follow our treatment protocol.

There is a disconnect between the way optometrists and their patients perceive the extent of this problem: "Patients perceive their dry eye as much more severe than their practitioner," according to Robin L. Chalmers, OD in a paper she presented to the American Academy of Optometry[14]. In her study 19% said their symptoms were severe whereas the optometrists in the study said only 9% of the subjects displayed severe symptoms. Although it is generally not sight threatening, it does cause our patients significant discomfort and we must treat and educate our patients about ocular surface disease even though this is somewhat tedious.

Believe it or not, what we call "dry eye" is, in my opinion, part of the problem. William Shakespeare wrote: "*What's in a name? That which we call a rose by any other word would smell as sweet.*" This may have been true in the Elizabethan era but I do not think the Bard of Avon's famous verse is applicable to modern day "dry eye".

I think that doctors and patients alike are underwhelmed with the diagnosis of "dry eye". In addition to the fact that the name does not sound clinical it is also a misnomer in that it tends to suggest only an aqueous deficiency. Also, patients with "wet dry eye" are easily confused by this moniker. I like the term ocular surface disease better than dry eye syndrome. It sounds more morbid as it should make doctors and patients take it more seriously and hopefully there would be a concomitant increase in counseling and compliance.

Let's Shed a Tear for our "Dry Eye" Patients

Artificial tears, in addition to managing lid disease, remains the mainstay therapy for dry eye syndrome. For currently available ocular lubricant drops to be effective they must be used q 2-3 hrs; we often fail to adequately convey this to our patients and it is tedious for them to instill drops this often. As a result patients tend use their drops infrequently or often not at all. I do not think it is possible to over-emphasize the frequency of instillation.

Historically, we have essentially considered two things when dealing with artificial tear products: preservatives and viscosity agents. We now have several brands of artificial tears with excellent preservatives in that they don't cause toxicity. The best known are: Tears Nauturale, Genteal, Theratears and Refresh lines of products.

I tend to favor the higher viscosity artificial tears like Systane, Tears Naturale Forte (Alcon) and Refresh Liquigel (Allergan). Most tend to blur vision for a few minutes. If patients are forewarned about this they tend to be more accepting of this treatment.

I tend to use punctal plugs less frequently than I did several years ago although they remain an excellent option for patients with low tear volume. In addition to increasing the residence time of naturally produced tears, they do the same for artificial tears supplementation. Artificial tears must still be used as otherwise we may create a cesspool of pro-inflammatory cytokines and other inflammatory mediators[15]. This is the reason that I tend to utilize them less frequently.

Omega-3 fatty acid supplementation has become a cornerstone of ocular surface disease treatment in my practice in the past several years. "Evaporative dry eye" occurs in the presence of meibomian gland dysfunction and this tends to be pervasive. Oral doxycycline and omega-3 fatty acids[16] enhance meibomian gland function and result in a more stable film.

David Star Jordan a physician and educator at Stanford University once stated: "Wisdom is knowing what to do next, skill is knowing how to do it, and virtue is doing it." Optometrists have the wisdom and skill to treat ocular surface disease; however, we all could be a little more virtuous in this regard.

Dr. Barbara Caffery: I think that a healthy body is an important aspect in the management of of dry eye disease. My advice is don't smoke, drink plenty of water during the day, eat fruits and vegetables and exercise.

Dr. Lucie Lesault: I think sleep patterns have a huge effect on people's symptoms and, at times,clinical signs as well. Sleep deprivation and stress may be linked to dry eye.

Dr. Trefford Simpson: I would like to add an accurate refraction and a good pair of glasses to avoid eye strain.

Dr. Barbara Caffery: Perhaps patients are not very compliant because the products we recommend are available OTC. If tear supplements were prescription items it might change their attitude.

Q *Dr Desmond Fonn:* How have the new treatments for mild/moderate dry eye performed?

Dr Gerry Leinweber : In general, the new generation of products have performed well. I am pleased to see we have many more options for providing relief to patients with dry eye. The new treatments that include Systane, are moving beyond simple lubricants to formulations that improve the quality of the tears over a longer period of time. Having non-preserved products is also a real benefit, as many patients are sensitive to preservatives, plus the single dose products are convenient.

Canada is a very big country. The climate in Alberta where I practice is very dry compared to other parts of Canada, and we can have very cold winters. I know that in speaking to practitioners across the country, the demands of our various local climates can greatly affect which products are of most benefit. In areas with more smog issues, a more frequent drop during the day seems to help, while in other areas, lid scrubs seem to be of more benefit. If there is a lot of conjunctival staining, the gels are of more benefit.

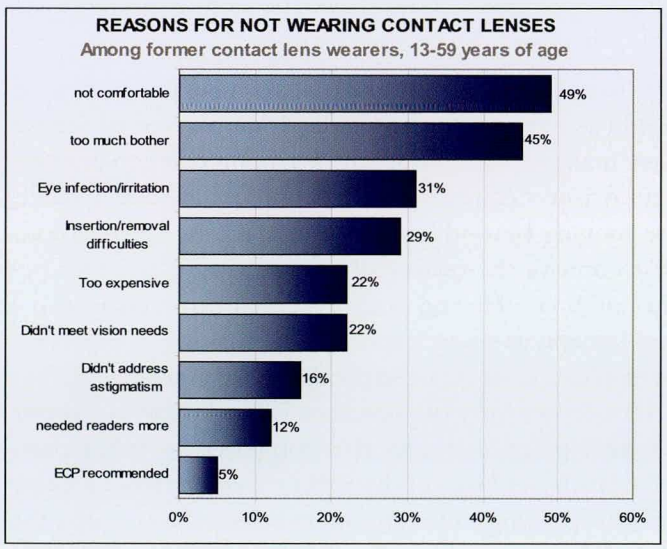
We have used NSAIDS but usually not for mild or moderate problems. I prefer to reserve these medications or steroids for more serious or stubborn problems but keeping the doses short. I would not consider Pulse Dosing as standard treatment for mild or moderate dry eye, but in stubborn cases, where a combination of first line treatments did not resolve the problem, then pulse dosing can be used.

There certainly is great logic in using the combination of lid scrubs bid to enhance natural tear production,

with drops or gels qid or prn and this is my preference when treating most moderate cases of dry eye. The next stage is to consider punctual occlusion to further enhance the benefits of therapy if this is not effective, and finally if still no relief, to consider TPA options.

Dr Desmond Fonn: What strategies do you use to treat contact lens related dryness and is this a major problem amongst your contact lens patients?

Dr Trevor Miranda: Lets tackle the second part of the question first. The short answer is yes. It contributes to increased numbers of contact lens dropouts and also to lower comfort and overall satisfaction amongst those patients that continue to wear their lenses.



The results above from Vistakon's Attitude and Usage Study of Vision Corrected Consumers 2002, 49% cited the lenses not being comfortable. Dryness causes at least half of all contact lens related discomfort issues[17].

Dryness in the discussion of contact lens wear can be divided into pre-existing dry eye and contact lens induced
dry eye (CLIDE). CLIDE is characterized by dryness and discomfort at the end of the wearing time; decreased wearing times; burning; lens intolerance; corneal and conjunctival staining and rapid TBUT. Dryness is a problem because we are fitting more presbyopic patients than ever before with mulitifocal contact lens options. Many patients want to wear their lenses longer or even on a continuous wear basis.

Strategies for treatment:

It is vital to determine the cause firstly. Is it the low production of tears as found by a Schirmer's test or is it pre-exisiting lid disease? Just asking how your lenses feel is not enough. Here are some of the strategies I employ for treating dryness in my contact lens practice:

Fit new low dehydration, high Dk/t lenses. I fit a lot of silicone hydrogel lenses whether or not the patient is considering overnight wear. This helps to reduce hypoxic effects on the cornea, which may contribute to symptoms of dryness. Simple and easy to follow instructions will help increase compliance. We recommend regular replacement schedules.

We often provide lubricating drops for patients when they are wearing contacts and Systane before and after contact lens wear. Dr Lutzi has found that drops containing sodium hyaluronate have provided patients with improved comfort and longer wearing times.

- We recommend sunwear over contacts to reduce external drying forces such as wind and sun.

- Recommend lid hygiene and lid scrubs for any lid disease.

- We try single use lenses either on a daily disposable or continuous wear basis to avoid solutions sensitivities and corneal inflammation that contribute to discomfort and dryness

- Decrease the wearing times.

- Reduce eye makeup that can cause irritation and local inflammation.

- Recommend oral omega 3 fatty acid intake. Patients who are deficient in Omega 3s have meibomian glands with very thick secretion. Consequently people who are deficient in omega-3 oils end up with an evaporative tear loss and dry eye syndrome.

- Consider punctual occlusion for highly motivated contact lens patients as a last resort.

- Future strategies may include topical cyclosporin A to reduce local inflammation.

Dr Desmond Fonn: Do contact lens disinfecting systems contribute to dryness/discomfort symptoms and if so what strategies do you use to minimize/eliminate the symptoms?

Dr. Kerby Kelly: Historically, preservatives have caused some adverse effects to contact lens wearers and to the contact lens material itself.

We can remember the toxic or hypersensitivity reactions to thimerosal and benzalkonium chloride. Fortunately

Pr Visudyne*
verteporfin for injection

PRESCRIBING INFORMATION (September 2004)

Pr Visudyne* Verteporfin for Injection for Intravenous Use

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CAUTION: Visudyne* Therapy should only be used by physicians trained in the treatment of age-related macular degeneration and pathologic myopia using photodynamic therapy with verteporfin for injection and specified lasers. Following VISUDYNE* injection, residual photosensitivity for 48 hours or more may result in erythema and blistering of the skin when exposed to sunlight or brightly focused indoor light.

INDICATIONS AND CLINICAL USE Visudyne* Therapy is indicated for the treatment of age-related macular degeneration, pathologic myopia and presumed ocular histoplasmosis in patients with predominantly classic subfoveal choroidal neovascularization.

CONTRAINDICATIONS VISUDYNE* (verteporfin) is contraindicated for patients with porphyria or a known hypersensitivity to any component of this preparation, and in patients with severe hepatic impairment.

WARNINGS Following injection with VISUDYNE* (verteporfin), care should be taken to avoid exposure of skin or eyes to direct sunlight or bright indoor light for 2 days. In the event of extravasation during infusion, the extravasation area must be thoroughly protected from direct light until the swelling and discoloration have faded in order to prevent the occurrence of a local burn which could be severe. If emergency surgery is necessary within 48 hours after treatment, as much of the internal tissue as possible should be protected from intense light. Patients who experience severe decrease of vision of 4 lines or more within 1 week after treatment should not be retreated, at least until their vision completely recovers to pretreatment levels and the potential benefits and risks of subsequent treatment are carefully considered by the treating physician.

Caution should be exercised when Visudyne* Treatment under general anesthesia is considered (See PRECAUTIONS).

Use of incompatible lasers that do not provide the required characteristics of light for the photoactivation of VISUDYNE* could result in incomplete treatment due to partial photoactivation of VISUDYNE*, overtreatment due to overactivation of VISUDYNE*, or damage to surrounding normal tissue.

Pregnancy TERATOGENIC EFFECTS There are no adequate and well-controlled studies in pregnant women. VISUDYNE* should be used during pregnancy only if the benefit justifies the potential risk to the fetus. Rat fetuses of dams administered verteporfin for injection intravenously at ≥10 mg/kg/day during organogenesis (approximately 40-fold the human exposure at 6 mg/m^2 based on AUC_{inf} in female rats) exhibit an increase in the incidence of anophthalmia/microphthalmia. Rat fetuses of dams administered 25 mg/kg/day (approximately 125-fold the human exposure at 6 mg/m^2 based on AUC_{inf} in female rats) had an increased incidence of wavy ribs and fetal alterations. In pregnant rabbits, a decrease in body weight gain and food consumption was observed in animals that received verteporfin for injection intravenously at 10 mg/kg/day during organogenesis. The no observed adverse effect level (NOAEL) for maternal toxicity was 3 mg/kg/day (approximately 7-fold the human exposure at 6 g/m^2 based on body surface area). There were no teratogenic effects observed in rabbits at doses up to 10 mg/kg/day.

Nursing Mothers Verteporfin and its diacid metabolite have been found in the breast milk of one woman after a 6 mg/m^2 infusion. The verteporfin breast milk levels were up to 66% of the corresponding plasma levels. Verteporfin was undetectable after 12 hours. The diacid metabolite had lower peak concentrations but persisted up to at least 48 hours. Because the effects of verteporfin and its metabolite on neonates are unknown, either nursing should be interrupted or treatment postponed, taking into account the risks of delayed treatment to the mother. Women should not nurse for 96 hours after Visudyne* Therapy.

Pediatric Use Safety and effectiveness in pediatric patients have not been established.

PRECAUTIONS

General Extravasation of VISUDYNE*, especially if the affected area is exposed to light, can cause severe pain, inflammation, swelling or discoloration at the injection site. The relief of pain may require analgesic treatment.

Standard precautions should be taken during infusion of VISUDYNE* (verteporfin) to avoid extravasation. Examples of standard precautions include, but are not limited to:

- A free-flowing intravenous (IV) line should be established before starting VISUDYNE* infusion and the line should be carefully monitored.
- Due to the possible fragility of vein walls of some elderly patients, it is strongly recommended that the largest arm vein possible, preferably antecubital, be used for injection.
- Small veins in the back of the hand should be avoided.

If extravasation does occur, the infusion should be stopped immediately. The extravasation area must be thoroughly protected from direct light until the swelling and discoloration have faded in order to prevent the occurrence of a local burn which could be severe. Cold compresses should be applied to the injection site (see Warnings).

Visudyne* Therapy should be considered carefully in patients with moderate hepatic impairment or biliary obstruction since there is no clinical experience with verteporfin in such patients.

Chest pain, vaso-vagal reactions and hypersensitivity reactions, which on rare occasion can be severe, have been reported. Both vaso-vagal and hypersensitivity reactions are associated with general symptoms such as syncope, sweating, dizziness, rash, dyspnea, flushing, and changes in blood pressure and heart rate.

There is no clinical data related to the use of VISUDYNE* in anesthetized patients. At a >10-fold higher dose given by bolus injection to sedated or anesthetized pigs, verteporfin caused severe hemodynamic effects, including death, probably as a result of complement activation. These effects were diminished or abolished by pretreatment with antihistamine and they were not seen in conscious non-sedated pigs or in any other species, whether conscious or under general anesthesia. Caution should be exercised when Visudyne* Treatment under general anesthesia is considered (see WARNINGS).

VISUDYNE* at >5 times the expected maximum plasma concentration in treated patients caused a low level of complement activation in human blood in vitro. VISUDYNE* resulted in a concentration-dependent increase in complement activation in human blood in vitro. At 10 µg/ml (approximately 5 times the expected plasma concentration in human patients), there was mild to moderate complement activation. At ≥ 100 µg/mL, there was significant complement activation. Signs (chest pain, syncope, dyspnea, and flushing) consistent with complement activation have been observed in < 1% of patients administered VISUDYNE*. Patients should be supervised during VISUDYNE* infusion.

Photosensitivity Patients who receive VISUDYNE will become temporarily photosensitive for 2 days after the infusion. During that period, patients should avoid exposure of unprotected skin, eyes or other body organs to direct sunlight or bright indoor light. This includes, but is not limited to, tanning salons, bright halogen lighting and high power lighting used in surgical operating rooms or dental offices (see Warnings). Prolonged exposure to light from light emitting medical devices such as pulse oximeters should also be avoided for 48 hours following VISUDYNE* administration. If treated patients must go outdoors in daylight during the first 2 days after treatment, they should protect all parts of their skin and their eyes by wearing protective clothing and dark sunglasses. UV sunscreens are not effective in protecting against photosensitivity reactions because photoactivation of the residual drug in the skin can be caused by visible light. Patients should not stay in the dark and should be encouraged to expose their skin to ambient indoor light, as it will help inactivate the drug in the skin through a process called photobleaching.

Drug Interactions Drug interaction studies in humans have not been conducted with VISUDYNE*. Verteporfin is rapidly eliminated by the liver, mainly as unchanged drug. Metabolism is limited and occurs by liver and plasma esterases. Microsomal cytochrome P450 does not appear to play a role in verteporfin metabolism. Based on the mechanism of action of verteporfin, many drugs used concomitantly could influence the effect of Visudyne Therapy. Possible examples include the following. Calcium channel blockers, polymyxin B or radiation therapy could enhance the rate of VISUDYNE* uptake by the vascular endothelium. Other photosensitizing agents (e.g., tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide diuretics and griseofulvin) could increase the potential for skin photosensitivity reactions. Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulfoxide, b-carotene, ethanol, formate and mannitol, would be expected to decrease VISUDYNE* activity. Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A_2 inhibitors, could also decrease the efficacy of Visudyne Therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility No studies have been conducted to evaluate the carcinogenic potential of verteporfin. Verteporfin was not mutagenic, in the absence or presence of light, when studied in microbial mutagenicity, unscheduled DNA synthesis, mammalian point mutation, chromosome aberration, and mouse micronucleus assays.

Photodynamic therapy (PDT) as a class has been reported to result in DNA damage including DNA strand breaks, alkali-labile sites, DNA degradation, and DNA-protein cross links which may result in chromosomal aberrations, sister chromatid exchanges (SCE), and mutations. In addition, other photodynamic therapeutic agents have been shown to increase the incidence of SCE in Chinese hamster ovary (CHO) cells irradiated with visible light and in Chinese hamster lung fibroblasts irradiated with near UV light, increase mutations and DNA-protein cross-linking in mouse L5178 cells, and increase DNA-strand breaks in malignant human cervical carcinoma cells, but not in normal cells. Verteporfin was not evaluated in these latter systems. It is not known how the potential for DNA damage with PDT agents translates into human risk.

No effect on male or female reproduction has been observed in rats following intravenous administration of verteporfin for injection up to 10 mg/kg/day (approximately 60- and 40-fold human exposure at 6 mg/m^2 based on AUC_{inf} in male and female rats, respectively). Males were dosed 28 days prior to and during mating until necropsy (approximately 60 days). Females were dosed for 14 days prior to and during mating until Gestation Day 7.

Geriatric Use Approximately 90% of the patients treated with VISUDYNE* in the clinical efficacy trials were over the age of 65. A reduced treatment effect was seen with increasing age.

Fluorescein Angiography Standard precautions for fluorescein angiography should be observed. Certain medical conditions (such as pregnancy or allergy to fluorescein) may make the injection of fluorescein dye for a particular patient inadvisable in the opinion of the ophthalmologist. Approximately 1/225,000 patients may experience a severe reaction resulting in a heart attack, stroke, or death. Most reactions are mild, such as temporary nausea or vomiting in a few patients and a rash, hives, or wheezing in about 1%.

Effects on ability to drive and use machines Following Visudyne* Therapy, patients may develop transient visual disturbances such as abnormal vision, vision decrease, or visual field defects that may interfere with their ability to drive or use machines. Patients should be advised to not drive or use machines as long as these symptoms persist.

ADVERSE REACTIONS In randomized clinical trials in choroidal neovascularization, mainly in patients with age-related macular degeneration (AMD), the most frequently reported adverse events to VISUDYNE* (verteporfin) are injection site reactions (including pain, edema, inflammation, extravasation, rashes, and less commonly, hemorrhage and discoloration) and visual disturbances (including blurred vision, flashes of light, decreased visual acuity and visual field defects such as grey or dark haloes, scotoma and black spots). These events occurred in approximately 10-30% of patients. The following events, listed by Body System, occurred in 1-10% of patients:

Ocular Treatment Site: Blepharitis, cataracts, conjunctivitis/conjunctival injection, dry eyes, ocular itching, severe vision decrease with or without subretinal or vitreous hemorrhage

Body as a Whole:	Asthenia, infusion related pain primarily presenting as back pain, fever, flu syndrome, photosensitivity reactions.
Cardiovascular:	Atrial fibrillation, hypertension, peripheral vascular disorder, varicose veins
Dermatologic:	Eczema
Digestive:	Constipation, nausea
Hemic and Lymphatic:	Anemia, white blood cell count decreased, white blood cell count increased
Hepatic:	Elevated liver function tests
Metabolic/Nutritional:	Albuminuria, creatinine increased
Musculoskeletal:	Arthralgia, arthrosis, myasthenia
Nervous System:	Hypesthesia, sleep disorder, vertigo
Respiratory:	Cough, pharyngitis, pneumonia
Special Senses:	Cataracts, decreased hearing, diplopia, lacrimation disorder
Urogenital:	Prostatic disorder

Severe vision decrease, equivalent of 4 lines or more, within 7 days has been reported in 1-4% of patients. At least partial recovery of vision, defined as more than one line improvement of vision following the event, occurred in most patients (approximately 75% of patients).

Photosensitivity reactions usually occurred in the form of skin sunburn following exposure to sunlight during the first 2 days after treatment usually within 24 hours of VISUDYNE* infusion. The higher incidence of back pain in the VISUDYNE* group occurred primarily during infusion and was not associated with any evidence of hemolysis or allergic reaction and usually resolved by the end of the infusion.

The following adverse events have occurred either at low incidence (<1%) during clinical trials or have been reported during the use of VISUDYNE* in clinical practice where these events were reported voluntarily from a population of unknown size and hence the frequency of occurrence cannot be determined precisely. They have been chosen for inclusion based on factors such as seriousness, frequency of reporting, possible causal connection to VISUDYNE*, or a combination of these factors:

Ocular Treatment Site: Retinal detachment (nonrhegmatogenous), retinal or choroidal vessel nonperfusion, severe vision decrease with retinal hemorrhage.

Nonocular Events: Chest and back pain (which may radiate to other areas including but not limited to pelvis, shoulder, girdle or rib cage) and other musculoskeletal pain during infusion.

Vaso-vagal and hypersensitivity reactions can occur, which on rare occasions can be severe. General symptoms can include headache, malaise, syncope, sweating, dizziness, rash, urticaria, pruritus, dyspnea, flushing and changes in blood pressure or heart rate.

Adverse reactions reported in treated eyes in patients with pathologic myopia or presumed ocular histoplasmosis were similar to those reported in AMD patients.

SYMPTOMS AND TREATMENT OF OVERDOSAGE Overdose of drug and/or light in the treated eye may result in nonperfusion of normal retinal vessels with the possibility of severe decrease in vision that could be permanent. An overdose of drug will also result in the prolongation of the period during which the patient remains photosensitive to bright light. In such cases, it is recommended to extend the photosensitivity precautions for a time proportional to the overdose.

DOSAGE AND ADMINISTRATION A course of Visudyne* Therapy is a two-step process requiring administration of both drug and light. The first step is the intravenous infusion of VISUDYNE* (verteporfin). The second step is the activation of VISUDYNE* with light from a nonthermal diode laser. The physician should re-evaluate the patient every 3 months and if choroidal neovascular leakage is detected on fluorescein angiography, therapy should be repeated.

Lesion Size Determination The greatest linear dimension (GLD) of the lesion is estimated by fluorescein angiography and color fundus photography. All classic and occult CNV, blood and/or blocked fluorescence, and any serous detachments of the retinal pigment epithelium should be included for this measurement. Fundus cameras with magnification within the range of 2.4-2.6X are recommended. The GLD of the lesion on the fluorescein angiogram must be corrected for the magnification of the fundus camera to obtain the GLD of the lesion on the retina.

Spot Size Determination The treatment spot size should be 1000 microns larger than the GLD of the lesion on the retina to allow a 500 micron border, ensuring full coverage of the lesion. The maximum spot size used in the clinical trials was 6400 microns. The nasal edge of the treatment spot must be positioned at least 200 microns from the temporal edge of the optic disc, even if this will result in lack of photoactivation of CNV within 200 microns of the optic nerve. For treatment of lesions that are larger than the maximum treatment spot size, apply the light to the greatest possible area of active lesion.

VISUDYNE* Administration VISUDYNE* should be reconstituted according to the directions given under PHARMACEUTICAL INFORMATION, Reconstitution. The volume of reconstituted VISUDYNE* required to achieve the desired dose of 6 mg/m^2 body surface area is withdrawn from the vial and diluted with 5% Dextrose for Injection to a total infusion volume of 30 mL. The full infusion volume is administered intravenously over 10 minutes at a rate of 3 mL/minute, using an appropriate syringe pump and in-line filter. The clinical studies were conducted using a standard infusion line filter of 1.2 microns. Precautions should be taken to prevent extravasation at the injection site. If extravasation occurs, protect the site from light (see Precautions).

Light Administration Initiate 689 nm wavelength laser light delivery to the patient 15 minutes after the start of the 10-minute infusion with VISUDYNE*. Photoactivation of VISUDYNE* is controlled by the total light dose delivered. In the treatment of choroidal neovascularization, the recommended light dose is 50 J/cm^2 of neovascular lesion administered at an intensity of 600 mW/cm^2 . This dose is administered over 83 seconds. Light dose, light intensity, ophthalmic lens magnification factor and zoom lens setting are important parameters for the appropriate delivery of light to the predetermined treatment spot. Follow the laser system manuals for procedure set up and operation. The laser system must be acceptable for the delivery of a stable power output at a wavelength of 689±3 nm. Light is delivered to the retina as a single circular spot via a fiber optic and a slit lamp, using a suitable ophthalmic magnification lens. The following laser systems have been tested for compatibility with VISUDYNE* and are acceptable for the delivery of a stable power output at a wavelength of 689±3 nm:

Lumenis Opal Photoactivator laser console and modified LaserLink adapter, Manufactured by Lumenis, Inc., Santa Clara, CA

Zeiss VISULAS 690s laser and VISULINK PDT adapter, Manufactured by Carl Zeiss, Inc., Thornwood, NY.

Concurrent Bilateral Treatment The controlled trials only allowed treatment of one eye per patient. In patients who present with eligible lesions in both eyes, physicians should evaluate the potential benefits and risks of treating both eyes concurrently. If the patient has already received previous Visudyne* Therapy in one eye with an acceptable safety profile, both eyes can be treated concurrently after a single administration of VISUDYNE*. The more aggressive lesion should be treated first, at 15 minutes after the start of infusion. Immediately at the end of light application to the first eye, the laser settings should be adjusted to introduce the treatment parameters for the second eye, with the same light dose and intensity as for the first eye, starting no later than 20 minutes from the start of infusion. In patients who present for the first time with eligible lesions in both eyes without prior Visudyne* Therapy, it is prudent to treat only one eye (the most aggressive lesion) at the first course. One week after the first course, if no significant safety issues were identified, the second eye can be treated using the same treatment regimen after a second VISUDYNE* infusion. Approximately 3 months later, both eyes can be evaluated and concurrent treatment following a new VISUDYNE* infusion can be started if both lesions still show evidence of leakage.

AVAILABILITY OF DOSAGE FORMS VISUDYNE* (verteporfin) is supplied in a single-use glass vial with a gray bromobutyl stopper and aluminium flip-off cap. It contains a lyophilized cake with 15 mg verteporfin. The product is intended for intravenous injection only.

Product monograph available upon request. September 2004.

QLT Inc. Vancouver Canada V5T 4T5

Co-developed and distributed by:

NOVARTIS OPHTHALMICS

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today's preservatives have a large molecular weight and size which precludes them from entering the matrix of hydrophilic lenses. These preservatives cause more damage to microbes making them as effective at lower concentrations. There are fewer solution problems, however, reactions still occur. The SiliconeHydrogels.org web site is a great resource of information on studies comparing the similarities and differences between conventional hydrogel and silicone hydrogel lenses. It appears that some solutions may not work as well with silicone hydrogels as conventional hydrogels but its unclear whether symptoms are manifested.

Adverse reactions to older contact lens solutions were often easier to find and identify. There was more of a diffuse SPK apparent. With newer formulations there might only be slight dryness or perhaps mild discharge. Sometimes you'll see low-grade inflammation of the tarsal plate as well. So it is somewhat more difficult now to figure out if it's the solution that's causing the problem.

Apparently many contact lens wearers in the U.S. use generic brands that are not prescribed by the practitioner. Patients may often ignore our recommendations and purchase the cheapest alternative. Many of the generic brands change the formulation without notice to the consumer. It may make more sense to retail the solution ourselves to ensure patient compliance.

Most care systems now are advertised as *no-rub* and unfortunately often equated in the patient's mind as *no care*. Digital cleaning is an important step with the new silicone hydrogel materials especially as they may attract more lipid deposition. Another useful tip is to have the patient rinse the contact lens as it may actually get rid of about 90 percent of the contaminants.

Depending on the severity of the symptoms patients may try rewetting or rewetting/surfactant combination drops or perhaps graduate to preservative-free alternatives such as peroxide or ultraviolet disinfection systems. Another good tip is to simply have the patient rinse their lenses with a non-preserved saline before insertion. This may solve some of the initial stinging and burning often experienced first thing in the morning.

Dr. Etty Bitton: I really want to reinforce the use of the Wratten yellow barrier filter to make it easier to observe mild SPK changes as it may otherwise go undetected.

When things go wrong with contact lenses we, as practitioners, have a knee-jerk reaction to change the contact lens without considering the disinfecting system.

Dr. Gerald Leinweber: Interestingly for some people who have had solution sensitivities - "no solution" seems to be the answer for those people, and the other solution is extended wear, 30 days.

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