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BCLA CLEAR presbyopia: Management with scleral techniques, lens softening, pharmaceutical and nutritional therapies

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ABSTRACT

The aging eye undergoes the same progressive crosslinking which occurs throughout the body, resulting in increased rigidity of ocular connective tissues including the lens and the sclera which impact ocular functions. This offers the potential for a scleral treatment that is based on restoring normal biomechanical movements. Laser Scleral Microporation is a laser therapy that evaporates fractional areas of crosslinked tissues in the sclera, reducing ocular rigidity over critical anatomical zones of the accommodation apparatus, restoring the natural dynamic range of focus of the eye.

Although controversial and challenged, an alternative theory for presbyopia is Schachar's theory that suggests a reduction in the space between the ciliary processes and the crystalline lens. Widening of this space with expansion bands has been shown to aid near vision in people with presbyopia, a technique that has been used in the past but seems to be obsolete now.

The use of drugs has been used in the treatment of presbyopia, either to cause pupil miosis to increase depth of focus, or an alteration in refractive error (to induce myopia in one eye to create monovision). Drugs and laser ablation of the crystalline lens have been used with the aim of softening the hardened lens. Poor nutrition and excess exposure to ultraviolet light have been implicated in the onset of presbyopia. Dietary nutritional supplements, lifestyle changes have also been shown to improve accommodation and the question arises whether these could be harnessed in a treatment for presbyopia as well.

1. Overall purpose

Presbyopia has been defined by the BCLA CLEAR Presbyopia as the physiologically normal age-related reduction in the eye's focusing range when it reaches a point that, when optimally corrected for far vision, the clarity of vision at near is insufficient to satisfy the individual's requirement [1]. The eye's focusing ability is regulated by the accommodation of the eye and the mechanisms to describe accommodation and accommodation biomechanics are detailed in the BCLA CLEAR Presbyopia paper on this topic [2]. Helmholtz's theory and clinical data suggests hardening of the crystalline lens, however hardening also occurs in the sclera, therefore, the sclera has been implicated in the eye's loss of accommodation, as it suffers from the natural aging process just as the lens incurs enlargement and hardening. The techniques to manage presbyopia discussed in this paper, such as Laser Scleral Microporation, lens softening with a laser and pharmaceutical drugs to soften the lens,

Abbreviations: BMCC, Bruch's Membrane-Choroid Complex; DRoF, Dynamic Range of Focus; DCNVA, Distant Corrected Near Visual Acuity; Er:YAG, Erbium-doped Yttrium Aluminium Garnet; FDA, Food Drug Administration.

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all respect the classic Helmholtz theory of the development of presbyopia. Other pharmaceutical drugs discussed also follow accepted theories, such as drugs causing a myopic shift or pupil miosis to increase depth of focus. One technique in this paper relies on a different mechanism for presbyopia, namely Schachar's theory [2], which suggests crystalline lens growth and a reduction in the space between the ciliary processes and the lens equator being the main cause of presbyopia and an increase in this space being able to treat presbyopia. The BCLA CLEAR Presbyopia paper on epidemiology suggests that poor nutrition may play a part in the onset of presbyopia [3], so here nutritional impact on presbyopia is addressed.

2. Crosslinking and biomechanical stiffness

Collagen is the major extracellular matrix protein and one of the most abundant proteins in the human body. Individual collagen molecules are formed as a triple helix of protein strands [4]. Collagen molecules are then covalently bound together by crosslinks to form collagen fibrils and fibres. Crosslinking is thus a normal feature of collagen and can occur enzymatically or spontaneously in reactions with glucose [5]. The stiffness of the sclera is created by its dense collagenous structure of approximately 90 % Type I collagen and 10 % Type III collagen, and scleral laminae are made up of collagen fibrils [6]. The mechanical behaviour of the collagen fibrils exhibits a nonlinear stress–strain response that causes the fibres to be straightened under high load and wavy under low load [7].

Aging increases the amount of crosslinking in connective tissue by the accumulation of advanced glycation end products (Fig. 1) [8]. Their production results in reactive oxygen species, oxidative stress, inflammation and structure damage. Advanced glycation end products also accumulate in collagenous tissues resulting in high levels of crosslinking. Lysine residues in collagen are susceptible to this crosslinking, whereby they are irreversibly covalently bound to adjacent molecules. Additionally, with aging comes reduced matrix production, reduced collagen turnover, and damage, all of which are associated with increased levels of crosslinking [8–10].

Much like woven fabric, increased levels of crosslinking lead to increased tissue stiffness. Inarguably, age-related increases in crosslinking are the major drivers of the increased stiffness observed with age [8]. Moreover, the increase in crosslinking and subsequent stiffness leads to ocular rigidity, an important and overlooked driver of presbyopia. Ocular rigidity is the stiffness of the eye, either as a whole or of its component tissues. At a whole-eye level, ocular rigidity refers to the resistance to increasing volume with increasing intraocular pressure [11]. Increased ocular rigidity is correlated with age and presbyopia, and therefore, may be a causative factor of age-related biomechanical and physiological dysfunctions of the eye [11–13].

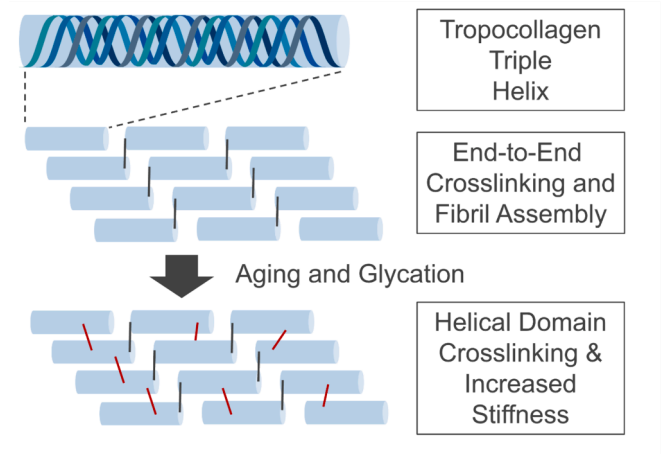

Fig. 1. Collagen structure and crosslinking. Collagen, a major matrix protein, is formed from triple-helix tropocollagen molecules. During fibril self-assembly, these undergo enzymatic crosslinking, primarily at the ends of tropocollagen units. During aging, matrix collagen acquires more crosslinks, often occurring in the helical domains and driven by glycation events. This crosslinking leads to greater tissue stiffness.

2.1. Dynamic range of focus

To understand the importance of ocular rigidity as it relates to age and presbyopia, one must understand the inherent biomechanical functions that lead to the eye's ability to focus at various distances. Dynamic Range of Focus (DRoF) is a term to describe the eye's ability to adjust focus and maintain clear vision across a range of distances. Positive DRoF or accommodation occurs when the key lenticular and extra-lenticular structures move dynamically and exert forces that allow the lens shape to shift from being relatively flattened to more rounded to shift focus from far to near. Conversely, negative DRoF or relaxation of accommodation occurs when the key lenticular and extra-lenticular structures move dynamically and exert forces allowing the lens shape to shift from being relatively rounded to more flattened to change focus from near distances to far distances. The ability to shift DRoF in either direction includes accommodative lens movements, pupil responses, aberrations, depth of focus and other factors affecting vision quality. It entails precise adjustments to allow focus across a continuum, rather than simply having "near" and "far" points of focus, and involves movements, intraocular fluidics, elastic biomechanical functions of the Bruch's Choroid Complex (BMCC), and tissue material properties. These integral ocular functions must be considered to properly approach the progressive problem of presbyopia, which is fundamentally an issue of biomechanic dysfunction.

Changing focus across a range of distances involves movement at its core: movement of the ciliary muscle, movement and shape changes of the lens and lens capsule, inward bowing movements of the sclera, and stretching and elastic recoil of the Bruch's membrane-choroid complex. These movements can be described in terms of "phases of accommodation" (Fig. 2). There are 3 phases: (Phase 0) pre-stretch; (Phase 1) accommodation; and (Phase 2) accommodative relaxation. In phase 0, the lens is in its most flattened or non-accommodating state and focused for far vision. In this phase, the zonules keep the lens pulled taut and in a relatively flattened shape, and the BMCC pulls on the posterior zonules and ciliary body to keep them in their resting positions. During phase 1 (+DRoF or accommodation), the ciliary muscle moves forward and centripetally, slackening the anterior zonules and allowing the lens capsule to round up, increasing central optical power [14]. The sclera bows inward transiently as the ciliary muscle contracts [15]. The ciliary muscle also pulls the elastic BMCC forward, stretching it like a spring. During Phase 2 (−DRoF or accommodative relaxation), the ciliary muscle relaxes, and the elastic energy stored in the BMCC pulls the entire apparatus backwards toward the non-accommodative position. While this description applies to young healthy eyes, the events of these phases are altered by the biomechanical changes that occur during presbyopia [16,17].

2.2. Ocular rigidity and the loss of dynamic range of focus due to age-related crosslinking

The stiffness of individual ocular tissues (particularly the sclera) plays a key role in affecting whole-eye ocular rigidity as well as directly affecting the accommodation and relaxation functions of DRoF. The movements that are so critical to achieving DRoF are not as efficient with the stiff tissues associated with presbyopia and the loss of elastic recoil of the BMCC (Figs. 2 and 3). A stiffer sclera pulls back against the ciliary muscle creating a drag force, and thus shows less inward bowing movement in a presbyopic eye [15]. The BMCC, having lost its elasticity [18], resists movement during Phase 1. In Phase 2, the BMCC, having less stored energy, fails to produce enough recoil force to pull the lens

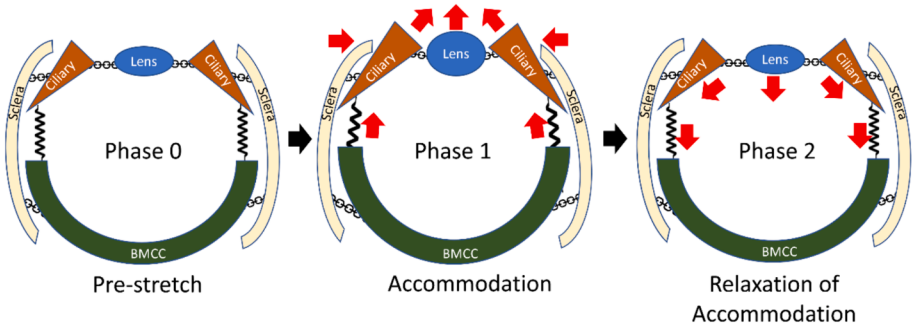

Fig. 2. Phases of accommodation in healthy young eyes.

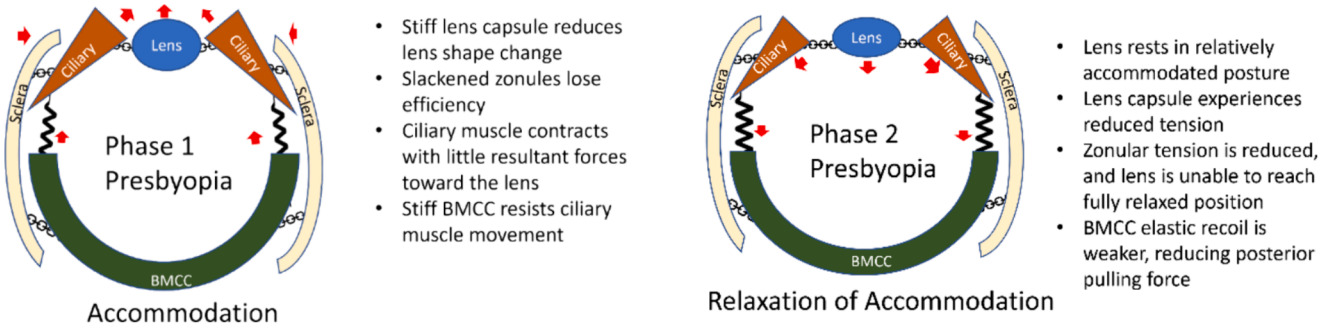

Fig. 3. Phase 1 and 2 of accommodation in the presbyopic eye. BMCC = Bruch's membrane-choroid complex.

back fully into its relaxed position, explaining why the lens posture in a presbyopic adult rests in a more accommodated position instead of a fully relaxed flattened position [19]. In addition, a stiffer lens capsule and/or lens substance loses its ability to undergo the shape changes that are necessary to accomplish a full range of DRoF [20–22]. Despite having a ciliary contraction force that is similar to that of a young person [17,20], a presbyope thus fails to achieve the proper lens posture and biomechanical forces necessary for DRoF. Furthermore, presbyopes undergo pathophysiological changes related to hydrodynamics and ocular pulsatile blood flow [23]. Thus, presbyopia is a manifestation of the biomechanical changes to tissue stiffness that occur with age.

Seen through the lens of biomechanics, an approach for treating presbyopia becomes readily apparent, addressing the root cause of presbyopia being the crosslinking and tissue stiffness that occurs with age. Doing so will restore biomechanical efficiency and DRoF. Early studies show promising results [24].

3. Scleral techniques for presbyopia

3.1. Laser Scleral Microporation

One mechanism for achieving this is Laser Scleral Microporation. This therapy has the goal of reducing scleral stiffness, and therefore, reducing ocular rigidity. Laser Scleral Microporation utilises arrays of laser-generated micropores in the sclera overlying critical accommodative anatomy, including the scleral spur and all three fibres of the ciliary muscle from origin to insertion of the tendons into the BMCC near the posterior portion of the pars plana [25–27]. By creating these micropores, Laser Scleral Microporation removes a fractional area of crossliniking rejuvenating the tissue creating negative stiffness that makes the scleral tissue more compliant alllowing the sclera to deform and respond to stress. For this reason, the sclera can move with the ciliary muscle forces and reduce resistance to the forces produced during DRoF. Reducing ocular rigidity potentially allows the biomechanical system to become more efficient.

One major technological underpinning of Laser Scleral Microporation is the erbium-doped yttrium aluminium garnet (Er:YAG) laser; the 2.94 μm wavelength coincides with the peak absorption of water (3.00 μm), making it ideal for evaporisation of connective tissues since they are almost all comprised of approximately 90 % water [28]. The Er:YAG laser is able to effectively vaporize the water out of the tissue with very little collateral thermal damage when compared to other lasers in the electromagnetic spectrum (Fig. 4). Er:YAG lasers with 250–350 μs pulse lengths were Food Drug Administration of the united States of America (FDA)-approved in 1996 for cutaneous resurfacing, and Er:YAG lasers with extended pulse widths of 500 μs to 10 ms were approved in 1999 [29]. Modern applications of these lasers include dermatological, dental, and ophthalmological procedures.

The Laser Scleral Microporation approach addresses the progressive loss of DRoF, which is caused in part, by progressive ocular rigidity occurring with presbyopia, is to create four matrices of micropores in the

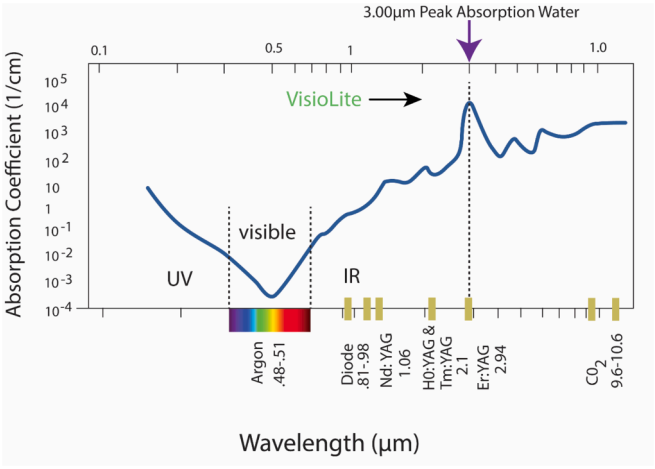

Fig. 4. Peak absorption of light from various lasers with respect to the absorption coefficient of water. (Data from [28]).

oblique quadrants of the eye including the superior nasal, superior temporal, inferior nasal, and inferior temporal. Targeting these oblique quadrants helps to avoid the extraocular muscles and the larger vessels present in the meridional quadrants of the eye and creates a "hoop stress" which allows the sclera to become flexible again responding to the ciliary muscle contracts supporting the inward and upward movements of the lens to change shape to achieve both positive DRoF and negative DRoF. Each matrix consists of 40–50 micropores, each targeted to a depth of 85 % of the scleral depth within a 5 mm x 5 mm diamond matrix, which begins approximately 0.5 μm from the anatomical limbus and extends just posterior to the pars plana. The pore density within the matrix is 10 % with a pore volume fraction of 10.4 %. The matrices are placed over five critical anatomical zones of physiological significance in the sclera (Fig. 5):

- Zone 0) 0.0–1.3 mm from the anatomical limbus, corresponding to the distance from the anatomical limbus to the superior boundary of ciliary muscle/scleral spur;
- Zone 1) 1.3–2.8 mm from anatomical limbus, corresponding to the distance from the sclera spur to the inferior boundary of the circular muscle;
- Zone 2) 2.8–4.7 mm from anatomical limbus, corresponding to the distance from the inferior boundary of the circular muscle to the inferior boundary of the radial muscle;
- Zone 3) 4.7–6.6 mm from anatomical limbus, corresponding to the inferior boundary of the radial muscle to the superior boundary of the posterior vitreous zonule zone
- Zone 4) 6.6–7.3 mm from anatomical limbus, corresponding to the superior boundary of the posterior vitreous zonule zone to the superior boundary of the ora serrata.

The critical zones are the location of the key anatomy being impinged upon by the increased ocular rigidity, thus providing the best treatment location to rejuvenate the biomechanical properties of the tissues involved in DRoF. Investigation of the capability of Laser Scleral Microporation therapy to rejuvenate DRoF has been conducted on eight eyes from four elderly cynomolgus monkeys followed for up to 7 months post-procedure, as shown in Fig. 6 [27]. An increase in the DRoF was measured with aberrometry, used to assess refraction and calculate spherical equivalent before and after instillation of pilocarpine to induce 'accommodative' effort [6]. No significant complications were noted, and intraocular pressure was significantly lower at postoperative visits.

One advantage of Laser Scleral Microporation therapy is that there is no change to the cornea or lens and no loss of visual quality. Neither the visual line of sight nor the refractive error is affected. Corneal procedures may manipulate optics to create multifocality using an excimer laser or inlays [30], whereas intraocular lenses use refraction, diffraction, extended depth of focus or a combination [31] to extend the range of clear vision; however, all corneal and lens procedures have the risk of a loss of far vision, nighttime photopsia or glare [32]. Another essential advantage of Laser Scleral Microporation is the ability to repeat the therapy as progressive aging results in additional crosslinking, progressive stiffening, and continued loss of DRoF over time. Minimal adverse tissue responses have been shown in animal models [33].

3.2. Scleral expansion bands

Scleral expansion bands have been used to increase the space between the ciliary body and the crystalline lens [34]. However, previous studies have demonstrated inconsistent and limited results [35–37]. This surgical approach is based on the accommodation theory developed by Schachar [38,39]. This model states that presbyopia is the result of a progressive increase of the crystalline lens equatorial diameter with age, which decreases the distance between the ciliary body and the lens, thus limiting the amount of force that the ciliary muscle can exert upon the lens [40]. Scleral expansion bands widen this space and therefore restore zonular tension. It is worth noting that although Laser Scleral Microporation, as described above, and scleral expansion bands both target the sclera, they are based theoretically upon different mechanisms of presbyopia.

A two year clinical trial (ClinicalTrials identifier NCT02374671) evaluating the safety and effectiveness of the VisAbility™ Micro-Insert System (Refocus group, Inc) for the improvement of near visual acuity in presbyopic patients reported the results of 360 participants. Eighty-

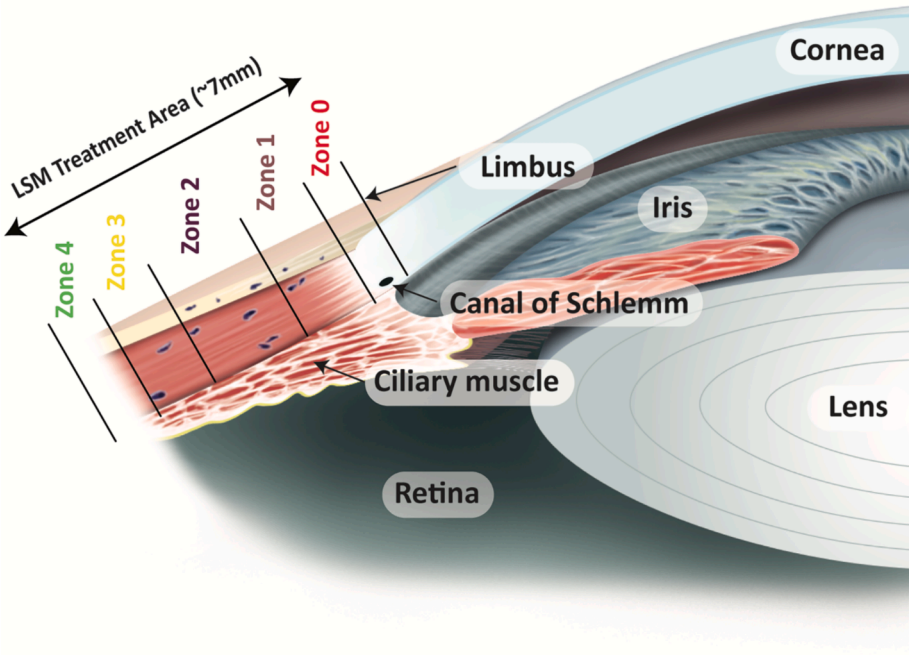

Fig. 5. Zones of clinical significance.

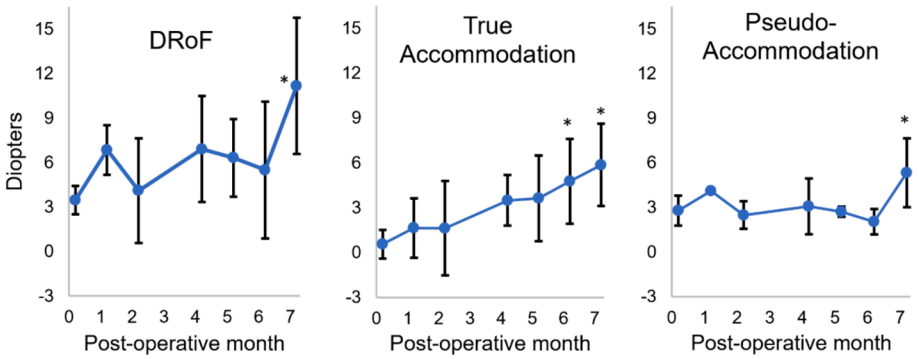

Fig. 6. Dynamic Range of Focus (DRoF), True accommodation, and Pseudoaccommodation in monkeys treated with Laser Scleral Microporation. True accommodation improved steadily after treatment. * = timepoints differ significantly from baseline. Figure adapted from Ting et al 2022 [27].

four percent of 344 participants analysed achieved a distance corrected near visual acuity (DCNVA) of 20/40 at 40 cm and a gain of at least 10 letters at 24 months for the primary eye. Anterior segment ischemia was reported in some cases in the FDA study, but most patients did not experience serious ocular adverse events [41]. The same group is currently enrolling participants to obtain an additional 36 months of safety and effectiveness data from all subjects who were implanted with the VisAbility Micro Insert in the previous clinical trial.

4. Pharmaceutical approaches

4.1. Treatments directed to soften the crystalline lens

This pharmacological approach to correct presbyopia and restore some accommodation is directed to soften the crystalline lens, based on the hypothesis that crystalline lens loss of flexibility and stiffening are the main causes of presbyopia [42–44]. Lipoic acid choline ester has shown to chemically reduce disulphide bonds in the crystalline lens [45], thought to be responsible for progressive lens stiffening. A preclinical study with lipoic acid choline ester (EV06 Ophthalmic Solution, 1.5 %) showed an increase of lens elasticity and a reduction of protein disulphides in mice, and this increase in lens elasticity was dosage dependant [46].

Results from a prospective, randomised, double masked, multicentre clinical trial (ClinicalTrials identifier NCT02516306) [47] assessing the safety of the topical lipoic acid choline ester (UNR844, 1.5 % formally known as EV06) and its efficacy in improving near visual acuity in presbyopic patients [45] demonstrated that UNR844 administration produced no safety concerns and was well tolerated, with no clinically relevant changes in best corrected distance visual acuity, pupil size and intraocular pressure or discontinuation due to adverse events. DCNVA improved in the UNR844 group (n = 50) compared to placebo (n = 25) during the 91 days of treatment (UNR844 versus placebo, mean change in LogMAR (standard deviation); −0.159 (0.120) versus −0.079 (0.116), p = 0.007). Bilaterally, the percentage of subjects with a gain of ≥10 letters in DCNVA was 53.1 % in the UNR844 group compared to 21.7 % in the placebo group (p = 0.021). Improvements in DCNVA were sustained at 5 and 7 months after UNR844 dosing ceased.

A later phase 2 trial (Clinical Trial Identifier NCT03809611) [48] including a total of 124 presbyopic participants, UNR844 Chloride (UNR844-Cl) group and placebo group, did not show a significant difference in binocular DCNVA at 3 months (UNR844-CI (n = 40) compared to the placebo (n = 38), number of letters (standard deviation); 6.1 letters (1.24) versus 4.5 letters (1.27), p = 0.183). Furthermore, no significant difference was observed in the number and percentage of subjects achieving 75 or more LogMAR letters in binocular DCNVA at month 3 (UNR844-CI versus placebo, n = 10 (25.0 %) versus n = 6 (15.8 %), p = 0.283).

Femtosecond lasers have also been used for lenticular softening as the pulse vaporises tissue within the ablation zone spheroid (of about 20 μm depth and 5 μm depth) [49] and creates a gas vacuole, which is absorbed into the surrounding tissue over time. By creating a series of these internal lenticular micro-incisions in the lens periphery, away from the line of sight, lamellar-type plates can be formed which act as 'gliding planes' [50] and allow the lens to deform on accommodation [51]. *In vitro* studies on human donor [51,52] and porcine [53–55] crystalline lenses have shown promise, with improvements in lens malleability and little or no change in central lenticular transparency. Further *in vivo* studies on rabbit [50,56] and monkey [57] eyes also reported no significant cataract formation over study periods ranging from 3 months to 4 years. However, little research has been reported since these studies.

4.2. Pharmaceutically induced monovision

Monovision has been a long-used concept whereby one eye is corrected for distance vision and the other eye for near work, the later effectively having induced myopia. Most often, monovision is a method of correction used with contact lenses [58], refractive surgery [30] or corrective cataract surgery [31]. The potential for inducing unilateral myopia to create monovision, by using a therapeutic agent exists only if the treatment was able to induce unilateral myopia; a systemic agent by definition would induce myopia in both eyes. A topical therapeutic agent could potentially be effective as the patient could simply instil the therapeutic agent as an eye drop in their non-dominant eye to induce myopia and achieve monovision.

There are currently no approved therapeutic agents available that have induced myopia as an indication of use to induce monovision. However, there are a series of case reports where induced myopia is listed as an adverse side effect for a number of drugs. These drugs are all prescribed systemically and include treatments for: acne, antibiotics, anti-inflammatory, antipsychotic antivirals, diuretics, epilepsy, migraine, immunosuppressants and weight loss. The incidence of induced myopia appears to be idiosyncratic, a sensitivity type of reaction and very uncommon. The level of myopia reported is variable and unpredictable. For all the cases reported, any induced myopia is reversed once the therapy was withdrawn. A detailed list of these drugs and associated case reports are shown in Table 1.

Common reported mechanisms for the induced myopia included ciliary body and peripheral uveal effusion [59,60], ciliary spasm, lens swelling and forward lens displacement [61]. These suggested mechanisms were supported with the use of cycloplegia resulting in a decrease in the myopic shift in the case of the ciliary spasm and B scan ultrasonography documenting the peripheral choroidal effusion and lens changes.

Currently, the suitability for any of these drugs to have an indication for producing reliable monovision would be unlikely due to the facts that they are generally only used systemically, induce myopia due to an

Table 1
Drugs with the reported side effect of inducing myopia, listed by drug class.

Drug class	Drug(s)	Treatment	Myopia level	Reported side effects	Citation
Anorexiants	Phendimetrazine Ephedrine	Weight loss	Acute myopia	Ciliochoroidal effusion, shallow anterior chamber	Case report (n = 1), [62].
Anticonvulsant	Topiramate (Sulphamate)	Epilepsy	Acute myopia	Shallow anterior chamber, uveal effusion, lens thickening, angle closure glaucoma	Case report (n = 1), [62]
	Lamotrigine	Migraine	−1.00D to −12.00D of myopia		Case Series (n = 2), [63]
	Zonisamide	Weight loss			Case report (n = 1), [64] Case report (n = 1) and review [65] Case report (n = 1), [66] Case series (n = 7), [67] Review, [68] Case report (n = 1), [69] Case report (n = 1), [70] Case report (n = 1), [71] Case report (n = 1), [72] Case series (n = 2), [73] Case Series (n = 5), [74] Case report (n = 1), [75] Case report (n = 1) [76] Review [77]
Antimicrobial drugs (synthetic)	Co-trimoxazole Sulfonamide Trimethoprim Sulfamethoxazole	Infections	Acute myopia	Shallow anterior chamber, lens thickening, ciliary body edema, supraciliary choroidal effusion	Case report (n = 1) [78] Case report (n = 1) [61] Case report (n = 1) [79] Case report (n = 1) [80]
Antipsychotic (second generation)	Amisulpride Aripiprazole	Acute and chronic schizophrenic disorders	Acute myopia −3.00 to −8.00D	From None to shallow anterior chamber, ciliary spasm, ciliary bodies effusion, peripheral uveal effusion and effects of ocular serotonergic intraneural fibres	Case report (n = 1) [81] Case report (n = 1) [82] Case report (n = 1) [83] Case report (n = 1) [84] Case report (n = 1) [85] Review [86] Case report (n = 1) [87]
Cholinergic agonists	Pilocarpine	Reversal of Mydriasis (Pilocarpine, 1 and 2 %)	Acute myopia	Miosis	Clinical study (n = 12), [88]
Disease-modifying antirheumatic drugs (DMARDs)	Sulfasalazine	Long-standing ulcerative colitis	Acute myopia	None	Case report (n = 1) [89]
		Rheumatoid arthritis	−1.00 to −4.00D		Case report (n = 1) [90]
Diuretics	Hydrochlorothiazide	Tinnitus	Acute myopia −0.50 to −17.0D	Shallow anterior chamber, choroidal detachments, ciliochoroidal effusion, raised IOPs, lens thickening	Case report (n = 1) [60]
	Triamterene	Systemic hypertension			Case report (n = 2) [59]
	indapamide (combined with amlodipine)				Case report (n = 1) [91]
	Chlorthalidone				Case report (n = 1) [92]
	Triplixam				Case Series (n = 5) [74]
	Methazolamide				Case report (n = 1), [93]
					Case report (n = 1) [94]
Herb	Ma-huang (Ephedra)	Weight loss	Acute myopia	Edematous cornea, raised IOPs, shallow anterior chamber, and thickened choroid	Case report (n = 1) [95]
Immunosuppressants	Equine antilymphocyte globulins	Aplastic anaemia	Acute myopia	None	Case report (n = 1) [96]
Neuraminidase inhibitor	Relenza	Antiviral agent	Acute myopia		Case report (n = 1) [97]
Non-steroidal anti-inflammatory (NSAID)	Mefenamic acid	Pain	Acute myopia −0.50 to −17.00D	Angle closure glaucoma choroidal detachment	Case report (n = 1), [98] Case Series (n = 5) [74]
Retinoids	Isotretinoin	Acne treatment	Corneal steepening, and myopia	None	Case report (n = 1) [99]
Sympathomimetic amines	Phendimetrazine	Weight loss	Acute myopia − 0.5 to − 17.0D	Acute angle-closure glaucoma, shallow anterior chamber, ciliochoroidal effusion	Case Series (n = 5), [74]
Selective serotonin receptor agonists	Zolmitriptan	Migraine	Acute myopia	Raised IOPs, shallow anterior chamber, ciliochoroidal effusion	Case report (n = 1) [62]

unpredictable inflammatory response and all would have a range of now unwanted side effects both ocular and systemic. Some do offer potential but only once the action for inducing myopia can be made safe, controllable, predictable, deliverable topically with minimal systemic side effects.

4.3. Use of miotics in presbyopia

There has been recent renewed interest in the use of miotics, such as pilocarpine, for the correction of presbyopia. A miotic pupil increases the depth of field, but at the expense of reducing retinal luminance [100,101]. Pilocarpine is a cholinergic agonist that directly stimulates

cholinergic receptors, acting on a subtype of muscarinic receptor (M3) found on the iris sphincter muscle and ciliary muscle, causing the muscle to contract and produce miosis and a relaxation of the zonules [102]. Pilocarpine is available as ophthalmic eyedrops and gels formulated as pilocarpine nitrate 2 % and pilocarpine hydrochloride 1 %, 2 % and 4 % (weight/volume). These formulations are indicated for usage as a miotic and in glaucoma management. In addition to miosis, in a clinical study it was noted when pilocarpine was used to reverse pupil dilation in young adults and it also induced significant levels of reversible myopia, which was found to be of greater intensity with the higher dosage drops (2 %) especially on a light-coloured iris [88].

In October 2021 Vuity 1.25 % (Pilocarpine HCl Ophthalmic solution) was approved by the FDA for the treatment of presbyopia. This approval was based on two Phase 3 clinical studies GEMINI 1 and GEMINI 2 [103]. One study reported on the formulation development of Vuity as having superior comfort compared with the formulations traditionally used for the treatment of glaucoma [104]. Various formulations of pilocarpine hydrochloride have been investigated and reported. One study showed that over a 30-day period there was improved efficacy with the 1.25 % [105]. This evidence was supported by a retrospective analysis of clinical data collected and reported the same year [106]. A study that reported on the patient reported outcomes for the Phase 3 study investigating Vuity on a sample of 323 participants, in a double masked randomised multicentre clinical study, confirmed significant improvements for the participants randomised to the treatment group compared to the participants randomised to the control group (using vehicle) by the 30 day time point [107]. Additional formulations appear to be in development. In a phase 2 study (VEGA-1, Ocuphire Pharma Inc), a combination of phentolamine ophthalmic solution (0.75 %) and pilocarpine (0.4 %), was able to demonstrate significantly improved unaided near vision up to 6 h post instillation and is awaiting Phase 3 study results [108]. An animal model using minipigs and the application of a cream-based pilocarpine ointment to the upper eyelids concluded the delivery mechanism to be safe and able to deliver an effective dose [109].

Pilocarpine does have some well reported side effects such as blurred vision, poor night vision and headaches. Regarding the long-term safety and efficacy in the treatment of presbyopia, that is not yet known [110]. A major concern relating to the use of long-term pilocarpine is the development of vitreofoveal traction and while none of the randomised clinical studies investigating the use of pilocarpine to treat presbyopia have reported such an adverse effect, a case of a female patient that developed a vitreomacular traction following the initiation of treatment using Vuity has been reported [111]. This concern has also been echoed by other authors, where retinal detachments associated with the use of pilocarpine have been shown [112]. Pilocarpine and other miotics have long been suspected to be associated with an increased risk of retinal detachment and at-risk patients should not be prescribed this treatment for presbyopia [113].

The study protocols relating to the clinical trials investigating the use of pilocarpine in the treatment of presbyopia have only reported distant correction aided and/or unaided near visual acuity as the main outcomes measured. Accommodation measurements have not been reported and it is not known whether the treatment action is by the pinhole effect from the pharmacological action on the muscarinic receptors on the sphincter muscle of the iris or if there is any effect from the action on the ciliary body, the relaxation of the lens zonules and potentially adding additional accommodation capacity per se [114].

5. Dietary supplementation and the management of presbyopia

Astaxanthin is a red orange carotenoid found in fish such as salmon, and seafood such as shrimp, and crab. It has been shown to act as an antioxidant in the human aqueous humour [25]. It is thought to enter the crystalline lens via the aqueous, having diffused from the blood plasma where it reduces sunlight related oxidative damage to the lens proteins [115]. A study of oral astaxanthin 5 mg/day for four weeks supplementation alone ($n = 13$ presbyopes) found an increase in accommodation amplitude (from 2.3 ± 1.4 D to 2.8 ± 1.6 D; $p < 0.01$) compared to a control group ($n = 13$) taking no supplementation (2.2 ± 1.0 D to 2.3 ± 1.1 D) [116]. Other researchers conducted a randomised prospective double-masked placebo-controlled trial to investigate the relationship between a multi-component dietary supplement (containing beta-carotene, lutein, vitamins B2, B3 [niacin], B6, B9 [folic acid], C, E, blueberry extract, copper, zinc selenium, chromium, astaxanthin and zeaxanthin daily for four weeks) and accommodative changes in 20 presbyopia computer users compared to a matched control group taking a starch placebo (both daily, for 4 weeks) [117]. Lutein is a natural antioxidant found in spinach, kale and yellow peppers and it has been found in the crystalline lens where it may reduce stiffening of lens proteins from oxidation [118]. Cyanidin-3-glucoside is a member of the anthocyanin family and is found in bilberries and black soybean hull, the outer shell of the bean. It is considered to have antioxidant and anti-inflammatory properties [119]. The mean accommodation of the intervention group increased from 3.26 ± 0.84 D to 3.46 ± 0.95 D ($p < 0.05$), while in the control group it decreased from 3.39 ± 1.08 D to 3.27 ± 1.04 D.

In another randomised double-masked randomised controlled trial, presbyopic participants took a placebo ($n = 24$) or dietary supplement ($n = 24$) consisting of a daily dose of lutein 10 mg, astaxanthin 4 mg, bilberry extract 20 mg, black soybean hull extract 26.5 mg and docosahexaenoic acid 50 mg for four weeks of dietary supplementation [120]. The bilberry and black soybean hull extracts provided 2.3 mg of cyanidin-3-glucoside. Docosahexaenoic acid is an omega-3 fatty acid found in cold-water, fatty fish, such as salmon and also in seaweed. The near point of accommodation increased to 1.32 ± 0.39 D for the intervention group compared to 0.11 ± 0.34 D for the placebo group after four weeks. There was a decrease in reported 'eye strain' in both groups, but only the dietary supplementation group reported an improvement in 'blurred vision', 'stiff shoulders or neck' 'heaviness of head' and 'difficult to focus on objects'. Interestingly, the placebo group also reported a reduced 'difficult to see in low light condition'. The authors proposed that astaxanthin may have improved the near point of accommodation because it increased blood flow in the ciliary and short posterior ciliary arteries which deliver nutrients to the ciliary muscle, and reduced the inflammatory response that results in loss of ciliary muscle function by suppressing tumour necrosis factor in the ciliary muscle. The authors further proposed that vasorelaxant properties of cyanidin-3-glucoside relaxed the ciliary muscles, leading to an increase in near point of accommodation, that lutein augmented the antioxidant properties of astaxanthin and that as docosahexaenoic acid had been found to occur in the ciliary body, it's inclusion in the dietary supplement had improved its effectiveness. However, no evidence for these proposed mechanisms were provided.

It is often not clear in these studies whether the participants were wearing optimal refractive correction during the assessments. Objective measurement has indicated a linear decline in accommodative amplitude of around 2.3 dioptres per decade, culminating in a complete loss of accommodation by around 51 years of age [109]. It is debatable whether the mean increases in accommodative amplitude measured in these studies is of clinical and real-world significance. The mechanism of action of the supplements is not fully understood, nor the optimum duration or use or daily dose. It is also unknown if the improvement in accommodative amplitude was maintained or decayed following cessation of supplementation.

Other supplementation investigated includes: methylcobalamin (a type of vitamin B12 and has been proposed to prevent neural degeneration and to enhance neural regeneration) in a study of in five pre-presbyopic male participant (mean age 30 years; range 23 to 35) finding that the increase in the low frequency component of accommodative microfluctuations with computer use when taking a placebo were supressed when taking 3 mg daily methylcobalamin for seven days

[121]; and α-glucosyl hesperidin consumption by mice increased crystalline lens elasticity and plasma antioxidants (by a similar amount for 1 % and 2 % preparations) [122]. Previously, they had shown that α-glucosyl hesperidin consumption prevented induced cataract formation in the rat model [123].

6. Recommendations and future directions

The field of presbyopia research is developing novel solutions for a problem that will be faced by everyone. This paper has reviewed some of the less mainstream solutions away from the main core of optical aids such as contact lenses and spectacles [58], or intraocular lenses [31]. Laser Scleral Microporation is showing emerging promising results. Pharmaceutics and nutrition will play an interesting role in management of patients with presbyopia. When imagining what types of novel solutions may be available in the future, especially those that may be considered as more peripheral options, then it is worth investigating patents that have been filed.

The pharmacological management of presbyopia is nearly exclusively via the maintenance of a miotic pupil regardless of luminance, to increase depth of focus to improve the near vision of emmetrope presbyopes or presbyopes using distance vision correction. There are a large number of applications and granted patents. Due to the large IP volume for a small field of invention, individual patents often represent minor variations from the exiting technology either in term of formulation or manufacturing process. Typically, the patents are based upon the formulation to produce miosis and additional formulations to achieve optimal clinical performance by controlling the unwanted effects of the miotic agents, principally irritation and decreased distance visual acuity. All the patents in this field are based upon the stimulation of the parasympathomimetic innervation via the use of cholinergic agents targeting the muscarinic acetylcholine receptors. Many cholinergic agents are listed in the various patents, with, however in all cases [1–12 124–134] but one [135,136] pilocarpine in different concentrations as the cholinergic agent used as the leading agent; the exception puts forward carbachol as the key agent in the claim. As in all patents a large range of possible agents are also listed as possible embodiments to expand the intellectual property protection, carbachol being specifically mentioned as an alternative in some patents for which the principal embodiment is pilocarpine [124,130].

The second group of agents listed in patents are those agents used to counter the undesired effects of the continuous use of cholinergic miotic agents: ocular pain, redness, excessive miosis under low light condition and distance blur due to induced myopia associated with the collateral effect of the cholinergic agents on the ciliary muscle. The agents used fall into two main classes: alpha agonist to reduce redness and prolong the miotic effect and non-steroidal anti-inflammatory agents, usually COX-2 selective to reduce the amplitude of the miosis but prolong its effect in time, reduce distance vision blur and ocular inflammation. A number of patents only claim the use of alpha agonists [128–130,135,136] the most common agent listed being Brimonidine, other only the use of non-steroidal anti-inflammatories [124,125,131], diclofenac being often cited while other claims the use of both classes of agents is revealed [124,132].

The third group of agents listed in the majority of patents are excipients to improve the acceptance the eyedrops by controlling other factors, such as viscosity, pH, non-Newtonian properties and ocular tissue penetration, affecting their interaction with the tear film and the ocular surface [124–130,132–136].

The pharmacological management via softening the crystalline lens intellectual property filing is from a continuous program with, however, a number of changing assignees from its inception to the latest filing. The program is based upon the theory that the loss of accommodation leading to presbyopia is due to loss of elasticity and hardening of the crystalline lens produced by an increase in viscosity between the lens fibres. The change in viscosity is hypothesised to be due to an increase in protein-to-protein disulfide bonds. The overall program and supporting intellectual property deal with firstly breaking the disulfide bonds to increase elasticity and subsequently or simultaneously protonate the sulphur moity that forms as the result of breaking the bonds via a reducing agent to prevent from the reformation of the disulfide bonds. The early intellectual property assumed that it was likely that in addition to delivering the biologically suitable chemical agents necessary, additional external activation would be required such as ionophoresis or electric voltage [137–140]. Even though the modes of application of the pharmaceutical compounds listed included eyedrop from the onset, a specific claim for the use of an eyedrop with suggested compositions was only mentioned in an intellectual property filing in 2014 [141] with choline ester as a reducing agent, preferably lipoic acid or derivatives. Subsequent patents and filings describe refinements in formulation associated with on-going program learning [142–146] including low dosage formulations of lipoic acid [21] and dithiol compounds and derivatives [145].

Declaration of competing interest

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