Review

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New insights in presbyopia: impact of correction strategies

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ABSTRACT

Presbyopia occurs when the physiologically normal age-related reduction in the eyes focusing range reaches a point, when optimally corrected for distance vision, that the clarity of vision at near is insufficient to satisfy an individual's requirements. Hence, it is more about the impact it has on an individual's visual ability to function in their environment to maintain their lifestyle than a measured loss of focusing ability. Presbyopia has a significant impact on an individual's quality of life and emotional state. While a range of amelioration strategies exist, they are often difficult to access in the developing world and prescribing is generally not optimal even in developed countries. This review identified the need for a standardised definition of presbyopia to be adopted. An appropriate battery of tests should be applied in evaluating presbyopic management options and the results of clinical trials should be published (even if unsuccessful) to accelerate the provision of better outcomes for presbyopes.

INTRODUCTION

Presbyopia and its impact on visual impairment, particularly in countries such as China,[1] is increasing due to population ageing.[2] Presbyopia is more than just near visual loss or a functional decline in the crystalline lens' ability to accommodate. As presbyopia is derived from Ancient Greek πρέσβυς translated into Latin (présbus, 'old man') and ὤψ (ṓps, 'eye' or to 'see like'),[3] a definition, centred on the patient's functional experience to fit this etymology has been proposed. Here, 'presbyopia occurs when the physiologically normal age-related reduction in the eyes focusing range reaches a point, when optimally corrected for distance vision, that the clarity and comfort of vision at near is insufficient to satisfy an individual's requirements'.[4] The definition acknowledges that presbyopia is defined by the impact of the tasks that an individual conducts rather than physiological ocular changes in isolation. Hence, this review assimilates the contemporary evidence-base concerning correction strategies and their impact on presbyopia. Despite not explicitly defining presbyopia as relating to the inability to perform near tasks, Mah[5] argues presbyopia is a medical condition and a disease. A recent ophthalmic consensus group proposed the average characteristics related to mild, moderate and advanced presbyopia should be based on the near add requirement, distance corrected near vision and Jaegar equivalent in photopic and mesopic conditions, behavioural adjustments, age and refractive error considerations; the rationale for this mainly clinical measurement-based approach was to 'facilitate consistency between healthcare practitioners and their ability to best match patients to the optimal treatment', but this needs to be task demand and environment specific.[6]

IMPACT OF PRESBYOPIA AND ITS MEASUREMENT

Presbyopia is associated with individual, societal and economic burdens. With between 1.09 billion and 1.80 billion individuals estimated to be affected by presbyopia globally,[7–9] its impact is both far-reaching and variable. In a recent systematic review of the burden of presbyopia,[9] the paucity of data regarding productivity and economic issues was highlighted, along with the need for primary studies to address local and global economic impacts of presbyopia. Estimates from a single modelling study indicated that global productivity losses of US$25 billion could be attributed to uncorrected presbyopia, equivalent to 0.037 % of the global gross domestic product (GDP) for presbyopic working-age adults aged 65 years and under.[10] Donaldson[11] highlighted the often inadequate correction of presbyopia in lower-income countries, which results in substantial societal impact. In a large randomised trial based in rural Assam, India, a significant increase in productivity (and associated income) of tea pickers aged 40 years and older was achieved with spectacle correction of presbyopia, compared with those who remained uncorrected during the study.[12] However, the burden of presbyopia on productivity is variable across regions, and potential loss of GDP depends on factors including prevalence, mortality and employment rates, in addition to the nation's level of development.[10] Even in economically developed countries, uncorrected presbyopia can be problematic due to a lack of awareness of the condition.[13]

The negative patient impact of presbyopia on visual function and quality of life is of global significance. A range of patient-reported outcome measures (PROMs) have been applied in presbyopia to evaluate the impact of the condition and the efficacy of treatment modalities from a patient perspective, and to support regulatory evaluation and marketing claims. In a recent review of PROMs in presbyopia research, the shortage of presbyopia-specific instruments was acknowledged, with many studies having applied generic eye disease measures.[14] Of 13 PROMs identified that had been used to assess vision outcomes in presbyopia or similar visual conditions, only the 11-item Near Activity Visual Questionnaire (NAVQ)[15] was presbyopia-specific. The NAVQ is now undergoing an update to reflect technological change since its development and validation among an entirely phakic cohort, to optimise its value in presbyopia research and supporting product label claims.

As an alternative to conventional PROMs, Kandel *et al*[16 17] described the development and evaluation of refractive error item banks (consisting of fixed sets of items administered to all participants) implemented using computerised adaptive testing (CAT). Individually tailored items can be administered to participants and with just a few items, refractive error quality of life domains may be measured using a staircase method.[16] Item banking with CAT has been proposed to have the potential to supersede conventional PROMs and be of value in routine clinical work and research environments.[18 19] However, question-based approaches to the evaluation of vision-related quality of life rely on patient memory of visual experiences. The Multifocal Acceptance Score MAS-2EV[20] has been described recently, and involves participants making judgements of the quality of their vision based on a set of digitised images representing different visual activity areas in daily life, as well as a near stereoacuity test. The MAS-2EV approach may be of particular value in evaluating and comparing presbyopic correction options for an individual and further work is ongoing to evaluate the metric further and compare with validated questionnaire-based approaches.

In recent years, significant increases in myopia prevalence and severity have been widely reported in several regions, most notably East Asia.[21] In affected regions, an increasing proportion of presbyopes will therefore have myopic refractive errors. Using the Refractive Status and Vision Profile PROM, Yang *et al*[22] examined the impact of myopia severity and form of visual correction on vision-related quality of life in presbyopic adults in Singapore. High myopes (spherical equivalent (SE) ≤–5.00 D) were found to have significantly poorer overall quality of life than low myopes (SE≤–0.50 D to SE>–5.00 D) as well as poorer functionality with and without spectacles. Myopic presbyopes wearing progressive addition spectacle lenses (PALs) reported significantly better quality of life scores in some areas compared with those wearing single vision distance lenses; in low myopes, overall quality of life was better in PAL wearers, and among high myopes, functionality scores were better in the PALs group. While these findings indicate that PALs may be a favourable form of spectacle correction in myopic presbyopes, care is needed in selecting the best strategy for presbyopia correction in older adults.[23] Falls represent a significant risk of morbidity and mortality around the world, particularly in the older population.[18] Both multifocal/ PAL and monovision correction options may be associated with an increased risk of falling[23] due to factors such as monocular blur, reduced stereoacuity, prismatic effects and/or variable refractive power across the visual field.

PREVALENCE AND REMEDIATION ADOPTION

The reported prevalence of presbyopia is variable, in part due to the lack of alignment with a single definition. In terms of correctable near visual impairment, it increases steadily from 40 years, reaching a maximum of about 80% by 55 years of age.[24] This is presumably due to the number of people with low to moderate myopia who can remove their glasses to conduct near tasks (see above), and this number is projected to increase to approximately half the world's population by 2050.[25] There is a decline in correctable near vision after this point in many low-income and middle-income countries due to untreated ocular pathology. The onset is earlier in some regions, such as in subcontinental and African populations, but this has been attributed to ethnic variations rather than environmental differences.[24] Differences in the onset of presbyopia between male and females has been noted in some country-based studies, but not in multinational analysis.[24] Other risk factors associated with presbyopia include dry eye disease (even matching for age and sex)[26–28] and diabetic glycaemic level.[29] One study has also reported associations with cigarette smoking, pregnancy, refractive error, sunglasses use and alcohol consumption.[30]

Presbyopia is undercorrected in many low-income and middle-income countries, with reading correction available for only 6%–45% of those who require this due to a lack of adequate diagnosis and affordable treatment.[24 31] The Global Burden of Disease Study[32] estimated in 2020 that approximately 510 million people worldwide have visual impairment from uncorrected presbyopia (defined as worse than N6 or N8 near acuity at 40 cm when best-corrected distance visual acuity was 6/12 or better). This represented a 6.3% increase over the past three decades (largely in Eastern Europe and Africa) and this is predicted to increase to 866 million in 2050 due to population ageing.

A near spectacle correction is rarely worn in low-income and middle-income countries (<10%) compared with reading glasses being worn by 63% in Guangzhou (and 5% with correction for distance and near) and 39% in Los Angeles (with 33% with correction for distance and near).[33] In reality, 88%–99% of people in low-income and middle-income countries had no refractive correction compared with 27% in the developed countries examined.[33] However, a more recent study found 26.5% had spectacles in a state in India[34] and 28% had presbyopia correcting spectacles in southwest Nigeria.[35] As previously noted, the myopia epidemic,[25] particularly across Asia, may reduce some of the burden of presbyopia although will further exacerbate visual impairment through poor access to refractive correction for distance.

Few studies have examined the real-world use of presbyopic corrections in developed countries. A study of over 500 presbyopes in London found that many used a combination of refractive corrections, predominantly near and multifocal spectacles, but 55% wore no correction for on average 64% of the day. Surprisingly, over half identified their principal tasks as generally being at far distances and these individuals reported a consistently better quality of vision than those who identified their primary tasks as being at closer distances.[36]

THE PATIENT EXPERIENCE OF / JOURNEY THROUGH PRESBYOPIA

While much previous research has evaluated the impact of presbyopia and its correction on quality of life using various quantitative instruments,[14] there are few published qualitative studies specific to the lived experience of the condition. Social media reviews can enable identification of relevant topics and themes in an area, with a large sample size that may span multiple countries[37]; across over 2000 relevant social media posts, the impacts on life most commonly reported by presbyopes were difficulties reading (56.8 %) and using digital devices (25.9 %), particularly mobile phones, along with limitations in sport and leisure activities (9.9 %). Of posts linked to the emotional impact, sadness (61.4 %) was most frequently cited, with other negative emotions including anger (12.3 %) and fear (10.5 %).[38] An in-depth qualitative study using a focus group approach to evaluate patient attitudes and knowledge of presbyopia along with preferred correction options, reported a similar level of negativity.[39] While general acceptance of the condition was apparent, 44 % of those who did not yet use a near correction had a reluctant outlook. The word 'presbyopia' was unfamiliar or not understood by around two-thirds of participants and the consensus was that information on presbyopia should originate from eye care practitioners. Regarding options for the correction of presbyopia, comfort, convenience and standard of vision were felt to be more important than cost.

Patient experience of, and progression through presbyopia may be influenced by factors including sex, ethnicity and refractive correction. In a large scale survey of 2000 presbyopes in Japan, the mean age at which symptoms such as 'hard to see small letters up close' and 'see better when I increase distance from the object' were first experienced ranged between 43.9 years and 46.7 years, with males becoming aware of symptoms at a younger age than females and experiencing a greater burden on near vision.[40] Accompanying clinical data from contact lens wearers indicated that females were more likely to tolerate early presbyopia through undercorrection of myopic refractive errors, compared with males who preferred full myopic correction. The mean age at which first reading glasses were obtained was around 48 years. In a smaller prospective study, also based in Japan, awareness of presbyopia was present in 50 % of participants aged 45–49 years, rising to 87.5 % in those aged 50–54 years and 100% in the 55–59 years age group.[13] None of the 15 participants aged 44 years and under were aware of presbyopia, in contrast to the report of Negishi *et al*[40] where 38% of respondents indicated that that they had become aware of difficulties focusing before 40 years of age, although these data were based on historical recall. Notably, the work of Tsuneyoshi *et al*[13] highlighted that patient awareness of presbyopia and difficulty with near tasks increased dramatically when binocular near visual acuity with habitual correction reduced to 0.0 logMAR (20/20); at this level, more than 80 % of patients were aware of presbyopia, and most had difficulty reading a newspaper or reading a book for an extended period. The data indicate that a near visual acuity of better than 0.0 logMAR is needed for comfortable near vision and it was proposed this may represent a useful threshold in the diagnosis of presbyopia and clinical analysis of treatment options. Interestingly, presbyopia also seems to have developed earlier during the COVID-19 pandemic, perhaps due to stress and increased digitalisation.[41]

Studies of presbyopia progression are relatively scarce; conventionally, the typical rate of progression of near add power has been cited as +0.10 D/year, based on data largely derived from Caucasian individuals.[42,43] Presbyopia progression over 6 years within the large-scale Singapore Epidemiology of Eye Diseases study[44] was lower than the anticipated mean add of +0.60 D, at +0.25 D. Younger presbyopes (40–49 years) were more likely to experience progression compared with those aged 60 years or over. Ethnic variation was also observed, with Malays more likely to experience add progression than Chinese or Indian individuals. In the Chinese participants, the near vision power change over 6 years (+0.16 D) was almost identical to the +0.15 D reported by Han *et al*[45] in a cohort of 303 Chinese. Further work is required to understand fully the variation in presbyopia progression with ethnicity, and it has been recommended that near addition prescription guidelines tailored for different ethnicities are developed.[44]

Digital eye strain (DES, a.k.a computer vision syndrome) refers to the spectrum of visual and ocular symptoms that may be experienced with prolonged use of digital devices. Symptoms may be broadly classified as external or internal[46]; external symptoms are closely linked to dry eye and include burning, irritation and tearing, while internal symptoms of eye strain and head/eye ache have been linked to accommodative and/or binocular vision stress. Presbyopes may face particular challenges with use of digital devices due to reduced accommodative amplitude, postural issues which can result from bifocal or progressive addition spectacle corrections[47] and the increased prevalence of dry eye disease in presbyopic age groups.[26–28] The prevalence of DES in presbyopes appears to be very high, with recent studies that have employed a validated questionnaire to identify the syndrome,[48] reporting prevalences of 68.1 %[49] and 74.3 %.[47]

Among a presbyopic population using PALs, being female, working under inadequate lighting and having a non-neutral neck posture were associated with significantly greater odds of experiencing DES.[47] Workplace training on lighting and ergonomic postures has been suggested to reduce the occurrence of symptoms.[47] Furthermore, usage of occupational spectacle lenses designed for more intensive intermediate and near work demands, rather than conventional PALs, has been shown to be effective in reducing the DES.[49 50] The beneficial effects of occupational lenses in reducing DES in presbyopes are apparent even in those with minimal/small distance refractive errors.[49 50] The choice of correction modality (single vision spectacles, PALs or contact lenses) does not appear to influence preferred viewing distance for smartphone use in presbyopes, and while the average viewing distance reported by Boccardo[51] was significantly longer in presbyopes (39.0±6.1 cm) compared with prepresbyopes (35.0±6.4 cm), the 0.29 D mean difference in accommodative demand levels is of little clinical relevance. Similarly, Lan *et al*[52] reported a weak positive association between smartphone viewing distance and age in a Chinese population, but highlighted the variety of visual demands and the need for eye care practitioners to gather a detailed history from patients to establish the working distance(s) being adopted to assess refractive and binocular vision functions at these distances.

Treatments for presbyopia

Strategies for ameliorating presbyopia include monovision (adding a near plus power addition to one eye), modified monovision (a combination of monovision and other strategies), moving the eyes to look though a segment of a lens with an increased optical power (typically with spectacles), extending the depth of focus with simultaneous images (typically with bi or multifocal contact lenses or intraocular lenses) asphericity or narrowing the optical aperture, or trying to restore active ocular accommodation (such as with accommodating intraocular lenses or scleral expansion surgery (figure 1).[4]

Spectacles

PALs for the correction of presbyopia vary in refractive power across the lens surface to provide in-focus vision at difference distances. However, the integration of multiple lens curvatures to provide additional powers in PALs induces undesired peripheral aberrations.[53 54] Compared with other forms of refractive correction for presbyopia, published clinical comparisons have been limited. Lens power profile aspects such as the far viewing zone width, near viewing zone width, blur gradient smoothness and the amount of distortion can be varied and lead to higher satisfaction when personalised (in 82% of n=51 participants)[55] and designs have been successfully modified to better suit computer users.[56]

Pharmaceutical treatments

Arguably, one of the most promising treatment approaches with potential to ameliorate presbyopia symptoms rests with the use of pharmaceutical agents. Indeed,

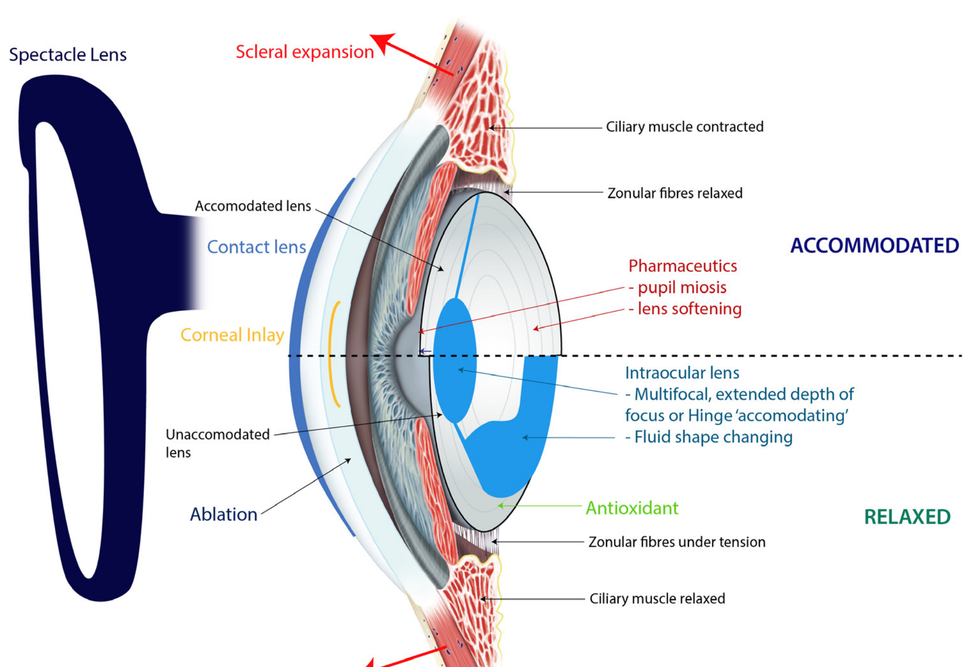

Figure 1 Treatments for presbyopia and where they are located/act (copyright Aston University 2023).

a cocktail of drugs are currently under investigation (see table 1). Of these, two main options appear to be gaining increasing interest: drugs that modify pupil size (and therefore depth-of-focus with a potential secondary myopic shift in reaction),[57] and those that aim to restore dynamic accommodation to the ageing eye via crystalline lens softening.[58]

Many of the drug formulations in current and recently completed clinical trials (table 1) are designed to modify pupil size and, in some cases, stimulate ciliary muscle function for a limited period of time each day (up to 8 hours in most cases). A recent retrospective, non-randomised case series to evaluate the safety and efficacy of patients treated topically with 'Benozzi's method' for presbyopia (ie, pilocarpine and diclofenac preservative-free eye-drops) from January 2011 to June 2018, showed a trend towards near vision spectacle independence.[59] Based on data from 910 participants (aged 40–59 years), baseline uncorrected near visual acuity (UNVA) over the 8-year period (as measured by Jaeger scale) improved from 4.74 (SD 1.53) to 1.36 (SD 0.48), while binocular uncorrected distance visual acuity remained stable (baseline 0.00 (SD 0.01) logMAR, 8 years 0.03 (SD 0.04) logMAR. Although some side effects were reported (such as decrease of light perception, headaches, symptoms of ocular surface dryness and dizziness) these resolved in those patients who continued with the treatment. Of note Allergan's VUITY (1.25% pilocarpine) presbyopia treatment received Food and Drug Administration (FDA) approval at the end of October 2021.

A further study reporting near vision, optical quality and pupil diameter of a new pharmacological therapy (FOV tears) in 177 presbyopic individuals (41–65 years old) found a significant ($p < 0.001$) improvement in UNVA from 0.35 LogMAR to 0.16 LogMAR at 2 hours of FOV drug use.[60] Nine individuals did not show an improvement in UNVA, while approximately 12 % (n=14) reported headaches as a side effect of the drug. The study observed that the group with the youngest participants gained more lines than the group with the oldest, which suggests a secondary mechanism in addition to pupil miosis (ie, a small myopic shift in refractive error) may also contribute to the outcome. A subsequent study from the same clinical research group on patients who had previously undergone corneal refractive surgery with either laser-assisted in-situ keratomileusis (LASIK), monovision or PresbyLASIK in addition to a nonsurgical control group,[61] demonstrated a statistically significant improvement in the uncorrected near vision of individuals in all groups ($p = 0.001$).

With phase 3 trial data for the muscarinic agonist AGN-190584 still unpublished (NCT03857542 and NCT03804268), phase 2 outcomes for AGN-199201 and AGN-190584 (NCT02780115) demonstrate a significant increase in UNVA from baseline compared with placebo with medium ($p < 0.001$) and higher ($p < 0.005$) doses of AGN-199201 and AGN-190584. No difference was observed with lower doses ($p = 0.1663$). Further, although no serious adverse events were reported, approximately 30 % of participants experiencing 'other' adverse events such as headache, blurred vision and irritation sensation on drug instillation. These drugs all adopt pupil miosis as the mechanism to address presbyopia. However, although pupil miosis induced in the iris plane increases depth-of-focus with minimal impact on peripheral vision,[62] its impact on retinal luminance and, therefore, UNVA in mesopic and photopic conditions remains largely unknown and a challenge for this particular therapeutic treatment. It is, therefore, clear that further studies are required to determine the overall impact these interventions have on near visual function. Indeed, as with many other approaches tested hitherto, it is likely that the effect of miotics on the amplitude and latency of dynamic accommodation will be limited. Perhaps the most promising approach for patients is the opportunity to employ miotic agents, synergistically, with complementary pharmaceutical and non-pharmaceutical interventions.

The proposed lens-softening approach to treat presbyopia symptoms uses lipoic acid and choline ester chloride to release disulfide bonds, thought to be responsible for progressive lens stiffening. In mice, use of this approach leads to a concentration-dependent decrease in lens protein disulfides concurrent with an increase in lens elasticity.[63] A clinical study[64] in presbyopes using the drug EV06 demonstrated improvement in distance corrected near vision acuity over a 90-day, two times per day (after day 7) dosing compared with a control. A follow-up 7 months after cessation of the drops in 34 patients compared with 18 controls indicated the visual benefit was maintained for 5–7 months after the last dose of EV06.[65]

Results from a study examining the efficacy of the topical lipoic acid choline ester (UNR844, 1.5%) in a prospective, multicentre clinical trial of 75 presbyopes,[66] demonstrated that the use of UNR844 produced no safety concerns, with no clinically relevant changes in BCDVA, pupil size or intraocular pressure. Distance corrected near visual acuity (DCNVA) improved in the study eye in the UNR844 group compared with placebo during the 91 days of treatment (UNR844 vs placebo, mean change in LogMAR (SD); −0.159 (0.120) vs −0.079 (0.116)). Bilateral DCNVA improved, with 53.1 % UNR844 vs 21.7 % placebo participants gaining 10 letters or more. Importantly, improvements in DCNVA were sustained at 5 and 7 months after UNR844 dosing ceased. However, a larger (n=124) phase 2 clinical trial (NCT03809611) on presbyopes aged 45–55, failed to detect a significant difference in binocular DNCVA from baseline (UNR844: 6.1 letters, Placebo: 4.5 letters, p=0.183). Moreover, no significant difference was observed in the number and percentage of participants achieving ≥75 Early Treatment Diabetic Retinopathy Study letters in binocular DCNVA at month 3 (UNR844: n=10 (25.0 %), placebo: n=6 (15.8 %), p = 0.283).

Efforts to improve lens malleability offer an encouraging alternative to established methods of correcting

Table 1 New and emerging topical pharmaceutical approaches aimed at either restoring, or ameliorating the symptoms of presbyopia

Intervention	Mechanism	Current status	No	Age (years)	Findings	Clinical trial information
UNR844 Chloride (UNR844-Cl)	Lipoic acid choline ester chloride	Phase 2	124	45–55	▶ No significant difference in binocular DCNVA from baseline (UNR844-Cl: 6.1 letters, Placebo: 4.5 letters, p=0.183) ▶ No significant difference in number and percentage of participants achieving ≥75 Early Treatment Diabetic Retinopathy Study letters in binocular DCNVA at Month 3 (UNR844-Cl: n=10 (25.0), Placebo: n=6 (15.8), p=0.283) ▶ No serious adverse events. Other adverse events (UNR844-Cl: 14/62, Placebo: 5/62) ▶ Study completed 16 December 2019	Novartis Pharmaceuticals NCT03809611(a)
AGN-241622 (Phase 1) AGN-190584 (Phase 2) ophthalmic solution	Muscarinic agonist	Phase 1/2	144	40–65	▶ Recruiting ▶ Study start date: 27 July 2020 ▶ Estimated study completion date: 28 June 2023	Allergan NCT04403763(b)
Phentolamine (Nyxol, 0.75%) and pilocarpine ophthalmic solution	Non-selective α–1 and α–2 adrenergic antagonist/ M3 muscarinic agonist	Phase 2	150	40–64	▶ Active, not recruiting ▶ Study start date: 15 February 2021 ▶ Estimated study completion date: September 2021	Ocuphire Pharma, Inc. NCT04675151(c)
AGN-190584	Muscarinic agonist	Phase 3	200	40–55	▶ Recruiting ▶ Study start date: second September 2021 ▶ Estimated study completion date: 30 January 2022	Allergan NCT04983589(d)
Pilocarpine, Brimonidine, Oxymetazoline	M3 muscarinic agonist/ α2 adrenergic agonist/ selective α1 and, partially, α2 adrenergic receptor agonist	Phase 1	11	40–60	▶ Complete; no results posted ▶ Study start date: 1 June 2020 ▶ Study completion date: 1 July 2020	Optall Vision NCT05006898(e)
UNR844	Lipoic acid choline ester chloride	Phase 2	225	45–55	▶ Recruiting ▶ Study start date: 30 June 2021 ▶ Estimated study completion date: 22 March 2023	Novartis Pharmaceuticals NCT04806503(f)
Pilocarpine, Brimonidine, Oxymetazoline	M3 muscarinic agonist/ α2 adrenergic agonist/ selective α1 and, partially, α2 adrenergic receptor agonist	Phase 1	11	40–60	▶ Recruiting ▶ Study start date: 14 August 2021 ▶ Estimated study completion date: 15 September 2021	Optall Vision NCT05006911(g)

Continued

Table 1 Continued

Intervention	Mechanism	Current status	No	Age (years)	Findings	Clinical trial information
CSF-1	Muscarinic agonist	Phase 3	300	45–64	▶ Recruiting ▶ Study start date: 26 October 2020 ▶ Estimated study completion date: 14 December 2021	Orasis Pharmaceuticals NCT04599972(h)
CSF-1	Muscarinic agonist	Phase 3	300	45–64	▶ Recruiting ▶ Study start date: 19 October 2020 ▶ Estimated study completion date: 14 December 2021	Orasis Pharmaceuticals NCT04599933(i)
Brimochol	Cholinergic agonist (both muscarinic and nicotinic)	Phase 2	40	45–80	▶ Recruiting ▶ Study start date: 24 March 2021 ▶ Estimated study completion date: 19 October 2021	Visus Therapeutics NCT04774237(j)
CSF-1	Muscarinic agonist	Phase 2	166	45–64	▶ Complete; no results posted ▶ Study start date: 26 February 2019 ▶ Study completion date: 26 July 2019	Orasis Pharmaceuticals NCT03885011(k)
AGN-190584	Muscarinic agonist	Phase 3	427	40–55	▶ Complete; no results posted ▶ Study start date: 1 March 2019 ▶ Study completion date: 10 September 2020	Allergan NCT03857542(l)
AGN-190584	Muscarinic agonist	Phase 3	323	40–55	▶ Complete; no results posted ▶ Study start date: 21 December 2018 ▶ Study completion date: 31 October 2019	Allergan NCT03804268(m)
PRX-100	Muscarinic acetylcholine receptor agonist	Phase 2	58	48–64	▶ A significant difference ($p<0.005$) in the proportion of participants with at least three line (15 letter) improvement in NVA (aceclidine+tropicamide combination: 47.22%, aceclidine: 47.22%; placebo: 2.38%) ▶ No serious adverse events. Other adverse events (aceclidine+tropicamide combination: 22/54, aceclidine: 22/54, placebo: 10/57) ▶ Study completed: 20 May 2018	Presbyopia Therapies NCT03201562(n)

Continued

Table 1 Continued

Intervention	Mechanism	Current status	No	Age (years)	Findings	Clinical trial information
AGN-199201 and AGN-190584	Muscarinic agonist	Phase 2	151	40–55	▶ A significant increase in UNVA from baseline compared with placebo with medium (p<0.001) and higher (p<0.005) doses of AGN-199201 and AGN-190584. No difference with lower doses (p=0.1663) ▶ No serious adverse events. Other adverse events (aceclidine+tropicamide low dose: 8/30, medium dose: 10/30, higher dose: 11/32) ▶ Study completed: 31 October 2017	Allergan NCT02780115(o)
CSF-1	Muscarinic agonist	Phase 2	20	40–65	▶ Complete; no results posted ▶ Study start date: July 2016 ▶ Study completed: June 2017	Orasis Pharmaceuticals NCT02745223(p)
Pilocarpine, Brimonidine, Oxymetazoline	M3 muscarinic agonist/ α2 adrenergic agonist/ selective α1 and, partially, α2 adrenergic receptor agonist	Phase 1	11	40–60	▶ Recruiting ▶ Study start date: 10 August 2021 ▶ Estimated study completion date: 10 September 2021	Optall Vision NCT05001243(q)
AGN-190584 and AGN-199201	Muscarinic agonist	Phase 2	163	40–50	▶ Study completed: 18 October 2017	NCT02595528(r)
EV06	Lipoic acid choline ester chloride	Phase 2	75	45–55	▶ Study completed 10 March 2016	NCT02516306

The table includes clinical studies that commenced on or after 1 January 2016 even where clinical data are unavailable.
CSF, Contrast Sensitivity Function; DCNVA, distance corrected near visual acuity; NVA, near visual acuity; UNVA, uncorrected near visual acuity.

presbyopia by restoring the eye's natural focusing ability in the ageing eye. It is clear, however, that while these methods are gaining pace with many ongoing studies, more data are required to affirm these as mainstream treatment modalities. Indeed, future studies will need to demonstrate not only the improvements in near vision, but also the time over which any improvements are sustained.

Nutrition

As with systemic ageing, oxidative stress is known to be one of the primary mechanisms for crystalline lens opacification.[67] Indeed, a range of observational studies have investigated the association between micronutrients and cataract formation, for example, vitamin A,[68] vitamin C,[69] vitamin E,[70] lutein,[71] zeaxanthin,[72] and α-carotene and β-carotene.[73] Although meta-analyses show an inverse relationship between these antioxidants and cataract development,[74] further interventional studies are required. Perhaps unsurprisingly, the impact of modifying nutritional intake on the genesis, progression and treatment of presbyopia remains underdeveloped.

A recent randomised controlled study examined the effects of a food supplement containing anthocyanin, astaxanthin and lutein on eye function in healthy Japanese adults,[75] appeared to show an improvement in symptoms over the study period. Although the authors state that the 6-week consumption of the supplement inhibited a decrease in the accommodative function caused by visual display terminal operation, their assumptions were based on changes to their participants' relative pupil size in response to an accommodative target, rather than an objective measure of any optical change to the eye. It is, therefore, most likely that any benefit experienced by the active group in the study was a consequence of increased depth-of-focus, rather than accommodative function per se.

Work in an animal (mouse) model has investigated the role α-glucosyl-hesperidin (G-Hsd) may play in maintaining lens antioxidant levels to prevent cataract formation and presbyopia development. Building on a previous study reporting that G-Hsd prevents nuclear cataract formation in 37 weeks old mice,[76] the same laboratory demonstrated that lens elasticity retains a higher level of malleability when compared with those mice administered orally with both 1 % and 2 % G-Hsd.[77] The mechanism appears to be mediated through an affected distribution of Transient Receptor Potential Vanilloid 1 feedback pathways that control lens intracellular pressure.[78] Although these data await replication in humans, the findings suggest that G-Hsd is a potential oral compound to prevent presbyopia and cataract formation. Similarly, Nagashima *et al* examined the effects orally administered resveratrol and two lactic acid bacteria (WB2000 and TJ515) have on rat lens stiffness. Both the short-term and long-term administration of resveratrol and WB2000 mitigated the increase in lens stiffness, whereas the administration of TJ515 alone decreased the lens stiffness with long-term, but not short-term administration.[79] These results indicate that the oral supplementation of an antioxidative diet could be a potential candidate to ameliorate near vision impairment encountered during presbyopia.

In recent years, the worldwide use of herbal medicines for eye diseases has become popular, with studies considering their use to treat age-related macular degeneration,[80] Behçet's disease[81] and diabetic retinopathy.[82] In terms of presbyopia, a 6-month study used a mixed formulation of herbal drugs (Cassiae Semen (200 g), L. barbarum (200 g) and Dendrobium huoshanense (40 g)) to modify autonomic input to the accommodative system.[83] Delivered orally to a cohort of uncorrected emmetropic (within ±1.00 DS) presbyopes aged 45–70 years, the study demonstrated a modest (~0.5 D) improvement in subjective accommodative amplitude (using an RAF rule) with supplement use. In addition to the participants' uncorrected ametropia, however, the methodological approach with Jaeger uncorrected far and UNVA as outcome measures is unable to rule out refractive error and changes in pupil size as confounding variables.

Contact lenses

The benefit of contact lenses to correct presbyopia, due to properties such as the stability of their optics on the visual axis with eye movement, cosmesis and lack of fogging, have been identified as the greatest opportunity to extend the contact lens market.[84] Recent designs can perform as well as PALs,[85] although this is not always the case, and vision and comfort are interrelated.[86] The BCLA Contact Lens Evidence-based Academic Report on contact lens optics[87] recently reviewed the optical designs for the correction of presbyopia. More recent design have focused on an extended depth of focus, through manipulation of the optical aberrations to create a single elongated focal point rather than several foci with multifocal lens designs,[88] with some benefits over the latter design.[89 90]

In terms of real-world performance, a driving simulator study showed no difference in sign identification between progressive addition spectacles and multifocal contact lenses.[91] A pinhole contact lens in the non-dominant eye has demonstrated enhanced intermediate a near vision in patients with presbyopia.[92–94] Although it has been proposed that patient psychological and physical parameters (such as pupil size) should dictate presbyopic contact lens performance and preferences, this has not been found to be the case with current clinical measures.[95 96]

Accommodating intraocular lenses

Early hinged and dual optic designs failed, largely due to fibrosis within the capsule as well as challenges in sizing to effectively couple with the natural changes in the capsule dimensions driven by the ciliary muscle[97]; newer designs have focused on shape changing optics.[98–100]

Soft polymers to replace the hardened crystalline lens are still being worked on[101] and with lenses powered by a membrane-shaped ion polymer metal composite actuator,[102] but this would need connection to an external battery and a method to detect ciliary muscle stimulation. However, human testing of these designs has, as yet, not been reported. ClinicalTrial.gov identifies five Crystalens trials reporting in the mid-2010's, 3 FluidVision trials completing between ~2015 and 2019 (not all the results have been posted) and some terminated trials of dual optic and other designs. Of the studies that have attempted to measure true objective accommodation (not including suggested 'objective' techniques such as dynamic retinoscopy), the only FDA-approved intraocular lens with an 'accommodating' indication was found to move backwards rather than the intended forward direction with accommodative effort[103] and while it was suggested some dynamic objective accommodation (assessed with dynamic wavefront aberrometry) could be measured in the first couple of months after implantation,[104] as also seen with another hinge optic 'accommodating intraocular lens,[105] no dynamic accommodation was detected using a similar measurement technique in another study[106] or with autorefraction.[107–109] Other implanted 'accommodating' lens designs have also found to display no significant dynamic optical change with accommodative effort.[109 110] Hence, the holy grail of restoring more natural eye focusing with an 'accommodating' intraocular lenses still seems far off.

Multifocal and extended depth of focus intraocular lenses

A recent review[111] addressed the influx of over 100 multifocal (with a discrete near and potentially a supplementary intermediate focal near addition) and extended depth of focus (with a single, but extended clear focus range) intraocular lens designs now available on the market. Extended depth of focus lenses do not provide a sufficient range of clear focus for sustained near task performance, whereas for multifocal intraocular lenses, in-focus (providing suitable vision for the distance of interest) and out-of-focus images (which must be suppressed) are presented at the retina simultaneously. Refractive multifocal designs have zones of different power, aspheric optics or a combination of both. Such optical systems are dependent on pupil dynamics and centration, and can cause photic phenomena such as halos and glare. Diffractive designs can cover the entire optic of the lens overcoming pupil dependency and the eschelets can be alternated in height profile to create trifocal designs.[112] Small apertures can also increase the depth of focus[113] and decentred optics can provide multifocality with less dysphotopsia.[114]

Two recent systematic review both concluded that multifocal intraocular lenses provide improved uncorrected near vision and a higher proportion of spectacle independence than monofocals, but with a greater risk of unwanted visual phenomena, with newer diffractive designs performing best.[115 116] However, as cross-over trials are not possible and lens comparison studies generally examine only a small range of lenses in a limited number of patients, clinical selection of the best lens for a patient is largely between monofocals, extended depth of focus lenses and full multifocals, rather than within these categories. Lens aberations need to be considered in conjunction with the individual's aberrations,[117] but seem to predict visual outcomes well[118] so offer the opportunity for enhanced clinical prediction. Machine learning has recently been applied to intraocular lens power calculations[119] and could also in future assist clinicians in synthesising large amounts of clinical data including optical coherence tomography (OCT) biometry and aberration data, to identify the best multifocal intraocular lens for an individual patient.

Ablation

While monocular use of LASIK can be used to correct near vision in a similar way to that adopted by monovision contact lenses,[120] presbyLASIK is a technique where the cornea is ablated using multifocal ablation profiles to correct ametropia and presbyopia bilaterally.[121] Typically, patients undergoing presbyLASIK do not present with clinically significant cataract, and their resulting vision often maintains satisfactory levels of stereopsis.[122122] Having increased in popularity in recent years, the technique can be classified into three broad approaches: central presbyLASIK; peripheral presbyLASIK and Laser Blended Vision (LBV).

As the most commonly performed corneal laser surgery to treat presbyopia,[123] central presbyLASIK adopts a centre-near design to the corneal ablation pattern (eg, AMO VISX,[105] SCHWIND PresbyMAX,[106] and Technolas SUPRACOR),[107] while peripheral presbyLASIK adopts a centre-distance approach.[124] The LBV technique increases depth of focus by modifying either spherical aberration (eg, Presbyond)[109] or asphericity (eg, Custom Q).[108] Although the aforementioned techniques each have their own set of advantages and disadvantages, in terms of baseline refractive error correction, Shetty and colleagues[122] suggest the preferred choice for myopes and emmetropes would be PresbyMAX hybrid, Presbyond and monovision LASIK, while for hyperopes, clinicians and patients may elect for Supracor, PresbyMAX symmetric, Custom-Q and Presbyond.

Scleral implants

Based on the somewhat controversial theory that presbyopia occurs largely due to an expansion of the crystalline lens with age, reducing circumlental space between the lens equator and the ciliary muscle and, in turn, releasing the tension on the ciliary zonules,[125 126] scleral expansion bands have been developed to attempt to reverse this effect. Despite work questioning the role of age-related changes to the circumlental space,[127] studies have shown an improvement in near acuity and measurable range of eye focus postimplant insertion, although this decreased with time and the research to date is limited.[128 129] A more recent clinical trial[130] posted results in 2020, with 84 % of 360 participants implanted with VisiAbility microinserts with 24 months follow-up achieving 20/40 at 40 cm and a gain of at least 10 letters, although this was lower for the randomised substudy.

Corneal Inlays

Despite recent recalls of corneal inlays for presbyopia and long-term data showing late onset regression, loss of distance acuity and occasional haze,[131 132] further designs are being developed including diffractive and trifocal designs.[133 134] Corneal inlays provide a reversible, minimally invasive surgical approach for the management of presbyopia, and may be used in conjunction with laser refractive surgery or cataract surgery.

Overall, small aperture inlays, based on the pinhole effect to increase depth of focus (eg, KAMRA, AcuFocus, Irvine, California, USA) provide good near visual outcomes in the majority of patients, with minimal reduction in distance vision in the implanted eye.[135] However, explantation rates of up to 10% have been reported,[132 136] due to complications such as haze, refractive shift or flap complications. Analysis of patients postexplantation indicates that a return to pre-implantation CDVA can be expected in the most individuals, supporting the reversibility of the procedure, although some degree of haze may persist.[132] A recent preliminary systematic review[137] of outcomes with refractive inlays (eg, Flexivue Microlens, Presbia Cooperatief, UA, Irvine, California, USA) which induce corneal multifocality reported good efficacy and safety, with an overall explantation rate of 8.7%. Explantations were mainly attributed to reduced contrast sensitivity, increased higher order aberrations and impact on distance vision. Regarding registered clinical trials, recruitment to a study of the new CorVision reshaping inlay (to steepen anterior corneal curvature; NCT04465409), comprised of biosynthetic collagen to overcome previous biocompatibility issues with inlays, is currently underway.[138]

While the evidence is clear that corneal inlays can improve near visual acuity in presbyopic patients, a significant minority encounter complications and require explantation. Notably, inlays do not restore true dynamic eye focus, and given the progressive nature of presbyopia, patients may eventually require supplementary near vision spectacles. Further developmental work in this field is underway to explore the potential of trifocal diffractive inlays (Furlan *et al*, 2021).[134]

Optofluidics and optoelectronics

The geometry of lenses made of soft elastomers (such as polydimethylsiloxane), fluid or gels encapsulated within rigid or deformable enclosures, with a refractive index higher than the surround, can be modified by changing the internal gas pressure or applying an electrical field.[139] This has been proposed as a basis for variable-focus technology for presbyopia correcting adaptive spectacles.[140] Optoelectronic lenses consist of lenses displaced by a motor so that their optical power is controllable as a function of the applied voltage. They have an increasing dioptric range (up to 10 D), but currently a limited field of view (eg, 43.6°) and are bulky for continual wear, so only the potential for presbyopia correction has been demonstrated to date.[141] Liquid crystal (birefringent material that bend light dependent on the orientation of the molecules) spectacle lenses have also been proposed for presbyopic correction,[142] but are also currently limited by their field of view and still require significant refinement and testing before widespread application. Electro-optic diffractive multifocal lens has been demonstrated that provides multiple focal planes simultaneously that are electrically switchable without compromising the field of view when combined with a refractive lens such as a human crystalline lens.[143]

Similar technology implanted intraocularly (rather than incorporated into spectacles) could restore dynamic eye focus to the presbyopic eye, but significant challenges relating to the delivery of power within the eye and receipt of the biological signal sent to the ciliary muscle relating to the distance at which the host wishes to focus at, must be overcome for this potential to be realised.

CLINICAL OUTCOME MEASURES AND RECOMMENDATIONS

Clinical studies of devices and treatments designed to restore dynamic accommodation to the ageing eye should incorporate appropriate clinical tests capable of demonstrating the existence of accommodation.[144] Despite the American Academy of Ophthalmology's Task Force Recommendations,[145] a principal limitation of studies examining the efficacy of interventions designed to restore ocular accommodation to the ageing eye, is their over-reliance on subjective visual acuity measures (eg, DCNVA) as the main outcome measure, without the inclusion of complementary objective techniques. As accommodation is defined as a change in optical power of the eye,[146 147] clinical trials of new interventions to restore eye focus should, at the very least, include an objective measurement of ocular accommodation.[105 148] While some restorative methods used to ameliorate presbyopia symptoms rely on extended depth-of-focus through multifocal optics[112] or the use of apertures,[149] others are designed to afford functional distance and near vision through an actual change in optical power of the human eye.[150] Although subjective measures such as DCNVA and defocus curves[151] have their place in representing the participants subjective experience, they are unable to prove undeniably that any near vision benefit is a result of a change in optical power of the eye.

Any accommodative stimulus should be reproducible, as amplitude of accommodation is modified differentially by stimulus characteristics.[152 153] For example, a high contrast target moved proximally under either monocular (in either free space or with the aid of a Badal system) or binocular conditions provides blur, proximity and, when under binocular conditions, convergence cues. Targets that induce or modify cognitive load should not be used, as mental effort can modify the accommodative response.[154 155] While accommodation can be stimulated pharmacologically with parasympathomimetics (such as pilocarpine), this approach should be used with caution, particularly with phakic presbyopes, as the effects of stimulating the ciliary muscle in this way can overestimate any refractive or biometric change.[156]

Where accommodation is restored through either an implantable device or method to modify the accommodative apparatus (such as crystalline lens, zonules or ciliary muscle), any resultant dioptric change in the eye's optical power may result from axial or curvature changes of the lens. Power changes to the eye can be measured with a validated open-field autorefractor,[157] a photorefractor[158] or an aberrometer.[159 160] To determine whether a restorative method has led to a physical biometric change (for example changes in anterior chamber depth, crystalline lens thickness, intraocular lens position or lens surface curvature), studies should use imaging techniques to quantify the underpinning morphological adaptations. Instruments that can be used include ultrasound biomicroscopy,[161] OCT,[162 163] Scheimpflug photography,[164] partial coherence interferometry,[165] optical low coherence reflectometry[166] and MRI.[167] An appropriate battery of objective (static and dynamic) and subjective tests to be used in clinical trials to assess the efficacy of methods to restore ocular accommodation or ameliorate the symptoms of presbyopia have been proposed for different management approached.[4]

There have been no comparative studies across strategies to guide clinicians on the most appropriate approach to take with patients depending on, for example, their lifestyle, environment, personality, residual accommodation, refractive error, pupil size and ocular aberrations. However, while PALs are the main presbyopia correction strategy, there is strong evidence from randomised controlled trials that multifocal contact lenses can provide high visual satisfaction and good levels of vision across all distances, without the loss of stereopsis which occurs with monovision. They can potentially help patients to assess their preferred correction strategy, and the balance of multifocality against possible dysphotopsia and loss of contract, for when they require an intraocular lens due to cataract formation. The research on corneal ablations and inlays, as well as scleral implants, is less well developed. Pharmaceutical approaches offer promise, perhaps as an adjunct therapy, but there are advantages of lens softening over pupil constriction mechanisms. A truly accommodating intraocular lenses has still to be commercialised.

CONCLUSION

Presbyopia has a significant impact on an individual's quality of life and emotional state. While a range of amelioration strategies exist, they are often difficult to access in the developing world and prescribing is generally not optimal even in developed countries. A standardised definition of presbyopia should be adopted, an appropriate battery of tests should be applied in evaluating presbyopic management options and the results of clinical trials should be published (even if unsuccessful) to accelerate the provision of better outcomes for presbyopes. Further, while the majority of techniques described herein are designed to restore near vision, we are yet to see a clinically approved method that restores dynamic accommodation to the presbyopic eye. Hitherto, a range of candidate methods using hydrogel,[168] thermopneumatic,[169] thermoelectric,[170] electrohydrodynamic,[171] electroactive polymer[172] and magnetic[173] actuators have been explored to create a tuneable, artificial crystalline lens. Perhaps one emerging approach that may gain further traction can be seen in work using graphene-based compound eyes inspired by vertebrates[174] that allow programmable and remote focusing of crystalline lens-shaped lenslet arrays.[175] Although these remain laboratory studies, whether triggered by the environment, an applied voltage and/ or the response of the autonomic nervous system to a proximal, blurred stimulus, such tuneable devices could mimic ocular accommodation with fast and accurate changes in lens curvature and size, resulting in a corresponding increase in the eye's dioptric power. Whether such devices could be used as implanted or worn optical appliances with adequate image quality, an acceptable focal range, and a wide field of view remains untested.

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