JANUARY 2017 # 37

the Ophthalmologist

Refractive Surgery's Holy Grail

Eyedrops for presbyopia. Myth or medicine?

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Perfect Refraction

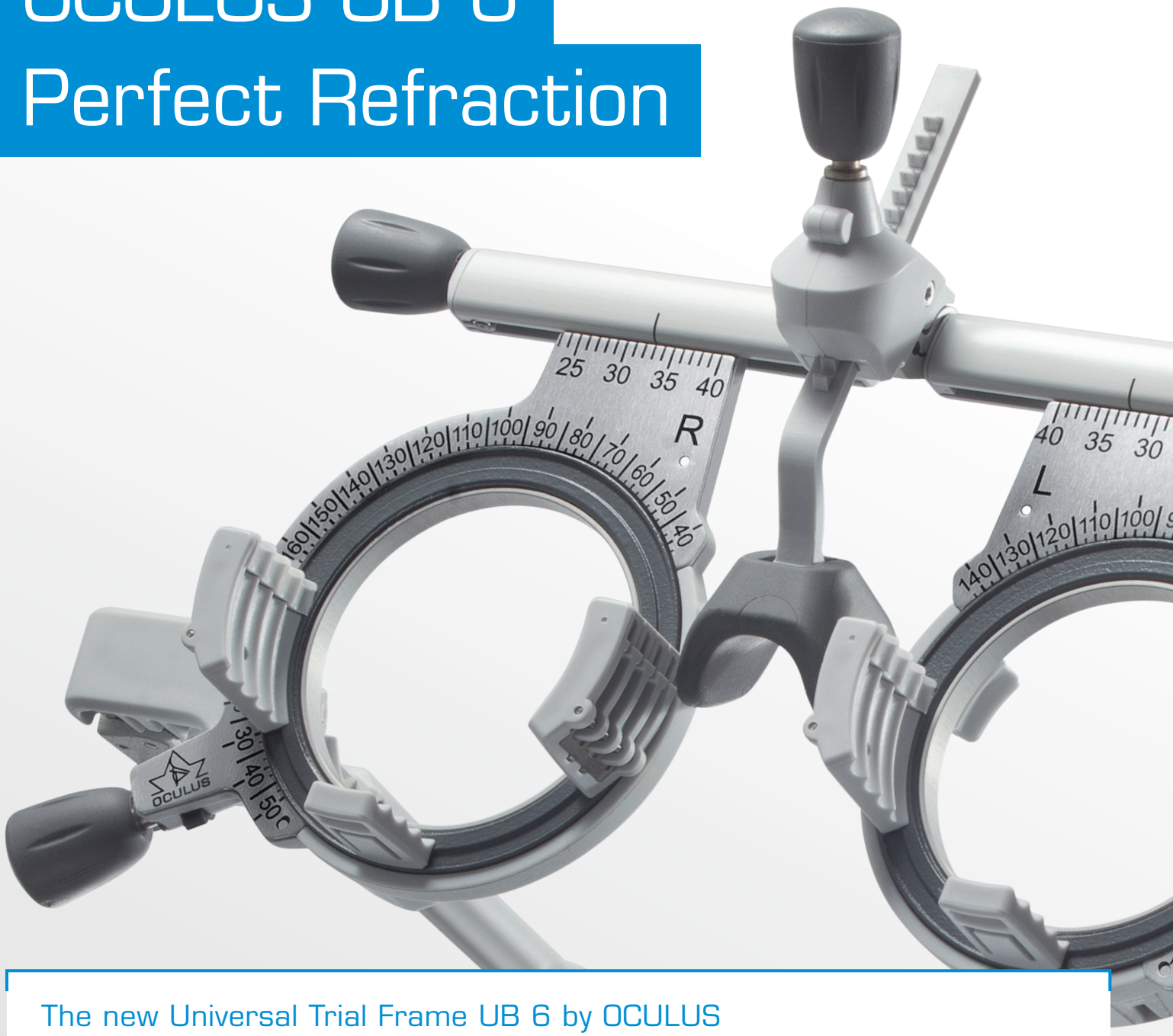

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Image of the Month

An Artistic Simulation of Sight with AMD

This image is a painted frame from "Ocular Bionica," an animated film about age-related macular degeneration (AMD) and digital retinal implants by artist Lucy Burscough. Lucy says "I wanted to show people what seeing with macular degeneration and the 'bionic eye' implant was like. This image shows UK-based Paulo Stanga, retinal surgeon at Manchester Royal Eye Hospital and Manchester Vision Regeneration (MVR) Lab at NIHR/Wellcome Trust Manchester Clinical Research Facility, as seen by his patient Ray." Lucy hopes that her work will raise awareness of AMD and encourage more patients to participate in clinical trials. Ocular Bionica can be viewed at www.LucysArt.co.uk/Ocular-Bionica.

Image courtesy of Lucy Burscough.

Do you have an image you'd like to see featured in The Ophthalmologist?
Contact edit@theophthalmologist.com

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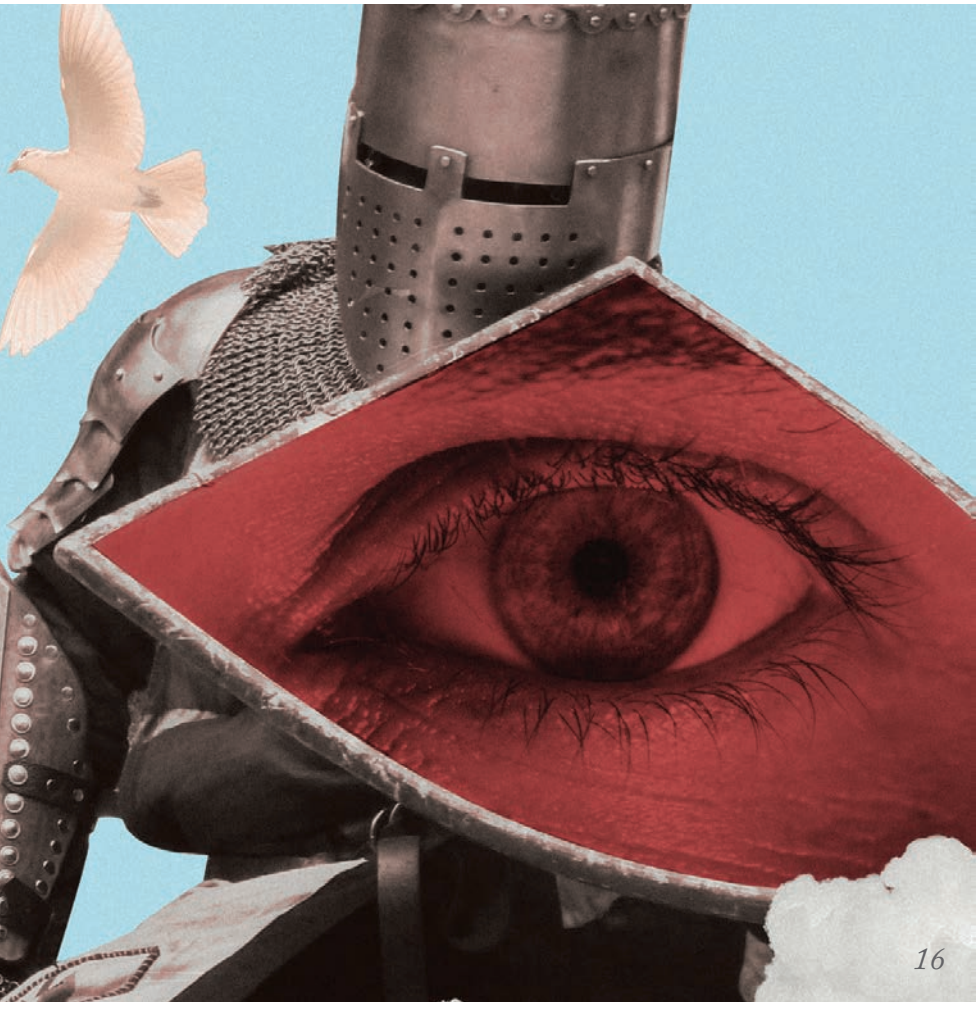

On The Cover

Art inspired by the Latin origin of the word presbyopia, and a little bit of Monty Python and the Holy Grail added in for good measure.

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Distribution:
The Ophthalmologist (ISSN 2051-4093) is published monthly except July, by Texere Publishing Ltd and is distributed in the USA by UKP Worldwide, 1637 Stelton Road B2, Piscataway, NJ 08854.
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Hindsight for Foresight

Looking back at 2016's predictions of the future

Happy New Year – and what a year last year was! Let's forget all about the politics and populism, and focus on some of the ground-breaking stories that we were honored to report in The Ophthalmologist in 2016. Looking back, there's a common thread that links our most popular feature articles of the last 12 months: the future. I'm repeatedly told that people read The Ophthalmologist to find out what's next, and I've picked three articles that I believe showcased precisely that.

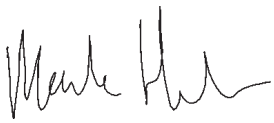
The first… was a world first. Robert MacLaren performing the first-ever robotic assisted surgery in the human eye – and we were in the operating theater to witness, record and report it (1). The interviews with the key players spoke to how robotic assistants will not only extend the capabilities of the surgeon far beyond what's possible now, but also their useful working life. The wonderful thing is that this is no longer the realm of the distant future; we're at the first-adopter stage. Whether you're ready or not, it's highly likely that surgical robots will be coming to an operating theater near you – soon.

The second was Pearse Keane and Alex Walsh explaining how they're going to revolutionize the eye exam (2). They're building – in the form of a pair of binoculars – binocular OCT. But it's more than just OCT; this display-toting, internet-connected pair of bins (plus its extensive cloud infrastructure) will enable visual field and acuity testing, amblyopia detection and much more – and the aim is to make the technology affordable so that patients can feasibly take one home too. Imagine what this could do; as well as the huge potential for disease screening and detection, this device could reduce the strain on healthcare resources. I find when something is described as a "paradigm shift," it's usually cliché. I don't believe that for a moment here.

My final pick of the year was Alex Huang's exposition on aqueous angiography (3). MIGS devices have transformed what's possible in the gap between eyedrops and filtration surgery, but many are inserted "blind" to where the patients' point of optimal aqueous outflow actually is. Alex has taken an innovative approach to map those outflow pathways in vivo by OCT – and it looks set to transform the efficacy of those MIGS devices that exploit the outflow pathways. In short, this could allow true customization of each procedure.

These are just three of the great stories that we have been privileged to cover this year, but 2016 has been full of, what I believe will be, practice-changing developments. I cannot wait to see what 2017 might bring. Here's to the future and a fantastic new year in ophthalmology!

Mark Hillen
Editor



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Upfront

Reporting on the innovations in medicine and surgery, the research policies and personalities that shape the practice of ophthalmology.

We welcome suggestions on anything that's impactful on ophthalmology; please email edit@theophthalmologist.com

Diagnosis: Color

Could a color-changing implant monitor IOP in patients at risk of developing glaucoma?

Glaucoma could be considered a "silent assassin" – it displays almost no early warning signs, and if it isn't detected early, it quietly inflicts irreparable damage to the optic nerve over many years. By the time it's noticed, all that can be done is to try to maintain what vision remains. The key to success is catching the disease as early as possible, and intervening before irreversible damage occurs. A team at Florida International University (FIU) has come forward with a potential solution – an intraocular device that monitors IOP and changes color with eye pressure.

Their low-cost device is comprised of flexible gel and elastomer layers supported by a rigid base with fixed patterns that functions as a reference line system. "The basic concept is that the elastic system is like a balloon – as it expands, it stretches the membrane across the reference line system, and this changes the color pattern," explains Sitharama Iyengar, one of the co-inventors. It requires no batteries or power supply, and the team intend their device to be surgically implanted between the cornea and iris. "Our aim is for it to be observable in users' eyes, which will help patients monitor their IOP without needing to visit an ophthalmologist," says Iyengar.

Their device is intended for use in people who are at a high-risk of developing glaucoma, such as those with diabetes and hypertension, and it's hoped that it will be useful for patients in rural communities and developing countries. "We anticipate that ophthalmologists would travel to potential rural areas to diagnose at-risk patients and implant the device within a sterile, mobile medical environment," says Iyengar. He adds, "We want it to be 'self-diagnosing' from this point for at least two years, upon which time the medical team could return to these outlying areas."

The team are still at the design stage. "We are currently exploring investment opportunities to enable us to produce the device and complete the required clinical analysis," Iyengar says, acknowledging that "there are optimization issues that must be addressed to minimize the potential for related irritation and corneal issues." *RS*

Same Difference

Real-world observational study comparing ranibizumab and aflibercept shows similar outcomes

In the fight against neovascular age-related macular degeneration (AMD), there are three heavyweights in the arena: ranibizumab, aflibercept, and bevacizumab. Although bevacizumab is commonly used off-label, ranibizumab and aflibercept are both indicated for the treatment of neovascular AMD. But which to choose?

It's known that all three are roughly similar in terms of efficacy and safety – aflibercept's approval was based on the Phase III VIEW trials which found that it was non-inferior to ranibizumab (1,2), and the CATT trial showed comparable outcomes with both ranibizumab and bevacizumab (3). But we also know that the real-world outcomes of patients receiving ranibizumab for the treatment of neovascular AMD don't match those in the clinical trials (4). So across all of the "heavyweights," is there a best choice amongst them in the real world?

To address this question, a multinational team mined the Fight Retinal Blindness registry to directly compare outcomes of patients treated with ranibizumab versus those treated with aflibercept (5). What they found was that patients' outcomes were similar after 12 months of treatment, irrespective of the drug used: there were no significant differences in visual acuity (VA) improvement nor frequency of treatment between eyes treated with either drug (Figure 1). They also found that more patients switched from ranibizumab to aflibercept than aflibercept to ranibizumab (13.7 percent vs. 3 percent, respectively), but that there was no VA benefit associated with the switch.

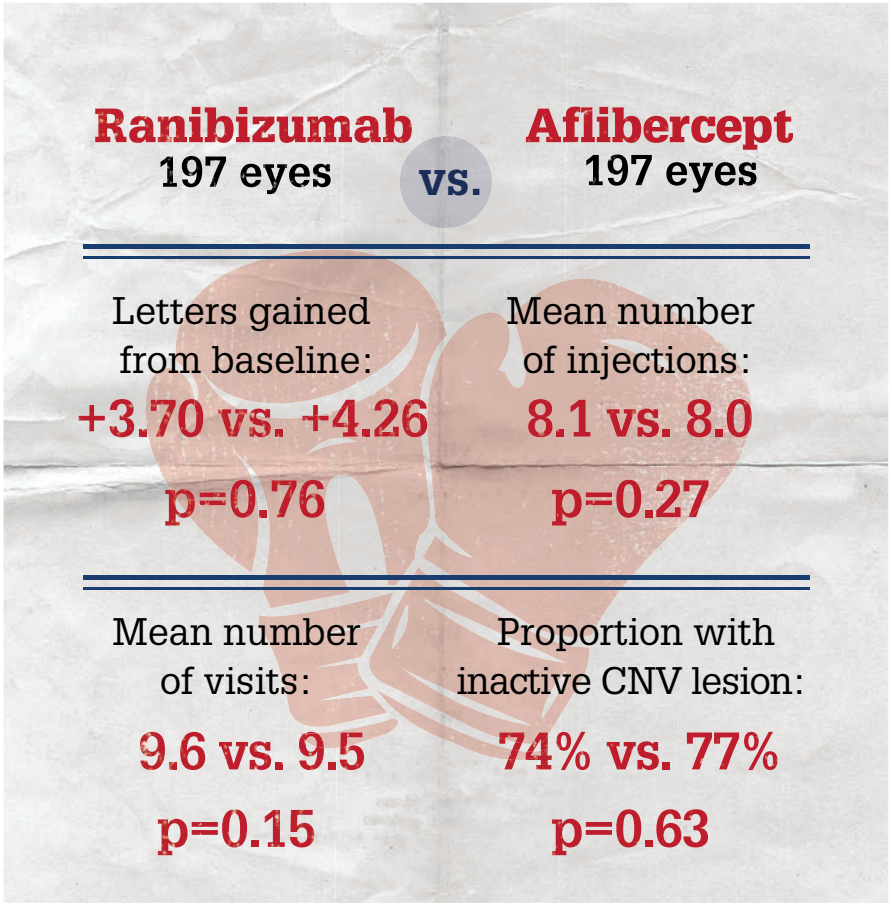

Figure 1. Summary of key results from the observational study after patients received 12 months of treatment with ranibizumab or aflibercept. A total of 394 eyes from 372 patients were followed between December 1, 2013 and January 31, 2015. CNV, choroidal neovascular membrane (5).

Concluding that both drugs "delivered similar, good outcomes in routine clinical practice," the authors acknowledge that "a randomized controlled trial would be required to demonstrate the superiority of one drug formally; however, numbers would be prohibitively large based on event estimates from this study." *RS*

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"Miami, We Have a Problem"

A Florida-based team provides the first quantitative evidence for the role of CSF in spaceflight-induced ocular changes

Since that "one small step," mankind has made giant leaps forward in space science. Today, astronauts regularly check in and out of the International Space Station (ISS), and the time they spend there is becoming longer and longer. But extended spaceflight brings with it a specter: visual impairment due to intracranial pressure (VIIP) syndrome, giving space agencies another vital mission… to characterize the syndrome and to figure out how to protect their astronauts from it.

Associated with globe flattening, hyperopic shift, choroidal folds, and optic disc edema, VIIP is thought to result from microgravity-induced cephalad vascular fluid shift, with symptoms being reported by up to two-thirds of astronauts during or after space flight (1, 2). But to date, the actual etiology of VIIP syndrome has not been defined. Now, a team from the University of Miami who have been studying ocular shape and cerebrospinal fluid (CSF) volume changes in astronauts, have provided the first quantitative evidence for a direct role of CSF in spaceflight-induced ocular changes (Figure 1; 3). Noam Alperin, Professor of Radiology and Biomedical Engineering at University of Miami Miller School of Medicine, and lead author of the study, tells us more…

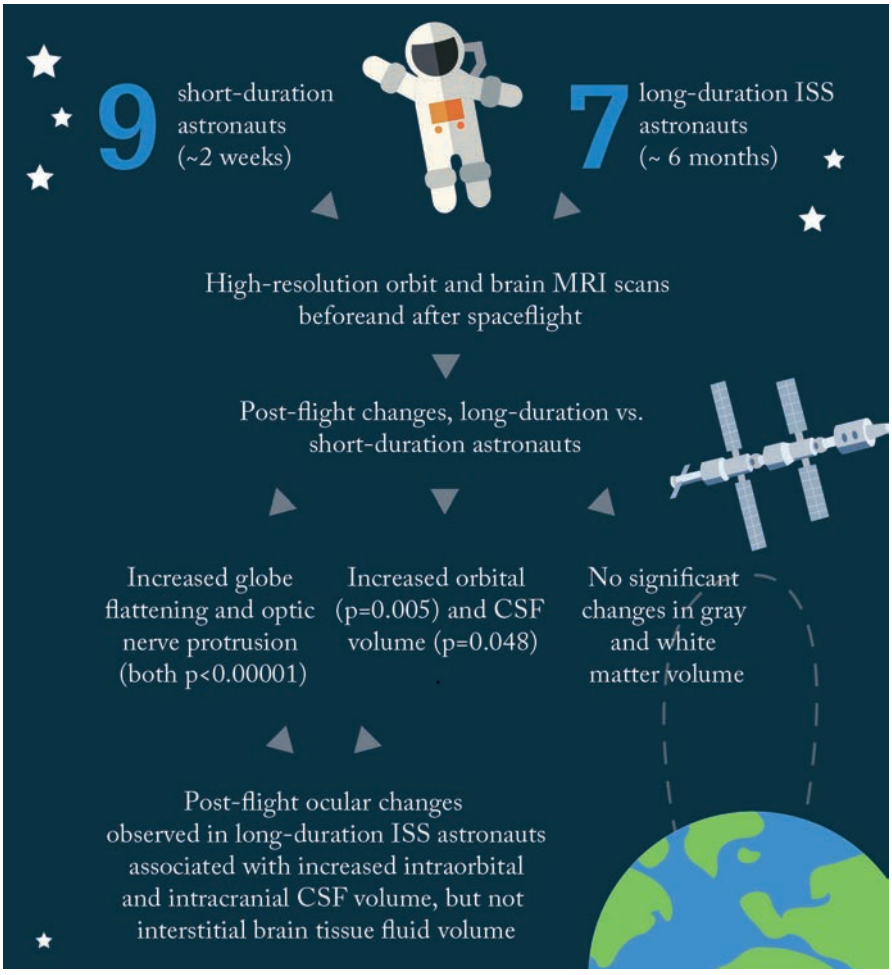

Figure 1. Study design and summary of key results. The team used quantitative imaging algorithms to analyze MRI scans and establish correlation between changes in CSF volume and ocular structure (3).

Why?

Our group has been investigating the CSF system for a long time, and we'd developed a method to measure intracranial pressure (ICP) non-invasively by magnetic resonance imaging (MRI). In 2010, I received a call from NASA, "Miami, we have a problem."

How?

We installed a protocol in their MRI scanner that's located near the Houston space center. For four years, we studied astronauts before and after space flights, collecting data from short-duration and long-duration astronauts. The algorithm we've developed to assess morphological changes provides a quantitative measure, and is much more accurate, reliable and reproducible than previous methods which involved "eyeballing the eyeball."

When?

We saw that most astronauts developed VIIP to a certain severity by six months. From studying short-duration astronauts who have been in spaceflight for two weeks, we know that VIIP starts after a much longer duration than this – I would say after several months of time in space and we expect that the longer the flight, the worse the deformations.

What's next?

We're already starting to use our approach to study glaucoma, and we've done a lot of work that will hopefully be published soon. We think our method of measuring

CSF volume is a consistent way to assess the balance between the eye and the brain. We'll also continue working with NASA to examine the effects of "head down tilt" on the globe. In this study, subjects will spend 30 days in bed with a head-down tilt of six degrees to simulate the movement of fluids from the legs to the head, and we'll measure and quantify the deformation that occurs. *RS*

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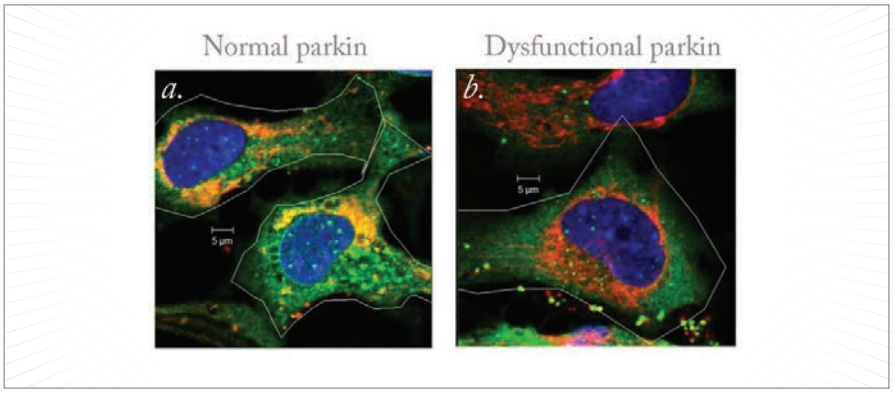
The Clear Lens Warden

A gene associated with early-onset Parkinson's disease appears to act against cataract formation



Credit: Florida Atlantic University.

Figure 1. When LECs expressing wild-type parkin protein are exposed to hydrogen peroxide-induced oxidative stress, parkin colocalizes with mitochondria and recruits proteins (such as p62/SQSTM1) to degrade the damaged mitochondria (yellow puncta) (a) whereas LECs expressing dysfunctional mutated parkin (C431N) do not (b).

Parkin is an interesting protein. Encoded in humans by the *PARK2* gene, it is implicated in several disease states, including Parkinson's disease. How *PARK2* mutations lead to dopaminergic cell death and early Parkinsonian symptoms isn't clear, though – it appears to play a role in the degradation of free-radical-damaged mitochondria, but what's now clear is that parkin also plays a central role in keeping the lens… clear.

Intrigued by the protein's potential role in lens opacity, researchers from the Charles E Schmidt College of Medicine at Florida Atlantic University decided to delve deeper. They performed cell culture experiments in which lens epithelial cells (LECs) expressing either normal or mutated forms of the *PARK2* gene were assessed. What they found was this: *PARK2* is expressed when LECs are exposed to cataract-causing, free radical-generating environmental insults (in this case, oxidative stress caused by hydrogen peroxide exposure). Parkin removes damaged mitochondria (see Figure 1), and by doing so, helps prevent the formation of free radicals in LECs. This increases the ability of the LECs to survive free radical formation, and presumably, the reactive oxygen species-mediated aging.

"Our findings suggest that parkin plays a direct role in the prevention of oxidative stress through its ability to maintain cellular mitochondrial populations, and that the gene encoding parkin is induced by environmental damage," says Marc Kantorow, lead author of the associated paper (1). What could this mean? "Drugs or genetic methods that increase parkin levels and function could prove effective in preventing cataracts and other age-related degenerative diseases, including neurological conditions like Parkinson's disease," he explains.

According to Kantorow, the team now plans to "establish how parkin regulates the growth and development of the lens by controlling mitochondrial populations that are required for lens cell growth." He adds, "We want to identify the genetic mechanisms that regulate the production of parkin in cells and see if they can be manipulated to increase parkin levels, thereby increasing cell survival to prevent disease." *RM*

Reference

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Hidden Depths

How much information do we retain about what we don't see?

To remember something, do you need to consciously see it? The belief in a strong link between something being visible to the eye, and the maintenance of corresponding neuronal activity is supported by several theories of visual awareness. But recent work is challenging this notion: it would appear that things that seem "invisible" to the naked eye can still be stored by the brain.

A group of researchers used magnetoencephalography (MEG) to monitor 16 healthy adult subjects while they were being shown patterns of lines that quickly appeared and disappeared on a screen (Figure 1). The subjects were then asked questions about the visibility and orientation of the images – meanwhile MEG was being used to measure the magnetic fields created by their brain activity.

The answers given by the study participants showed that stimuli reported as "unseen" were actually remembered by the brain. How? When the participants answered questions about images that they said they didn't detect, they managed to perform better than if they were answering at random (1). The MEG data provided even more interesting results: neuronal activity elicited by the images (even those only on screen for around 150 ms) moved from the primary visual cortex to high visual regions, ending up at the parietal and frontal cortex, suggesting the information was briefly maintained. "Undoubtedly, these results suggest that our current understanding of the neural mechanisms of conscious perception may need to be revised," says Jean-Rémi King, co-first author of the paper. *RM*

Reference

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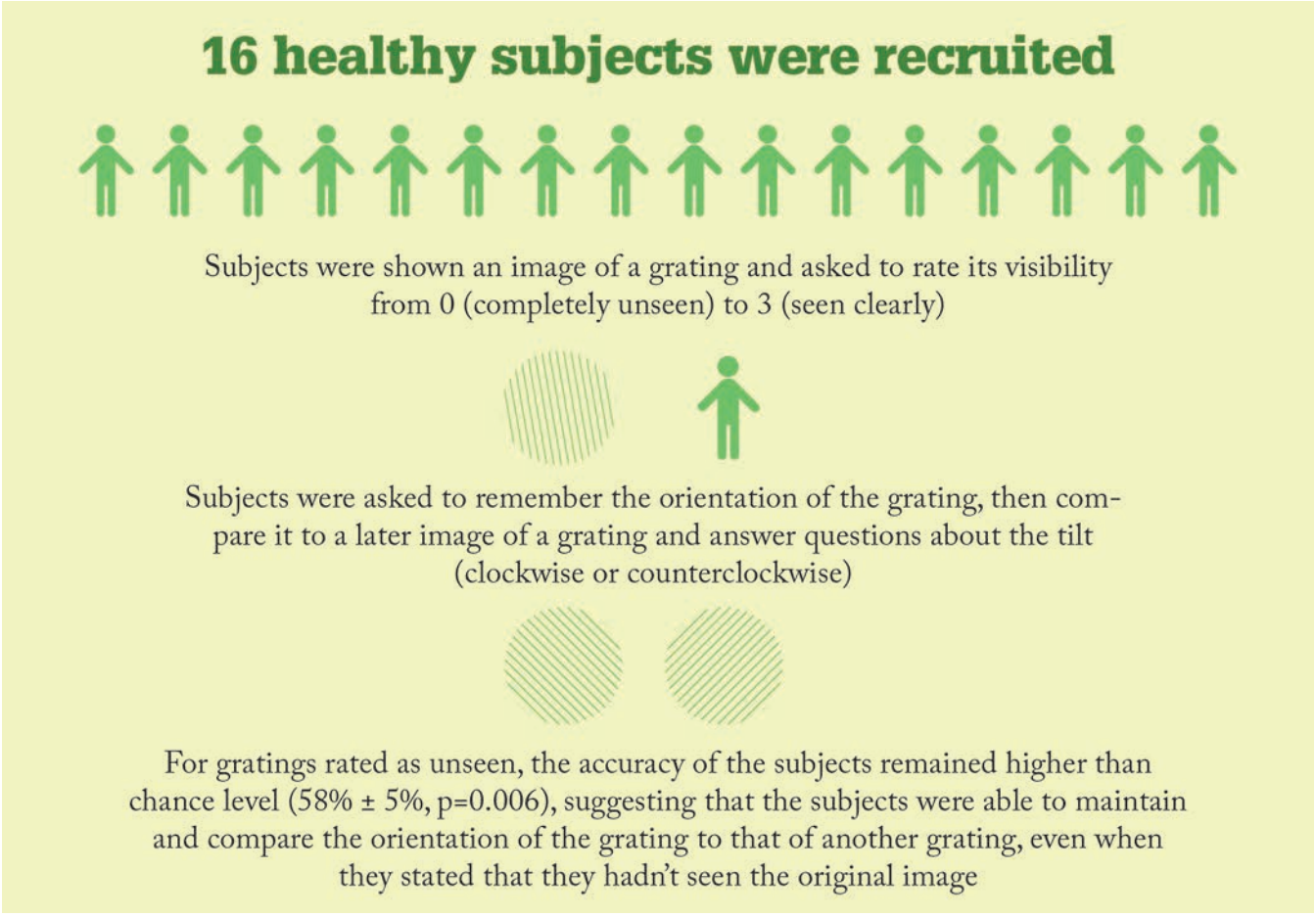

No Synergy

In theory, pegpleranib + ranibizumab is better than ranibizumab alone. But Phase III results suggest otherwise…

Pegpleranib (E10030; Fovista) had the potential to be worth a billion dollars to Ophthotech. The rationale was obvious. Platelet-derived growth factor (PDGF) is the enemy of sustained anti-VEGF therapy: it causes pericytes to proliferate and engulf the new macular vasculature, thereby protecting the vessels against the effects of the anti-VEGF agents. Fovista blocks PDGF, disrupting the pericytes and stripping them from the blood vessels, rendering them vulnerable once again to anti-VEGF drugs.

It was looking good – Phase II results of the CAPELLA study (in which pegpleranib and ranibizumab was compared with ranibizumab monotherapy in patients with treatment-naïve neovascular AMD) showed favorable outcomes for the combination (1). But, now, Ophthotech and Novartis have announced that the combination has failed to show superiority over ranibizumab monotherapy in a pair of Phase III trials (NCT01944839 and NCT01940900; 2, 3). The two multisite, randomized controlled trials assessed the anti-PDGF and anti-VEGF combination therapy in over 1,200 patients with neovascular AMD. Here are the topline results from the pooled analysis:

- The pre-specified primary endpoint of mean change in visual acuity at 12 months was not achieved (Figure 1). Patients receiving combination therapy gained a mean of 10.24 ETDRS letters at 12 months compared with 10.01 letters in patients receiving ranibizumab monotherapy.
- At month 12, 24.2 percent of patients receiving combination therapy gained 20 or more ETDRS letters from baseline, compared with 22.1 percent of patients receiving monotherapy.
- More patients in the combination therapy group lost five or more letters at month 12 (12.1 percent vs. 11.2 percent in the monotherapy group).
- In the combination therapy group, 13.5 percent of patients achieved a VA of 20/25 compared with 13.9 percent in the monotherapy group.
- Both treatments were well tolerated at one year. Ocular adverse events reported more frequently in the combination group were related to the injection procedure.

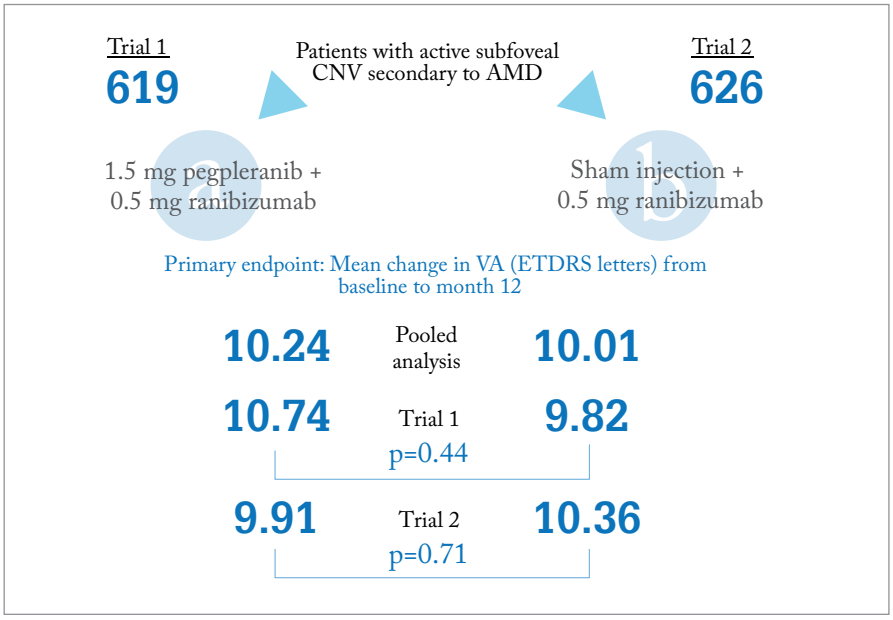

Figure 1. Summary of topline primary endpoint results from the two Phase III trials. Trial 1, NCT01944839; Trial 2, NCT01940900. CNV, choroidal neovascularization (2,3).

Ophthotech's CEO, David Guyer comments, "We will continue to analyze the data from these two studies to better understand the trial results." Vasant Narasimhan, Global Head of Drug Development and Chief Medical Officer at Novartis (who partnered with Ophthotech) adds, "We are confident that underlying data will provide further understanding and guidance on how best to help patients with this disease." Novartis has other irons in the fire, though: RTH258, a single chain antibody fragment anti-VEGF agent, which is currently undergoing Phase III trial evaluation, with results expected early this year. *RS*

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In My View

In this opinion section, experts from across the world share a single strongly-held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of ophthalmology. They can be up to 600 words in length and written in the first person.

Contact the team at edit@theophthalmologist.com

The Right Angle

Why anterior segment imaging is my gold standard method for diagnosing and monitoring angle-closure glaucoma

By Hiroshi Ishikawa, Professor of Ophthalmology at New York University Schools of Medicine and Engineering, New York, NY, USA

Most of you reading this probably view gonioscopy as the gold standard method for determining if an eye has an occludable angle. I would argue that anterior segment imaging through ultrasound biomicroscopy (UBM) and/or optical coherence tomography (OCT) is better – and has several clear advantages. Here are my reasons why.

First, anterior segment imaging is objective: you can make quantitative assessments through measuring the angle, anterior chamber depth, corneal thickness, and so on. Second, several publications have shown that imaging is better than gonioscopy in terms of reproducibility and agreement: intra-observer repeatability is higher with imaging (1) and there is a high agreement between gonioscopy and UBM when both are performed in a darkened room (2). Third, anterior segment imaging can be a great patient education tool – patients can see their angle closure and response to treatment.

Although I think UBM and OCT are both great, it's difficult to say which is best; they each have their own benefits. As OCT is a non-contact method, it can be performed in post-operative eyes as soon as a day after surgery – obviously UBM isn't recommended for this. OCT also has a higher axial resolution than UBM – 5 µm versus 25 µm. On the other hand, you can't always see the scleral spur with OCT, but it can be located consistently with UBM. Penetration is also better with UBM, meaning that it can help diagnose cases of plateau iris. Whilst you can visualize the angle and the flat iris with OCT, you may not be able to see the ciliary body processes, but with UBM, you can see the process very clearly, and you can also assess whether there is space in the sulcus. So to diagnose plateau iris, you need to use UBM – you would sometimes struggle to accurately diagnose these cases with gonioscopy alone even with indentation.

To me, using anterior segment imaging instead of gonioscopy is a no-brainer. It's more precise, it offers greater consistency with angle assessment and it represents the true angle. I also find that the cross-sectional view is more robust when variations in the iris profile are present. We know that the agreement between gonioscopy and anterior imaging is high (2), meaning that sensitivity and specificity of the two are similar. So why not choose the method with higher reproducibility and precision?

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Buy One, Get One (Almost) Free?

Why I believe it's time to finally embrace immediate sequential bilateral cataract surgery

By Charles Claoué, Consultant Ophthalmic Surgeon, 119 Harley Street, London, UK

"Nothing is more powerful than an idea whose time has come!" – Victor Hugo.

Immediate Sequential Bilateral Cataract Surgery (ISBCS) isn't new – it was topical when Jacques Daviel invented cataract extraction in 1752. But it's still a subject of discussion in 2017. Why? Cataract hasn't really changed; it's still predominantly a bilateral disease. Patients haven't really changed either, and they still question why a bilateral disease needs separate episodes of care. In repeated surveys, around eight in every 10 of patients would prefer ISBCS. This is because they want rapid visual rehabilitation (days rather than weeks or months), reduced costs for travel and spectacles, and reduced payments if they're funding the treatment themselves. What's not to like? Unfortunately, surgeons haven't really changed their views on the subject, with many not reviewing the evidence for years. This often means their objections haven't changed in over a decade! Predictably, the concerns include the risk of infection, toxic anterior segment syndrome (TASS), corneal or retinal edema, and refractive surprise…

However, if the recommendations of The International Society of Bilateral Cataract Surgeons (1) are followed, all these risks are minimized to such an extent that they become acceptable to most patients. The recommendations also specify that patients at risk of cystoid macular edema or corneal decompensation should not be offered ISBCS, and nor should those at risk of refractive surprises (e.g. post-LASIK patients). And with the advent of optical biometry and the newest IOL formulas such as the Hill-RBF calculator, the predictability of IOL power for normal eyes is so high that the refractive surprise argument simply doesn't hold up.

We're also beyond the era of high-risk IOL exchange for refractive surprises, with tools such as supplemental (piggy-back) IOLs and LASIK at our disposal. TASS remains an "unknowable unknown" – it's a systems failure, not a random event. The guidelines make it clear that nothing used for surgery can be changed without consultation. Under these circumstances, in the unlikely event of an occurrence should there be a "bad batch" of a regular product, it can be argued that it becomes a product liability issue, rather than a medical one.

Finally, infection remains the front-line argument for non-believers. We all have mental scars from patients with fulminant endophthalmitis and a bad outcome, and I believe this prevents us from thinking rationally about the issue. The risk of infectious endophthalmitis with the use of intracameral antibiotics is around 1 in 5,000, or better (2). It follows that, as a chance event, the risk of bilateral simultaneous endophthalmitis is just 1 in 25,000,000! And of course, the risk is identical for bilateral sequential endophthalmitis. Compare this to the risk of unexpected death from a general anesthetic in a healthy adult – a risk of 1 in 100,000. And even if endophthalmitis occurs, a third of eyes will regain sufficient vision to be able to drive, making the risk of functional blindness even lower. Compared with the other risks people face on a daily basis, this is a very remote risk, and our patients understand this.

Looking at the financial aspect, it is well documented that ISBCS carries financial disadvantages for surgeons in many countries. But in addition to the financial savings for the patient, there are some major societal financial advantages to ISBCS. Healthcare providers can save about €500 per patient, and hospitals can increase throughput, as one ISBCS takes less time than two unilateral cases. The increasing demand for cataract surgery is relentless, and funding is limited – making the widespread adoption of ISBCS seem even more attractive. I believe that once healthcare providers start to appreciate the productivity and financial advantages of ISBCS, they will start to exert pressure on ophthalmologists to take ISBCS into consideration in appropriate cases. And who knows, we might even be offered a premium for ISBCS in the future. Time will tell whether this is a realistic possibility, or simply a joke!

"A wise man changes his mind, a fool never does." – Spanish proverb.

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REFRACTIVE SURGERY'S HOLY GRAIL...

Eyedrops for presbyopia

By Shafi Balal, Raquel Gil-Cazorla, Shehzad A. Naroo, Anant Sharma, Sunil Shah

Twenty-five years old is a good age to be. Any older and your hearing starts to decline; the loss may be barely detectable at that stage – but it's only going in one direction. By the start of your fourth decade, your bone and skeletal muscle mass starts to decline, and by your mid-forties, a number of ocular diseases start to manifest: incipient cataract, slight drusen deposits, a small raise in IOP... and presbyopia. Some people experience it in their forties, others in their fifties. It's most definitely age-related, and for now, almost certainly inescapable.

The progressive loss of accommodation (Table 1) is the big issue with presbyopia because it brings with it the inability to focus on near visual tasks (1). In developed countries, that's easily dealt with: you wear spectacles. But having to wear them for near tasks can be a pain, and we all know that there's a great appetite for being "spectacle-free" – it's what drove the LASIK boom of the early 2000s. Glasses cost money, prescriptions change, they can get broken and lost, they need to be cleaned and cared for, and you might not like how you look wearing them – all valid complaints. But if you are in a developing country, presbyopia is more of a problem. If your livelihood or survival requires the use of near vision and you don't have access to spectacles, you're in trouble. Clearly, solving the presbyopia problem has the potential to transform many lives, which is why presbyopia correction is often referred to as the "Holy Grail of refractive surgery" (2).

Over the years, many surgical strategies have been developed in an attempt to correct presbyopia, but none have truly solved the problem, with each having risks and limitations, and all resulting in some compromise in visual function. But what about a pharmacological approach to reduce the impact of presbyopia?

Appreciating the anatomy

To understand how drugs might be used to treat presbyopia, it's worthwhile considering the main anatomical units involved in accommodation: the ciliary muscle, lens and zonular fibers.

The ciliary muscle is predominantly under parasympathetic control, with sympathetic innervation playing a minor role in relaxation only (by inhibiting accommodation). The contraction of the ciliary muscle alters the shape and position of the lens, thereby invoking the accommodative capacity. Notably, the ciliary muscle also contains muscarinic-3 acetylcholine receptors (M_3).

It's important to note that the iris is also under heavy influence of the parasympathetic system – cholinergic stimulation of the M_3 receptors on the iris sphincter muscle causes miosis. Conversely, the iris dilator muscle is sympathetically innervated and contains α-adrenergic receptors. If these receptors are antagonized, it allows the parasympathetically innervated pupillary sphincter to predominate (as it is unopposed), resulting in miosis.

Depth of focus: the pinhole effect

Most pharmacological approaches for the treatment of presbyopia are based on reducing the aperture of the pupil. Small aperture optics have long been known to increase near visual acuity (VA) by increasing the depth of focus. Peripheral light waves are most distorted by refractive error: by blocking these and allowing only the most central rays of light to reach the retina, this results in not only clearer vision, but also an increase in the depth of field of clear vision. It's this principle that underpins the surgical approaches of AcuFocus' small aperture corneal inlays and intraocular lenses (IOLs). Their Kamra corneal inlay features a central 1.6 mm aperture (a size AcuFocus claim achieves an expanded depth of focus without significant visual degradation) and their IC-8 IOL contains a 1.36 mm central aperture and is implanted in the non-dominant eye – and has shown promising early results. Clearly, for a pharmacological option to be successful it must create a similar and long-lasting effect on pupil size (3).

However, manipulating pupil size is not without undesired consequences. A constricted pupil (understandably) decreases vision at night – less light enters the eye, and diffraction at very small pupil sizes can degrade overall vision quality. For elderly patients in particular, decreasing the amount of light falling on the retina worsens vision.

Understanding accommodation

To appreciate why some pharmacological formulations may or may not work in presbyopia, it is essential to understand accommodation. Accommodation isn't a completely settled topic: there are a number of competing theories that seek to explain the mechanism(s), with Hermann von Helmholtz's 166 year-old theory being the most widely accepted.

Von Helmholtz suggested that when the eye is at rest and focused for distance, the ciliary muscle is relaxed (Figure 1). To focus on a near object, the ciliary muscle contracts, causing the ciliary body to move forward and towards the axis of the eye. Simultaneously, the tension of the zonular fibers around the lens equator relaxes, which allows a soft lens to be molded by the elastic capsule into a more spherical and accommodative form. A larger, stiffer lens – such as one that arises from ageing – will not change shape as much, thereby compromising accommodation.

Ronald Schachar proposed an alternative theory: that only the equatorial zonules are under tension during accommodation (Figure 1). When the ciliary muscle contracts, equatorial zonular tension is increased, causing the central surfaces of the crystalline lens to steepen, the central thickness of the lens to increase, and the peripheral surfaces of the lens to flatten. The increased equatorial zonular tension keeps the lens stable and flattens the peripheral lens surface during accommodation. In this scenario, presbyopia occurs because the equatorial diameter increases with age. However, this theory is opposed by the well-documented occurrence of lens stiffening and failure of scleral surgical approaches (which are based on Schachar's theory) to correct presbyopia. Furthermore, studies have shown that it is axial thickness that is increased and not equatorial diameter.

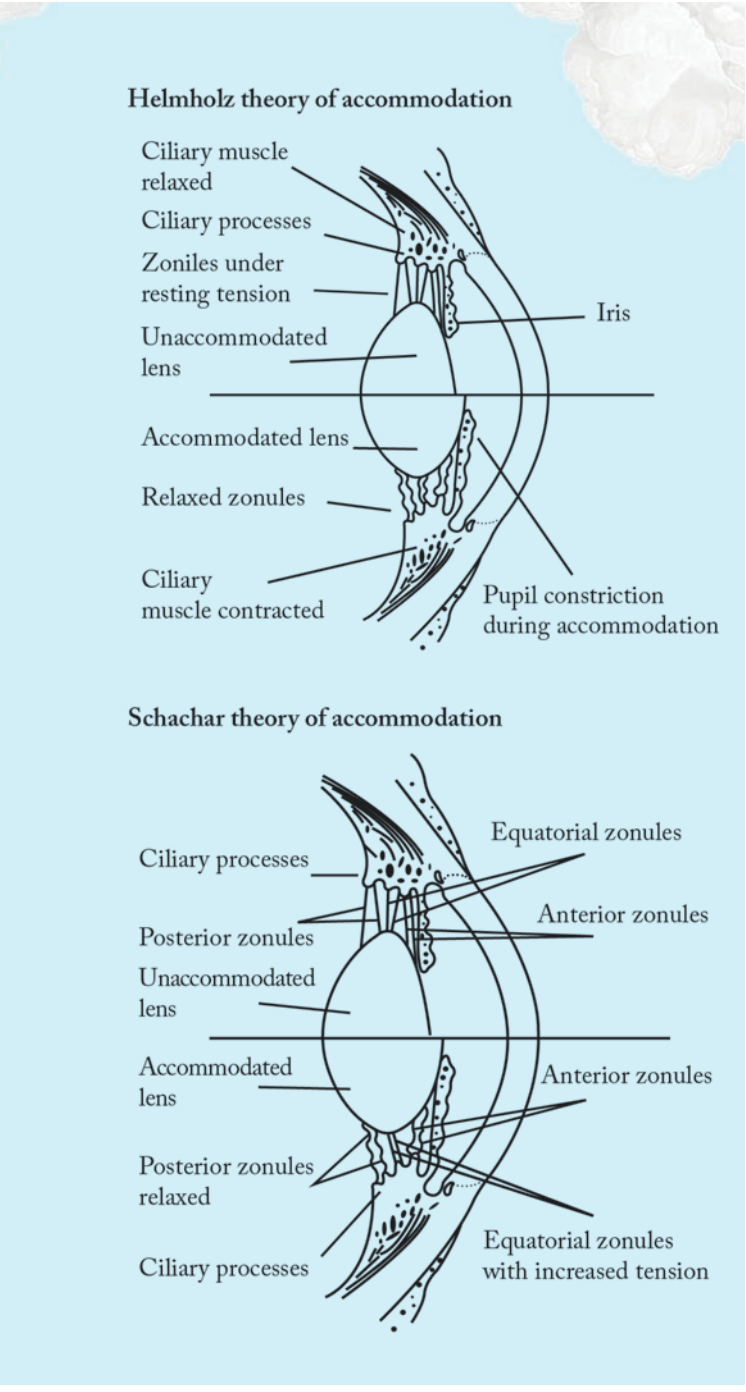

Figure 1. In the Helmholz theory of accommodation (top), ciliary muscle contraction leads to a relaxation of the zonular fibers; the reduced zonular tension lets the elastic lens capsule contract, increasing anterior and posterior lens curvature. In the Schachar theory (bottom), the equatorial zonules are under tension only during accommodation, and the anterior and posterior zonular fibers offer only passive support structures for the lens.

The most important aspect to remember is that true accommodation results in a dioptric change in the power of the eye. Most interventions achieve pseudoaccommodation: functional near vision from non-accommodative factors like small pupils, against-the-rule astigmatism and spherical aberration. Indeed, most pharmacological treatments attempt to exploit pseudoaccommodation from a small pupil.

"Accommodation isn't a completely settled topic: there are a number of competing theories that seek to explain the mechanism(s)."

Pharmacological potential

1. Muscarinic agonists with non-steroidal anti-inflammatory (NSAID) agents

Many groups have investigated this combination over the years (Table 2), the rationale being that a muscarinic agonist causes the ciliary muscle to contract (with a corresponding increase in lens thickness). However, this may only be achievable in younger presbyopes, as stiffer lenses are less easily induced into accommodation. Muscarinic agonists also cause miosis with resulting increase in depth of focus and pseudoaccommodation.

What about the NSAIDs? Jorge Benozzi's group has advocated the use of diclofenac for the inhibition of inflammation in the anterior uveal tract, claiming that it decreases spasmodic ciliary contraction, pigment dispersion and posterior synechia formation secondary to parasympathomimetic drugs (9). However, it must be noted that our group was unable to find any evidence to substantiate that NSAIDs achieve this, and pilocarpine is not known to cause pigment dispersion or posterior synechiae in normal eyes.

Similarly, Patel et al. (10) have claimed that including NSAIDs with muscarinic agents prolongs the effects of the parasympathomimetic agent through the inhibition of prostaglandin synthesis in the anterior uvea. This seems counterintuitive – NSAIDs are used in cataract surgery to help prevent miosis – but nevertheless, Patel and Salamun believe

Unit	*Change with age*	*Effect*
Lens	Less elasticity Greater size	Less ability to deform under accommodation
Lens capsule	Decreased elasticity	Inability to deform lens Other investigations indicate mechanical properties may remain the same with age
Zonules	Reduced number Increased fragility More anterior insertion	Surprisingly no effect on zonular tension with age
Ciliary muscle	Decreased strength	Reduced muscle movement
Bruch's membrane capsule	Less elastic	Restriction of ciliary muscle mobility
Vitreous	Liquefaction	Reduced peripheral compression of lens

Table 1. Possible contributing factors in etiology of presbyopia. Adapted from (4–6).

it shows promise and have patented the approach along with Claes Feinbaum. They are currently attempting to minimize any adverse effects by using an intravitreal micro-insert to slowly release low concentrations of the insert's ingredients. The micro-insert should have a number of advantages over repeated drop instillation: topical administration is associated with drug loss through the eye's natural drainage channels, and this permits lower drug concentrations to be used. To date, no study data has been published on this device (10).

Juan-Carlos Abad (13) has attempted to exploit the pharmacology of NSAIDs one step further. NSAIDs inhibit the cyclooxygenase (COX) enzyme family, which are responsible for prostaglandin and thromboxane synthesis. Humans have two functional COX isoforms, COX-1 and COX-2, with COX-2 typically being expressed in inflamed tissue. Abad's patent identifies using COX-2 specific inhibitors in combination with a cholinergic or muscarinic agent in an attempt to target COX-2 specific pro-inflammatory mediator production, but sparing COX-1's "housekeeping" prostanoid production. Whether there is an advantage in this targeted approach over non-specific NSAIDS remains to be seen.

A slightly different drug combination approach was taken by Humberto Carrera, who combined pilocarpine with the NSAID, bromfenac. His rationale was that bromfenac's duration of action can be as long as 24 hours, and this should allow for a once-daily topical application – unlike diclofenac, which has an ocular half-life of under two hours. However, once again, no published studies are available on this formulation to date (14).

We must note here that presbyopia is a benign condition, so it is essential not to advocate potentially iatrogenic therapies. NSAID drops such as diclofenac have been associated with devastating adverse effects, such as corneal melt, epithelial defect and sterile infiltrates, so extensive patient evaluation is required before long-term treatment initiation is warranted.

2. Muscarinic agonist with sympathetic agonist

Carbachol is a parasympathomimetic agent and, unlike pilocarpine, is a full agonist that also promotes release of acetylcholine from parasympathetic nerve endings. Additionally, its carbamate structure means it may also inhibit cholinesterase enzymes (15). In terms of inducing miosis, the most commonly used strength of carbachol is 2.25% (which is equivalent in effect to about 3% pilocarpine; 16). Brimonidine is an α_2-receptor agonist, licensed in glaucoma, exhibits pupillary action, and can produce significant miosis, typically in low light conditions.

Kaufman (18,19) presented a study (summarized in Table 3) of the combination of both classes of drugs. Kaufman states "each combination was tested in each patient" but it is unclear if this was a true cross-over study or why uncorrected near visual acuity (UNVA) rather than best distance corrected near visual acuity (BDCNVA) was used. The near and distance visual acuities were measured 1, 2, 4, and 8 hours after instillation of the drugs. The results demonstrate the preparation is effective – but that adverse effects remain an issue.

In what appears to be an extension of Kaufman's work, Abdelkader (20) looked at carbachol 2.25% in combination with brimonidine 0.2%. The drops resulted in statistically significant UNVA improvements, and all patients stated they would continue to use the drops if available (whereas none were prepared to continue using the placebo drops). It's well known from pilocarpine use in glaucoma that patients experience a dull headache on initiation with pilocarpine therapy, but that this should improve with time. The group have recently published another clinical trial (23), which compares the 3% carbachol formulation with brimonidine 0.2% in only 10 patients – but again, statistically significant results were shown. Given that they recruited almost five times as many patients for the 2.25% formulation (20), one can infer the formulation they likely favor. Interestingly, the trial was registered on November 11, 2016 but received by the journal in July 2016. Retrospective trial registration has been discouraged for some time by the ICJME (24).

Allergic reactions to ophthalmic agents for the treatment of presbyopia have not been extensively studied. However, brimonidine (when used for the treatment of glaucoma), has. Blondeau (25) found that that up to 25.7 percent of patients with glaucoma experienced such a reaction in his study.

Another combination of a muscarinic agonist with a sympathetic agent (pilocarpine and phenylephrine) has also

How much accommodation do we need to restore?

A 45 year-old will have around 4 D of accommodative power but only uses around 2 D of this comfortably (Figure 2). The usual reading distance is around 40 cm and this requires 2.5 D of accommodation. Therefore a recovery of only 1–2 D would be sufficient to treat most presbyopic patients.

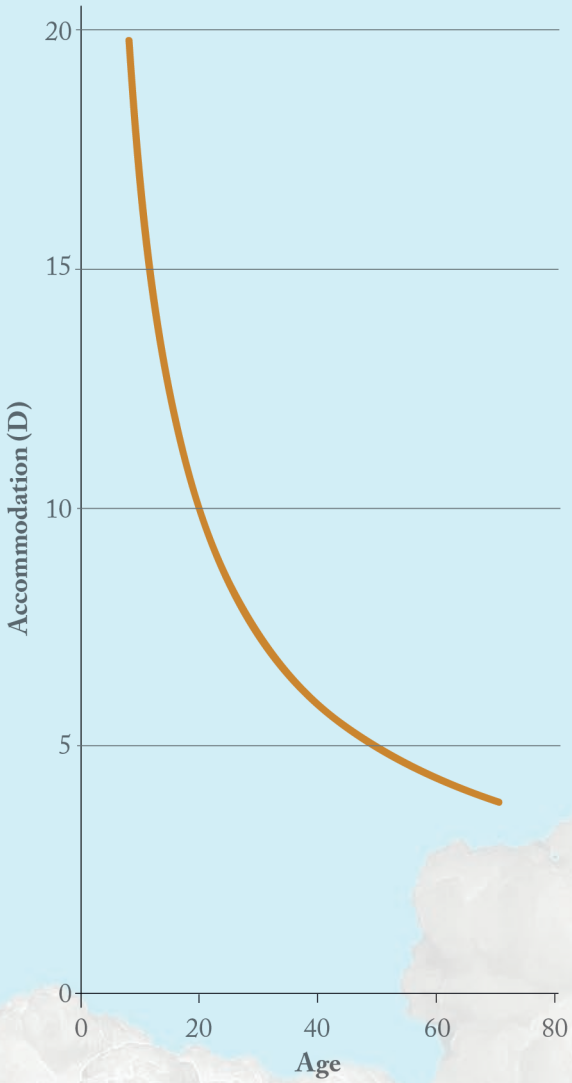

Figure 2. Mean Accommodation versus age. Adapted from (7).

been evaluated as a presbyopia therapy (21). Phenylephrine is a α_1-adrenergic agent – but has shown little to no effect on the ciliary muscle or the centrally stimulated accommodative response. In the past, this combination was used as the Mapstone test, which consists of phenylephrine 10% and pilocarpine 2%, as provocation of closed-angle glaucoma. The proponent of this combination, Vejarano (22), has anecdotally stated that he has used the drops on himself for over five years with no change to his distant UCVA and a 2 line improvement in UNVA.

Vejarano has not reported any adverse effects (such as brow ache or headache), but if pilocarpine does cause ciliary spasm leading to these adverse effects, they may remain unresolved by the addition of phenylephrine. It is also unclear how well patients tolerate the worsening of distance vision in the first hour of instillation, which has implications on, for example, operating heavy machinery and driving. The worsening may be caused by a delay in maximal pilocarpine action, resulting in an initial unopposed phenylephrine-induced mydriasis – the iris' melanin acts as a pilocarpine reservoir, delaying it from working on the ciliary muscle immediately (26).

"If pilocarpine does cause ciliary spasm leading to adverse effects, they may remain unresolved by the addition of phenylephrine."

3. Muscarinic agonist with muscarinic antagonist

The combination of a muscarinic agonist with a muscarinic antagonist is found in PRX-100, a proprietary preparation developed by 'Presbyopia Therapies', which contains aceclidine and tropicamide. Aceclidine is a muscarinic agonist that is less potent than pilocarpine and carbachol; tropicamide is an anti-muscarinic agent. The combination is reported to effectively cause miosis without stimulating accommodation and, according to Presbyopia Therapies' internal data, 1.6–1.9 mm is the optimum pupil diameter. Results reported in an article by Steven Dell are summarized in Table 4. Dell attributes the beneficial effects of PRX-100 under scotopic conditions to the reduction in light that's received by retina, which is thanks to the smaller pupil

Active agents	*Patients*	*Outcomes*	*Adverse effects*	*Authors/Patent*
Pilocarpine 1%, Diclofenac 0.1% 6 hourly	100 patients of both sexes, aged 45–50 with no ocular or systemic disease	All study patients had a near vision of Jaeger 1 (J1). Distance vision remained 20/20	1 discontinued due to ocular discomfort and burning, 4 discontinued due to preference for spectacles	Benozzi (8,9)
'Presbyeye drops' (unknown exact active ingredients; authors state combination of parasympathomimetic and NSAID)	15 eyes recruited in Sweden	Pupil size reduced from 4.1 mm to 2.7 mm ($p<0.001$). Statistically significant improvements in UCVA for near and distance; improved depth of focus reported	Transient nausea and ocular discomfort	Patel, Salamun (10)
Diclofenac 0.006% to 0.12%, Pilocarpine 0.2% to 0.4% and Sodium hyaluronate 0.1% to 0.9% intravitreal insert	N/A	N/A	N/A	Feinbaum, Patel, Salamun (11)
'PresbiDrops' (unknown exact active ingredients; authors state combination of parasympathomimetic and NSAID)	81 patients; 10 pseudophakic, 4 with cataracts, 10 post LASIK; 57 eyes without opacity	1 mm reduction in pupil size associated with a 0.9 D increase in depth of field. Effects lasted up to 14 hours. Near and distant VA also 'significantly improve.' Post LASIK patients maintained 20/20 distant UCVA	25% patients with 4 cases each of nausea, headache, dryness or burning, stinging, blurry vision. All these dissipated within 5 minutes	Feinbaum, FEPASAET group (12)
Muscarinic agonist and α-agonist or a COX-2 selective NSAID	N/A	N/A	N/A; adverse effect sparing effect of the COX-1 enzyme remains to be elucidated	Abad (13)
Pilocarpine 1%, Bromfenac 0.0018%	N/A	N/A	N/A	Carrera (14)

Table 2. Summary of results for muscarinic agonists and NSAID combinations. NSAID, non-steroidal anti-inflammatory; UCVA, mean uncorrected visual acuity.

diameter being offset by an improvement in contrast sensitivity and the elimination of stray light (27). However, this effect remains poorly understood: the amount of light entering is decreased, so presumably retinal adaptation is also occurring. This latter formulation perhaps has shown the most promise for patients given that it has progressed through various stages of regulatory approval. Indeed, a Phase II US clinical trial has been completed but (at the time of writing this article) is still unpublished (28).

The mydriatic, tropicamide, has the opposite effect of aceclidine. Its use can appear counterintuitive, but a closer look at its pharmacology reveals why it may have been chosen. A study by German et al., (26) found that tropicamide displays a much higher affinity for iris M_3 receptors (as opposed to ciliary M_3 receptors) compared with other anti-muscarinic agents. What this allows is pupil dilation with minimal influence upon accommodation. This predilection for the iris may reduce the sphincter pupillae spasm with the minimal undesired antagonism of ciliary contraction, which is required for accommodation. In addition, its small effect on the ciliary muscle may explain why no brow or headache has been reported. The effect is well recognized and is exploited in the use of cyclopentolate, another muscarinic antagonist, to reduce aching pain caused by ciliary and iris spasm in corneal abrasion.

4. AGN-199201 and AGN-190584

AGN-199201 (presumed to be oxymetazoline, an α-sympathomimetic agent [29]) and AGN-190584 (a currently unknown agent) are two compounds, used together, currently under investigation by Allergan. The first of two Phase II clinical trials has been completed – and some results have been published (30). A second has been registered but, at the time of writing, patient recruitment has yet to begin (31). Oxymetazoline's α-adrenergic action causes vasoconstriction, which is exploited for its use as a nasal decongestant and ocular anti-hyperemia agent. Its use is often restricted to several days due to rebound nasal congestion – an effect seen even with ocular use.

However, α-receptor agonism in the eye acts on the iris dilator muscles to produce mydriasis – which is undesirable when you're trying to treat presbyopia, as it decreases the depth of focus. It may be that AGN-199201 is only being included to attenuate an adverse effect caused by AGN-190584, such as hyperemia, or to allow AGN-190584 to remain in the eye longer and slow systemic absorption; it may even induce synergy.

Allergan recruited 65 participants in a trial with the above mentioned agents (30), the results of which are summarized in Table 4. Combining AGN-190584 with oxymetazoline did not appear to negate the formers' adverse effects. But the

Active agents	*Patients*	*Outcomes*	*Adverse effects*	*Authors/Patent*
Carbachol 2.25%/3% and brimonidine 0.2%	Masked placebo study of 12 patients using non-dominant eye only	Carbachol 2.25% and 3% alone group mean improvement was 6.3J; 3% had longer duration of action. Brimonidine 0.2% with carbachol (strength not stated) mean improvement 6.3J but had the longest duration of effect (up to 8 hours)	Ocular discomfort was seen in 10 to 30% of all patients, including in the placebo group; 90% of patients stated they would use the drops if available	Kaufman (17–19)
Pilocarpine 1% and brimonidine 0.2%	Masked placebo study of 12 patients using non-dominant eye only	In pilocarpine 1% alone mean UNVA improved by 2.3J lines. Pilocarpine 1% with brimonidine 0.2% resulted in a mean improvement of 3J lines	As above	Kaufman (17–19)
Carbachol 2.25% and brimonidine 0.2%	Double blind placebo trial on non-dominant 48 emmetropic and presbyopic eyes. All had 20/20 UDVA and no ocular pathology	Acuity tested at various time points for distance and near vision. Significant improvement in UNVA ($p<0.0001$). No loss of effect was observed over a three month period. The control group received only placebo drops	Dull headache in 10% of patients and one person reported difficulty seeing in dim light for the first couple of weeks. Mild ocular burning was reported in all groups but most frequently in the carbachol group	Abdelkader (20)
Pilocarpine and phenylephrine (PE) (unknown strengths) 'PresbV drops'	20 patients, 9 emmetropes and 11 prior LASIK. Observed for 30 days	UNVA improved by about 2 to 3 mean Jaeger lines in each eye and binocularly by 2J. Mean distant UCVA worse for the first hour and then improved by average of 1 line in each eye	No adverse effects reported. Tear film quality/quantity, endothelial cell count, intraocular pressure (IOP) and contrast sensitivity unaffected	Vejarano (21, 22)

Table 3. Summary of results for muscarinic agonists with sympathetic agonists. UCVA, mean uncorrected visual acuity.

combination from Allergan has clearly shown some promise and are pursuing it in a second Phase II study.

5. Sympathetic antagonist with muscarinic agonist

It is possible that a muscarinic agonist and an α-sympathetic antagonist agent could act synergistically to allow miosis; not only would that assist in increasing pseudoaccommodation but would also reduce ciliary body spasm (because of a reduced muscarinic dose and possible opposing effects of the drugs at the ciliary muscle) and its putatively associated adverse effects, such as brow ache. The decrease in pupil size is the mechanism to increase the depth of focus and hence improve UNVA. It is a combination of drug classes that has been proposed by Anant Sharma in two formulations: pilocarpine with dapiprazole and pilocarpine with thymoxamine (33).

Thymoxamine is a competitive post-junctional α_1-antagonist that has been investigated for the discernment between angle-closure and open-angle glaucoma, and to reverse phenylephrine-induced pupil dilation. As sympathetic innervation has very little influence on the ciliary muscle (although opposite to muscarinic agonism), thymoxamine allows the size of the pupil to be affected without significantly affecting the ciliary muscle. The half-life is about 10 hours which is much longer than that of pilocarpine, which is about 1 hour (34). Susan Small and her colleagues showed back in 1976 that after 90 minutes, mean reduction in pupil size with thymoxamine was 1.6 mm with a 1 D increase in accommodation (35).

The other proposed sympathetic antagonist, dapiprazole, has been studied for reversal of pharmacologically induced mydriasis and shares thymoxamine's mechanism of action. When Wilcox (36) used dapiprazole 0.5%, the greatest increase in accommodation was gained with two drops as opposed to one drop. Notably, brown eyes were slower in their reversal of mydriasis.

β-blockers, such as timolol, are another class of sympathetic

Active agents	*Patients*	*Outcomes*	*Adverse effects*	*Authors/Patent*
PRX-100 (aceclidine and tropicamide)	Castillejos et al. (27,28) study in Mexico. Recruited 9 subjects, mean age of 51.3 years	Investigated at undisclosed concentrations. Drops achieve rapid pupillary constriction to a stable diameter of 1.6 mm, lasting approximately 8 hours in a majority of participants. UNVA was in the range of Jaeger 1 to Jaeger 1+. Distance acuity improved without glare or halos, as did vision at night	Participants did not report brow ache or reduction in distance acuity. The only adverse effects reported were conjunctival injection and stinging	Horn, Nordan Presbyopia Therapies (32)
AGN-199201 (presumed to be oxymetazoline) with AGN-190584	65 participants. Mean age of patients was 49.2 years	Percentage of participants with at least a 2 line improvement from baseline UNVA 70.6% (AGN-190584 alone), 68.8% when both agents were used in both eyes and only 46.7% in AGN-199201 alone group	No serious adverse. Eyelid retraction in 26% oxymetazoline alone users, none in the combined group. AGN-190584 group had 1 case each of blurred vision, hyperemia, increased lacrimation and eye irritation	Abad (13)

Table 4. Summary of results for PRX-100 and AGN-199201 with AGN-190584.

agents that could be used. The iris and, to a lesser extent, the ciliary muscle also have β-adrenergic receptors, which when antagonized cause contraction, miosis and an increase in accommodation. However, timolol's use may be limited as it can cause significant systemic adverse effects. Despite the drawbacks, Neufeld patented a preparation consisting of a β-blockers only (37), but no trials evaluating its effect on presbyopia have been performed.

Direct lens manipulation: softening

As noted earlier, perhaps the most significant hampering of accommodation occurs due to lens stiffening, which is caused by the crystalline protein's sulfhydryl groups undergoing oxidation to disulfides as the human lens ages (38).

Topically administered ester derivatives of lipoic acid have been investigated as lens softening agents. In fact, the choline ester of lipoid acid (LACE) was patented (as EV06) by Encore Vision for this purpose (39). LACE is a prodrug; it penetrates the cornea where it is quickly metabolized into choline and lipoic acid. Enzymes within the lens fiber cells chemically reduce the lipoic acid to dihydrolipoic acid, which is thought to reduce the disulfide bonds in the lens, restoring the lens' "softness" – and, hopefully, natural accommodation.

Encore Vision announced some (as yet) unpublished results from their Phase I/II randomized, double-masked, multicenter study, which examines the safety and efficacy of EV06/LACE 1.5% (compared with placebo) in 75 patients aged 45–55 years, over a 90 day period for the treatment of presbyopia and the primary endpoint of BDCNVA. In the EV06 group, mean change from baseline was a 0.191 LogMAR improvement and 0.095 LogMAR with placebo. The drops were "well tolerated and not associated with any significant adverse effects" (40). The group still needs to ascertain dosing frequency in a Phase III study. Initial results are encouraging and perhaps underline that lens stiffening plays a prominent part in the etiology of presbyopia – and this may explain Novartis' announcement at the end of 2016 that they are to acquire Encore Vision (41).

"There are only two approaches: generating a small pupil size, and lens softening."

Are we nearly there yet?

Pharmacological presbyopia therapy continues to evolve – but it hasn't matured to a point where widespread adoption is on the horizon. Although there are data available on the

various formulations mentioned in this article, they are often from unpublished studies and/or only available through news articles. The lack of peer-reviewed information – and a general absence of large-scale studies with robust data – makes appraisal of this approach to presbyopia therapy frustrating.

It appears that there are only two approaches to the pharmacological treatment of presbyopia: generating a small pupil size, and lens softening. Any intervention that takes the first approach has to tick a number of boxes to be successful: it must be long-acting, produce significant miosis, have minimal or no myopic shift and be relatively side-effect free. To achieve this, it seems that the active ingredients must not only act synergistically but also allay any shortcomings (or side effects) of their counterparts; the combination of a muscarinic agonist and sympathetic antagonist appears to best create this synergy.

We all know that we can increase the depth of focus by reducing aperture. Even monocular pharmacologic treatment with a single miotic agent has been shown to result in acceptable reading vision for many presbyopes, even in older recipients. And this same increase in the depth of defocus may improve distance vision in low hyperopes. It is also important to consider whether there would be an effect from other potential variables; for example, different colored irides and different ethnicities.

Perhaps the most exciting formulations remain the lens softeners, which address presbyopia at a fundamental (and potentially longer-lasting) level. Although this is a much newer approach than the pharmacological induction of small aperture optics, safe and effective lens softening holds immense promise as a presbyopia intervention. Even if the accommodative outcomes and implications are currently difficult to predict, it's still exciting times for topical 'presbyopic' treatments.

Shafi Balal is a trainee doctor in North Central Thames London Deanery, UK. Raquel Gil-Cazorla is a clinical and research optometrist at Aston University, Birmingham, UK. Shehzad Naroo is a Reader at Aston University, UK. Anant Sharma is a consultant ophthalmic surgeon at Moorfields Eye hospital, Bedford, UK. Sunil Shah is a consultant ophthalmologist at the Birmingham and Midland Eye Centre, Birmingham, UK.

Declaration

Shafi Balal declares no conflict of interest. Shehzad Naroo has been awarded a research grant to investigate lens softening using femtosecond laser and a research grant to investigate scleral surgery to help presbyopia and grants to investigate intraocular lenses for presbyopic patients. Anant Sharma is an intellectual property (IP) holder of related technologies and products. Sunil Shah is a shareholder in company holding IP for presbyopia related technologies and products.

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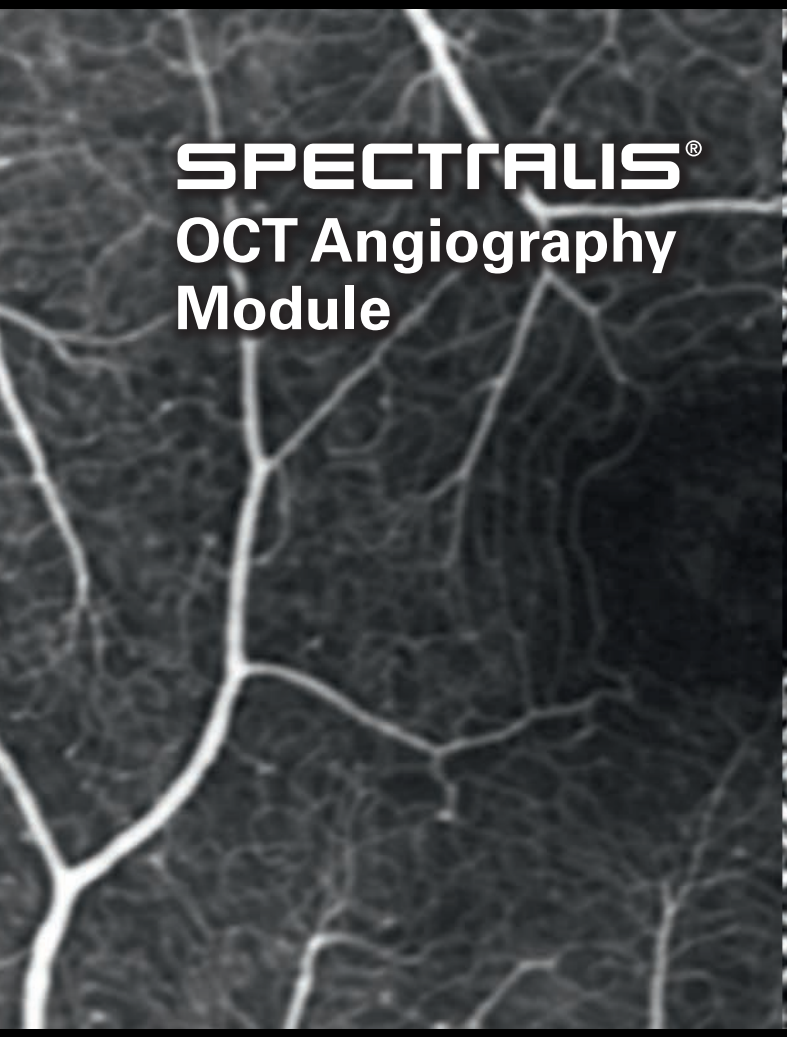

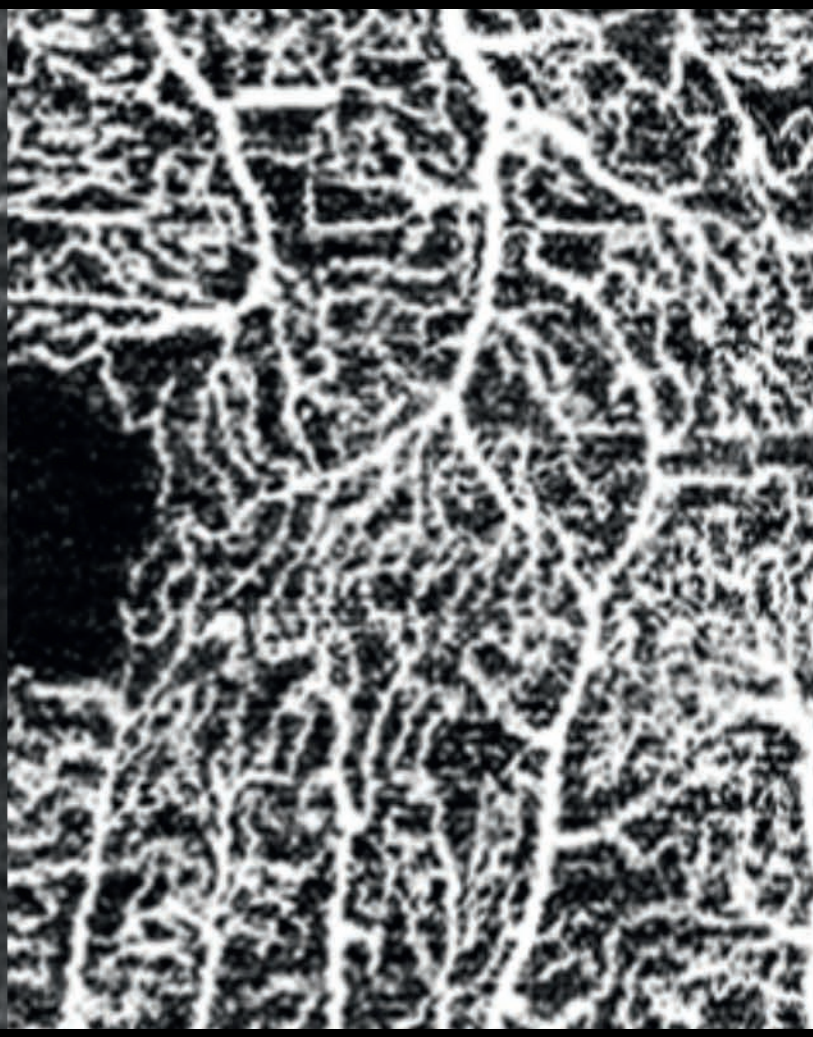

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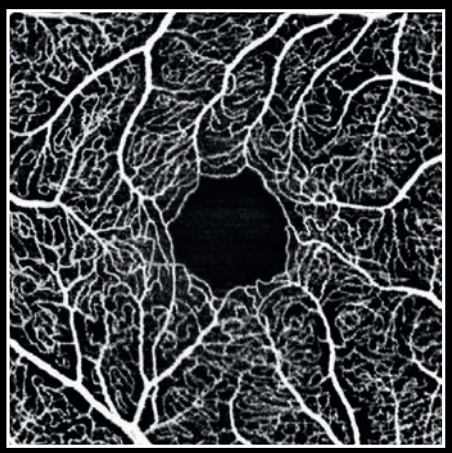

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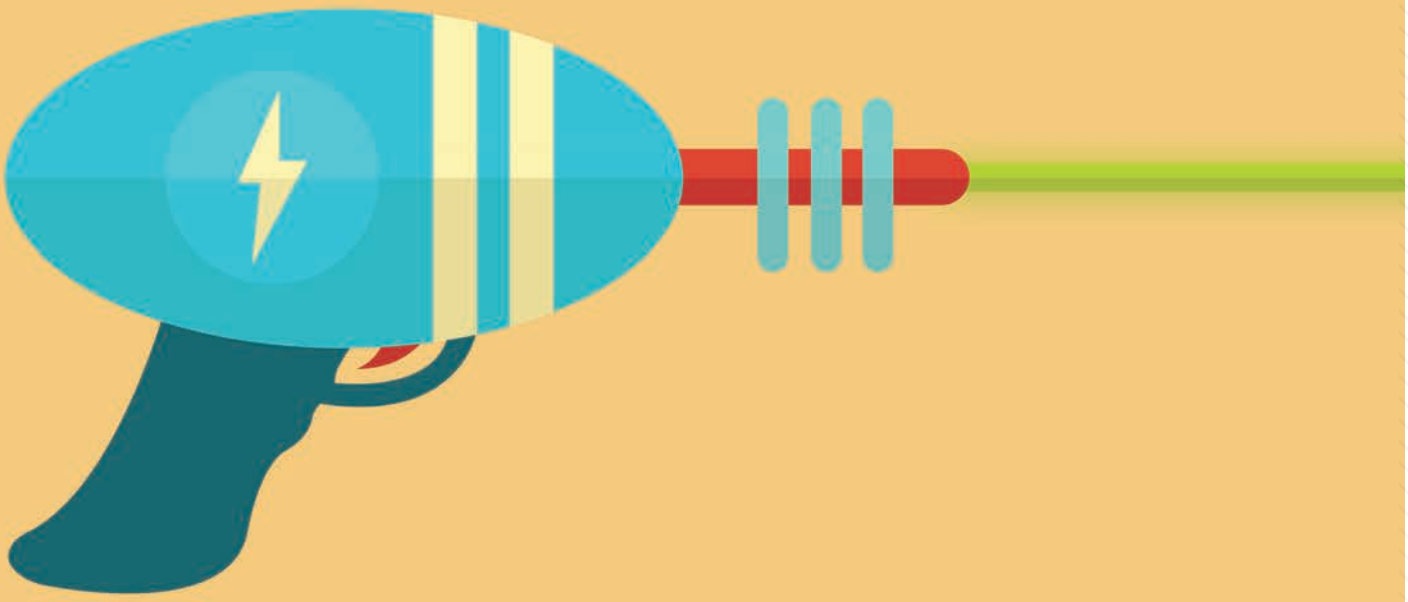

The Laser Quest for a Happy Medium

In glaucoma, medical management is plagued with noncompliance, and filtration surgery can be complex and risky. Could laser-based treatments offer a happy medium?

Few people under your care are "model patients." Almost everyone misses a dose now and then, and it's understandable. People have busy lives to lead, and some things get forgotten. The problem is, glaucoma is a progressive disease. Missed doses soon add up to progression, and unless the disease has been caught by screening measures (perhaps because of a family history), it's likely that the disease is first diagnosed at a relatively advanced stage (and age) – as that's when people start noticing vision loss. So this renders a predominantly elderly population, some of whom might be forgetful, with stiff fingers, and who need to take a considerable number of other medications to take each day (in addition to their eyedrops) just to get by – yet they are at a critical stage of their disease, where any progression equals vision loss.

Compared with only a decade ago, there are considerably more treatment options available today for glaucoma specialists to choose from. There's no longer the simple dichotomy of eyedrops and filtration surgery: there's a number of laser and micro-incisional, minimally invasive approaches that can be taken today – the challenge is to determine which approach is most suited to your patient. We asked two glaucoma surgeons to discuss the laser-based treatments that they offer, in order to understand which patients are most suitable for their procedure of choice: Dan Lindfield discusses his use of selective laser trabeculoplasty (SLT) in the clinic, and Noa Geffen reviews 5 year results of using the CO_2-based CLASS laser.

At a Glance

- *Topical glaucoma therapy is usually very effective at lowering IOP – so long as the patient follows the regimen, and self-administers the drops correctly.*
- *Even though eyedrop use can be associated with adverse events which reduce patients' quality of life, filtration surgery is still viewed by some as risky, and an "option of last resort"*
- *Is there a happy medium? An approach that lowers IOP and reduces patients' reliance on drops without requiring invasive surgery?*
- *Two glaucoma specialists review two laser-based techniques occupying the middle ground between drops and penetrating incisional techniques: SLT and CLASS*

A User's Guide to SLT

What benefits can SLT offer, and which patients are eligible?

By Dan Lindfield

I don't believe in waiting to offer surgical intervention. It's clear that any intervention that achieves IOP control early in the disease process translates to better outcomes, so I routinely offer non-pharmacological interventions to my patients. I find that by treating early, less visual loss has occurred, and the target IOP is easier to reach – and I find that very often, this is achievable using SLT, rather than traditional filtration surgery. SLT use is not without risk (cases of transient anterior chamber inflammation, mild uveitis and cystoid macular edema have been reported), but the risks are infrequent, manageable, and are all front-loaded. This contrasts with the daily instillation of topical therapy – in fact, I think you could argue that overall, SLT has the superior risk profile.

When SLT was first introduced, there were concerns about its duration of action and its repeatability, and this stopped many glaucoma specialists from adopting the technology. But research continued, the technology advanced, and most of the issues previously identified with SLT have now been addressed. Indeed, using SLT as a primary treatment for ocular hypertension (OHT) and glaucoma was previously controversial but recent data has questioned this (1), and results from the forthcoming LiGHT (Laser in Glaucoma and Ocular Hypertension) study that's comparing SLT versus drops as first-line treatment for OHT/Glaucoma should help further clarify SLT's role in glaucoma management (2).

My patient population

I mainly use SLT to improve IOP control for patients on medication(s) to prevent them needing further medication or surgery, and I also use SLT to reduce medication dependence for patients with controlled IOP. For patients using drops who have problems with compliance, memory, side effects (ocular or systemic) or allergies, SLT is a useful option to use in order to reduce the number of medications needed for IOP control. In this setting, SLT can prove a cost-effective

option, as the cost of an SLT procedure may be lower than the cost of monthly eyedrops. Indeed, patients are increasingly asking me about SLT as an alternative to using multiple eyedrops for precisely this reason.

SLT after cataract surgery?

The question of exactly how laser energy modulates trabecular function after trabeculoplasty is still debated. In my opinion, the effects of both cataract surgery and SLT can be attributed to a "trabecular meshwork modulation" process. In cataract surgery, the high volume of fluid flowing around the anterior chamber "washes out" trabecular debris, and a postoperative cytokine reaction is seen – this is similar to what happens in SLT. This means that performing SLT after cataract surgery is usually much less effective, as the outflow has already been improved. Anecdotally, three years or more post-phaco, I begin to see SLT become more effective again. I suspect that this is because, like SLT, the effect of the phaco-related trabecular modulation persists for two to three years before trabecular outflow resistance increases again. In practice, this means I usually reserve SLT for phakic patients, or those who have had cataract surgery over three years previously.

Champagne bubbles and pressure spikes

In my practice I use the OptoYag & SLT M (Optotek). Patients all receive written information about the procedure in advance. On arrival, they have their IOP checked for baseline, and pilocarpine 2% and apraclonidine 1% drops are instilled. I use a Latina gonio lens for this procedure and typically use an initial energy of 0.8 mJ, treating the inferior angle first, as it is usually the most open and the gonioscopic landmarks are clearest. I work up the power until I see what looks like fine champagne bubbles. If the bubbles are adherent or any changes on the trabecular meshwork surface persist, then I reduce the power. The power can be adjusted to the visible bubble response (in contrast to some clinicians who use a constant power throughout) – higher power is needed nasally and temporally than inferiorly and superiorly because of the changes in angle pigmentation.

I apply approximately 110 shots to each eye and usually treat the full 360 degrees. Immediately post procedure, I apply another drop of apraclonidine 1% and prescribe a topical NSAID (four times daily for five days). A spike in IOP is seen in approximately 3 percent of patients, so IOP should be checked 60 minutes after the procedure. If an IOP spike does occur, then use acetazolamide to control it. In patients with advanced field loss or heavily pigmented angles, I also use acetazolamide prophylactically 30 minutes before the procedure, to reduce the risk of a transient pressure rise. I routinely review patients after 6 weeks to assess the effect of treatment, or after 48 hours if a spike has occurred. In patients who have had the procedure with the aim of reducing topical medication, I ask them to stop using their drops one week prior to the review appointment, in order to more accurately determine the outcome of the treatment.

It is also advisable to warn patients that the average duration of SLT is two to two-and-a-half years, but the effects have been known to persist for up to five. However, since the procedure can be repeated, a customized schedule can be developed for individual patients – this usually involves retreatment every couple of years.

Getting started

I have performed over 90 cases in my first six months with an SLT laser, which I believe to be a significant demand for the procedure. In this time, I have had three non-responders and two pressure spikes, both of which settled within 90 minutes with acetazolamide and normalized by 48 hours. Indeed, in my patients, I have found that IOP reduction from SLT outperforms prostaglandin monotherapy. It is of course clear that this cohort are self-selected to be poor responders since they required SLT, as they are likely to have poor compliance or poor tolerance for topical therapy, but this biased data is a useful consideration for real life practice.

There is always some anxiety when first offering a new procedure to your patients. However, SLT is relatively easy to learn and combines two skills that glaucoma surgeons will be very familiar with – gonioscopy, and laser skills that are similar to Nd:YAG capsulotomy. Patient selection is key: always ensure that the angle is easily visible and there are no peripheral anterior synechiae. SLT requires gonio lens contact for approximately 5 minutes per eye so it is vital to select patients who will tolerate gonioscopy comfortably. Patients with tremor, or those who have difficulty with positioning make treatment more challenging, and hence are best avoided until the surgeon is very comfortable with the procedure.

These challenges aside, I have found SLT to be a useful and cost-effective alternative to medical therapy in my practice, helping me to control patient IOP, and in some cases reduce the need for eyedrops.

Dan Lindfield is a consultant ophthalmic surgeon at Optegra, and glaucoma lead at Royal Surrey County Hospital, England, UK.

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A Long Term Look at CLASS

The 5-year trial results are in. How safe and effective is the CLASS procedure?

By Noa Geffen

CO_2 Laser-Assisted Sclerectomy Surgery (CLASS) is an outpatient procedure that provides significant IOP-lowering efficacy with a safety profile similar to those of manual non-penetrating deep sclerectomy. CLASS is performed through a standard, manually created superficial scleral flap, followed by repeated ablations of the scleral tissue at a depth of approximately 30 µm in a predefined pattern (see Box: The CLASS procedure). This exposes Schlemm's canal, and facilitates aqueous fluid outflow through the remaining thin trabeculodescemet membrane. Prior to unroofing Schlemm's canal, the CO_2 laser is used to create a reservoir inside the scleral flap window which is intended to reduce the final bleb size and to increase the secondary (subchoroidal) aqueous humor absorption pathway. This means that the bleb created is much less elevated than what trabeculectomy or tube shunt surgery achieves, and helps to mitigate against some of the bleb-related complications associated with trabeculectomy.

It's worth reviewing how CLASS works. It uses a CO_2 laser, which is extremely effective at ablating dry tissue. But the laser energy is also highly absorbed by water and aqueous solutions, which in effect creates a self-regulating mechanism: once the aqueous humor starts to percolate from the remaining thin membrane, it absorbs the laser energy and prevents it penetrating to deeper layers – which explains why the procedure is non-penetrating.

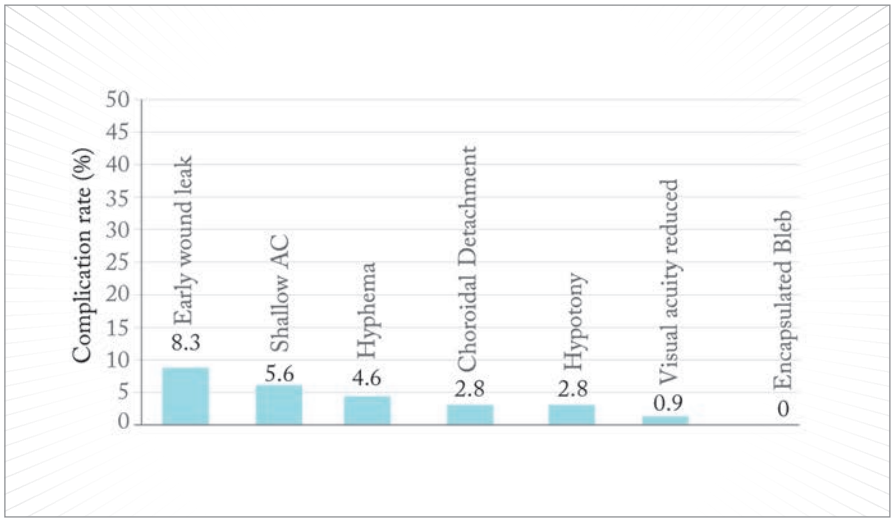

Figure 1. Complication rates in a 5-year clinical trial of CLASS. Other complications included iris incarcerations (8.3%), peripheral anterior synechiae (5.6%), transient superficial clerato keratitis (3.8%), macular edema (0.9%), and perforation by laser (4.6%). AC, anterior chamber.

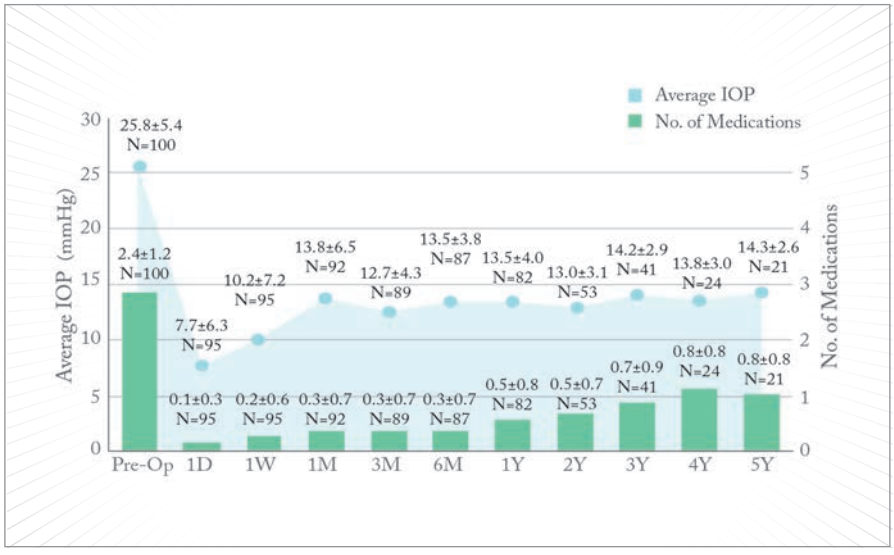

Figure 2. CLASS' efficacy over 5 years of follow-up (1). P<0.008 using Bonferroni correction for multiple comparisons.

Looking at the long term…

A five-year clinical trial of the long-term effects of CLASS has recently been presented (1). It was a prospective, multicenter trial that involved 111 patients with primary open angle or pseudoexfoliative glaucoma and who had baseline IOPs of over 18 mmHg. Of the 111 patients, 11 were excluded from the efficacy analysis: five because of protocol deviations and six because the operator failed to manually create an adequate scleral flap.

At the conclusion of the study, the CLASS procedure was shown to be relatively safe with few complications (Figure 1), and was successful in lowering IOP and reducing the average number

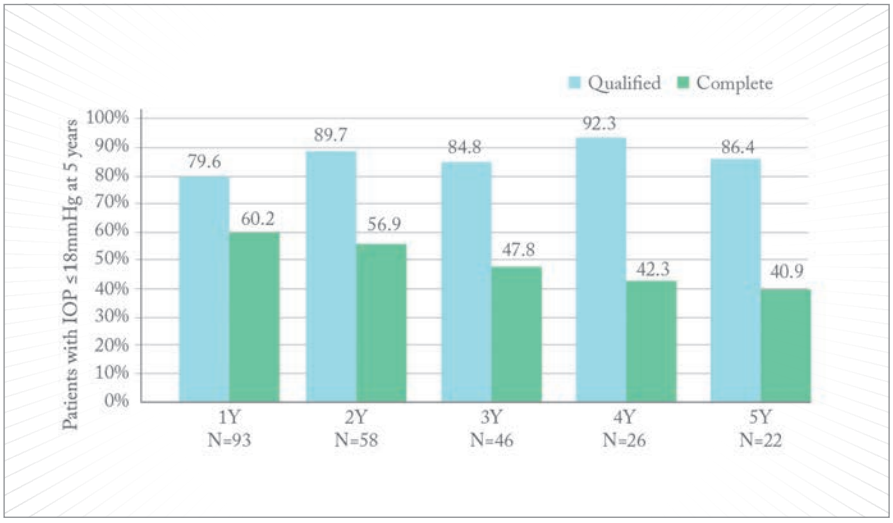

Figure 3. CLASS procedure's success rate (IOP ≤18 mmHg at 5 years) (1).

of medications in the vast majority of patients (Figures 2 and 3). There were no intraoperative safety issues noted, and postoperatively, complications were mostly mild and transitory with no sequelae. So far, there have not been any cases of endophthalmitis or blebitis. Scarring at the incision site was reported, although not unexpected; because ablation takes place below the limbus, corneal scarring near the limbus is also possible. Compared with what might be expected after the standard filtration procedures, bleb-related complications (i.e., vascular blebs and late leakage) were virtually nonexistent, and in general, blebs were diffuse with posterior location.

… and at the limitations

The single-arm nature of this study limited the ability to judge the outcomes in comparison to incisional procedures, but previous studies have suggested that CLASS is similar to trabeculectomy in terms of efficacy, and to manual non-penetrating deep sclerectomy in terms of safety (2). During the first year, the trial was prospective, but after the first year, treating surgeons were given latitude to use their own follow up protocols. This potentially introduced several confounding factors that might complicate analysis of the data. However, the IOP curves from each treatment center were almost identical at the end of five years, which appears to indicate a high degree of predictability and reproducibility. Although patients with treatment-naïve glaucoma (in terms of surgery) were studied in the trial, we do not believe that prior treatment should be a contraindication to performing CLASS. I believe CLASS is therefore a viable, effective and non-penetrating alternative to trabeculectomy in patients with glaucoma.

Noa Geffen is an ophthalmologist at the Department of Ophthalmology, Meir Medical Center, Kfar Saba, and the Ein-Tal Eye Center, Tel Aviv, Israel.

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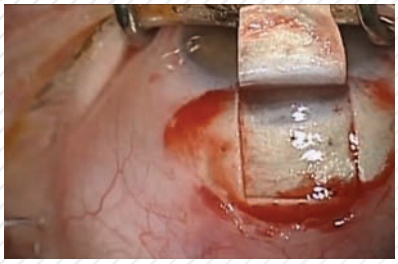
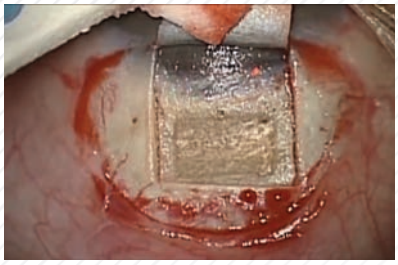
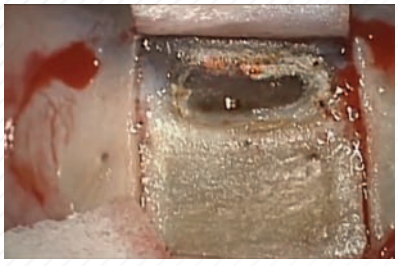
The CLASS procedure.



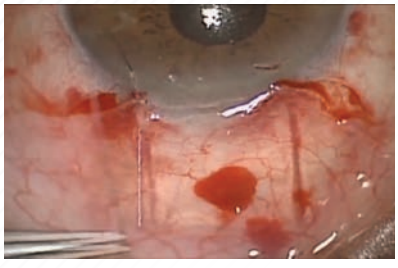
Step 1. Peritomy and superficial scleral flap dissection extending to the clear cornea.



Step 2. A 90% deep scleral reservoir is created by laser ablation at the bottom of the flap.



Step 3. Laser ablation aimed at Schlemm's canal until percolation is achieved throughout the treatment area.



Step 4. Scleral flap and conjunctiva suturing.

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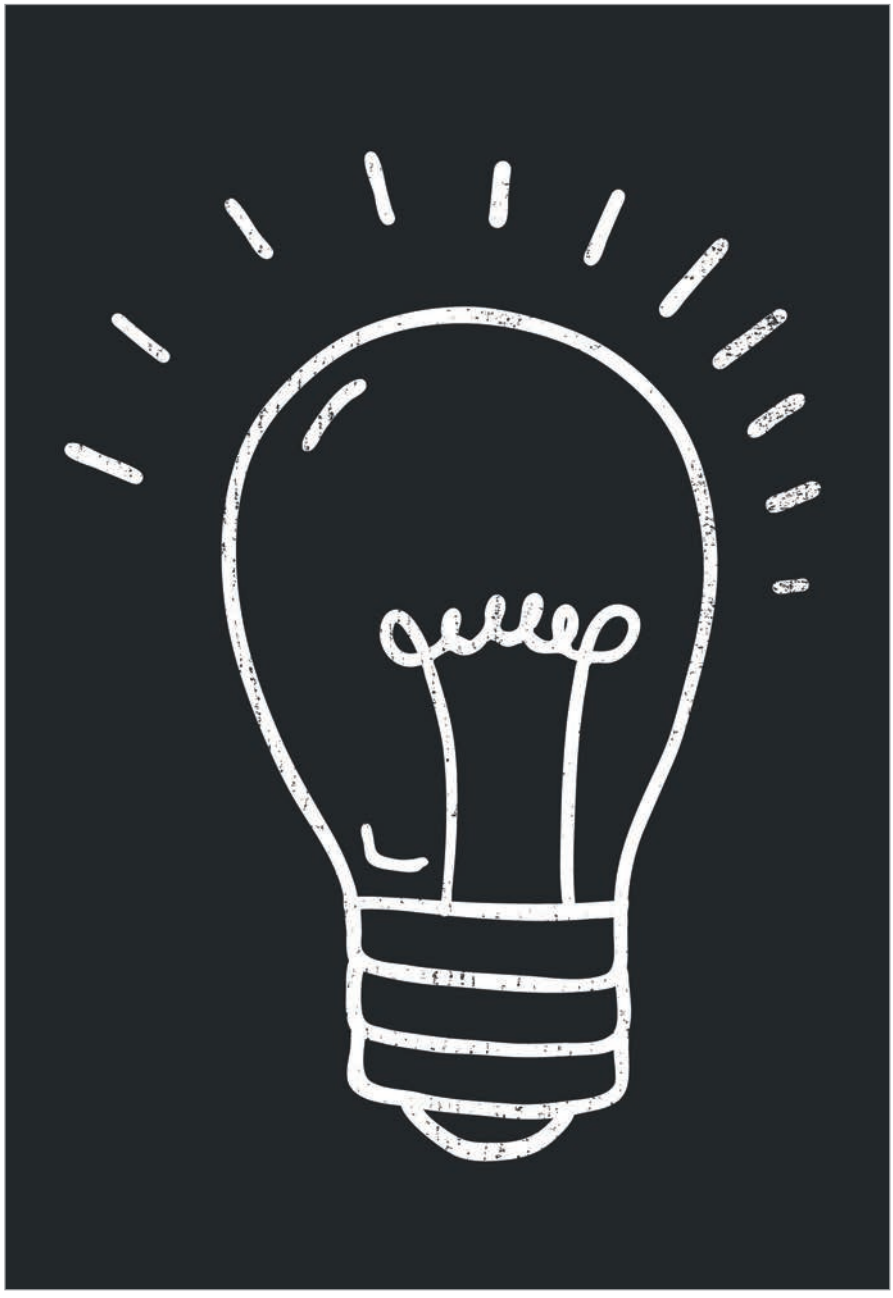
A New Approach to Motion That Might Cause Commotion

Might we have hit on the right method to achieve true accommodation?

By Paul Beer



When it comes to cataract surgery, I have a different perspective on the procedure: I'm a retinal surgeon. When I see an IOL in the capsular bag, it's months or years after it was implanted and it's no longer the elastic item cataract surgeons interact with. Instead, I usually see something that's encased in a rigid and fibrosed disc. The lens is, effectively, straight-jacketed, so any chance of ciliary muscle-induced accommodation is long gone. I always thought that this was a shame – and the observation stuck with me. Might this be something that a simple solution could fix?

I discussed this with a friend who, at the time was an IP attorney, but who had been a nuclear physicist and ophthalmologist in prior careers, who connected me the head of the College of Nanoscale Science and Engineering institute at SUNY Poly in Albany, New York, in order to start a brain trust for innovation. We started to bounce around some ideas; he thought we should develop some advanced technology like a retinal prosthesis, but I suggested something simpler, a mechanical device like an accommodating IOL. Surely if

At a Glance

- *Most cataract surgeons usually see an elastic capsular bag during a cataract procedure – retinal surgeons see a stiff, fibrosed bag months to years later*
- *The fibrosed bag, sectioned appropriately, can actually help the right IOL vault forwards and backwards in response to ciliary muscle tension*
- *Primate studies suggest that this approach results in IOL accommodation–disaccommodation similar to that of the crystalline lens*
- *Getting an accommodative IOL right has the potential to be transformative, if only we can achieve true accommodation*

we could get the design right, this might be a solution. The meeting didn't go anywhere back then, but it didn't stop me from wondering how this issue of rigidity might be overcome, and indeed what role other factors might play – nanofibers, materials, the capsular bag, elasticity and accommodation, and ultimately, zonular capture haptics.

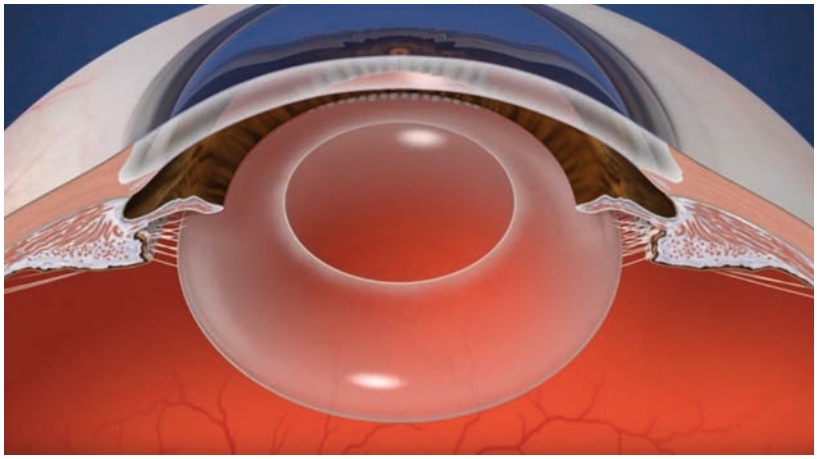
"Embracing the fibrosis further, we could utilize it to attach zonules to the individually mobile haptics like Velcro."

The birth of a concept

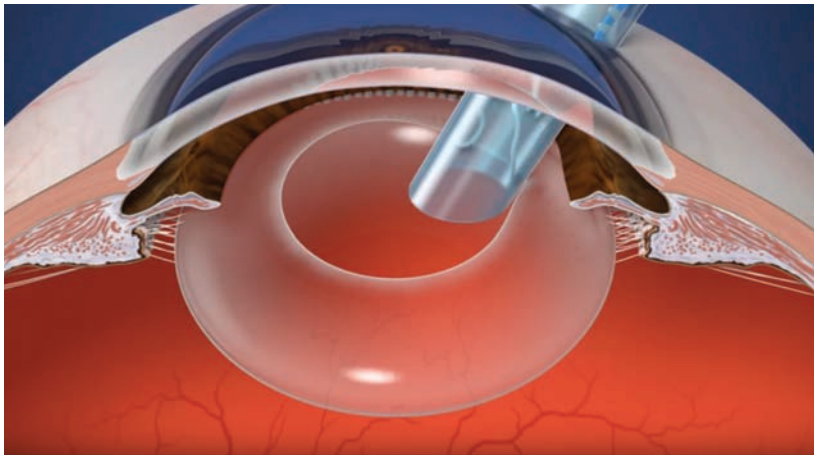
My thinking was this. The fibrosed capsular bag restricts movement. But if it was cut into sections (with radial capsulotomies), then each section is able separate from the others during disaccommodation. When the ciliary muscles contract and relax, this should mean that the IOL (with appropriate, flexible haptics) could vault forwards and backwards, respectively. Embracing the fibrosis further, we could utilize it to attach zonules to the individually mobile haptics like Velcro. And so the zonular capture haptics concept – and idea of how to design an IOL that could utilize it – was born.

I drew my concept and had it notarized, and then almost forgot about it. But two years later, I decided to pursue it. As this was not my field at all, I went to

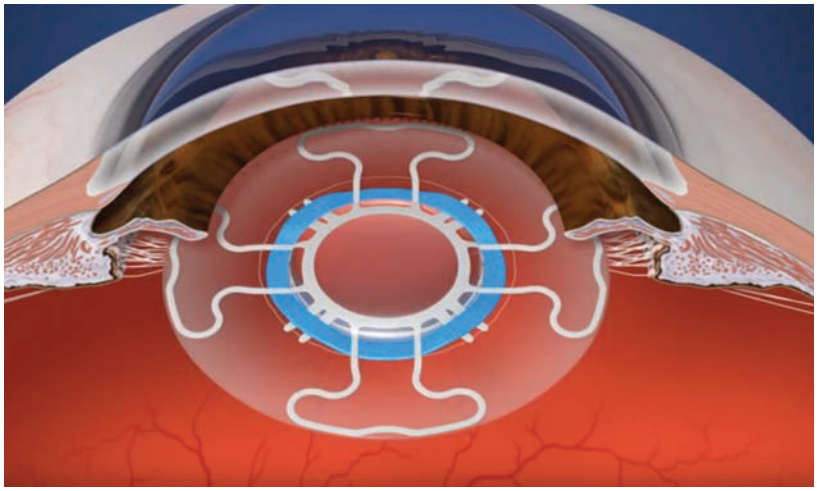
Box: The Z Lens IOL implantation and activation steps



Step 1. The cataract is removed using standard phacoemulsification techniques.

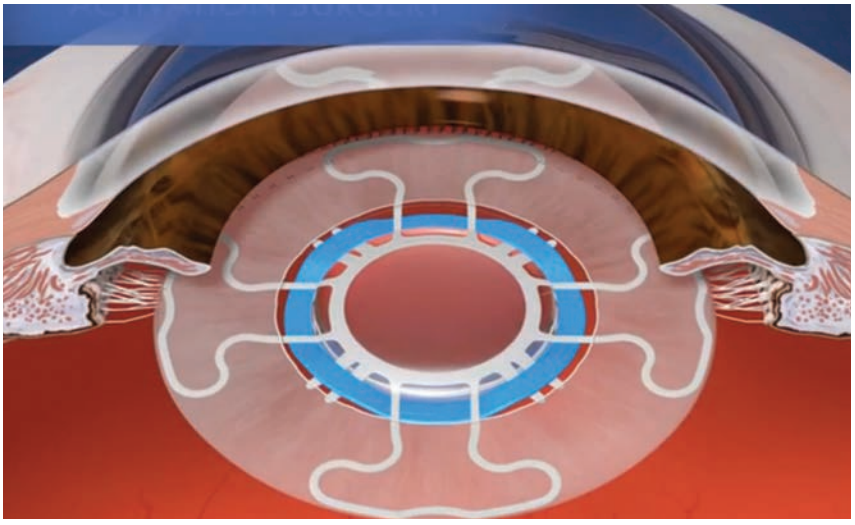


Step 2. The (folded) Z Lens IOL is inserted and introduced into the capsular bag.

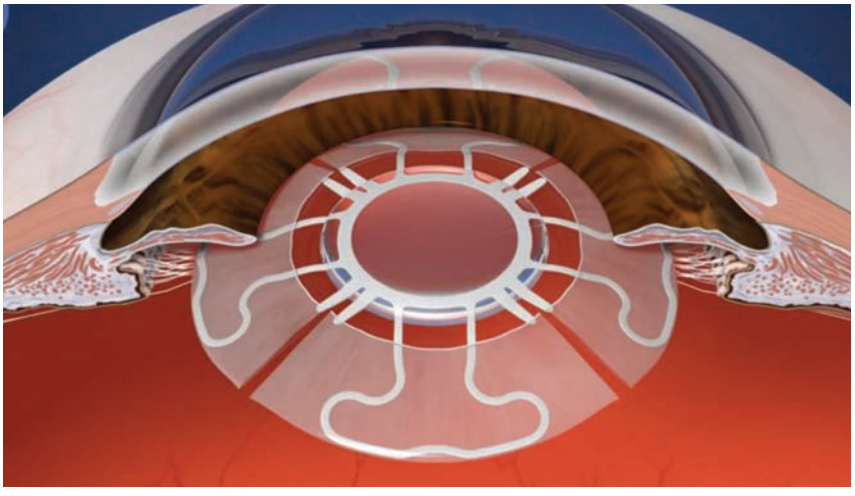


Step 3. The Z Lens IOL occupies the empty capsular bag and with the restraining device (blue) in place. It (initially) functions like a monofocal IOL.

Box: The Z Lens IOL implantation and activation steps (continued)



Step 4. A few weeks later, the capsular bag has fibrosed and hardened.



Step 5. A femtosecond or Nd:YAG laser is used to non-invasively remove the restraining device and perform the radial capsulotomy incisions.

an ISOP meeting in Barcelona in 2009 to hear what the presbyopia and cataract specialists were working on. None voiced similar ideas to mine – so this made me confident that my idea was unique. I came back home and filed a preliminary patent application with a friend of the family who was a patent attorney. My daughter helped make a conceptual animation for me in college and my son, who was a professional artist, made illustrations. I then contacted Alcon and presented my concepts to them. The company liked my idea and encouraged me to get back in touch when I had some results.

An idea only gets you so far

It was then when I realized that just having a good idea is absolutely not enough. So Z Lens LLC was incorporated, and then things really got moving...

I visited Paul Kaufman and Mary Ann Croft in Madison, Wisconsin, as they are leaders of one of the best presbyopia research groups in the US. I presented my idea to them and proposed a proof-of-principle study. They were intrigued, so much so that they were interested in doing an animal study. I paid for the first animal study out of my own pocket. We implanted a handmade ring haptic structure that I made from surgical Prolene in two primate eyes, let the capsular bag fibrose, whereupon they sectioned it and measured changes in the haptic upon accommodation. The handmade haptic dilated and constricted almost 1:1 with the ciliary body, for over a year after implantation (see Box "Proving the Point").

"I paid for the first animal study out of my own pocket."

But I didn't have unlimited funds and primate studies are extremely expensive, so I inquired about government grants. During this time, I was introduced to the serial entrepreneur, Ted Eveleth, who became my partner, and has been the financial arm of Z Lens LLC ever since. Ted was an experienced grant writer – among many other things – and he helped secure all of the grants that allowed us to get as far as we have without any stock dilution. We recruited advisors: Tom McNicholas and Tom Dunlap (who have reputations that precede them), and the designer of our IOLs Rob Stupplebeen, a former Bausch + Lomb engineer. Dave Dudzinski, an incredible engineer at the Learner Research Institute at the Cleveland Clinic made all of our recent prototypes. They've all been huge assets to our company.

"The Z Lens mimics the movement of the natural lens by flattening out during disaccommodation and bolting forward during accommodation."

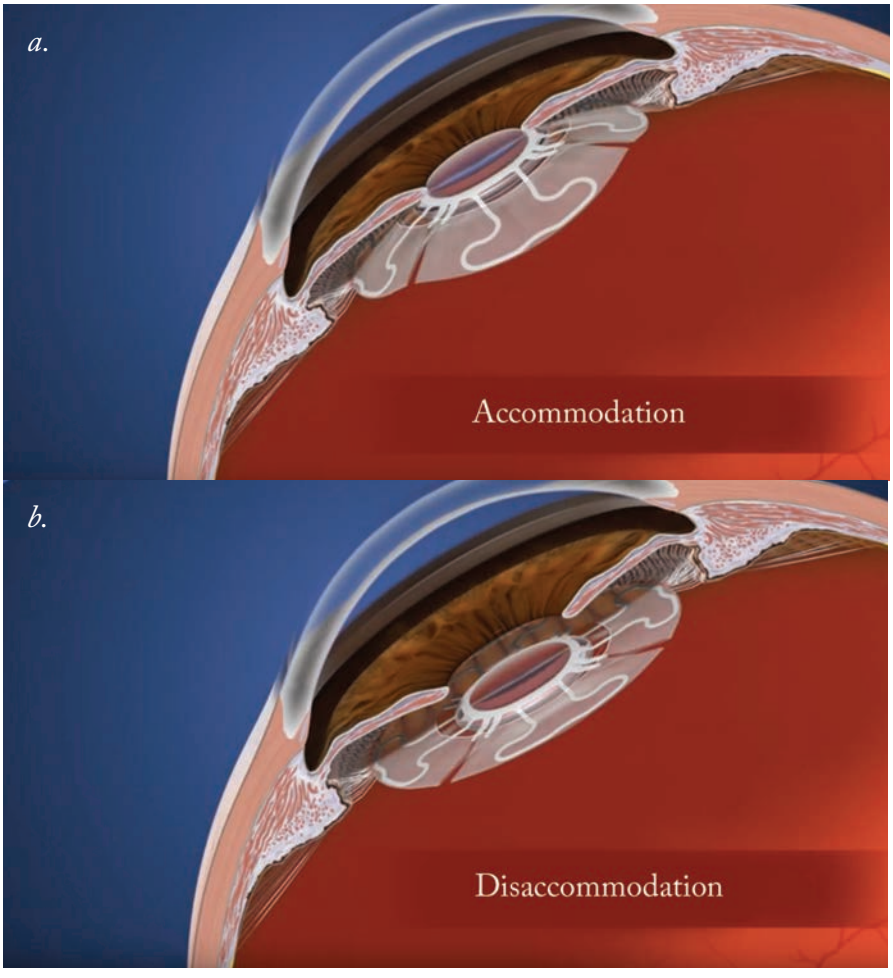


Figure 1. The Z Lens IOL vaulted forwards under accommodation (a), and flattened backwards during disaccommodation (b), entirely controlled by the ciliary muscles.

Fine-tuning the process

We've now refined the process (see Box: The Z Lens IOL implantation and activation steps): after capsulorhexis and phacoemulsification, the Z Lens is placed into the empty capsular bag – with a restraining device that holds it in a flat configuration. The surgery is then completed following normal procedures, then we wait. The lens acts like a traditional monofocal lens... but after a few weeks, the capsular bag becomes stiff and prevents movement. To restore movement, we activate the Z Lens by cutting the capsular bag in between the haptics and releasing the restraining device – and this can be done non-invasively with a YAG or femtosecond laser. The radial capsulotomies (also made with the laser) enable the bag to move once again in response to ciliary muscle movement – and with it, the Z Lens. In other words, the Z Lens now mimics the movement of the natural lens by flattening out during disaccommodation and bolting forward during accommodation (Figure 1).

We've now completed the animal work with our first-generation Z Lens IOL (see Box "Proving the Point"). We have more than a year's worth of data in nine animal eyes: an accommodating-disaccommodating IOL with a single rigid optic that would meet FDA label requirements, and is ready for resizing for human eyes.

One more thing. The crystalline lens doesn't just move backwards and forwards during accommodation and disaccommodation: it changes shape too. We now have a dual mode IOL in development that adds a shape-shifting optic to provide more accommodation, and in silico projections suggest it's capable of an accommodation range of 10 to 14 D, and we expect to be testing prototypes in primates very soon.

The accommodative IOL market is potentially worth $0.5 billion, and this will only increase – if we can offer true accommodation. With the work that we've completed so far and what we have in the pipeline, it's something that we hope to show in the not too distant future…

In addition to being the inventor of the Z Lens IOL, Paul Beer is a Professor of Ophthalmology at Albany Medical College, has received multiple teaching awards, merit awards from the AAO, ASRS, and was appointed the principal investigator for 25 multicenter clinical trials and conducted multiple investigator-sponsored trials.

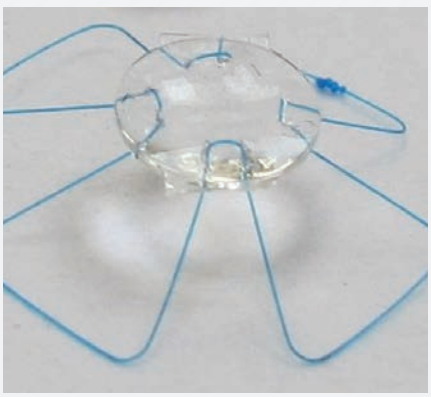
Proving the Point

A Proof of Principle, Unoptimized Z Lens IOL Prototype

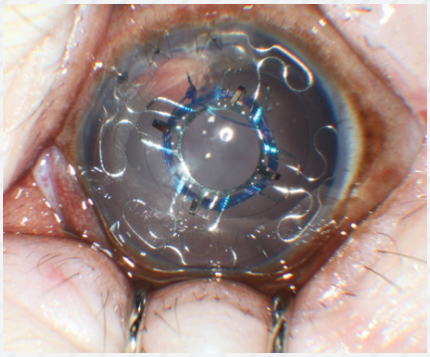
One of our early animal experiments involved implanting a "proof of principle" prototype of the Z Lens IOL concept into two Rhesus monkey eyes. This was a simple, un-optimized IOL with a "borrowed" 5 mm optic and Prolene haptics.

After waiting three weeks we sectioned the fused capsular bag. Two weeks after that, we performed ultrasound biomicroscopy (UBM) and plano perfusion lens and OCT imaging. Each time, we induced pharmacological accommodation via corneal iontophoresis of 40% carbachol in agar – a supramaximal dose for inducing accommodation.

What we found was that the pharmacological stimulation of accommodation yielded an average maximum accommodation of 4 D, which exceeded expectations, and both animals reached maximum accommodation by 10 minutes after carbachol administration. We observed a rapid return to near-baseline refractions after only 20 minutes.



Unoptimized Z lens IOL prototype



In vivo zonular capture haptic dynamometer

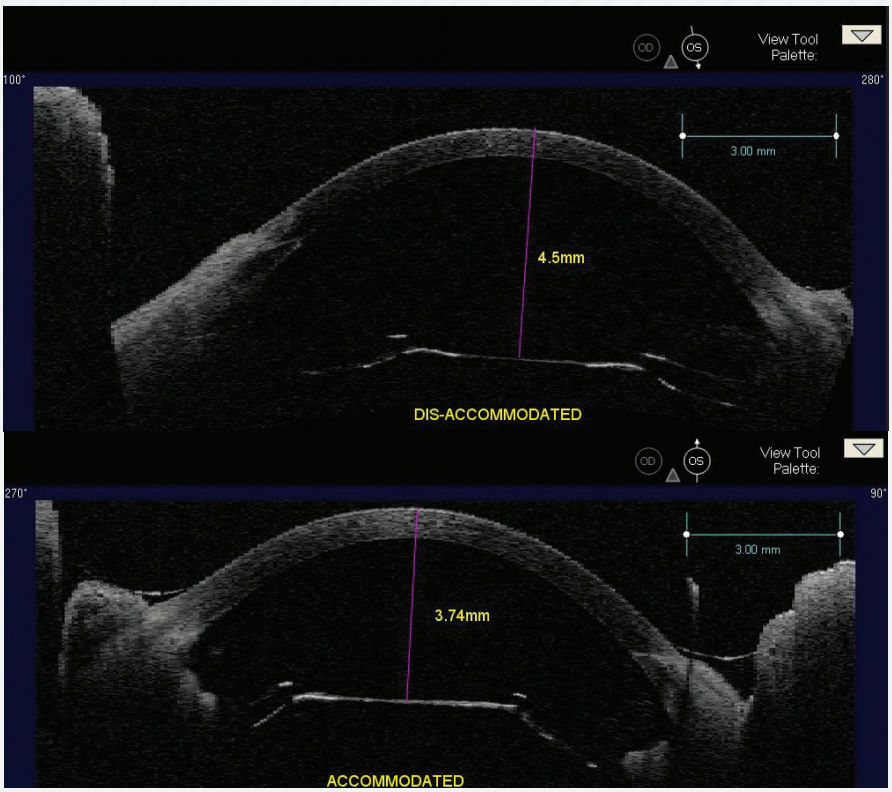
The in vivo Zonular Capture Haptic Dynamometer

Prolene is not an appropriate haptic material for a dynamic IOL. We designed and built a haptic structure from a super elastic, shape memory alloy that could cycle between accommodated to disaccommodated shape over millions and millions of cycles without loss. We have repeated the experiment with this device and we used it as an intraocular, in vivo dynamometer.

The data from this dynamometer allowed us to measure the actual forces exerted by the eye in vivo, on a fibrosed, post-surgical capsular bag, and optimize the haptic structure force response curves.

The Optimized Zonular Capture Haptic

We then tested the optimized Zonular Capture Haptics. As you can see, it integrates perfectly with the fibrosed capsular bag and it produced an axial shift of 0.76 mm on OCT, as seen. When we used a physiologic level of accommodation, via stimulation of the mid brain Edinger-Westphal (EW) nucleus, this optimized structure

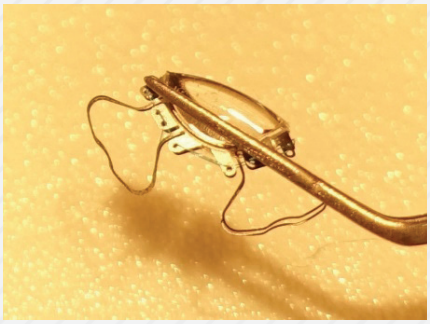


The optimized zonular capture haptic.

matched the movement dynamics of a young crystalline lens.

AD-IOL with Zonular Capture Haptics

The next experiment was to show that an integrated accommodating-disaccommodating (AD-) IOL, using the optimized haptic and custom made optic, could provide physiological levels of accommodative movement (in primates). Accommodation was achieved through either electrode stimulation of the EW midbrain nucleus or carbachol administration, and we assessed optic axial shift, haptic flexion, and refractive change by OCT, UBM, Scheimpflug imaging, and Hartinger objective refraction.



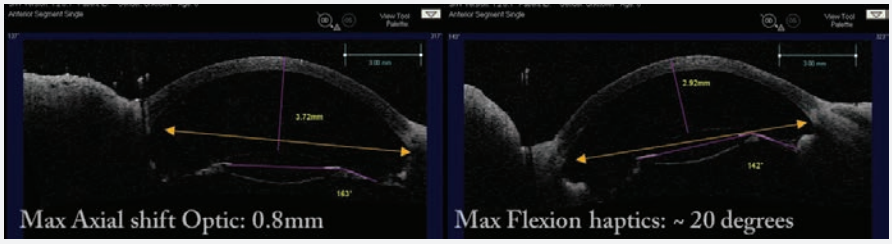
AD-IOL with zonular capture haptics

"We've shown physiological levels of accommodative movement in primates."

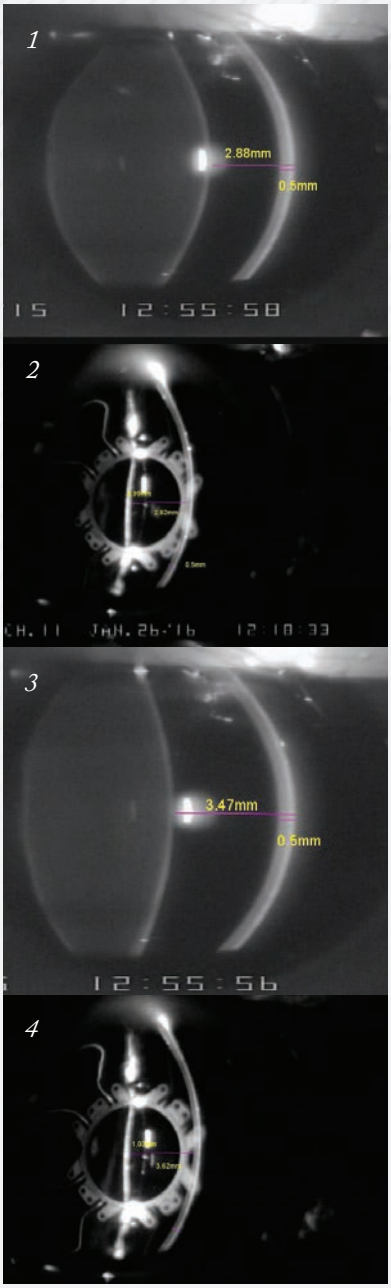
Here's what we found. When we compared the animal's crystalline lens in the same eye, using EW stimulation, before and after surgery, the crystalline anterior lens face shifted by 0.48 mm, and the anterior optic face by 0.47 mm (To view the Z Lens IOL undergoing EW-stimulation, visit: bit.ly/ZLensIOL).

In a different animal eye, seen to the right, the axial shift of the AD-IOL actually exceeded the axial shift of the crystalline lens.

One year after implantation, we found that we could produce a maximal axial shift in the optic of 0.8 mm and a maximal haptic flexion of 20°. Given that the biometrically predicted accommodation of the Z Lens IOL was 1 D per 1 mm of axial shift, we actually observed (using Hartinger objective refraction) a mean accommodation of ~2 D using electrode stimulation, and up to 4 D using carbachol – and this meets the FDA requirements for an accommodating IOL label.



One year post-implantation results. The biometrically predicted accommodation was 1 D/1 mm of axial shift; the observed accommodation was ~2 D/~0.5–0.8 mm (1–3 D EW, 4 D carbachol).



Physiologic level of accommodation via stimulation of an EW electrode, same eye before and after surgery: crystalline lens (panels 1–2) vs. Z Lens IOL (panels 3–4), accommodated (panels 1 and 3) disaccommodated (panels 2 and 4). Axial shift of the anterior crystalline lens face: 0.59 mm; axial shift in the anterior optic face: 0.80 mm.

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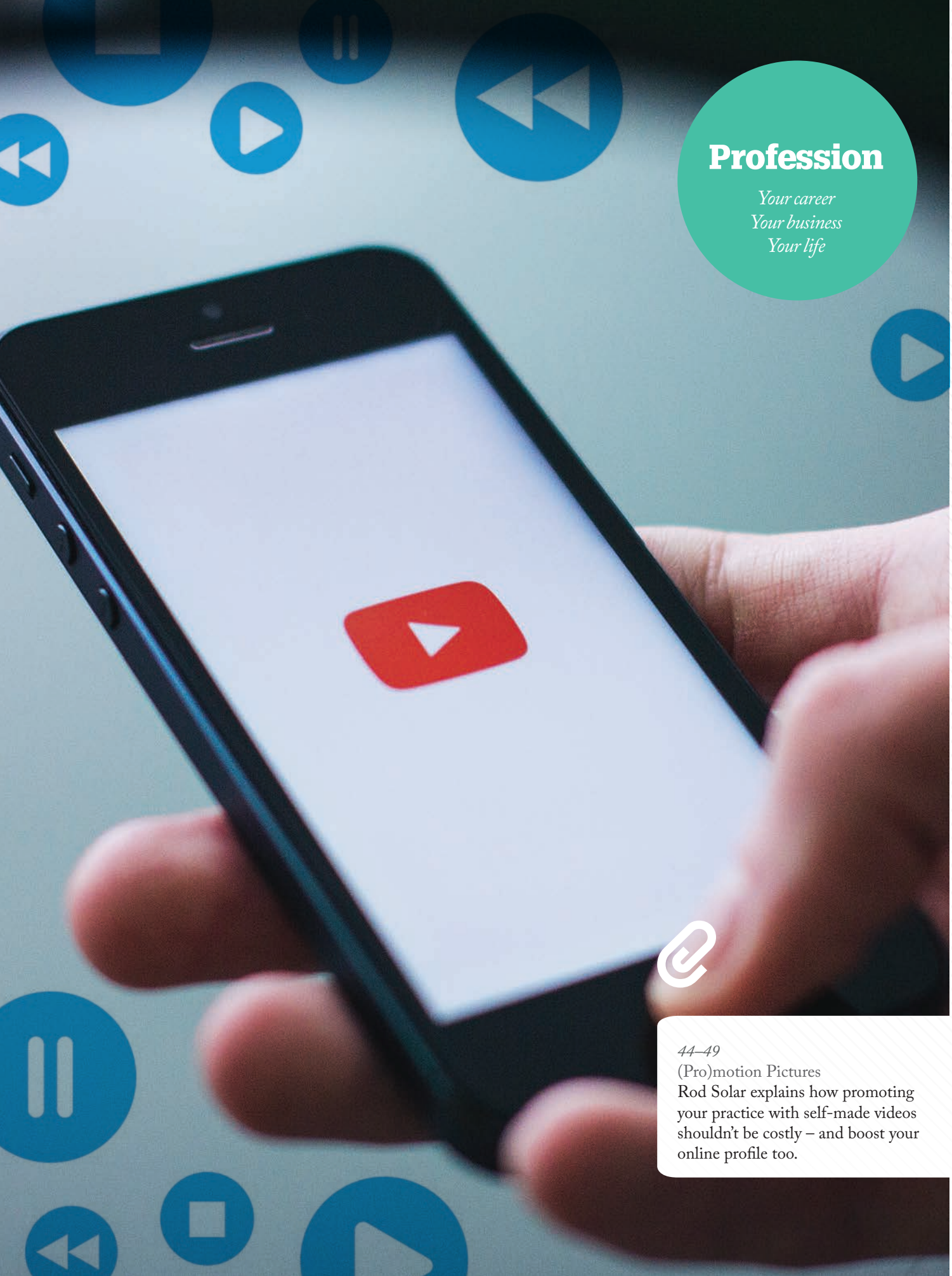


Profession

Your career
Your business
Your life

(Pro)motion Pictures

Producing your own videos isn't costly and could boost your profile online

By Rod Solar

Entrepreneur and public speaker Seth Godin once said "marketing is no longer about the stuff you make, but the stories you tell." In the digital age, one of the best mediums for telling our stories is video. Are you using it? If not, why not?

There's no denying that marketing has changed – the explosion of social media and self-generated content means we're seeing an appetite for something that feels authentic – something that Donald Trump has recently used very effectively. Gone are the days when people were solely interested in looking at a product, understanding its features and advantages and so on. Today, they're more interested in who you are. What's your story? What's the story behind this product or service? Anyone who's ever enjoyed a film or TV show can understand why video is an outstanding storytelling medium – so if you want to appeal to today's consumers, it's an invaluable way to promote yourself.

Ophthalmology is no exception – if you want to promote your practice and attract new patients, video can have a huge effect. Many practices are already online, with websites and a social media presence. But if you want to have the biggest impact, video could be the way to go. There are many ways you can use video, but there are also obstacles that can hold you back from trying (see "Barriers to Video"). Two of these – concerns about your brand, and about permanence, can be overcome by embracing video rather than fearing it. And as for the price – this isn't nearly the issue it was years ago.

"If you want to have the biggest impact, video could be the way to go."

At a Glance

- *Marketing has changed. Many consumers – and potential patients – would rather watch a video than read a website*
- *Pro-quality video production used to be expensive, but today, anyone with a good smartphone and some know-how can do a great job*
- *Creating amateur video and social media video streaming are two excellent ways of engaging and attracting potential clients into your practice*
- *Making and posting your own content may seem scary, but it's worth your while to embrace it – it's the future of marketing!*

Why Use Video?

Patient education
Many rather professional-looking videos are made for this purpose, with features such as animations to demonstrate how parts of the body work.

Profiles
These are typically the domain of large companies with very significant budgets – large corporations might spend thousands of dollars to get a big, high production value profile video done. Historically, these types of video have been out of the reach of most entrepreneurs and new businesses.

Service descriptions
Organizations may describe their services on video – either how things are done, or descriptions of the products they offer.

Testimonials
Patient testimonials are increasingly common – healthcare organizations ask patients to speak on video about their experiences.

Patient interviews
This is a more extended version of a testimonial, where someone interviews the patient about their experience. This can provide a little bit more depth than a testimonial, and can be an extremely useful exercise.

Case studies
Here, we follow the patient through the process involved in having a procedure. Many of these are quite heavily scripted – although this isn't always a negative point. They're prepared, they're polished, and they tell a story.

Frequently asked questions
These can be aimed at the patient, and relate to the questions they might ask, or can be used for internal training. If you have staff who are working in your clinic who aren't answering questions in the way you'd prefer, these videos can encourage them to use your words and methods when dealing with enquires.

Community engagement
This is where social media comes in to the mix – this type of video can engage patients or prospects with your brand, and help them understand a bit more about you and your background. More the domain of amateur video, whether

it's Facebook, Periscope, or any platform that allows you to create live video. The nice thing about these platforms is that they encourage real-time engagement and interaction from your audience. For example, a doctor could announce that they plan to hold a live Q&A at 8 o'clock on a Wednesday and answer any questions people pose to them about a particular subject area – that can be extremely engaging for your audience.

Webinars

This is a more formalized approach to community engagement that gives you a bit more control of the content. Often it will be in the form of a series of webinars, and also involves engaging with the community, who can communicate with you using the webinar software.

Counting the cost

The expense of producing video is all down to what you're making. There are three main levels: premium, professional, and amateur. Premium video is the type used by Hollywood – it's incredibly expensive, very high quality, and something you might use for a television advert. But it's overkill for everyday practice promotion. Why? It can cost between $20,000 and $50,000 for just a few minutes of film.

Next, there's professional video. The

benefits include the predictable, good quality: you know what it's going to look like before you pay for it. The risk is that it can be a little boring and self-centered – but it doesn't have to be! If you're careful about choosing the story the video follows, and keeping things as genuine as possible, it will be engaging. Don't just talk about yourself – talk directly to your audience, and try and empathize with your patients' needs. A few minutes of professional video could cost you $1,000 to $3,000, but if you're smart about how you plan and coordinate the filming, you can get the cost lowered.

Finally, there's amateur video; the footage you film yourself. It has a bit of a bad name, but it shouldn't – and it offers some great benefits. The risk is (of course) variable quality, which depends entirely on your own talent and the tools you use (see "Straight to Video"). That can be scary for people, but it's something you can overcome. You might not necessarily use this type of video for a business profile, or a service description, unless you're really confident you can deliver something close to professional. There is some practice involved, and you need to learn how to plan, film, produce, and upload video. However, it's well worth the effort.

The total cost of the kit I use (and you

Barriers to Video

"I'm protecting my brand"

This is a major reason why people hold back on producing video, even though they're happy to produce written or visual content. Video exposes you – you can't hide behind anything, and that can cause people to feel quite protective of the image that they have of themselves – and that's perfectly understandable.

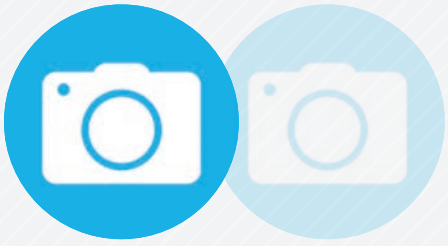
But here's the problem with that: you don't control your brand anymore. Today we have social media, review sites, comments, bloggers, vloggers, the list goes on – and this has completely changed the conversation. It's no longer a broadcasting model, where you talk to an audience about what you do. Now, the audience talks about you amongst themselves, and shares information, experiences and opinions with no input from you. Brands are elevated or demolished every day in the marketplace, and it's all done by the customer. If someone gets an impression of you, good or bad, they can share it. You can't control that, but you can definitely influence the process. So if people are going to be talking about you anyway, you might as well be part of the conversation. Don't sit outside – get in there and make your voice heard!

"I can't afford it"

In the past, you needed to spend a lot to get good quality video, but that's changed. Quality has increased, and cost has come down. Video is highly accessible now – which is good news for those of us who don't have an abundant budget.

"Once it's online, it's online forever"

Yes, once it's out there, it's extremely difficult to get rid of. So there's no easy answer for this. But it shouldn't stop you – just be confident that you're prepared; know what you want to say and how you're going to say it. And ultimately, if you're willing to say something to a patient, why shouldn't you be willing to say it to a bigger audience? You might make some mistakes, but the good news is that many, many people are making their own video now, which means audiences are a lot less judgmental about the type of mistakes you're likely to make.



"But I've got stage fright!"

It takes a lot of courage to get in front of a camera. But as an ophthalmologist, you walk into the OR every day and perform surgeries, some of which carry a lot of risks – and you don't seem to have much performance anxiety when it comes to that! With video, you just need a little practice. If you can create a video in which you feel confident, and look and sound as good as you can, you'll find it gets easier. And some people even end up finding it very enjoyable.

don't need everything – for example all of the tripods, or two lights or microphones), came to under $400 when I last priced it. That's incredibly affordable – even if you try it, and don't like it, it's not a big risk. So why not go for it?

Playing it straight

So we're ready to make a video. But what do people want to see? The answer, corny as it might sound, is: the real you. They want honesty. That means speaking off the cuff; talking from experience. You don't want to read rigidly from a script and pretend to be someone you're not. They also want honesty in patient testimonials – they want to hear the great, the good, and perhaps even the so-so. It doesn't all have to be perfect – although luckily, in ophthalmology there tend to be a lot of glowing testimonials.

People also want to get involved, and interact during live videos and webinars. They want the opportunity to comment and ask questions in real-time. This is where social media streaming options (such as Facebook Live and Periscope) can be invaluable.

In my opinion, consumers are changing (see "Video: Some Statistics"). They've become a lot more sophisticated, and they know nonsense when they see it. So if you're confident about your services and your practice, and feel good about what you do, there should be absolutely nothing in the way of you getting out there so that people can see that confidence in your eyes, and hear it in your voice. So why wait? Get filming and show them what you're all about.

Video: Some Statistics

Businesses using video grow company revenue 49% or faster year-on-year than organizations without video (1)

Video drives a ~157% increase in organic traffic from search engines (2)

70% of marketers now claim that video produces more conversions than any other type of content (3)

Social video generates ~1,200 more shares than text and images combined (1)

When text and video are both available on a webpage, 59% of senior executives prefer to watch the video instead of reading the text (4)

Video on a landing page can increase conversions by 80% or more (5)

74% of millennials find video helpful when comparison shopping, and 60% prefer to watch video over reading a newsletter (6)

Nearly two thirds of consumers (62%) are likely to have a negative perception of a brand that publishes poor quality video (7)

Rod Solar is the Director of Client Services with LiveseySolar (www.liveseysolar.com), and is responsible for delivering sales, customer service and communications training to LiveseySolar's clients.

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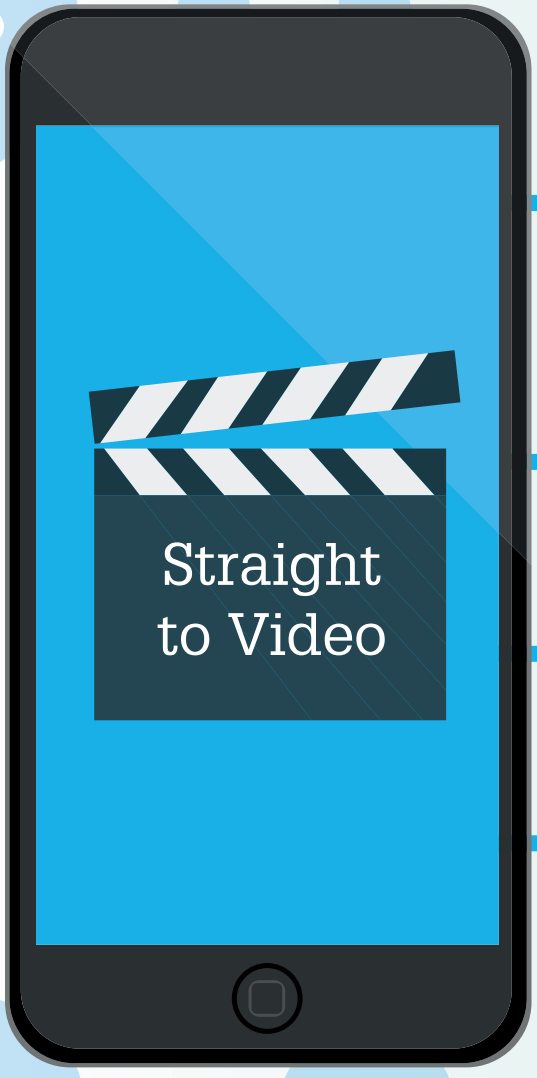


What you need

- Your smartphone's camera
- A tripod
- Good lighting
- A microphone
- Editing software
- A YouTube or Vimeo account

Why you need it	What I use
Many people don't know this, but you can get excellent quality video from your smartphone	A recent iPhone or premium Android smartphone, ideally with at least 16 or 32 GB of storage. Try and use the rear camera, as it's a far better lens and image sensor than the one on the front-facing camera. It can be tough to frame the show when you can't see the screen, but you can get a friend to help or use a screensharing app easily enough.
Holding your phone at arm's length is only okay for holiday selfies!	The JOBY GripTight GorillaPod (excellent for uneven surfaces). The Hama Star 62 Tripod (a standard lightweight tripod; very useful and inexpensive). iOgrapher cases (these are essentially two-handed stands). Great for video on the move or virtual tours. You can also put a microphone, lighting, or lenses on it – it's like a rig for your smartphone. A Bluetooth selfie stick (they can be a bit hit and miss, but they can be invaluable when you need to get that difficult angle or a wide shot).
This can't be underestimated. We only see what is lit, and if you're talking in the dark you'll turn people off	Newer CN 160 LED-based lamps, essentially power panels that are the size of a track pad. They need a battery that's rechargeable, but they can be held, sit on stands or be docked onto a camera's hot shoe flash attachment. They produce a nice, soft light, and they usually come with a couple of filters to warm the tone of light, if required.
A quality microphone is essential, as people are even more turned off by bad audio than they are by bad video	BOYA BY-M1 3.5 mm lavalier microphone. Made for smartphone use, they are high quality, and sound fantastic. I also use a Smays Extension Earphone 3-Pole 3.5 audio jack splitter, which lets me hook up two microphones into the same line for interviews.
This is how you put your videos together, and it doesn't need to be expensive	Apple iMovie. There's also Final Cut Pro, which is the kind of thing moviemakers use – but iMovie can meet your movie editing needs. It's simple to use, and it gets the job done, and there's even an iPhone and iPad app version of it.
You need somewhere to store the videos you make	I use a YouTube account chiefly for public videos, and Vimeo for more professional videos (such as training videos). This is because Vimeo offer some privacy and security features that you just don't get with YouTube. The number one thing you have to avoid is hosting video on your own website. Not only will it slow your website right down, you'll get people who are unable to access it at all. It will also cost you huge amounts of money, since video consumes a considerable amount of bandwidth – at considerable cost, if you're hosting it. Put videos you want to share on YouTube or Vimeo, then embed them on your website. Finally, buy some external hard drives and keep the video footage off your computer!

Family Man

Sitting Down With...
George O. Waring IV, Associate Professor of Ophthalmology and Director of Refractive Surgery, Medical University of South Carolina (MUSC) Storm Eye Institute, Medical Director, MUSC Magill Vision Center, and Adjunct Assistant Professor of Bioengineering, Clemson University, South Carolina, USA.

What excites you most about your work?

I work in a tertiary academic center where we are referred complex refractive and IOL patients who have had multiple surgeries, often after having sought multiple opinions. Rehabilitating these patients to improve their quality of life, often with a bioptic approach, is what excites me most about my work. Utilizing techniques and technologies on both lenses of the eye to rehabilitate and restore functionality of vision is what brings me the most satisfaction.

Being part of the development of new technology, and working to overcome the challenges, is a wonderful opportunity. In particular, being able to follow the process to the point where we actually see the benefits they bring to patients – sometimes first with implantations outside the United States pre-FDA approval, and then in our own patients after approval – is pleasing.

"To this day, my father is my role model for scientific excellence."

You studied economics and environmental science at Emory University – how has this influenced you?

In economics, cost-benefit analyses are a guiding principle, and I use these principles on a daily basis when looking at both cost- and also risk-benefit analyses. Every time we make a decision on how to advise a patient on their treatment choices, or on whether or not to perform surgery, we can use these principles to reason through our options in a logical fashion.

Environmental science utilizes the concept of "passive use" values – evaluating metrics such as quality of life, which are hard to assign a metric value to, but which are important in ophthalmology when we're considering things like patient satisfaction. My academic studies help me consider things from different angles, and to apply these principles to surgical decision making.

You were selected for the AAO's leadership development program in 2017. What do you hope to achieve in this role?

I want to help foster international growth and adoption of lens and cornea-based refractive surgery, and to spread awareness of the global health burden related to vision disorders like presbyopia. For example, if you look at the 2008 census data, there were around one billion presbyopes internationally. By the year 2020, that number will have doubled. Not only that, but around half of these existing presbyopes don't have access to reading glasses – something we take for granted in developed countries – leaving many of them unable to adequately perform their jobs. If we can raise awareness of the global burden and the social impact of presbyopia, we can find ways to help these patients.

What achievements are you most proud of?

My family.

We've just had our first son, George O. Waring V, and I would consider him my greatest achievement to date. My wife is my partner at work, and one of my most respected colleagues. So we have a very unique work-life balance and integration that brings us a tremendous amount of joy and satisfaction.

From a work perspective, I am fortunate to be able to aid in the research and development of a wide range of technologies, to help advance my field and my subspecialty in some way.

If you could go back in time and give yourself some advice, what would it be?

I'd tell myself to be patient, and to accept that every decision I made, whether it seemed like the correct one or not at the time, will eventually end up being a benefit in the long run. I think all too often we see young ophthalmologists hoping for results quickly – but progress takes years of hard work, dedication and focus (no pun intended), and there is no substitute for this.

I would also teach myself the 80/20 rule – that driving to consensus in personal and group decision making is more important in moving a process forward, even if the decision is not perfect. It's better to be 80 percent right and move forward, than to pursue 100 percent perfection and not move forward.

Who were your mentors, and how did they influence you?

I've been very fortunate to have many mentors and friends – more than I could list here. If I could mention three, the first would be my father. To this day, he is my role model for scientific excellence, by remaining objective and making good use of the scientific method and critical thinking. I am blessed to have Daniel Durrie as my mentor. It was just last night that I spent time with him and his family around a fire talking about my future – which is priceless.

Finally, Howard Fine was one of my first mentors, based on my father's recommendation. I'll always remember the conversations I had with him early on in my career. He would pull out crumpled pieces of paper with hand-sketched technologies, like the capsule refilling technology, and the first sketches of "the smart lens" over a decade and a half ago.

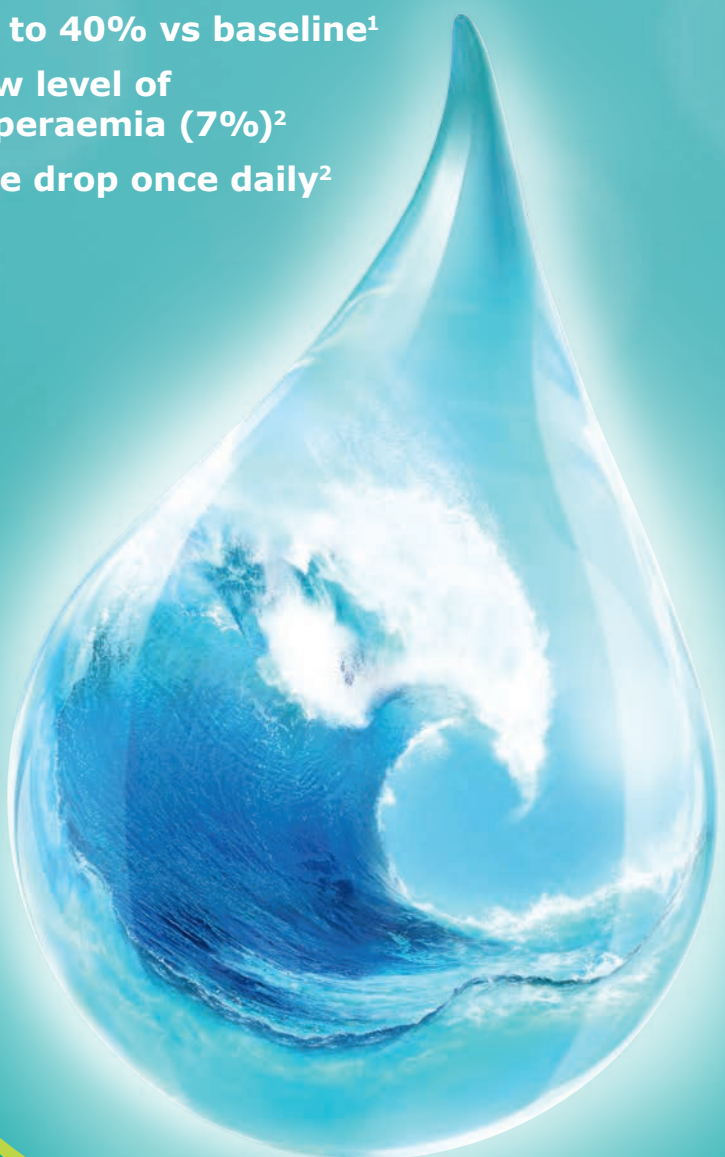
Being fortunate enough to have exposure to people like this, who are thinking decades in advance, and who cared enough to invest in my career, has greatly shaped my journey. I hope to be able to honor them by investing in the next generation in the same way.

TAPTIQOM®

(15µg/ml tafluprost + 5mg/ml timolol maleate eye drops)

THE NEXT STEP FOR POWERFUL IOP LOWERING

- **Up to 40% vs baseline[1]**
- **Low level of hyperaemia (7%)[2]**
- **One drop once daily[2]**



Santen

Product Name: TAPTIQOM® 15 micrograms/ml + 5 mg/ml eye drops, solution in single-dose container. **Composition:** One drop (about 30 µl) contains about 0.45 micrograms of taflupost and 0.15 mg of timolol. One single-dose container (0.3 ml) of eye drops contains 4.5 micrograms of taflupost and 1.5 mg of timolol. Please refer to the Summary of Product Characteristics (SmPC) for a full list of excipients. **Indication:** Reduction of intraocular pressure in adult patients with open angle glaucoma or ocular hypertension who are insufficientlyresponsive to topical monotherapy with beta-blockers or prostaglandin analogues and require a combination therapy, and who would benefitfrom preservative free eye drops. **Posology and method of administration:** Recommended dose is one drop in the conjunctival sac of the affected eye(s) once daily. Not to exceed one drop per day in the affected eye. Not recommended in children or adolescents (under the age of 18). In renal or hepatic impairment use with caution. To reduce systemic absorption, patients should be advised to use nasolacrimal occlusion or close the eyelids for 2 minutes after instillation. Excess solution should be wiped away to reduce the risk of darkening of eyelid skin. If more than one ophthalmic product is used, fiveminutes should separate their administration. Contact lenses should be removed before instillation. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. Reactive airway disease including bronchial asthma, or a history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, sick sinus syndrome, including sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker. Overt cardiac failure, cardiogenic shock. **Warnings and precautions**: Before initiating treatment, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation related to taflupost. These changes may be permanent, and lead to differences in appearance between the eyes if only one eye is treated. Similar cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-adrenergic blocking agents may occur. The incidence of systemic adverse reactions after topical ophthalmic administration is lower than with systemic administration. Caution should be exercised when prescribing TAPTIQOM® to patients with cardiac or severe peripheral vascular disorders eg Raynaud's disease or syndrome. Use with caution in patients with mild/moderate COPD and in patients subject to spontaneous hypoglycaemia or labile diabetes. Beta-blockers may mask signs of hyperthyroidism and block systemic beta-agonist effects such as those of adrenaline. Anaesthetists should be informed when a patient is receiving timolol. Patients with a history of severe anaphylactic reaction may be more reactive to repeated challenge with such allergens and be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions. The known effects of systemic beta blockers may be potentiated when TAPTIQOM® is given concomitantly. The use of two topical beta-blockers is not recommended. Patients with corneal disease should be treated with caution as ophthalmic beta-blockers may induce dry eyes. When timolol is used to reduce elevated intraocular pressure in angle-closure glaucoma, always use a miotic. Caution is recommended when using taflupost in aphakic patients, pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, and in patients with known risk factors for cystoid macular oedema or iritis/uveitis. Please see the SmPC for further information. **Interactions with other medicinal products:** Potential for hypotension / marked bradycardia when administered with oral calcium channel blockers, beta-adrenergic blockers, anti-arrhythmics, digitalis glycosides, parasympathomimetics and guanethedine. Please refer to the SmPC. **Pregnancy:** Do not use in women of childbearing age/potential unless adequate contraceptive measures are in place. **Breast-feeding:** It is not recommended to breast-feed if treatment with TAPTIQOM® is required. Driving and using machines: If transient blurred vision occurs on instillation, the patient should not drive or use machines until clear vision returns. **Undesirable effects:** Conjunctival/ocular hyperaemia occurred in approximately 7% of patients participating in clinical studies with TAPTIQOM®. Other common side effects include: eye pruritus, eye pain, change of eyelashes (increased length, thickness and number of lashes), eyelash discolouration, eye irritation, foreign body sensation, blurred vision, photophobia. Adverse reactions that have been seen with either of the active substances (taflupost or timolol) and may potentially occur also with TAPTIQOM® include: increased iris pigmentation, anterior chamber cells/flae, iritis/uveitis, deepening of eyelid sulcus, hypertrichosis of eyelid, exacerbation of asthma, dyspnea, allergy, angioedema, urticaria, anaphylaxis, hypoglycaemia, syncope, ptosis, bradycardia, chest pain, palpitations, oedema, cardiac arrest, heart block, AV block, cardiac failure. Please also see the SmPC. **Overdose:** Treatment should be symptomatic and supportive. **Special precautions for storage:** Store in a refrigerator (2°C - 8°C). After opening the foil pouch keep the single-dose containers in the original pouch and do not store above 25°C. Discard open single-dose containers with any remaining solution immediately after use. **Package quantities and price:** 30 x 0.3ml single-dose containers £14.50. **Marketing authorisation holder:** Santen Oy, Niittyhaankatu 20, 33720 Tampere, Finland. **Marketing authorisation number:** PA 0879/003/001. **Date of authorisation:** 28/11/2014. **Legal Category:** POM. **Prescribing information job code:** STN 0418 TAP 00001a Date of **prescribing information:** 14/04/2016.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Santen UK Limited (Email: medinfo@santen.co.uk or telephone: 0345 075 4863).

References:

1.Holló G et al. Fixed-Dose Combination of Tafluprost and Timolol in the Treatment of Open-Angle Glaucoma and Ocular Hypertension: Comparison with Other Fixed-Combination Products. Adv Ther. 2014; 31: 932-944

2.Taptiqom SPC, last changed October 2014

Job code: STN 0918 TAP 00038 Date of preparation: September 2016