Presbyopia-Correcting Eyedrops Move Ahead

With at least 2 billion people affected globally, presbyopia is the world's leading cause of visual loss. In the United States alone, close to 130 million adults live with the progressive eye condition, a number that is expected to surpass 150 million within the next two decades.[1,2]

A technical challenge. Despite these statistics, current treatment options are relatively limited and somewhat flawed. Glasses and contact lenses are more common than surgical alternatives such as monovision LASIK, multifocal corneal ablations, intracorneal inlays, and refractive lens exchange, said John P. Berdahl, MD, at Vance Thompson Vision in Sioux Falls, South Dakota. And patients may be bothered by eyestrain, night vision disturbances, glare and halo, and a reduction in quality of vision.

"We really have yet to design a lens or manipulate optics in a way that's as effective as our naturally occurring flexible lens, and that's why presbyopia remains one of the biggest technical challenges we face," Dr. Berdahl said.

An untapped market. There's also another reason why a solution is considered one of ophthalmology's Holy Grails, said Dr. Berdahl. Consider the sheer size of the presbyopic market, he said: "It is enormous. It's basically every person in the world over age 50. There are very few markets, if any, that are this large."

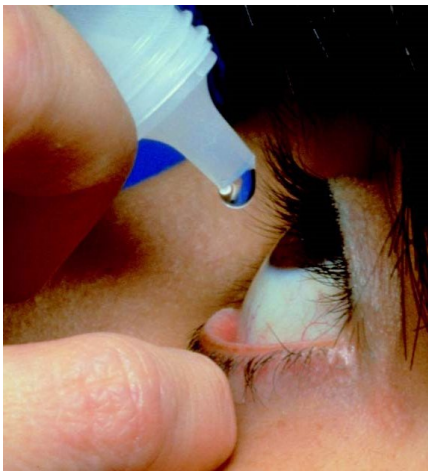
And U.S. pharmaceutical companies have taken notice. With several years of research completed, they're inching toward regulatory approval and readying the marketplace for a potential major breakthrough: topical therapies utilizing miotics and lens softening for noninvasive, real-time correction of presbyopia.

The Pinhole Approach

A large majority of the new pharmaceutical drops under investigation are within the category of pupillary miotics. Miosis is achieved through the use of specific muscarinic agonists such as pilocarpine, carbachol, or aceclidine, said Eric D. Donnenfeld, MD, at Ophthalmic Consultants of Long Island in Garden City, New York.

"By reducing the size of the pupil in this manner, you create a pinhole effect that creates depth of field without impairing the peripheral field," Dr. Donnenfeld said. "This is an exciting approach because it not only provides more near vision but also can improve distance vision, and it's all reversible."

Pilocarpine. The first drug that's likely to be approved by the FDA for the correction of presbyopia is AGN-190584 (AbbVie), a once-daily formulation of pilocarpine 1.25%. In a recent phase 3 clinical study, a statistically significant greater proportion of participants treated with the drop gained 3 or more lines in distance-corrected near visual acuity (DCNVA) under low-light conditions than with the placebo. Additional endpoints evaluated showed that 75% of participants treated with AGN-190584 achieved at least a 2-line improvement in mesopic DCNVA.[3]



NEW ERA. *Whether they act as miotics or lens softeners, eyedrops for presbyopia are poised to reshape the refractive landscape.*

"AGN-190584 also demonstrates good durability," said Jay S. Pepose, MD, PhD, at the Pepose Vision Institute in St. Louis. "What's particularly impressive is that these effects had a rapid onset of around 15 minutes and lasted up to six hours," Dr. Pepose said. "Adverse events, including tearing, blurred vision and headache, were reported more commonly in the treatment than placebo group, but the latter [events] were mostly mild and transient, and no patient discontinued treatment because of them."

BY MIKE MOTT, CONTRIBUTING WRITER, INTERVIEWING **JOHN P. BERDAHL, MD, ERIC D. DONNENFELD, MD,** AND **JAY S. PEPOSE, MD, PHD**.

Phentolamine + low-dose pilocarpine. Ocuphire is using a combination of phentolamine 0.75% (Nyxol, a nonselective alpha-1/alpha-2 adrenergic antagonist) with low-dose pilocarpine 0.4% to induce miosis. In a phase 2 clinical trial, 61% of presbyopic participants experienced at least a 3-line improvement in daytime binocular near vision compared with 28% of the placebo group. These results were achieved within 30 minutes and were sustained through at least six hours.[4]

Of note, this drug raises the potential for tunable pupil modulation, said Dr. Pepose. "There's a dual approach being taken here between the phentolamine, which inhibits the iris dilator muscle, and the pilocarpine, which activates the pupillary sphincter," he said. "And each of these drugs has a very different half-life—24 versus six hours. So there's some possibility for customization here in that you can provide a range of pupillary modulation by adjusting the timing of the drugs, providing synergy to phentolamine's 24- to 36-hour moderate miotic effect." This is relevant in that most patients function under different lighting conditions throughout the day and also need to be able to drive home in dim light, he added.

Ocuphire plans on initiating phase 3 trials in 2022.

Carbachol/brimonidine tartrate. Another contender is Brimochol (Visus), a fixed combination of carbachol and brimonidine tartrate. Although ongoing phase 2 trial results have not been reported, the formulation does appear to have durability, Dr. Donnenfeld said. "As a miotic, the cholinergic agent carbachol has a significantly longer-acting effect than pilocarpine," he said, "and here it's combined with brimonidine, an alpha-2 sympathomimetic, which prevents pupillary dilation and also inhibits ciliary body contraction." This combination increases the half-life of the carbachol and extends its bioavailability even further, potentially up to a minimum of eight hours.

Visus is planning to finish a phase 2 trial before end of this year.

Pilocarpine via novel dispenser. MicroLine (Eyenovia) is another pilocarpine-based presbyopic drug, but what's unique is the delivery vehicle, said Dr. Pepose. "A microdose mist of pilocarpine 2% is administered horizontally via the company's proprietary piezo-print dispenser." The dispenser reduces the amount of drug volume by 80%, potentially eliminating the excess overdosing and drug waste commonly associated with conventional eyedrops.

Earlier this year, Eyenovia announced results from a phase 3 trial, which showed promise in terms of both safety and efficacy, said Dr. Pepose. Although specifics were not provided, a higher proportion of participants achieved at least a 3-line improvement in DCNVA using MicroLine compared with placebo, and more than 70% self-reported a meaningful improvement in near vision.[5]

Next up: Eyenovia is conducting a second phase 3 trial later this year, with results expected mid-2022.

Rounding out the field. Two additional miotic-based pharmaceutical offerings are also making their way through the approval pipeline. CSF-1 (Orasis) is a low-dose pilocarpine formulation currently being tested in two phase 3 studies. In a 2019 phase 2 trial, the formulation demonstrated at least a 3-line gain in DCNVA as well as no reduction of distance or night vision in participants using the drop.[6]

In addition, Presbyopia Therapies has reemerged as Lenz Therapeutics following results from a 2018 phase 2 clinical study in which more than 47% of eyes treated with the company's PRX formulation gained at least 3 lines of improvement at one hour, with almost half maintaining at least 2 lines after seven hours.[7] "What sets this product apart from the competition is the use of aceclidine," said Dr. Pepose. "This induces miosis without the myopic shift and accommodative effect oftentimes associated with other cholinergic agonists, which can impair distance vision." The company is gearing up for a new trial in the future; no timeline has been disclosed.

Lens Softening

As an alternative to increasing the depth of field via miosis, the UNR844 eyedrop (Novartis) stands alone in the arena of lens softening for the temporary relief of presbyopia.

Restoring elasticity. In essence, this strategy aims to restore the elasticity of the lens that's been lost due to the effects of aging, said Dr. Pepose. "This is a prodrug designed to penetrate the cornea, and it breaks down into two components, lipoic acid and choline, which are hydrolyzed by the esterases in the tear film and reduced into dihydrolipoic acid within the lens fiber cells."

This antioxidant then hydrolyzes, breaking down the disulfide bonds between the lens crystalline proteins that form over time. "By allowing cytosol to regain its ability to flow more freely, you're pharmaceutically reversing the lens oxidative process and restoring the lens elasticity," Dr. Pepose said. "This results in the return of accommodative amplitude because now the lens can change shape and curvature."

Research update. UNR844 has moved from experimental studies to human trials over the last several years, but it's likely farther away from FDA approval than most of the miotic alternatives, said Dr. Donnenfeld.

The latest studies are nonetheless promising, he added: Recent results from an independent phase 1/2 dosing and safety study showed that patients treated with UNR844 had statistically significant improvements in DCNVA compared with the placebo—results that continued to increase through day 91.[8] However, these results were not repeated when Novartis conducted its own phase 2 safety and efficacy trial in which researchers saw only a 4-letter DCNVA increase in treated patients 45 to 55 years old compared with the placebo in a post hoc analysis.[9]

Novartis started a dose-ranging study of UNR844 this summer; it is expected to be completed by early 2023.

Patient Selection: Unknown Variables

One unknown factor at this point: who is and who isn't the best candidate for these treatment modalities, said Dr. Pepose.

What about age? Age will likely play a factor, Dr. Pepose said: "Will lens softening really work in eyes that are

already presbyopic and already have significant hardening of the lens? Or is it best suited for the treatment of early presbyopes in their late 30s and early 40s? We don't have the age-stratified data just yet to know the answers."

There's a similar age-related question regarding treatment with miotics, added Dr. Berdahl. "We don't know which patients are going to do the best here, but there's no evidence for ruling out anyone."

Nuances to consider. Dr. Berdahl imagines the best candidates will be those who are new to presbyopia—e.g., those patients with new-onset presbyopia and even maybe those with mild to moderate amounts of astigmatism who are not accustomed to wearing glasses. In addition, hyperopes and post-LASIK emmetropes in this same age range will likely appreciate these presbyopic drops based on the published study data, added Dr. Donnenfeld, as well as patients who have had previous cataract surgery.

What about side effects? Side effects will also play a role in patient selection, said Dr. Pepose. Although not enough is known about the long-term use of lens-softening agents, there's a history of adverse reactions to approved doses of muscarinic agonists such as pilocarpine, he said. These include the potential for brow ache, decreased night vision, redness and irritation, dry eye, and retinal tears in high myopes.

"We're still a bit unsure of the real-world effects of these miotic drops," Dr. Pepose added. "It's one thing to get through the FDA process, but it's another thing to see how these treatments work for different types of presbyopes interacting in different daytime and nighttime conditions, when very small pupils and resulting low retinal illumination can dramatically elevate neural contrast levels."

Looking Ahead

Ultimately, the drops' side effect profiles—along with cost and convenience—will drive clinicians' recommendations and patients' choices, said Dr. Pepose. As a result, the market will likely be one that's fragmented, similar to glaucoma drops.

"Once these treatments hit the U.S. market, we'll really start to see the differentiation in terms of onset, duration, and adverse events," Dr. Pepose said. "Some drops might just be better for certain lifestyles, in certain environments, and under certain lighting conditions. But there's going to be a variety of products, and that's great because there's plenty of room in this new marketplace."

1 Fricke TR et al. *Ophthalmology*. 2018;125(10):1492-1499.

2 Donaldson KE. *J Refract Surg*. 2021;37(S1):S17-S19.

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5 https://ir.eyenovia.com/news-releases/news-release-details/eyenovia-highlights-recent-progress-three-phase-3-programs-nda

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8 Korenfeld MS et al. *Eye (Lond)*. Published online Jan. 29, 2021.

9 https://clinicaltrials.gov/ct2/show/study/NCT03809611

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