

Presbyopia – A Review of Current Treatment Options and Emerging Therapies

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Abstract: Presbyopia is a common age-related vision disorder characterized by a progressive inability to focus on near objects. If uncorrected or under-corrected, presbyopia can significantly impact patients' quality of life. Presbyopia represents an area of considerable unmet need due to its rising prevalence worldwide as the population ages, the high proportion of under-treated individuals in some parts of the world, and the limitations of currently available corrective methods. Progressive or bifocal spectacles are associated with peripheral blur, a restricted visual field and impaired depth perception, which have been linked to an increased risk of falls in the elderly. Contact lens options can be difficult to maintain due to the development of age-related dry eye symptoms and reduced manual dexterity. Other corrective methods involve surgical interventions that modify the optics of the cornea, replace the crystalline lens, or attempt to restore active accommodation. While patients undergoing surgery report satisfactory outcomes post-operatively, many of them eventually require reading glasses. Non-invasive therapies with novel mechanisms of action are currently being investigated; these include miotic agents and UNR844, a lipoic acid choline ester. In this narrative review, available evidence on presbyopia prevalence, quality of life impact and risk factors are described, with a focus on observational studies in non-clinical settings. The diagnosis pathway and patient journey in presbyopia are outlined, and various treatment options are analyzed. The data reviewed herein reveals significant gaps in the provision of vision correction for this common condition, with a paucity of effective, non-invasive treatment options broadly accessible to presbyopic individuals.

Keywords: presbyopia, epidemiology, patient characterization, vision correction, pharmacological therapies

Plain Language Summary

This review was carried out to i) explore available evidence on the causes and risk factors of presbyopia, ii) summarize how the condition is currently diagnosed and managed, including residual unmet needs and iii) provide an overview of potential future treatment options that are currently in development. Presbyopia is an age-related decline in the ability to focus on near tasks, thought to be caused by a loss of flexibility, increase in size and hardening of the lens and/or the muscle fibers surrounding the lens inside the eye. Our research found that the onset of presbyopia may be earlier in women and in individuals who live closer to the equator. Presbyopia onset may also be influenced by an individual's distance glasses prescription. We discovered that presbyopia is typically diagnosed around 50 years of age, with optometrists being the major providers of vision correction. However, current treatment options for presbyopia, which include glasses, contact lenses and surgery, mostly manage the symptom of blurred near vision, without addressing the underlying cause of the condition. This review highlights the need for effective, broadly accessible, non-invasive presbyopic treatment options.

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Introduction

Presbyopia is a common, age-related vision disorder characterized by a progressive inability to focus on near objects. Presbyopia is hypothesized to be caused by either a weakening of the ciliary muscles or a loss of lens elasticity preventing focal point change.^{1,2} While the etiology of this condition is not fully elucidated, recent research suggests that an increase in lens rigidity is the primary causative mechanism.^{3,4}

Although corrective measures are available to restore near vision, access to treatment (most often in the form of reading glasses) is limited in some parts of the world. In 2015, 826 million of the 1.8 billion people estimated to have functional presbyopia were found to be living with uncorrected near vision impairment because they had no access to vision correction or were utilizing inadequate correction.⁵ Without optical correction, presbyopia can have multiple effects on quality of life, such as problems reading (inability to read fine print, need for increased lighting, diplopia, epiphora, headache fatigue or asthenopia), and other tasks, such as threading a needle or seeing fine details on proximal objects.⁶

This review encapsulates available evidence on presbyopia epidemiology, diagnosis and management, while highlighting the unmet need for an effective, broadly accessible, non-invasive presbyopic treatment options.

Presbyopia: Prevalence and Quality of Life Impact

The prevalence and severity of presbyopia increases with age, with up to ~85% of people aged 40 years or older developing presbyopia.⁵ In 2015, it was estimated that 1.8 billion people globally had presbyopia and the prevalence is expected to peak at approximately 2.1 billion in 2030.⁵ Although the measured prevalence of presbyopia is greater in regions with longer life expectancies,⁵ it is estimated that 94% of those with significant near vision disability due to uncorrected presbyopia live in developing countries.⁷

Studies have revealed that presbyopia is undercorrected in many countries, with reading glasses available for only 6–45% of patients living in developing countries.⁷ In these parts of the world, the high prevalence of uncorrected presbyopia is due to a lack of adequate diagnosis and affordable treatment.^{8–11}

Uncorrected or under-corrected presbyopia has a substantial impact on quality of life, regardless of the nature of daily activities performed.¹² However, affected

individuals can experience a dramatic increase in productivity in their daily activities when provided with an appropriate correction.¹³ At the same time, in developed countries, the broad accessibility of corrective devices such as reading glasses may mean that potential alternative presbyopic treatment options are often overlooked.¹⁴ Additionally, dependence on spectacles is one of the main causes of loss of quality of life in people over 45 years of age.¹⁵

Presbyopia Risk Factors Environment

The first symptoms of presbyopia are typically experienced around 40 years of age in Western societies, with an earlier age of onset reported in countries closer to the equator, such as Central/South American countries.¹⁶ It has been previously hypothesized that premature degradation of the crystalline lens may be caused by ultraviolet radiation exposure, thus contributing to premature onset presbyopia.^{17–19}

Refractive Status

There is a scarcity of literature relating to baseline refractive error in presbyopes. A prospective study of 473 subjects presenting with presbyopia at a rural tertiary teaching hospital in India revealed just under half (49.7%) were emmetropes, 30.3% had hyperopic correction, and 20% had a myopic correction.²⁰ A later study carried out in 1191 urban Chinese participants (mean age 50.4 years; 52.9% female) found a significantly higher prevalence (52.2%) and incidence (78.8%) of functional presbyopia among hyperopic individuals compared to the rest of the cohort.⁹ Results from this study also revealed a considerably lower overall prevalence of functional presbyopia (25.2%) compared to values reported in other studies; attributed to the socioeconomic gap between urban and rural areas.⁹

While hyperopia and presbyopia have different etiologies, low rates of undiagnosed hyperopia would manifest as an earlier need for near-vision correction with the onset of presbyopia.²¹

Sex

Women over 40 years of age have higher rates of presbyopia than men in the same age group.²¹ The increased need for presbyopia correction in women is hypothesized to be caused by differences in tasks performed and viewing

distance requirements, rather than physiological gender differences in accommodation mechanisms.²¹

Patient Diagnosis and Eye Care Provision

Globally, optometrists are the major providers of vision correction, though mainly in private practice rather than in community settings.²² However, there are substantial differences in optometric service provision between countries. Most US optometrists encounter presbyopes on a daily basis in private practices,²¹ compared to European primary eye care models which are more heterogeneous. Within Europe, eye care in France is almost exclusively provided by ophthalmologists, while optometrists are the main primary eye care providers in the UK. The German system is a mixed model, where ophthalmologists as well as optometrists provide essential elements of primary eye care.²³ The regulatory framework, education and scope of practice of ophthalmologists are similar in France, Germany, and the UK. However, the numbers of active ophthalmologists differ significantly between these countries, leading to differing roles for ophthalmologists in primary eye care.²³

Presbyopia is typically diagnosed around 50 years of age, with case studies indicating that individuals residing in developed countries who have never had an eye examination before 50 years of age are likely to be emmetropic or hyperopic.¹⁶ In India, patients with myopia have been found to seek intervention for presbyopia later than emmetropes and hyperopes within the same age group.⁵ In some cases, a decrease in the age-specific prevalence of presbyopia has been reported as a result of the increasing prevalence of myopia, which decreases the accommodative need of individuals without optical correction.⁵

Before presenting for an eye exam, presbyopes often self-diagnose and may resort to over the counter (OTC) reading (or magnifying) spectacles as an initial solution to a reduction in near visual acuity.⁶ This may be influenced by economic status, which was found to impact the frequency of accessing eye care services and obtaining spectacles among presbyopes in an American community.²⁴

With rising life expectancy, the increasing prevalence of age-related ocular conditions, such as glaucoma, diabetic retinopathy, age-related macular degeneration and presbyopia is anticipated to pose a challenge to eye care service providers in Europe, especially as the number of ophthalmologists are decreasing in some countries.²⁵

Presbyopic Treatment Options

Methods to correct presbyopia include both fixed- and variable focus lens systems, as well as surgical interventions that modify the optics of the cornea, replace the crystalline lens, or attempt to at least partially restore active accommodation, with ongoing efforts to improve the presbyopic visual experience.²⁶

Optical Appliances Spectacles

Spectacles are generally assumed to be the most accessible intervention for correcting the symptoms of presbyopia, however no currently available spectacle lens can fully restore the dynamic range of accommodation in the aging eye.^{14,27} Single near-vision spectacles, designed with a single focal point throughout the entire area of the lens appropriate to the distance of the object viewed, correct sight at one distance only, therefore requiring removal of spectacles or a separate pair of spectacles for distance viewing.²⁷

Bifocal, trifocal or progressive addition spectacle lenses (PALs) incorporate zones of various optical powers for viewing objects at chosen specific distances. As multiple prescriptions can be combined in one lens, variable lens systems are advantageous as typically only one pair of spectacles is required.^{14,27} Compared to single vision lenses, variable lens systems are typically more expensive and have restricted optical zones,²⁷ which can impact individuals' subjective visual experiences while driving and performing workplace tasks.^{28,29}

Contact Lenses

Contact lens options for presbyopia include single vision distance contact lens correction with reading spectacles providing the required near addition, monovision correction, or a bi-/multifocal correction based on alternating or simultaneous image principles.^{26,30}

The combination of a single vision soft or rigid gas permeable (RGP) contact lens correction with reading spectacles can provide optimum vision at distance and near with less expense and fitting complications compared to multifocal options. However, patients are still inconvenienced by taking on and off glasses to read.³¹

Monovision and enhanced monovision correction involves correcting one eye for optimal distance viewing and the alternate eye with a single vision near or bi-/multifocal contact lens.³¹ Although typically less expensive and perceived as easier to fit compared to multifocal

lens designs, a major limitation with monovision is a reduction in stereopsis and contrast sensitivity,^{32–35} both important for critical visual tasks such as driving.³⁶

Multifocal contact lenses accommodate multiple refractive prescriptions. Contact lens selection and a comprehensive pre-fitting evaluation are important in multifocal lens wear, due to patient satisfaction relying strongly on lens centration, pupil size, ocular optics, and neural adaptation.^{37,38} The success of multifocal contact lenses can vary substantially across individuals due to differences to blur tolerance, ocular aberrations and neural adaptation.³⁷

Although the extent to which multifocal and monovision lenses are prescribed for presbyopia varies considerably by country, an international survey report in 2011 revealed the rate of multifocal soft contact lens prescribing was over 3 times greater than that for monovision soft contact lenses (25% compared to 7%), with survey results revealing an overall low rate of presbyopic contact lenses prescribing.³⁹ However, in more recent years the multifocal market share has grown due to technological advances in lens design, materials and manufacturing methods, as well as the availability of various lens replacement options and the increased practitioner confidence.^{38–41} Although such technological advances may attempt to satisfy the complexity of presbyopic treatment requirements, the development of age-related conditions such as dry eye may hinder patients' lens-wearing experience in terms of vision and comfort.^{42,43}

Females are more likely than males to wear contact lenses for presbyopia, owing in part to cosmetic reasons.^{39,44} In a survey of 14,690 patients in the UK, women were twice as likely to have a presbyopic contact lens correction,⁴⁵ and an Irish study found that 65% of the patients (N=97) undergoing surgical compensation of presbyopia and additional ametropia were female.⁴⁶

Surgical Options

The increased use of digital devices, coupled with an increase in patients continuing to work past retirement, has resulted in permanent vision correction options becoming particularly attractive to the aging population.⁴⁷ Advancements in lens design alongside an increased variety of surgical options over the past decades have also led to its increased popularity.^{48–50}

Refractive Lens Exchange

Refractive lens exchange (RLE), in which the natural crystalline lens in the eye is replaced with an intra-ocular

lens (IOL), can effectively reduce or mitigate the need for reading glasses by using monovision, multifocal, extended depth of focus, or accommodating intraocular lens implants (Table 1).⁵¹ Monovision single vision lens implants are only appropriate for certain patient categories, and effective patient selection is crucial for a successful outcome of the procedure.^{52,53} Current multifocal IOL designs predominantly provide good visual outcomes,⁵⁴ with trifocal toric IOLs found to provide significantly better near vision than extended depth of focus IOLs while providing similar intermediate and distance VA outcomes.⁵⁵ Accommodating intraocular lens implants respond to ciliary body contraction, thus inducing accommodation, although current designs induce some inevitable side effects, such as limited amplitude of accommodation and a high rate of posterior capsular opacification.⁵⁶ New generation accommodating IOLs are now under investigation.⁵⁷ A recent development in RLE is the light adjustable lens, which permits post-operative titrations in IOL power after the eye has healed, facilitating customization and optimization of the lens to achieve the desired prescription (Table 1).⁵⁸

In terms of patient satisfaction after surgical correction for presbyopia, a multicenter study in 2015 reported that three months after undergoing RLE with a zonal refractive IOL, over 90% of (220) patients found the procedure improved their lives, and 93.5% were willing to

Table 1 Current Surgical Options for Presbyopia

Site	Surgical Options
Cornea ^{65,108–110}	<ul style="list-style-type: none"> • Monovision (LASIK) • Presbyopic LASIK* (multifocal laser ablation) • Photorefractive keratectomy (PRK) • Intracor Femtosecond Laser (LASIK) • KAMRA™ Corneal Inlay • Conductive keratoplasty
Lens: refractive lens exchange ^{26,111}	<ul style="list-style-type: none"> • Monovision (monofocal IOL) • Multifocal IOL • Accommodative IOL • Light adjustable lens
Sclera* ⁷⁵	<ul style="list-style-type: none"> • VisAbility Micro-Insert scleral implant (Refocus Group, Dallas, TX, USA) • Scleral laser anterior ciliary excision (LaserACE, Ace Vision Group, Newark, CA, USA) • Scleral laser micro-excision

Note: *Not FDA-approved

Abbreviations: IOL, intraocular lens; LASIK, laser-assisted in situ keratomileusis.

recommend it to friends and family.⁵¹ Similarly, in a more recent case series study, 96% of emmetropic participants would recommend unilateral RLE with multifocal IOL implantation to friends and family.⁵⁹ A separate retrospective chart review of 29 patients implanted with a diffractive multifocal IOL found that all patients who underwent bilateral RLE were spectacle-free at their 6 month check. Among these, the group with habitual spectacle use pre-operatively were the most satisfied with their post-operative visual performance.⁶⁰ In a medical record study of 304 patients implanted bilaterally with multifocal IOLs, patients' scores on the "Freedom from Spectacles Value Scale" questionnaire were between 3.8 and 4.4 (of a maximum of 5), indicating a high degree of satisfaction following surgery.⁶¹ In contrast, the most identifiable causes of dissatisfaction after implantation of presbyopia-correcting IOLs are residual refractive errors and dry eye symptoms.⁶²

Recent results on the implantation of a presbyopic phakic intraocular contact lens in the posterior chamber of 16 eyes (8 patients) have demonstrated that patients had good visual acuity and were fully independent of spectacles for both far and near distance four weeks following surgery. No significant change in intraocular pressure and no complaints of halo or glare were reported, with overall high patient satisfaction regarding the quality of vision. However, longer-term data are needed to assess the outcomes of this intervention.⁶³

Corneal Procedures for Presbyopia

Other surgical options for presbyopic individuals involve procedures such as corneal inlays and laser surgery (Table 1).

Corneal inlays consist of a minimally invasive surgical implantation of an inlay into the corneal stroma of one eye and has advantages including reversibility and repeatability while providing high levels of satisfaction and spectacle independence for near vision.^{14,53,64–67} The disadvantages of corneal inlays are a potential compromise of night vision and distance vision, and the long-term potential for corneal haze development. The three types of corneal inlays are corneal reshaping inlays, refractive inlays, and small-aperture inlays.⁶⁴ The Raindrop Near Vision Inlay, a corneal reshaping transparent hydrogel implant, was recalled by the FDA in 2018, due to an increased risk of corneal haze observed in a post-approval study of 150 patients who were followed for 5 years after implantation.⁶⁸ KAMRA™ (Acufocus, Inc.),

an FDA approved small-aperture inlay, currently has more data supporting its efficacy and safety than of any other inlay. In a cohort of 32 emmetropic presbyopic eyes, long-term results of monocular KAMRA™ inlay implantation showed maintenance of near vision acuity, with only one inlay removed at 36 months.⁶⁹ In a more recent study, KAMRA™ was found to be safe and effective among 507 emmetropic presbyopes, however, 44 (8.7%) inlays were removed from the full cohort within 3 years.⁷⁰ In contrast to monovision which also targets one eye, inlays do not compromise distance visual acuity, however small-aperture corneal inlays such as KAMRA™ can restrict light entering the eye which may reduce contrast and night vision.

While patients undergoing surgical interventions generally report satisfactory outcomes post-operatively, they may experience significant regression over time, with some reverting to their pre-operative refractive state.⁷¹ Many patients may eventually need reading glasses again after corneal inlay surgery,⁶⁴ and over half of patients undergoing unilateral RLE were found to require spectacles post-operatively.⁶⁰ Surgical correction strategies for presbyopia may also disrupt the corneal epithelium and ocular surface, which can impact outcomes and exacerbate dryness in the aging presbyopic eye.⁷²

In terms of laser surgery, monovision or multifocal laser in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK) can be used to remove corneal tissue and reshape the cornea to reduce the need for reading glasses in presbyopic individuals (Table 1). Monovision laser vision correction, in which one eye is optically corrected for distance and the other eye for near vision, often results in reduced binocular visual acuity and stereopsis.⁷³ In saying that, monovision laser correction in myopic individuals has been shown to result in sustained vision outcomes and good patient satisfaction.⁵² Multifocal (or presbyopic) LASIK and PRK aim to correct vision by changing the refractive power of the cornea by either increasing depth of focus by ablation of the peripheral cornea (transitional multifocality and peripheral presbyLasik) or by creating a bifocal cornea (central presbyLasik).⁷⁴

LASIK is also useful in that it can provide a minimally invasive option for conversion to bilateral distance correction or enhancement of the distance eye following surgical monovision correction, as patients who have had surgically induced monovision appear to be more sensitive to

changes in their distance eye, and thus are more likely to request enhancement for small residual refractive errors.⁶⁴

Scleral Correction Procedures for Presbyopia

Scleral approaches are based on the Schachar's theory of accommodation and attempt to preserve or restore the accommodative ability of the eye by expanding the equatorial scleral diameter overlying the ciliary body and restoring zonular tension.⁷⁵ Although, the theoretical justification of such procedures remains controversial, there has been increasing interest in scleral interventions, which use laser scleral micro-excisions and scleral micro-inserts (Table 1).⁷⁵

Unmet Needs of Presbyopic Patients

Even though the global prevalence of presbyopia is continuing to increase with population growth,⁵ patients' experience of presbyopic treatment options has been insufficiently investigated, although there is increasing interest in the topic. A recent social media listening study found that individuals with presbyopia experienced difficulties with reading and electronic devices, and felt inconvenienced by the use of varifocal glasses and contact lenses.⁷⁶ An online survey of pre-presbyopic and presbyopic volunteers perceived comfort and convenience of their optical correction as more important than cost, with spectacles preferred over multifocal contact lenses for near vision correction.⁷⁷ Multifocal IOLs have been shown to improve patients' quality of life, in contrast to patient satisfaction following presbyopic LASIK, which was found to be similar to reading glasses.⁷⁸

All currently available treatment methods require the patient to accept some compromises in the quality and flexibility of vision offered at different distances.²⁶ However, could such compromises increase the risk of falls and injury?⁷⁹ Falls among presbyopic age cohorts are identified as a significant public health concern.⁸⁰ Presbyopes wearing multifocal glasses can experience blurred vision when viewing distant objects through the lower part of the lens, as well as impaired depth perception, leading to a higher incidence of falls.^{81,82} A one-year prospective cohort study of 156 people aged 63 to 90 found that multifocal spectacle wearers were twice as likely to fall as those not wearing multifocal spectacles, due to impaired depth perception and edge-contrast sensitivity, especially in unfamiliar settings outside the home or when negotiating stairs.⁸³ A study of healthy individuals

found that monocular blur in monovision correction led to significant reductions in stereoacuity and spatial perception.⁸⁴ However, another study reported that spectacle magnification rather than lens blur was responsible for step negotiation and mobility problems experienced by elderly glass wearers.⁸⁵ The Visual Intervention Strategy Incorporating Bifocal & Long-distance Eyewear (VISIBLE) randomized controlled trial (N=606 patients, mean age 80 years) found that replacing multifocal spectacles with single vision spectacles for walking and outdoor activities in elderly individuals resulted in an 8% reduction in falls.⁸⁶ The provision of intermediate addition multifocal spectacles (of ~1.00–1.25 D) instead of a full addition lens, worn inside and outside the home, has been proposed to help reduce falls whilst avoiding continuous switching of glasses in elderly populations.⁸⁷ Furthermore, some clinicians recommend only prescribing partial changes in refractive error in older patients to help adaptation.⁷² However, these recommendations are not evidence-based, and further research is needed on the effect of ocular or spectacle magnification on mobility and falls.

Future Outlook for Presbyopia

Topical pharmacological options currently being investigated can be defined under two general categories: those working via pupil modulation and those aiming to restore accommodation.⁸⁸

Symptomatic Relief of Presbyopia Symptoms via Pupil Modulation

The majority of formulations under development are included in the first group, which involves increasing the depth of field by parasympathetic-mediated miosis and ciliary muscle stimulation, or lens softening to temporarily ameliorate the symptoms of presbyopia.^{89,90} These therapies, which include pilocarpine, carbachol, acetylcholine/brimonidine tartrate, FOV Tears, AGN-190584, AGN-199201, PRX ophthalmic solution, Nyxol, CSF-1 and VISION-1, rely on improving near vision for a period of 6 to 8 hours (Table 2).^{75,89–101} Pilocarpine formulations have varying concentrations, from less than 0.5% to above 1%. Higher concentrations may provide a longer duration of effect, whereas lower concentrations may show less adverse events or increased comfort.¹⁰² The Phase 3 trials (NCT03857542 and NCT03804268) of AGN-190584, a miotic agent, were completed in late 2019, and demonstrated a significant

Table 2 Topical Pharmacological Options Currently Under Investigation, Defined as Those Working via Pupil Modulation or Aiming to Restore Accommodation

Compound Name and Formulation	Mechanism of Action	Clinical Development Status	Key Findings	Manufacturer/ ClinicalTrials.gov
Pupil modulation				
Carbachol/brimonidine	Miotic	Phase 2	Statistically significant improvement in NVA over placebo; effect was maintained over 3 months (N=48)	Therapeutics press release 2020 ⁹¹ Abdelkader 2015 ⁹⁰ Visus
FOV Tears (pilocarpine/ phenylephrine/ polyethyleneglycol/nepafenac/ pheniramine/naphazoline)	Miotic	Phase 1; currently available in Columbia, with Phase 2 studies ongoing	Pupil size initially decreased and NVA improved up to 5 h (N=14)	Renna et al, 2016 ⁸⁹
AGN-190584 ophthalmic solution (pilocarpine)	Miotic	Phase 3 complete FDA registration	A statistically significant greater proportion of participants treated with AGN-190584 gained 3 lines or more in mesopic, high contrast, binocular DCNVA (N=327)	Allergan press release 2020 ⁹² NCT03857542 ⁹³
AGN-199201 ophthalmic solution (pilocarpine/ oxymetazoline)	Miotic	Phase 2	Up to 70% of patients had at least a 2-line improvement in uncorrected NVA (N=151)	NCT02780115 ⁹⁴
PRX ophthalmic solution (aceclidine/tropicamide)	Miotic	Phase 2b	Primary endpoint vs placebo was met; duration of effect was approximately 7 hrs	Presbyopia Therapies press release 2018 ⁹⁵
Nyxol (phentolamine ophthalmic solution)/ pilocarpine	Miotic	Phase 2	Primary endpoint is percentage of subjects with ≥ 15 letters of improvement in photopic binocular DCNVA	Ocuphire ⁹⁶ NCT04675151 ⁹⁷
CSF-1	Miotic	Phase 2b complete	Statistically significant improvement in DCNVA of a 3-line or greater gain.	Orasis Pharmaceuticals press release ⁹⁸ NCT03885011 ⁹⁹
VISION-1 (pilocarpine)	Miotic	Phase 3	Primary outcome is the proportion of subjects gaining ≥ 15 letters in mesopic, high contrast, binocular distance corrected near visual acuity (DCNVA) [Time Frame: 120 minutes post-dosing]	Eyenovia ¹⁰⁰ NCT04657172 ¹⁰¹
Treatments for the underlying cause of presbyopia				
UNR844	Lipoic acid choline ester	Phase 1/2	Bilateral DCNVA improved, with 53.1% UNR844 vs 21.7% placebo subjects gaining ≥ 10 letters. Improvements in DCNVA were sustained at 5 and 7 months after UNR844 dosing ceased.	Novartis NCT02516306 ¹⁰⁶
UNR844	Lipoic acid choline ester	Phase 2a	Bilateral DCNVA improved, with a four-letter median difference between UNR844 vs placebo groups ($p = 0.0924$), and no meaningful differences in side effects	Novartis NCT03809611 ^{105,112}

Notes: \geq , greater than or equal to; (DC)NVA, (distance-corrected) near vision acuity; N, study population sample size; P, statistically significance; vs, versus. This table only includes products for which clinical data is available.

improvement in near vision and patient-reported outcomes (PROs) with a once-daily bilateral administration of AGN-190584 ophthalmic solution for 30 days compared with placebo in presbyopic adults aged 40 to 55 years. The most common adverse effects were headache, conjunctival hyperaemia, blurred vision and eye pain, reported by $\geq 3\%$ of AGN-190584 treated participants.⁹² A further recent non-randomized, case series, 8-year retrospective study found that pilocarpine/diclofenac eye drops were an efficient treatment for emmetropic or presbyopic individuals, providing spectacle independence for near visual tasks.¹⁰³ A combination topical preparation of carbachol and brimonidine has been shown to provide a longer duration of action in correcting presbyopia than pilocarpine.¹⁰⁴

Treatments for the Underlying Cause of Presbyopia

The second group includes pharmaceutical treatments exploring novel mechanisms of action in presbyopia, in order to address the underlying causes of the condition, by investigating age-related lens stiffness and associated increasing lens disulfide content.^{3,105} The prodrug UNR844 is currently under investigation and in a Phase 1/2 study (NCT02516306) comprising 75 patients aged 45–55 years, the UNR844 treatment group gained an average of approximately one line (5 letters) over placebo and two lines (10 letters) over baseline after 90 days of treatment, with the benefit maintained until the final assessment, carried out 7 months after cessation of treatment (Table 2).¹⁰⁶ The results from this study demonstrate UNR844 to be a well-tolerated, effective pharmacological intervention for improving near visual acuity. These results, along with the subsequent Phase 2a study results, support the further development of this therapeutic approach as a potential treatment for presbyopia.¹⁰⁵

A further new chemical entity developed by ViewPoint Therapeutics targets protein misfolding and aggregation to treat and prevent lens disorders; this approach is being tested in cataract and potentially presbyopia.¹⁰⁷

Such approaches present an attractive alternative to near lenses or surgical interventions and, if successful, would mark a milestone in the management of presbyopia.³² However, while progress has been made in the development of non-invasive therapies, none of these are sufficiently developed to become routine interventions.²⁷

Conclusion

Presbyopia is a common condition with increasing prevalence in a globally aging population. Yet, all currently available presbyopic correction methods require the patient to accept compromises in the quality and flexibility of vision offered at different distances. Currently, there is no major pharmacologic therapy to address the unmet needs of presbyopic patients. As uncorrected or sub-optimally corrected presbyopia can have a considerable impact on patients' daily activities and quality of life, a unique and ideal solution, or a treatment that restores true accommodation, is a priority.

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