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BEST PRACTICES IN PRESBYOPIA:

Current and Future Management

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Thought leaders from the optometric and ophthalmic communities share their approaches to caring for patients with presbyopia and discuss how novel pipeline therapies may have a positive impact on the treatment paradigm.

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Best Practices in Presbyopia:
Current and Future Management

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CONTENT SOURCE

This continuing medical education (CME/CE) activity captures content from two webinars.

ACTIVITY DESCRIPTION

Emerging pharmaceutical options for the treatment of individuals with presbyopia are poised to enter the eye care landscape. This novel approach represents a completely new paradigm for eye care providers to consider when discussing the array of options available with patients.

TARGET AUDIENCE

This certified CE/CME activity is designed for optometrists and ophthalmologists who care for patients with presbyopia.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- **Define** the underlying mechanisms of presbyopic changes.
- **Interpret** the clinical trial experience published in the literature with pharmaceutical and nonpharmaceutical presbyopia-correcting (PC) options.
- **Differentiate** among the pharmacological properties of newly emerging presbyopia correcting drops and their mechanisms of action.
- **Explain** how PC drops are likely to affect categories of patients based on individual characteristics.
- **Compare** the side effects of pharmaceutical approaches to presbyopia correction with other treatment options to debate the pros and cons of each strategy.

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1. **Please rate your confidence in your ability to interpret clinical trial data published in the literature about pharmaceutical and nonpharmaceutical presbyopia-correcting options (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

2. **Mr. Smith is a 45-year-old man who presents to your office with complaints of difficulty reading his phone. He is very reluctant to try reading glasses and asks for a medication that may help him. Which of the following drops may alleviate his symptoms?**
   a. Timolol
   b. Latanoprost
   c. Pilocarpine
   d. Atropine

3. **Peripheral vision is least restricted when the pinhole is placed on _____.**
   a. The spectacle plane
   b. The corneal plane
   c. The iris plane
   d. Peripheral vision is equally restricted on all of these planes

4. **All of the following are benefits of a miotic EXCEPT:**
   a. Increase depth of field/depth of focus
   b. Works as a pinhole at the iris plane
   c. Works as a pinhole at the corneal plane
   d. Improves near vision without impacting IOP

5. **Which one of the following investigational pharmacological therapies for the treatment of presbyopia is NOT a miotic?**
   a. AGN 190584
   b. Carbachol + brimonidine tartrate
   c. CSF-1
   d. PRX-100
   e. UNR844

6. **What percent of presbyopes usually seek eye care?**
   a. 12%
   b. 32%
   c. 42%
   d. 62%

7. **Ms. Jones is a 38-year-old who presents to your office with fear about eventually needing reading correction. She asks about preventative measures she can take to delay onset of presbyopia. Which of the following may be a reasonable suggestion?**
   a. Limit exposure to high temperature environments, like saunas.
   b. Increase frequency of exposure to high temperature environments, like saunas.
   c. Preferentially live in high temperature environments
   d. No lifestyle measures can reduce the risk of presbyopia

8. **How many people globally are affected by presbyopia?**
   a. 1.1 billion
   b. 1.8 billion
   c. 2.1 billion
   d. 2.8 billion

9. **Which of the following terms refers to the stage of presbyopia where no accommodative ability is present?**
   a. Premature presbyopia
   b. Incipient presbyopia
   c. Functional presbyopia
   d. Absolute presbyopia

10. **All of the following are components of the near triad, EXCEPT:**
    a. Accommodation
    b. Convergence
    c. Miosis
    d. Mydriasis

11. **What is the optimal pupil size range?**
    a. 10-20% of the natural pupil size
    b. 20-30% of the natural pupil size
    c. 30-40% of the natural pupil size
    d. 40-50% of the natural pupil size

12. **Which of the following is a common side effect of miotics?**
    a. Headaches
    b. Discoloration
    c. Allergic Reaction
    d. Ptosis

13. **The phase 3 GEMINI 1 and 2 trials involving pilocarpine for treatment of presbyopia showed that a statistically significant greater proportion of patients in the treatment group compared to the control group:**
    a. Gained 1 line of near vision
    b. Gained 2 lines of near vision
    c. Gained 3 lines of near vision
    d. Lost one lines of near vision

14. **In a clinical trial examining PRX-100 use on patients, what percentage of trial participants gained at least 2 lines of near acuity after administration of this drop?**
    a. 41.7%
    b. 62.3%
    c. 75.9%
    d. 91.7%

PART ONE

Pharmaceutical Approaches to Presbyopia Management

I believe managing presbyopia with pharmaceuticals is going to be the next big thing in the coming months and years. This is sure to be a hot topic for both optometry and ophthalmology. This activity represents the first educational program dedicated to presbyopia management with pharmaceuticals. Our patients are not satisfied with the status quo that we have to offer—they absolutely hate presbyopia. When patients find out there is potentially a new drop that can help with their near vision, they are ecstatic.

In the articles that follow, based on a webinar, we discuss the prevalence of presbyopia, how to talk to patients about presbyopia, the presbyopic process, the mechanisms of action of the new drops, and ultimately, how to bring patients into your practice.

—Milton M. Hom, OD, FAAO, Program Co-Chair

THE YOUNG PRESBYOPES ARE COMING: PREVALENCE AND CURRENT OPTIONS

Our patients should not have to simply accept poor near vision.

BY SELINA R. MCGEE, OD, FAAO

Does anyone actually want to be reminded that they are "old?" The origin of presbyopia is from Classical Greek. "Presby" is a word-forming element meaning old; the combining form means elderly or aged as a noun. I learned this my first semester of optometry school. I was 21 and even then, I was horrified. That impression has never waned. How well do our patients accept this verbiage? Words matter!

Early presbyopes, 40- to 50-year-olds, are at the height of their income-making years as their visual demands continue to increase. Millennials are starting to grapple with this sign of aging: they turn 40 this year and they are certainly concerned about their appearance. We can consider presbyopia a "lifestyle" problem. Researchers have found that people who feel old tend to age faster, in fact, people who think aging means declining tend to develop cardiovascular and memory problems. People in this age range are already grappling with "The Midife Unraveling" as Brene Brown calls it.

THERE ARE HOW MANY OF THESE PEOPLE?

The prevalence of presbyopia is stunning—approximately 1.8 billion people[1] globally are affected, with 826 million of those having near vision loss because of no, or inadequate, vision correction.[1] In America, we have about 128 million people[2-4] with presbyopia. We know that 30.9 million of these adults wear over-the-counter readers, purchasing about 51.2 million pairs a year.[5]

None of our presbyopic patients want to wear glasses and be reminded they are getting older, and they do not enjoy keeping up with several pairs of readers they can never find or enlisting their children to help read recipes. And what about us? Do we think emmetropic presbyopes are fun? Do we love spending extra chair time with multifocal contact lens patients who read 20/20 but can't "see" anything?

WE ARE SPENDING HOW MUCH TIME ON SCREENS?

Presbyopia seems more prevalent than ever, partly due to the ubiquitous nature of digital media and communication. American adults spend more than 11 hours per day watching, reading, listening to, or simply interacting with media.[6,7] Americans now check their phones 96 times a day—that's once every 10 minutes.[8] This means they're potentially being reminded up to 96 times a day that their near vision isn't perfect and that they're getting old. Texting is the preferred mode of communication: even baby boomers are 7 times more likely to text versus talking in person.[8]

A survey of 1,339 patients ages 40 to 55 found that 62% of presbyopes saw an eye care professional in the past 12 months, and 79% of them initiated a discussion about near vision loss symptoms.[9] Only half, however, say they received the information they needed and just 15% received printed information about presbyopia.[9] This gulf presents an opportunity for us to intentionally reach out to these patients—already in our offices—to improve their satisfaction with presbyopia options.

WATCH IT NOW

Part 1 of this supplement is based on a CE webinar (1.5 COPE credits) available on EvolveMedEd.com. Go to the link below to view the full webinar presentation followed by a question-and-answer session with the audience.

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Conversely, if a patient has never been to an eye care provider, how do we encourage them to come in? Pharmaceutical agents to treat presbyopia are that doorway.

WE NEED TO BE INTENTIONAL

When these patients are in our chairs, we need to purposefully discuss with them how they feel about presbyopia. I do not believe we or our patients are completely satisfied with our solutions. Now is the time to start helping, potentially, 31 million people improve their near vision and at the same time improve their quality of life.

Emmetropic presbyopes do not usually seek out our services; only 13% see an eye exam as a preventive measure and have regular exams.[10] If we can get them in the door, imagine how many other diseases—glaucoma, dry eye, age-related macular degeneration, cataracts—we would potentially diagnose, treat, or prevent. We would then be able to initiate conversations around skin cancer and the importance of regular exams for them and their loved ones. I see presbyopia-correcting drops as a "gateway drug" for our practices.

CONCLUSION

Current options to manage presbyopia can be considered surgical and nonsurgical (Figure). It is time for us to take a step back and ask ourselves if any of our patients are truly happy with these and how much time it takes to review these options with patients. Those who are not even having these conversations or who treat it as an afterthought need to change their thinking. Presbyopia cannot be glossed over; it must be treated like a real condition. Optometrists prescribe 90% of corrective devices.

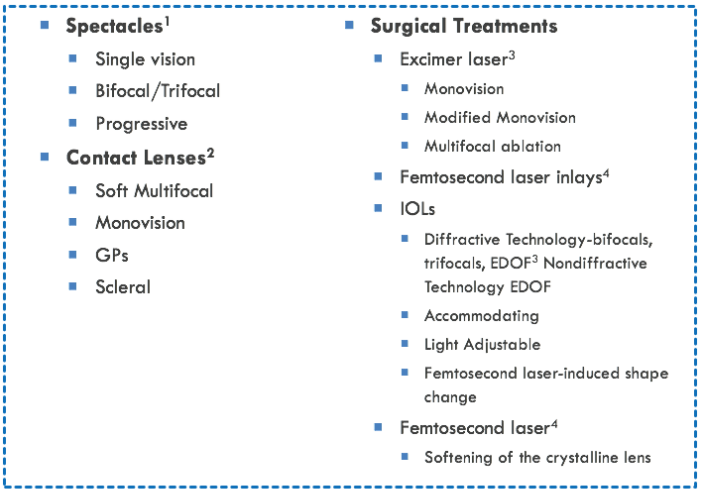

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Figure. The current list of options for managing presbyopia.

We need to step up and own this disease—presbyopia is not complicated! We cannot miss this opportunity. ■

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MECHANISMS OF PRESBYOPIA

Denatured proteins make the lens hard and stiff.

BY MILTON M. HOM, OD, FAAO

How do you take a three-dimensional environment and place it on a two-dimensional retina and see at multiple distances? It's called the near triad: accommodation, convergence, and miosis. For us to see at multiple distances, the lens changes power. To do this, however, it has to be flexible. As time goes by, the nucleus becomes harder and less flexible.

Heys and colleagues reported that in people younger than 30 years, the nucleus was softer than the cortex; those in their 30s had similar cortical and nuclear stiffness values; and those older than 50 had lenses with nuclei that were typically an order of magnitude more rigid.[1] Over time, the stiffness values of the nucleus can increase over 1,000 times that of the cortex. All of the difficulties that we have with presbyopia center around the nucleus.

LIVE LONG - WON'T PROSPER

Mr. Spock may have said, "live long and prosper," but when it comes to the crystalline lens, it's "live long, won't prosper," according to Toyama and Hetzer.[2] Proteins have a certain longevity before they need to be replaced or become denatured, which is what happens in the lens. In other words, they become harder and stiffer.

A cross section of the lens is similar to a tree with its age lines, ie, the center rings are of the young tree and the outer rings are the older tree. The center of the lens is the fetal nucleus, and the cortex comes later. The proteins in the nucleus denature much faster than the cortex because of the lack of blood supply to renew the proteins.

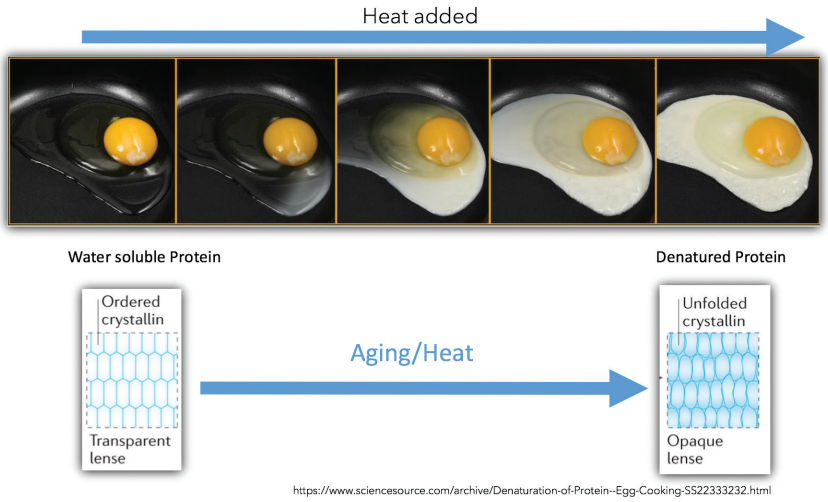

Figure. The lens has been compared to an egg.

SOME DON'T LIKE IT HOT

Another reason for denaturation may be heat.[1] In a subsequent study, Heys found that as the human lens is heated, stiffness increases.[3] The hypothesis is that over time, the buildup of heat contributes to the denaturation of the protein, which brings on the stiffness of the nucleus, which brings on presbyopia.

The lens has been compared to an egg (Figure). The lens begins as water soluble and clear. The crystallin in the lens is actually transparent. As it is heated, the protein denatures, it becomes stiffer and turns more opaque. Is the heat's impact due to cumulative effect of aging or does the ambient temperature play a role and influence the onset of presbyopia?

In 1979, Miranda plotted the average age of the onset of presbyopia in a group of doctors living in various countries.[4] He showed that the higher the ambient temperature, the earlier the onset of presbyopia. In fact, the closer you are to the equator, the more likely you are to develop presbyopia at a younger age. Heys went on to recommend living in colder climates and avoiding heated environments like saunas as ways to delay the onset of presbyopia. ■

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CAN MIOTICS LEVERAGE THE PINHOLE EFFECT TO BENEFIT NEAR VISION?

A review of small-aperture optics.

BY SELINA R. MCGEE, OD, FAAO

As an alternative to natural accommodation, the eye's iris can be employed to create a pinhole effect, which extends the depth of focus.[1] Ideally, a method of correcting presbyopia employing a small aperture would not restrict peripheral vision.

A large aperture or dilated pupil creates blur in the retinal image and a narrow depth of focus. Making the pupil smaller allows for a range of depth of focus. The pinhole allows improved image quality on the retina due to blocked stray light. Because the pinhole can restrict peripheral vision, where it is placed matters. Placing a pinhole pupil in front of the eye at the spectacle plane severely restricts the peripheral focus, which is still restricted at the corneal plane. Only a small pupil in or very near to the iris plane can extend depth of focus without restricting peripheral focus.[1]

Regarding the size of a pupil, one size does not fit all. Rather than an absolute number for pupil size, it is best to describe pupil size as a percentage of the natural pupil, based on the individual and the light. The optimal pupil size range considers maximum image quality for both near and distance vision (Figure).

Xu et al showed that in high light, as the pupil size gets smaller, near-vision image quality improves, while distance-vision stays stable until the pupil gets so small that distance-vision image quality starts to decline.[2] Extrapolating from that work, a focused eye, constricting the pupil size to about 50% to 60%

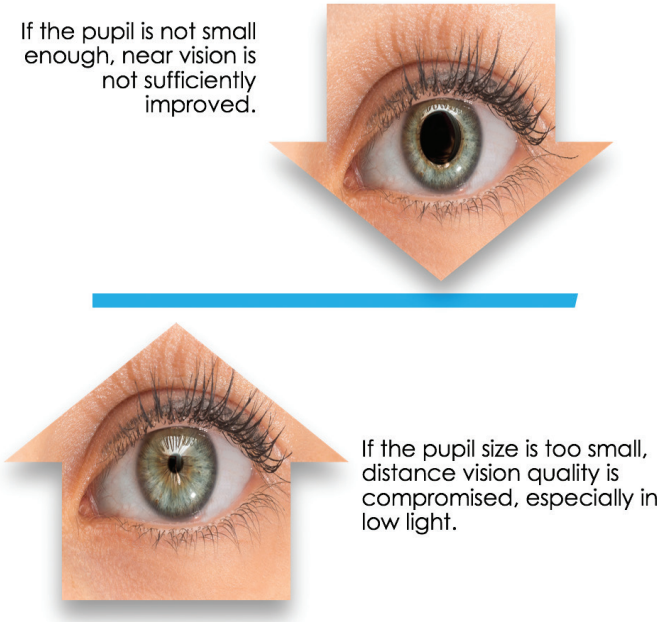

Figure. The optimal pupil size range considers maximum image quality for both near and distance vision.

of its natural size, generates the best image quality for bright, mesopic, and low-light levels (1.2- to 1.6-mm pupil diameter). The improvement over the natural pupil is very small, however.

When considering the overall visual challenges faced by a distance-corrected presbyope, we might consider a pupil miosis between 30 and 40% of natural size as optimum, even though

MODULATING PUPIL SIZE: MIOTICS
By Ian Benjamin Gaddie, OD, FAAO

When we think about modulating pupil size, we think of miotics. Historically, the prototypical drug in that class has been pilocarpine. Before pilocarpine, glaucoma drops were largely toxic, required excessive administration intervals, and were largely ineffective. In 1975, we finally had the ability to suppress aqueous when Tom Zimmerman, MD, PhD, created timolol for Merck. It was a blockbuster drug at the time, and beta-blockers are still the comparator drug today for all FDA pivotal trials in glaucoma.

Pilocarpine acts as a muscarinic receptor agonist, causing miosis and ciliary muscle contraction. The ciliary muscle acts independently to pull on the lens to cause accommodation.

This also is where the IOP-lowering effect occurs. Pilocarpine facilitates trabecular outflow via direct stimulation of the muscarinic cholinergic receptors. This is different than some of the new drugs glaucoma drugs that act in the trabecular meshwork directly by facilitating aqueous flow through the trabecular endothelial cells. Pilocarpine has a unique mechanism of action for someone who is in pupillary block glaucoma, as the miotic pulls the congested iris root from blockage.

As such, a miotic could be a viable option to treat presbyopia; several agents in the class could potentially be utilized to achieve temporary pupil modulation and improved near vision. Ideally, the drug would increase the depth of focus without restricting peripheral vision or affecting distance vision. The concentration of some miotic products may induce pseudomyopia and given the population that could be most interested in a presbyopic miotic agent, the concentration or number of miotics involved could impact the success of these agents. It should affect the pupil size to improve near vision, but not have an impact on distance vision. We will need to understand the effect on IOP of any presbyopia-lowering agent even though it is expected to be minimal at the concentration and dosing frequency being considered for these purposes.

Since miotics effectively work at the iris plane, they can be effective at a low concentration so as not to cause any unwanted short- or long-term effects. Ultimately, the pupil should return to normal size and normal function as the duration of effect wanes. Ideally, it should be able to modulate a little bit, to adapt to scotopic and mesopic conditions.

From a glaucoma historical perspective, one of the problems with miotics, and pilocarpine in particular, is the low pH of the agent and the poor penetration from the cornea to the anterior chamber. The manufacturers had to be made viscous to allow it to reside on the cornea long enough to transfer across the cornea. Low pH coupled with high viscosity left a lot to be desired in terms of blurred vision and local tolerability. Headaches or brow ache are common side effects from miotics, and may cause a myopic refractive shift in some patients.

For presbyopic patients who still have some relative accommodation, one challenge will be mitigating or overcoming headaches relative to the pharmacologically induced miosis. If you think about patients' needs over a normal workday, 6 to 8 hours of effect could be a huge win for patients.

I do not view presbyopia-correcting drops as something that is going to completely replace what we do in terms of presbyopic optical or contact lens corrections. I think it's a reasonable expectation for patients to be free of glasses for 6 to 8 hours. We want patients to be able to see their phones, see their tablets, the TV—anything within arm's length would be the goal with a miotic product.

it is not optimal for either near or distance. Taking into account these ranges, it may be reasonable to interpolate that the best image quality without sacrificing distance vision may lie in the middle—40 to 50% of natural pupil size.

With the understanding that optimal pupil range is a percentage reduction rather than a number, we can conclude that pinhole placement at the iris plane provides the right balance—expanding depth of focus without restricting peripheral vision.

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MOST LIKELY CANDIDATES FOR APPROVAL IN THE PIPELINE

Key players appear poised for FDA approval.

BY MILE BRUJIC, OD, FAAO

New pharmaceuticals that seek to create miosis—or act in other ways—to provide improved near visual acuity for presbyopia must be comfortable and convenient for patients to use. This is where the engineering behind these products comes into play. I will summarize the agents in the pipeline that are most likely to be approved.

Allergan. Phase 2 trial results of Allergan's investigational product were presented at the 2020 (virtual) American Academy of Optometry meeting.[1] That study looked at various concentrations of a combination of pilocarpine, a parasympathomimetic agent, and oxymetazoline, a sympathomimetic. The low side-effect profile was a key finding

of the study, especially as it relates to brow aches and blurred vision most typically associated with pilocarpine. There was very little difference in both of those categories compared to placebo.

Phase 3 clinical trials, the placebo-controlled Gemini 1 and Gemini 2, included 750 patients, randomized in a one-to-one ratio of vehicle to AGN-190584 (pilocarpine 1.25%).[2,3] The study agent was administered once-daily bilaterally for 30 days. It demonstrated statistically significant gains of 3 lines near vision in low-light conditions without a loss of distance vision. There were no treatment-emergent serious adverse events observed in any participants treated with AGN-190584. Taken together, the outlook is optimistic for approval in the near future.

Novartis. UNR844-CL is a lipoic acid choline ester that acts to break disulfide bonds that are believed to cause the crystalline lens to lose its elasticity over time. Two registered clinical trials have been reported for this twice-daily drop.[4] After 3 months of use, 82% of 125 individuals in the trial had at least 20/40 visual acuity and 36% had at least 20/25.

Orasis Pharmaceuticals. CSF-1 is a parasympathomimetic that has completed phase 2 clinical trials.[5] The agent showed a statistically significant improvement in near visual acuity of at least 3 lines with a good safety and tolerability profile in the multicenter, double-masked investigation of 166 participants. The NEAR-1 and NEAR-2 phase 3 studies are multicenter, double-masked, parallel-group clinical trials enrolling approximately 600 participants with presbyopia to further evaluate the efficacy and safety of Orasis' eye drop candidate.

OSRX Pharmaceuticals. These drops are compounded combinations, which are not subject to the same FDA approval process as the other technologies discussed here.[6] The drop contains pilocarpine, phenylephrine, pheniramine, and ketorolac. There are two different versions of the combination drop: one contains 0.302% pilocarpine and the other 0.604% pilocarpine. Together the other molecules are meant to blunt the side effects of pilocarpine. According to the company, nine patients in a proof-of-concept study experienced improved near visual functionality. These drops are meant to be used every 4 hours.

Presbyopia Therapies. The active ingredient in PRX-100 is aceclidine, a parasympathomimetic like pilocarpine. As a muscarinic acetylcholine receptor agonist, it causes pupil constriction in the sphincter muscle of the iris. Phase 2b clinical trials enrolled 58 subjects and found that 47.2% gained 3 lines of near visual acuity and more than 90% gained at least 2 lines

POTENTIAL CLINICAL USE OF INVESTIGATIVE THERAPIES

Faculty shares thoughts on how to create intentional discussions with patients about presbyopia.

Counseling Patients on Presbyopia

Mile Brujic, OD, FAAO

It is important that we explain presbyopia to our patients in such a way that ensures they understand that it is progressive and that their vision will change over time regardless of treatments. Let them know what they can expect during the next 5, 10, 15, and 20 years in terms of their near visual acuity. We should inform them that we are here to help determine the best treatment options at each stage, including glasses, contact lenses, pharmaceuticals, and a combination of these approaches.

Pharmaceutical agents will add a level of sophistication to our current treatments. Emmetropes, for example, will likely do very well with a drug approach. For those individuals who may be having a difficult time transitioning into multifocal vision or are limited to certain materials, we can potentially keep them in single-vision lenses longer and supplement with a presbyopia-correcting agent. A strategy that would essentially make patients emmetropic and then layer these technologies on top. Presbyopia-correcting drops will give us the opportunity to further customize solutions for patients, and that excites me.

Finding Common Language

Selina R. McGee, OD, FAAO

As we discuss these treatment options with our patients, we all need to use a common language. Use the word presbyopia so that when a drug is FDA approved for presbyopia patients know what that is.

With these drops, we will be able to expand our services and our treatments. I think we will fit more contact lenses and patients will need different types of glasses if they are using them in conjunction with a pharmaceutical agent. The drops are not a panacea or a replacement for everything we do now, but they will enhance and expand what we are already doing. It comes down to thorough education so that we as optometrists can own this condition.

Keep an Open Mind About Patients Likely to Benefit

Ian Benjamin Gaddie, OD, FAAO

It is possible that some of these agents may have an effect for pseudophakic patients as well, so do not limit their use to any one patient type. The lowest hanging fruit are people who are older than 40 and see 20/15 distance but struggle to see anything up close. There are so many people in the category of needing near presbyopia correction, that I think they will comprise the bulk of the market. The potential of this therapy to improve quality of life for patients is obvious—just ask anyone you see who needs a variety of readers. Presbyopia has a profound effect on people's psyche, and I think these drops present a huge opportunity.

of near visual acuity.[7,8] Approximately half the patients maintained the 2-line improvement up to 7 hours after drop installation, and the treatment was well tolerated.

Visus Therapeutics. This company is developing a proprietary formulation of carbachol, a parasympathomimetic, and brimonidine, an alpha-2 adrenergic agonist, which keeps the dilator muscle from activating. Five clinical studies have been conducted evaluating the safety and efficacy of this combination.[9] In the most recent clinical study of 57 subjects, the investigative therapy demonstrated statistically significant improvement in near visual acuity of a 5 Jaeger-line or greater gain, with the effect lasting at least 12 hours. The same study found the drug was well tolerated with no reports of headache or brow. Phase 2 trials are slated to commence this year.

The pipeline for presbyopia-correcting pharmaceuticals is robust, providing us with an enormous opportunity to offer our patients a totally novel solution. Expect to hear more about the lines of near visual acuity improvement associated with the various drugs. This is a key metric that we will start hearing about as the manufacturers continue to meet with the FDA to develop the "rule book" for these agents. ■

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HOW TO PREPARE YOUR PRACTICE FOR NOVEL PRESBYOPIA-CORRECTING DROPS

Faculty members outline their game plans.

MILTON H. HOM, OD, FAAO

When a presbyopia-correcting drop is approved, we will include it in all of our social media posts. We plan to notify our patients who are presbyopic or patients who need reading glasses or bifocals about this new option when it becomes available.

We are formulating a patient list from our database to determine the patients who are the most appropriate candidates, based on clinical trial data.

SELINA R. MCGEE, OD, FAAO

I have already begun to discuss the drops with patients because I want to have an intentional and focused conversation. I use the word presbyopia and describe different ways we can manage it. I let them know that this is coming down the pipeline. I dig deeper, I ask in-depth questions about what bothers them.

Status quo does not fly in my office. This product category is a way for us to disrupt ourselves and think bigger and be able to offer more solutions for our patients. We have started a marketing campaign already so we will be a presbyopia practice internally and externally once the products become available.

MILE BRUJIC, OD, FAAO

I put a lot of effort into internal marketing because, in my mind, the worst thing that I could do for a patient is not tell them about a service that we provide. We do massive amounts of internal education with our staff members to get everyone on board. The demand for this product will be huge, and eye care practices need to figure out how we can deliver.

- Intentional focus on presbyopia
- Purposeful discussions about presbyopia with patients
- Presbyopia solutions
  - Glasses
  - Specialty Contact Lenses
  - Surgical Options
  - Pharmacological Agents
- Marketing: Internal and digital marketing

Figure. Approach to preparing an eye care practice for presbyopia-correcting drops.

My patients are already asking for a date as to when they can have presbyopia-correcting drops. I've started to think about how I'm going to communicate the benefits. Three lines of improvement might not mean anything to patient, so I will explain it to patients that it's like putting a +1.00 D pair of glasses over your eyes. I am already talking about how we can leverage the drop with contact lens and eyeglass wearers. Some people love office lenses because of the enhanced vision that it gives them at their computer, but for others who are up and down all day, office lenses can sometimes be difficult for them to work with. Having a presbyopia drop that we can leverage with a progressive addition lens at the computer is an awesome solution.

Ultimately, I tell my patients that I'm trying to simplify their lives. Our internal planning needs to make sure that we're tight and concise with what we tell patients we can deliver. We must formulate an

effective discussion about how this is actually going to be explained to patients so it's easy for them to digest and we don't overpromise and underdeliver. I want to ensure we meet the expectations I set.

IAN BENJAMIN GADDIE, OD, FAAO

I'm talking to patients about presbyopia-correcting drops and to everybody in my community about the innovations that are occurring. I think this is going to be one of those situations where we don't have to do much of anything. It is going to be such a huge market immediately. I think you need to be prepared to take the calls and explain to patients that they need a comprehensive eye examination and that's the route by which you are prescribed a medication like this. This is going to be a win for everybody involved. ■

PART TWO

Visualizing the Future of Presbyopia

Presbyopia is a highly prevalent condition that we deal with every day. We have 128 million presbyopes,[1-4] and as many as 89% of them are 45 years old and older.[4] Unfortunately, our presbyopia solutions are lacking. The use of pharmaceuticals to address presbyopic correction is a very exciting, brand new area. There has not been a whole lot of discussion regarding presbyopia the mechanism and how we treat it.

The articles that follow, which are based on a webinar, we review the mechanisms of presbyopia and also dig deeper, challenging us to think about how we approach presbyopia with our patients and what it means to our patients and our practices to have pharmaceutical options. We discuss some of the likely candidates, potential clinical uses, and discuss how we can incorporate them into our practices. A safe, reversible, and long-lasting pharmaceutical treatment for presbyopia represents a new frontier.

—Francis S. Mah, MD, Program Moderator

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PRESBYOPIA: PREVALENCE, IMPACT, AND TREATMENTS OPTIONS

We can't ignore the (presbyopic) elephant in the room.

BY DANIEL H. CHANG, MD

Since early in my practice, my career goal has been to "conquer presbyopia." Through the years, this has meant collaborations in the development of technology and in the training of surgeons. More recently, I have worked with others to help shape the way eye care providers approach the treatment of presbyopia. I believe we need a paradigm shift in the way we even think about this condition and its treatment. Presbyopia is more than just a nuisance; the real impact of presbyopia and its treatment on patients can literally be life-altering.

The global burden of presbyopia is huge, affecting 1.8 billion people worldwide.[1] Around 826 million people, or about 45% of presbyopes, have near vision impairment due to inadequate or no vision correction.[1] This has resulted in up to a 22% decrease in quality-of-life scores with accompanying economic losses of $11 to $25 billion annually.[2] In the United States alone, presbyopia affects 128 million people,[3-5] including 83 to 89% of adults 45 years of age and older.[2] Almost 31 million of these individuals buy over-the-counter readers.[6] In terms of sheer numbers, the presbyopic population is simply staggering.

WATCH IT NOW

Part 2 of this supplement is based on a CME webinar (1.25 credits) available on EvolveMedEd.com. Go to the link below to view the full webinar presentation followed by a question-and-answer session with the audience.

evolvemeded.com/online-courses/2031_md_enduring

WHAT DO WE KNOW ABOUT PRESBYOPES?

The vast majority of 40- to 55-year-olds have presbyopic symptoms. In a survey of 797 adults in this age group, 96% said they are somewhat affected by presbyopia, and nearly half said they

FALLS AND THEIR FALLOUT

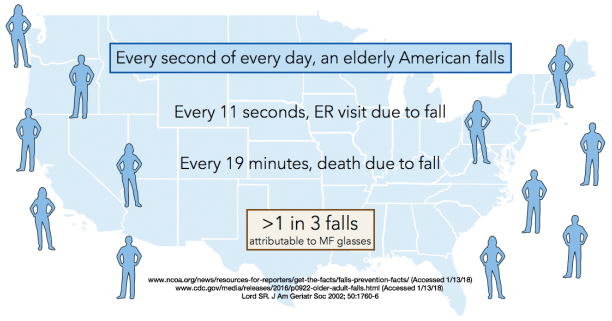

Figure. Falls and their fallout.

- Overall, one in four adults older than 65 falls every year and that increases to one in two for those older than 70 (Figure). [1-3]
- Nearly half of these falls can lead to injury, with 10 to 15% being serious, ie, hip fractures or traumatic head injuries.[1-3]
- Every second of every day, an elderly American falls, every 11 seconds there is an ER visit due to a fall, and every 19 minutes there is a death caused by a fall.[3-5]
- In the United States in 2014, there were 29 million falls, nearly 3 million ER visits, almost 1 million hospitalizations, and more than 27,000 deaths—greater than the number of deaths from breast or prostate cancer in that same age group.[3-5]
- If one in three of these falls can be attributed to multifocal glasses, that is roughly 10,000 deaths a year.
- Even for those who are not injured, one in three elderly adults who fall develop post-fall anxiety syndrome which leads to a reduced quality of life, functional decline, depression, social isolation, reduced activities of daily living, and increased institutionalization.[1-3]
- The financial impact of falls in 2014 was $31 billion, this number is expected to approach $70 billion this year.[3-5]

The good news is that these falls can be prevented. First-eye cataract surgery reduces the fall rate by about a third.[6,7] One study found that replacing bifocals with single-vision glasses reduced falls by up to 40% in the elderly who regularly took part in outdoor activities.[8] Removing that varying power across the visual field is protective for falling and is something we should consider.

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are extremely affected by their presbyopia.[7] Millennials, the largest demographic in the workplace, start turning 40 this year and are thus just entering the height of their income-making years as they start contending with this new challenge to their visual function.

Presbyopia is additionally a significant lifestyle issue. Younger presbyopes in particular are concerned about their appearance; and for many, presbyopia is the first unavoidable sign of aging. It has been shown that people who feel old tend to age faster. Presbyopia cannot be denied—it tells patients they are getting old.

Presbyopia has also become more disabling in the modern context because of increasing screen time: screens and the aging eye do not mix. American adults spend more than 11 hours per day watching,[8,9] reading and interacting with media, and that number goes up every year. On average, we check our phones 96 times per day,[10] once every 10 minutes; and we use tablets and smart phones nearly 4 hours a day.[9] All of this screen time makes the near-vision struggle constantly apparent.

Most presbyopes do visit eye care practitioners, with 60% having seen their doctor in the previous 12 months.[7] Two-thirds of these patients said they have initiated discussions with their eye care providers;[7] yet only half said they received the information they needed, and only 15% received printed information.[7] Unfortunately, many eye care providers do not ask our patients how they feel about their presbyopia, and most discussions on the matter are merely an afterthought. It is difficult to understand how patients feel about their current presbyopia-correcting solution if there are no purposeful discussions on the topic.

TRADE OFFS: CURRENT SOLUTIONS

To some extent, eye care providers may be avoiding discussions about presbyopia simply because currently available treatments are not well-suited for our patients. Reading and multifocal glasses are essentially just a workaround. Many patients in their 40s do not tolerate multifocal contacts, and most are not eager to have intraocular surgery. As such, many presbyopes would rather struggle with their near-vision activities: holding things further away, using more light, or increasing font size on their phones and tablets. Indeed, 90% of patients surveyed are frustrated or irritated by their presbyopia.[7] Eye care providers are likewise frustrated with the limited options for our presbyopia patients.

Presbyopia treatment options have traditionally been thought of as surgical versus nonsurgical. However, a mechanistic approach to categorization can be helpful to clinical decision-making. To increase depth of field, the eyes' refractive power can be varied in one of four ways:

1. Over time: true accommodation provides full focus on the object of fixation, regardless of distance, ideally with imperceptible lag time.

2. Between eyes: commonly referred to as monovision, offsetting the refractive power between eyes can be achieved with contact lenses, lasers, or IOLs.

3. Across the visual field: multifocal spectacles and some multifocal contact lens designs change their focal length based on the direction of gaze.

4. Through a range of distances: pseudoaccommodation can be achieved through several means, including pin-hole, refractive, and diffractive optics.

Regardless of the approach, every surgical and nonsurgical treatment for presbyopia leverages (at least) one of these four mechanisms to extend the range of focused vision. Each mechanism comes with benefits but has its own unique set of side effects inherent to that mechanism. For example, multifocal spectacles—bifocals, trifocals, and progressives—are associated with a loss of contrast sensitivity and depth perception in the inferior visual field. This more than doubles the risk of falling in the elderly population.[11] Put another way, one in three falls in the elderly can be attributed to the use of multifocal spectacles (see *Falls and Their Fallout*).

Therefore, instead of simply accepting multifocal glasses as the default approach to treating presbyopia, eye care providers should consider other approaches that may be safer for patients. Thankfully, as new treatments become available, we have an opportunity to better address our patients' needs. For example, the use of eye drops to treat presbyopia represents an exciting development. Whether the mechanism of action is pupil modulation, stimulating accommodation, or lens softening, a new medical therapy may represent a better approach to addressing this unavoidable, frustrating, and limiting condition of aging.

At the end of the day, eye care providers should embrace the growing repertoire of available treatments and engage in intentional conversations with patients to understand their specific needs. Only this way can we take full advantage of the advances in technology to provide each patient with the best possible treatment for their presbyopia. ■

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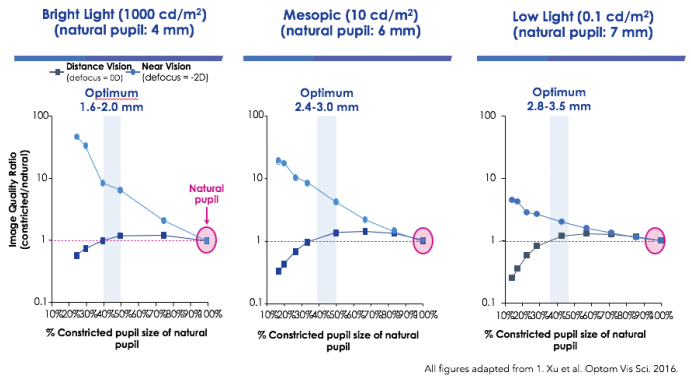
EMERGING PHARMACEUTICAL OPTIONS FOR PRESBYOPIA CORRECTION

Agents in the pipeline harness various mechanisms of action.

BY MARJAN FARID, MD

One way to affect the depth of focus is with pupil modulation. It has long been known that pharmaceuticals have the ability to leverage the iris to create a pinhole effect that extends the depth of focus. Doing so without restricting peripheral vision is the key.

A large aperture dilated pupil achieves a narrow depth of focus. Conversely, a constricted pupil provides more of a range of vision where the image is in focus. The depth of focus is created through pupil modulation. But, what about peripheral vision? In the clinic, if we put a pinhole in front of a patient's eye he or she can see more clearly, but peripheral vision is significantly restricted. That is why pinhole glasses never took off.



All figures adapted from 1. Xu et al. Optom Vis Sci. 2016.

Figure. Xu et al reported that the optimal pupil size range may be 40 to 50% of the natural pupil size.

Corneal inlays tried to take advantage of the pinhole effect at the corneal plane, with a depth of field increase and less restriction of peripheral vision. Putting the pinhole at the iris plane, however, is ideal for both extending the depth of focus and not impairing peripheral vision.

NO IDEAL PUPIL SIZE, BUT A RANGE

There is no single, absolute pupil size that is optimum, however, rather a percentage reduction of the natural pupil size. This varies based on the patient and on the lighting conditions. The goal is to maximize the image quality for both distance and near. Decreasing the size of the natural pupil results in an increase in near focus and the near range improves. But the smaller the pupil becomes, there is a point at which the quality of distance vision is diminished. It turns out that a 40 to 50% reduction in the pupil size tends to be the best range to maximize

near vision and not have an impact on distance in bright and mesopic conditions (Figure).

This means the ideal pharmaceutical agent for modulating the pupil will need to restrict the pupil enough to achieve a depth of focus without compromising peripheral vision, and also falls in the range where it does not affect the quality of distance vision.

TRADITIONAL AGENT PILOCARPINE

Pilocarpine, a cholinomimetic drug that works to facilitate trabecular outflow, historically has been used in glaucoma management. It also acts as a muscarinic cholinergic receptor agonist. Pilocarpine and carbachol are two cholinomimetics that have direct effects on accommodation by causing the ciliary muscle to contract. Echothiophate has indirect effects: it acts on the iris sphincter, which brings down the pupil. Pilocarpine is still used for its IOP lowering effects, but it may be of better service in the presbyopia world.

MAKING THE MOST OF MOA

Miotics are a viable presbyopia treatment option. Making the most of this mechanism of action, the ideal miotic to treat presbyopia would need to increase depth of field and depth of focus, being sensitive enough to ensure a pupil size in the 40 to 50% range, at the iris plane. The drop would be reversible, safe, comfortable, and convenient to use.

Based on these principles, pilocarpine in its current form does not fit the bill. It is irritating to the ocular surface, can cause headaches, and has a short acting time. Pilocarpine would need to be optimized it for better safety and tolerability: the pH balance is important, the vehicle cannot cause blur, and the formulation would need to minimize any compromise in distance vision. It would also have to reduce the potential for head and brow aches common with traditional pilocarpine. Duration of effect is important when looking at using this mechanism of action for presbyopia; 6 to 8 hours would be best. The greatest impact should be on functional near vision. Vision in dim light is important, with continuous improvement at all distances.

What agents are the likely contenders for FDA approval? Three companies have promising, pupil modulation products that will likely be approved: Allergan, Orasis, and Visus.

PUPIL MODULATION AGENTS IN THE PIPELINE

Allergan. The company has assessed various concentrations of pilocarpine with and without oxymetazoline and have recently released phase 3 trial data on their optimized formulation.[1] Compared with generic pilocarpine solution and older formulations studied in phase 1, AGN-190584 (pilocarpine 1.25% ophthalmic solution) achieves fast pH equilibration on the ocular surface, comfort was far superior with less ocular blur, and it was associated with a lower incidence of adverse effects.

Phase 3 GEMINI 1 and GEMINI 2 (N = 750) met their primary endpoints of a statistically significant 3-line or more gain in distance-corrected near visual acuity out to day 30 at hour 3 compared with vehicle. AGN-190584 demonstrated significant near vision gains in mesopic conditions without a loss of distance vision. There were no treatment-emergent serious adverse events, and the majority of secondary endpoints were also met in both studies, including a significant improvement in patient-reported outcomes such as an increase in vision-related reading ability, and reductions in the impact of presbyopia on daily life, and use of coping behaviors to manage presbyopia. Allergan expects to submit a New Drug Application during the first quarter of this year, with FDA approval hopefully by mid-year.

Orasis Pharmaceuticals. This product has a very low concentration of pilocarpine, less than 1%, with a proprietary multifaceted vehicle. Phase 2b clinical trials with 166 participants at US sites found a statistically significant improvement in near visual acuity of 3 lines or better with twice-daily administration and very minimal temporary adverse effects. Compared to vehicle, almost 50% achieved 3 lines improvement, and 80% achieved 2 lines of improvement.[2]

The company's phase 3 studies, NEAR-1 and NEAR-2, have commenced with enrollment of 300 subjects. They will look at the same primary and secondary outcomes, along with the impact on night vision and other safety and tolerability measurements.

Visus Therapeutics. Visus acquired two FDA-approved pharmaceuticals and created a proprietary formulation combining carbachol and brimonidine. Five clinical studies have been conducted evaluating the safety and efficacy of the combination, and the most recent trial of 57 patients demonstrated significant improvement of near visual acuity up to about 5 Jaeger lines of gain, with the effect lasting 8 to 12 hours. Its long-lasting effect makes this product unique. The thought is that the brimonidine, because it's an alpha agonist, helps diminish the dilating effect over time for the pupil so it maintains that pupil constriction longer.[2]

There's also decreased aqueous humor production so the concentration of the carbachol in the anterior chamber may be longer over time. The study showed the formulation was well tolerated with no reports of significant headaches or brow aches.

The company studied each ingredient separately to evaluate the individual effects. The combined drug was superior compared with each ingredient separately.

LENS MODULATION

Novartis. Novartis' novel drop is a lipoic acid choline ester the company acquired. It works by restoring lens function, a potential first-in-class treatment for presbyopia. Disulfide bonds are formed in the crystalline lens over time contributing to its stiffness. Breaking these bonds may restore the microfluidics of the crystalline lens over time and increase lens elasticity.

This is a twice-daily drop and their trials show that over time, out to 91 days, the drop was associated with a very significant improvement in mean bilateral distance-corrected near visual acuity versus placebo. By day 91, 82% of patients had 20/40 or better near vision and 36% had 20/25 or better near vision. The effect built with increased use and the improvement was sustained in 67% of patients at 7 months posttreatment. [4,5]

Will a drug like this have an impact on cataract formation long term? That needs to be worked out. Although the phase 2a studies did not meet the primary endpoint, there was a lot of variation in how the different sites looked at the distance corrected near visual acuity. A posthoc sensitivity analysis indicated that there was an effect, so the company has moved on to a phase 2b study.

CONCLUSION

The miotic presbyopia drops appear poised to hit the market in the next few months, and we can expect a stream of these therapies over the next several years. ■

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COUNSELING PATIENTS ABOUT PRESBYOPIA

Be prepared to engage patients on drops and other options.

I EMPATHIZE!

FRANCIS S. MAH, MD

With the coming availability of presbyopia-correcting drops, ophthalmologists will be tasked with having discussions with patients that we may have avoided previously. The tendency might have been for us to hand off these patients to optometrists or even send them to the drug store for readers. It is important that we prepare now to counsel these patients appropriately; they will be looking to us for guidance.

We need to think about how we will be discussing the condition of presbyopia with younger patients who are just starting to experience trouble with their near vision. Each of us will need to determine where the treatment options line up and how we will use them over time. Some options may be better early in the condition and others later. As surgeons, we are used to talking to patients about cataract surgery—the back end of the process—but now we must think about the front end—early presbyopia and even prepresbyopia.

I have a lot of empathy for my patients, and I can describe to them what they are going to go through because I am now dealing with presbyopia myself. I have tried glasses and contact lenses; I'm really looking forward to trying the pharmaceuticals, but not ready to have surgery yet. So, in trying to optimize solutions for patients, I know I am trying to do the same for myself.

NEW TREATMENT BRINGS IN A NEW PARADIGM

DANIEL H. CHANG, MD

When medical therapy for dry eye (cyclosporine 0.05%) was first introduced, doctors lacked a good framework for understanding or even discussing dry eye disease. It was only through a collaboration of physicians, societies, and even industry that a paradigm and language for addressing dry eye disease was developed. A specialty area can only develop as diagnostics and treatment options become available; but when they do, doctors should likewise evolve in the way we approach that condition. I am excited about development of presbyopia eye drops because we will soon have a brand-new category-defining treatment option.

Pharmaceuticals could be the bridge between a glasses-free prepresbyopic life and a more permanent and invasive surgical solution. Corneal refractive surgery and contact lenses work well for younger patients. Early to moderate presbyopes can use eye drops instead of reading glasses, bifocal glasses, and monovision. When patients are finally ready for lens surgery, presbyopia-correcting IOLs—or possibly eye drops with monofocal IOLs—can help. Patients no longer have to concede to glasses for presbyopia; and doctors should shift our mentality from simply giving glasses to considering options that can provide spectacle freedom over a lifetime. Of course, we should set expectations appropriately, avoid overpromising, and counsel on possible side effects. Let's all be good stewards of bringing this exciting technology to our patients!

OPPORTUNITY TO ENGAGE YOUNGER PATIENTS

MARJAN FARID, MD

We do tend to ignore early presbyopia until we have a way to treat the patient. With novel treatments for presbyopia, we have an opportunity to engage this group of 40- to 55-year-old patients in eye care. This group falls into a gray zone, but now we have a reason to engage with them and encourage them to come into the office. Once there, we can then provide appropriate treatment solutions and build their confidence. These will be future cataract patients as well, and ultimately, it will be very good for our practices and our industry to engage and build relationships with this group. As an early presbyope myself too, I am very excited. ■

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