BMJ Open Ophthalmology

New insights in presbyopia: impact of correction strategies

James S Wolffsohn , Leon N Davies , Amy L Sheppard

To cite: Wolffsohn JS, Davies LN, Sheppard AL. New insights in presbyopia: impact of correction strategies. *BMJ Open Ophthalmology* 2023;**8**:e001122. doi:10.1136/bmjophth-2022-001122

Received 21 July 2022
Accepted 15 January 2023

Optometry and Vision Sciences Research Group, Aston University, Birmingham, UK

Correspondence to
Professor James S Wolffsohn; j.s.w.wolffsohn@aston.ac.uk

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,

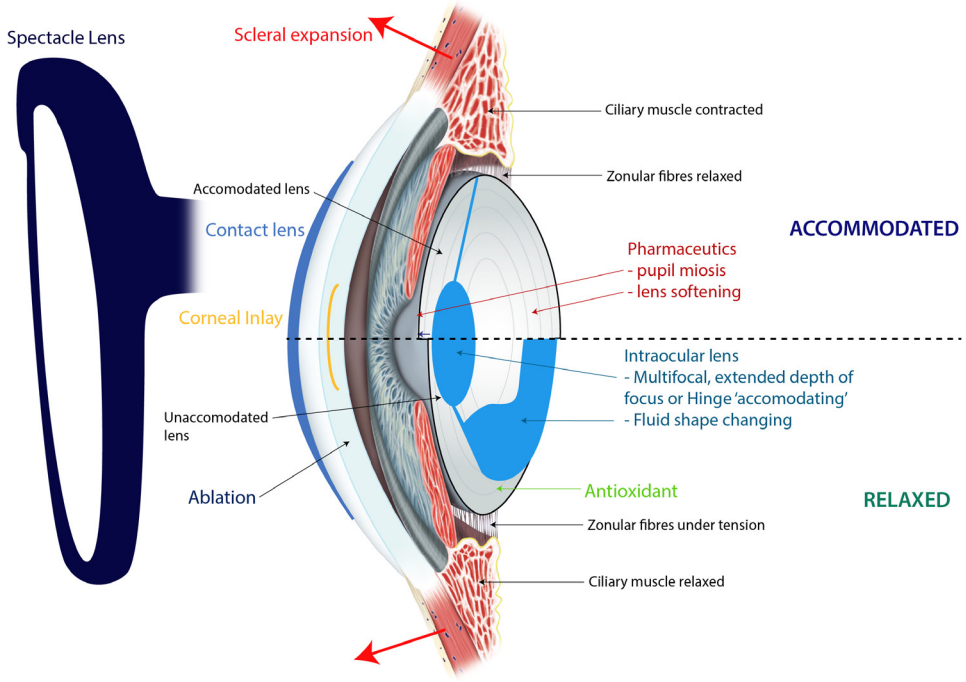

Figure 1 Treatments for presbyopia and where they are located/act (copyright Aston University 2023).

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.

Contributors All the authors (JSW, LND and ALS) were involved in the conception, design, literature searching and data interpretation.

Funding This review was part funded by Bausch and Lomb, but was written independently.

Competing interests The Optometry and Vision Sciences Research Group receives grant funding from Alcon, Atia Vision, Bausch and Lomb, Coopervision, Essilor and Rayner, who have presbyopia products.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
James S Wolffsohn http://orcid.org/0000-0003-4673-8927
Leon N Davies http://orcid.org/0000-0002-1554-0566

REFERENCES

1 Wang C, Wang X, Jin L, *et al*. Influence of presbyopia on smartphone usage among Chinese adults: a population study. *Clin Exp Ophthalmol* 2019;47:909–17.
2 Congdon N, Reddy PA, Mackenzie G, *et al*. Presbyopia and the sustainable development goals. *Lancet Glob Health* 2018;6:e1067.
3 Gualdi L, Gualdi F, Rusciano D, *et al*. Ciliary muscle electrostimulation to restore accommodation in patients with early presbyopia: preliminary results. *J Refract Surg* 2017;33:578–83.
4 Wolffsohn JS, Davies LN. Presbyopia: effectiveness of correction strategies. *Prog Retin Eye Res* 2019;68:124–43.
5 Mah FS. Clarifying the disease state of presbyopia. *J Refract Surg* 2021;37:S8–11.
6 McDonald MB, Barnett M, Gaddie IB, *et al*. Classification of presbyopia by severity. *Ophthalmol Ther* 2022;11:1–11.

7 Bourne RRA, Flaxman SR, Braithwaite T, *et al*. Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis. *Lancet Glob Health* 2017;5:e888–97.
8 Holden BA, Fricke TR, Ho SM, *et al*. Global vision impairment due to uncorrected presbyopia. *Arch Ophthalmol* 2008;126:1731–9.
9 Berdahl J, Bala C, Dhariwal M, *et al*. Patient and economic burden of presbyopia: a systematic literature review. *Clin Ophthalmol* 2020;14:3439–50.
10 Frick KD, Joy SM, Wilson DA, *et al*. The global burden of potential productivity loss from uncorrected presbyopia. *Ophthalmology* 2015;122:1706–10.
11 Donaldson KE. The economic impact of presbyopia. *J Refract Surg* 2021;37:S17–9.
12 Reddy PA, Congdon N, MacKenzie G, *et al*. Effect of providing near glasses on productivity among rural indian tea workers with presbyopia (prosper): a randomised trial. *Lancet Glob Health* 2018;6:e1019–27.
13 Tsuneyoshi Y, Masui S, Arai H, *et al*. Determination of the standard visual criterion for diagnosing and treating presbyopia according to subjective patient symptoms. *J Clin Med* 2021;10:3942.
14 Sharma G, Chiva-Razavi S, Viriato D, *et al*. Patient-reported outcome measures in presbyopia: a literature review. *BMJ Open Ophthalmol* 2020;5:e000453.
15 Buckhurst PJ, Wolffsohn JS, Gupta N, *et al*. Development of a questionnaire to assess the relative subjective benefits of presbyopia correction. *J Cataract Refract Surg* 2012;38:74–9.
16 Kandel H, Khadka J, Watson SL, *et al*. Item banks for measurement of refractive error-specific quality of life. *Ophthalmic Physiol Opt* 2021;41:591–602.
17 Kandel H, Khadka J, Fenwick EK, *et al*. Constructing item banks for measuring quality of life in refractive error. *Optom Vis Sci* 2018;95:575–87.
18 James SL, Lucchesi LR, Bisignano C, *et al*. The global burden of falls: global, regional and national estimates of morbidity and mortality from the global burden of disease study 2017. *Inj Prev* 2020;26:i3–11.
19 Pesudovs K. Item banking: a generational change in patient-reported outcome measurement. *Optom Vis Sci* 2010;87:285–93.
20 Barcala X, Vinas M, Romero M, *et al*. Multifocal acceptance score to evaluate vision: MAS-2EV. *Sci Rep* 2021;11:1397.
21 Rudnicka AR, Kapetanakis VV, Wathern AK, *et al*. Global variations and time trends in the prevalence of childhood myopia, a systematic review and quantitative meta-analysis: implications for aetiology and early prevention. *Br J Ophthalmol* 2016;100:882–90.
22 Yang A, Lim SY, Wong YL, *et al*. Quality of life in presbyopes with low and high myopia using single-vision and progressive-lens correction. *J Clin Med* 2021;10:1589.
23 Chang DH. Multifocal spectacle and monovision treatment of presbyopia and falls in the elderly. *J Refract Surg* 2021;37:S12–6.
24 He M, Abdou A, Ellwein LB, *et al*. Age-related prevalence and met need for correctable and uncorrectable near vision impairment in a multi-country study. *Ophthalmology* 2014;121:417–22.
25 Holden BA, Fricke TR, Wilson DA, *et al*. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology* 2016;123:1036–42.
26 Mai ELC, Lin C-C, Lian I, *et al*. Population-Based study on the epidemiology of dry eye disease and its association with presbyopia and other risk factors. *Int Ophthalmol* 2019;39:2731–9.
27 Kaido M, Kawashima M, Shigeno Y, *et al*. Relation of accommodative microfluctuation with dry eye symptoms in short tear break-up time dry eye. *PLoS One* 2017;12:e0184296.
28 Ayaki M, Negishi K. Short tear breakup time could exacerbate the progression of presbyopia in women. *Biomed Res Int* 2022;2022:8159669.
29 Srinivasan R, Paramasivan G, Sharma A, *et al*. Prevalence, risk factors and association with glycemic levels of presbyopia in South Indian population. *Indian J Ophthalmol* 2021;69:3173–7.
30 Andualem HB, Assefa NL, Weldemichael DZ, *et al*. Prevalence and associated factors of presbyopia among school teachers in gondar City, Northwest Ethiopia, 2016. *Clin Optom (Auckl)* 2017;9:85–90.
31 Goertz AD, Stewart WC, Burns WR, *et al*. Review of the impact of presbyopia on quality of life in the developing and developed world. *Acta Ophthalmol* 2014;92:497–500.
32 Blindness GBD, Vision Impairment C. Trends in prevalence of blindness and distance and near vision impairment over 30 years: an analysis for the global burden of disease study. *Lancet Glob Health* 2021;9:e130–43.
33 He M, Abdou A, Naidoo KS, *et al*. Prevalence and correction of near vision impairment at seven sites in china, india, nepal, niger, south africa, and the united states. *Am J Ophthalmol* 2012;154:107–16.
34 Marmamula S, Khanna RC, Kunuku E, *et al*. Spectacles use in a rural population in the state of Telangana in South India. *Indian J Ophthalmol* 2017;65:509–15.
35 Ajibode HA, Fakolujo VO, Onabolu OO, *et al*. A community-based prevalence of presbyopia and spectacle coverage in Southwest Nigeria. *J West Afr Coll Surg* 2016;6:66–82.
36 Sivardeen A, McAlinden C, Wolffsohn JS. Presbyopic correction use and its impact on quality of vision symptoms. *J Optom* 2020;13:29–34.
37 Snelson CL. Qualitative and mixed methods social media research. *International Journal of Qualitative Methods* 2016;15:160940691562457.
38 Wolffsohn JS, Leteneux-Pantais C, Chiva-Razavi S, *et al*. Social media listening to understand the lived experience of presbyopia: systematic search and content analysis study. *J Med Internet Res* 2020;22:e18306.
39 Hutchins B, Huntjens B. Patients' attitudes and beliefs to presbyopia and its correction. *J Optom* 2021;14:127–32.
40 Negishi K, Ayaki M, Kawashima M, *et al*. Sleep and subjective Happiness between the ages 40 and 59 in relation to presbyopia and dry eye. *PLoS One* 2021;16:e0250087.
41 Negishi K, Ayaki M. Presbyopia developed earlier during the COVID-19 pandemic. *PLoS One* 2021;16:e0259142.
42 Pointer JS. The presbyopic add. I. magnitude and distribution in a historical context. *Ophthalmic Physiol Opt* 1995;15:235–40.
43 Pointer JS. The presbyopic add. II. age-related trend and a gender difference. *Ophthalmic Physiol Opt* 1995;15:241–8.
44 Majithia S, Wong KH, Chee ML, *et al*. Normative patterns and factors associated with presbyopia progression in a multiethnic Asian population: the Singapore epidemiology of eye diseases study. *Br J Ophthalmol* 2020;104:1591–5.
45 Han X, Lee PY, Liu C, *et al*. Distribution and progression of add power among people in need of near correction. *Clin Exp Ophthalmol* 2018;46:882–7.
46 Sheedy JE, Hayes JN, Engle J. Is all asthenopia the same? *Optom Vis Sci* 2003;80:732–9.
47 Sánchez-Brau M, Domenech-Amigot B, Brocal-Fernández F, *et al*. Prevalence of computer vision syndrome and its relationship with ergonomic and individual factors in presbyopic VDT workers using progressive addition lenses. *Int J Environ Res Public Health* 2020;17:1003.
48 Seguí M del M, Cabrero-García J, Crespo A, *et al*. A reliable and valid questionnaire was developed to measure computer vision syndrome at the workplace. *J Clin Epidemiol* 2015;68:662–73.
49 Sánchez-Brau M, Domenech-Amigot B, Brocal-Fernández F, *et al*. Computer vision syndrome in presbyopic digital device workers and progressive lens design. *Ophthalmic Physiol Opt* 2021;41:922–31.
50 Kolbe O, Degle S. Presbyopic personal computer work: a comparison of progressive addition lenses for general purpose and personal computer work. *Optom Vis Sci* 2018;95:1046–53.
51 Boccardo L. Viewing distance of smartphones in presbyopic and non-presbyopic age. *J Optom* 2021;14:120–6.
52 Lan N, Rosenfield M, Liu L. Cell phone viewing distance and age in a chinese population. *Optometry and Visual Performance* 2018;6:203–5.
53 Sheedy JE, Campbell C, King-Smith E, *et al*. Progressive powered lenses: the minkwitz theorem. *Optom Vis Sci* 2005;82:916–22.
54 Villegas EA, Artal P. Comparison of aberrations in different types of progressive power lenses. *Ophthalmic Physiol Opt* 2004;24:419–26.
55 Forkel J, Reiniger JL, Muschielok A, *et al*. Personalized progressive addition lenses: correlation between performance and design. *Optom Vis Sci* 2017;94:208–18.
56 Jaschinski W, König M, Mekontso TM, *et al*. Comparison of progressive addition lenses for general purpose and for computer vision: an office field study. *Clin Exp Optom* 2015;98:234–43.
57 Montés-Micó R, Charman WN. Pharmacological strategies for presbyopia correction. *J Refract Surg* 2019;35:803–14.
58 Mercer RN, Milliken CM, Waring GO, *et al*. Future trends in presbyopia correction. *J Refract Surg* 2021;37:S28–34.
59 Benozzi G, Perez C, Leiro J, *et al*. Presbyopia treatment with eye drops: an eight year retrospective study. *Transl Vis Sci Technol* 2020;9:25.
60 Vargas V, Vejarano F, Alió JL. Near vision improvement with the use of A new topical compound for presbyopia correction: A prospective, consecutive interventional non-comparative clinical study. *Ophthalmol Ther* 2019;8:31–9.

61 Vargas V, Vejarano F, Alió J. Pharmacological therapy for presbyopia in patients with previous corneal refractive surgery: a pilot study. *Ophthalmol Ther* 2020;9:1003–10.
62 Charman WN. Pinholes and presbyopia: solution or sideshow? *Ophthalmic Physiol Opt* 2019;39:1–10.
63 Garner WH, Garner MH. Protein disulfide levels and lens elasticity modulation: applications for presbyopia. *Invest Ophthalmol Vis Sci* 2016;57:2851–63.
64 NCT02516306. ClinicalTrails.gov. A study to evaluate the safety and efficacy of EV06 ophthalmic solution in improving vision in subjects with presbyopia. 2021. Available: https://www.clinicaltrials.gov/ct2/show/NCT02516306
65 Stein JM, Robertson SM, Evans DG, *et al*. An observational follow-up study assessing the long-term effects of bilaterally dosed topical lipoic acid choline ester eye drops for the treatment of presbyopia. *Invest Ophthalmol Vis Sci* 2017;58:330.
66 Korenfeld MS, Robertson SM, Stein JM, *et al*. Topical lipoic acid choline ester eye drop for improvement of near visual acuity in subjects with presbyopia: a safety and preliminary efficacy trial. *Eye (Lond)* 2021;35:3292–301.
67 Mathew MC, Ervin A-M, Tao J, *et al*. Antioxidant vitamin supplementation for preventing and slowing the progression of age-related cataract. *Cochrane Database Syst Rev* 2012;6:CD004567.
68 Kuzniarz M, Mitchell P, Cumming RG, *et al*. Use of vitamin supplements and cataract: the blue Mountains eye study. *Am J Ophthalmol* 2001;132:19–26.
69 Rautiainen S, Lindblad BE, Morgenstern R, *et al*. Vitamin C supplements and the risk of age-related cataract: a population-based prospective cohort study in women. *Am J Clin Nutr* 2010;91:487–93.
70 Christen WG, Glynn RJ, Chew EY, *et al*. Vitamin E and age-related cataract in a randomized trial of women. *Ophthalmology* 2008;115:822–9.
71 Glaser TS, Doss LE, Shih G, *et al*. The association of dietary lutein plus zeaxanthin and B vitamins with cataracts in the age-related eye disease study: AREDS report no. 37 [AREDS Report no.37]. *Ophthalmology* 2015;122:1471–9.
72 Ma L, Hao Z, Liu R, *et al*. A dose-response meta-analysis of dietary lutein and zeaxanthin intake in relation to risk of age-related cataract. *Graefes Arch Clin Exp Ophthalmol* 2014;252:63–70.
73 Dherani M, Murthy GVS, Gupta SK, *et al*. Blood levels of vitamin C, carotenoids and retinol are inversely associated with cataract in a North Indian population. *Invest Ophthalmol Vis Sci* 2008;49:3328–35.
74 Sideri O, Tsaousis KT, Li HJ, *et al*. The potential role of nutrition on lens pathology: a systematic review and meta-analysis. *Surv Ophthalmol* 2019;64:668–78.
75 Kizawa Y, Sekikawa T, Kageyama M, *et al*. Effects of anthocyanin, astaxanthin, and lutein on eye functions: a randomized, double-blind, placebo-controlled study. *J Clin Biochem Nutr* 2021;69:77–90.
76 Nakazawa Y, Aoki M, Ishiwa S, *et al*. Oral intake of α-glucosyl-hesperidin ameliorates selenite-induced cataract formation. *Mol Med Rep* 2020;21:1258–66.
77 Nakazawa Y, Doki Y, Sugiyama Y, *et al*. Effect of alpha-glucosyl-hesperidin consumption on lens sclerosis and presbyopia. *Cells* 2021;10:382.
78 Nakazawa Y, Aoki M, Doki Y, *et al*. Oral consumption of α-glucosyl-hesperidin could prevent lens hardening, which causes presbyopia. *Biochem Biophys Rep* 2021;25:100885.
79 Nagashima H, Sasaki N, Amano S, *et al*. Oral administration of resveratrol or lactic acid bacterium improves lens elasticity. *Sci Rep* 2021;11:2174.
80 Evans JR. Ginkgo biloba extract for age-related macular degeneration. *Cochrane Database Syst Rev* 2013;2013:CD001775.
81 Jun JH, Choi TY, Lee HW, *et al*. Herbal medicine for Behçet's disease: a systematic review and meta-analysis. *Nutrients* 2020;13:46.
82 Zhang HW, Zhang H, Grant SJ, *et al*. Single herbal medicine for diabetic retinopathy. *Cochrane Database Syst Rev* 2018;12:CD007939.
83 Horng CT, Ma JW, Shieh PC. Improvement of presbyopia using a mixture of traditional chinese herbal medicines, including cassiae semen, wolfberry, and *dendrobium huoshanense*. *Evid Based Complement Alternat Med* 2021;2021:9902211.
84 Thite N, Desiato A, Shinde L, *et al*. Opportunities and threats to contact lens practice: a global survey perspective. *Cont Lens Anterior Eye* 2021;44:101496.
85 Fogt JS, Weisenberger K, Fogt N. Visual performance with multifocal contact lenses and progressive addition spectacles. *Cont Lens Anterior Eye* 2022;45:101472.
86 Diec J, Naduvilath T, Tilia D, *et al*. The relationship between vision and comfort in contact lens wear. *Eye Contact Lens* 2021;47:271–6.
87 Richdale K, Cox I, Kollbaum P, *et al*. CLEAR - contact lens optics. *Cont Lens Anterior Eye* 2021;44:220–39.
88 Martínez-Alberquilla I, García-Montero M, Ruiz-Alcocer J, *et al*. Visual function, ocular surface integrity and symptomatology of a new extended depth-of-focus and a conventional multifocal contact lens. *Cont Lens Anterior Eye* 2021;44:101384.
89 Sha J, Tilia D, Kho D, *et al*. Comparison of extended depth-of-focus prototype contact lenses with the 1-day ACUVUE moist multifocal after one week of wear. *Eye Contact Lens* 2018;44 Suppl 2:S157–63.
90 Bakaraju RC, Tilia D, Sha J, *et al*. Extended depth of focus contact lenses vs. two commercial multifocals: part 2. visual performance after 1 week of lens wear. *J Optom* 2018;11:21–32.
91 Fogt JS, Kerwin T, Wrabel C, *et al*. Driving performance and road sign identification by multifocal contact lens wearers in a driving simulator. *Cont Lens Anterior Eye* 2022;45:101493.
92 Jun I, Cho JS, Kang MG, *et al*. Clinical outcomes of a novel presbyopia-correcting soft contact lens with a small aperture. *Cont Lens Anterior Eye* 2020;43:497–502.
93 Park SY, Choi YJ, Jung JW, *et al*. Clinical efficacy of pinhole soft contact lenses for the correction of presbyopia. *Semin Ophthalmol* 2019;34:106–14.
94 Park SY, Kim T-I, Lung JW, *et al*. Clinical efficacy of pihhole soft contact lenses for correcting presbyopia. *Invest Ophthalmol Vis Sci* 2016;57:3121.
95 Woods J, Woods CA, Fonn D. Early symptomatic presbyopes -- what correction modality works best? *Eye Contact Lens* 2009;35:221–6.
96 Sivardeen A, Laughton D, Wolffsohn JS. Investigating the utility of clinical assessments to predict success with presbyopic contact lens correction. *Cont Lens Anterior Eye* 2016;39:322–30.
97 Sheppard AL, Bashir A, Wolffsohn JS, *et al*. Accommodating intraocular lenses: a review of design concepts, usage and assessment methods. *Clin Exp Optom* 2010;93:441–52.
98 Bontu S, Werner L, Kennedy S, *et al*. Long-Term uveal and capsular biocompatibility of a new fluid-filled, modular accommodating intraocular lens. *J Cataract Refract Surg* 2021;47:111–7.
99 Kennedy S, Werner L, Bontu S, *et al*. Explantation/exchange of the components of a new fluid-filled, modular, accommodating IOL. *J Cataract Refract Surg* 2021;47:238–44.
100 de la Hoz A, Germann J, Martinez-Enriquez E, *et al*. Design and ex situ performance of a shape-changing accommodating intraocular lens. *Optica* 2019;6:1050.
101 Riehle N, Thude S, Kandelbauer A, *et al*. Synthesis of soft polysiloxane-urea elastomers for intraocular lens application. *J Vis Exp* 2019;2019:145.
102 Horiuchi T, Mihashi T, Hoshi S, *et al*. Artificial accommodating intraocular lens powered by an ion polymer-metal composite actuator. *PLoS One* 2021;16:e0252986.
103 Marcos S, Ortiz S, Pérez-Merino P, *et al*. Three-dimensional evaluation of accommodating intraocular lens shift and alignment in vivo. *Ophthalmology* 2014;121:45–55.
104 Dick HB, Kaiser S. Dynamic aberrometry during accommodation of phakic eyes and eyes with potentially accommodative intraocular lenses. *Ophthalmologe* 2002;99:825–34.
105 Wolffsohn JS, Hunt OA, Naroo S, *et al*. Objective accommodative amplitude and dynamics with the 1CU accommodative intraocular lens. *Invest Ophthalmol Vis Sci* 2006;47:1230–5.
106 Pérez-Merino P, Birkenfeld J, Dorronsoro C, *et al*. Aberrometry in patients implanted with accommodative intraocular lenses. *Am J Ophthalmol* 2014;157:1077–89.
107 Zamora-Alejo KV, Moore SP, Parker DGA, *et al*. Objective accommodation measurement of the crystalens HD compared to monofocal intraocular lenses. *J Refract Surg* 2013;29:133–9.
108 Cleary G, Spalton DJ, Gala KB. A randomized intraindividual comparison of the accommodative performance of the bag-in-the-lens intraocular lens in presbyopic eyes. *Am J Ophthalmol* 2010;150:619–27.
109 Cleary G, Spalton DJ, Marshall J. Pilot study of new focus-shift accommodating intraocular lens. *J Cataract Refract Surg* 2010;36:762–70.
110 Alio JL, Simonov A, Plaza-Puche AB, *et al*. Visual outcomes and accommodative response of the lumina accommodative intraocular lens. *Am J Ophthalmol* 2016;164:37–48.
111 Rampat R, Gatinel D. Multifocal and extended depth-of-focus intraocular lenses in 2020. *Ophthalmology* 2021;128:e164–85.

112 Zhong Y, Wang K, Yu X, *et al*. Comparison of trifocal or hybrid multifocal-extended depth of focus intraocular lenses: a systematic review and meta-analysis. *Sci Rep* 2021;11:6699.
113 Kohnen T, Suryakumar R. Extended depth-of-focus technology in intraocular lenses. *J Cataract Refract Surg* 2020;46:298–304.
114 Oshika T, Arai H, Fujita Y, *et al*. One-Year clinical evaluation of rotationally asymmetric multifocal intraocular lens with +1.5 diopters near addition. *Sci Rep* 2019;9:13117.
115 Khandelwal SS, Jun JJ, Mak S, *et al*. Effectiveness of multifocal and monofocal intraocular lenses for cataract surgery and lens replacement: a systematic review and meta-analysis. *Graefes Arch Clin Exp Ophthalmol* 2019;257:863–75.
116 Schallhorn JM, Pantanelli SM, Lin CC, *et al*. Multifocal and accommodating intraocular lenses for the treatment of presbyopia: a report by the american academy of ophthalmology. *Ophthalmology* 2021;128:1469–82.
117 Lang A, Portney V. Interpreting multifocal intraocular lens modulation transfer functions. *J Cataract Refract Surg* 1993;19:505–12.
118 Alarcon A, Canovas C, Rosen R, *et al*. Preclinical metrics to predict through-focus visual acuity for pseudophakic patients. *Biomed Opt Express* 2016;7:1877–88.
119 Moutari S, Moore JE. An ensemble-based approach for estimating personalized intraocular lens power. *Sci Rep* 2021;11:22961.
120 Bennett ES. Contact lens correction of presbyopia. *Clin Exp Optom* 2008;91:265–78.
121 Paley GL, Chuck RS, Tsai LM. Corneal-based surgical presbyopic therapies and their application in pseudophakic patients. *J Ophthalmol* 2016;2016:5263870.
122 Shetty R, Brar S, Sharma M, *et al*. PresbyLASIK: a review of presbymax, supracor, and laser blended vision: principles, planning, and outcomes. *Indian J Ophthalmol* 2020;68:2723–31.
123 Wang Yin GH, McAlinden C, Pieri E, *et al*. Surgical treatment of presbyopia with central presbyopic keratomileusis: one-year results. *J Cataract Refract Surg* 2016;42:1415–23.
124 Epstein RL, Gurgos MA. Presbyopia treatment by monocular peripheral presbylasik. *J Refract Surg* 2009;25:516–23.
125 Schachar RA. Cause and treatment of presbyopia with a method for increasing the amplitude of accommodation. *Ann Ophthalmol* 1992;24:445–7.
126 Schachar RA, Cudmore DP, Black TD. Experimental support for schachar's hypothesis of accommodation. *Ann Ophthalmol* 1993;25:404–9.
127 Croft MA, Glasser A, Heatley G, *et al*. The zonula, lens, and circumlental space in the normal iridectomized rhesus monkey eye. *Invest Ophthalmol Vis Sci* 2006;47:1087–95.
128 Qazi MA, Pepose JS, Shuster JJ. Implantation of scleral expansion band segments for the treatment of presbyopia. *Am J Ophthalmol* 2002;134:808–15.
129 Tunc Z, Helvacioglu F, Ercalik Y, *et al*. Supraciliary contraction segments: a new method for the treatment of presbyopia. *Indian J Ophthalmol* 2014;62:116–23.
130 USNIoHC Trials. A clinical trial of the visability micro insert system for presbyopic patients. 2018. Available: https://clinicaltrials.gov/ct2/show/NCT02374671
131 Abdul Fattah M, Mehanna C-J, Antonios R, *et al*. Five-year results of combined small-aperture corneal inlay implantation and LASIK for the treatment of hyperopic presbyopic eyes. *J Refract Surg* 2020;36:498–505.
132 Moshirfar M, Buckner B, Rosen DB, *et al*. Visual prognosis after explantation of a corneal shape-changing hydrogel inlay in presbyopic eyes. *Med Hypothesis Discov Innov Ophthalmol* 2019;8:139–44.
133 Furlan WD, García-Delpech S, Udaondo P, *et al*. Diffractive corneal inlay for presbyopia. *J Biophotonics* 2017;10:1110–4.
134 Furlan WD, Montagud-Martínez D, Ferrando V, *et al*. A new trifocal corneal inlay for presbyopia. *Sci Rep* 2021;11:6620.
135 Davidson RS, Dhaliwal D, Hamilton DR, *et al*. Surgical correction of presbyopia. *J Cataract Refract Surg* 2016;42:920–30.
136 Yılmaz OF, Alagöz N, Pekel G, *et al*. Intracorneal inlay to correct presbyopia: long-term results. *J Cataract Refract Surg* 2011;37:1275–81.
137 Sánchez-González J-M, Borroni D, Rachwani-Anil R, *et al*. Refractive corneal inlay implantation outcomes: a preliminary systematic review. *Int Ophthalmol* 2022;42:713–22.
138 ClinicalTrials.gov. Evaluation of safety and efficacy of intrastromal implantation of corvision® bioengineered corneal inlay for correction of presbyopia. 2022. Available: https://clinicaltrials.gov/ct2/show/NCT04465409?term=inlay&cond=Presbyopia&draw=2&rank=1
139 Levy U, Shamai R. Tunable optofluidic devices. *Microfluid Nanofluid* 2008;4:97–105.
140 Jarosz J, Molliex N, Chenon G, *et al*. Adaptive eyeglasses for presbyopia correction: an original variable-focus technology. *Opt Express* 2019;27:10533–52.
141 Mompeán J, Aragón JL, Artal P. Portable device for presbyopia correction with optoelectronic lenses driven by pupil response. *Sci Rep* 2020;10:20293.
142 Jamali A, Bryant D, Bhowmick AK, *et al*. Large area liquid crystal lenses for correction of presbyopia. *Opt Express* 2020;28:33982–93.
143 Bharath Kumar M, Kang D, Adeshina MA, *et al*. Electro-Optic diffractive multifocal lens with electrically reconfigurable multifocal planes. *Optics and Lasers in Engineering* 2021;139:106459.
144 Glasser A, Hilmantel G, Calogero D, *et al*. Special report: american academy of ophthalmology task force recommendations for test methods to assess accommodation produced by intraocular lenses. *Ophthalmology* 2017;124:134–9.
145 Lum F, Holladay JT, Glasser A, *et al*. Special report: the american academy of ophthalmology task force for developing novel end points for premium intraocular lenses introduction. *Ophthalmology* 2017;124:133–4.
146 Atchison DA. Accommodation and presbyopia. *Ophthalmic Physiol Opt* 1995;15:255–72.
147 Charman WN. The eye in focus: accommodation and presbyopia. *Clin Exp Optom* 2008;91:207–25.
148 Wolffsohn JS, Naroo SA, Motwani NK, *et al*. Subjective and objective performance of the lenstec KH-3500 " accommodative " intraocular lens. *Br J Ophthalmol* 2006;90:693–6.
149 Dick HB. Small-aperture strategies for the correction of presbyopia. *Curr Opin Ophthalmol* 2019;30:236–42.
150 Liang YL, Jia SB. Clinical application of accommodating intraocular lens. *Int J Ophthalmol* 2018;11:1028–37.
151 Dhallu SK, Sheppard AL, Drew T, *et al*. Factors influencing pseudo-accommodation-the difference between subjectively reported range of clear focus and objectively measured accommodation range. *Vision (Basel)* 2019;3:34.
152 Radhakrishnan H, Hartwig A, Charman WN, *et al*. Accommodation response to Chinese and Latin characters in chinese-illiterate young adults. *Clin Exp Optom* 2015;98:527–34.
153 Otero C, Aldaba M, Vera-Diaz FA, *et al*. Effect of experimental conditions in the accommodation response in myopia. *Optom Vis Sci* 2017;94:1120–8.
154 Davies LN, Wolffsohn JS, Gilmartin B. Cognition, ocular accommodation, and cardiovascular function in emmetropes and late-onset myopes. *Invest Ophthalmol Vis Sci* 2005;46:1791–6.
155 Redondo B, Vera J, Molina R, *et al*. Accommodative dynamics and attention: the influence of manipulating attentional capacity on accommodative lag and variability. *Ophthalmic Physiol Opt* 2020;40:510–8.
156 Koeppl C, Findl O, Kriechbaum K, *et al*. Comparison of pilocarpine-induced and stimulus-driven accommodation in phakic eyes. *Exp Eye Res* 2005;80:795–800.
157 Wolffsohn JS, Davies LN, Naroo SA, *et al*. Evaluation of an open-field autorefractor's ability to measure refraction and hence potential to assess objective accommodation in pseudophakes. *Br J Ophthalmol* 2011;95:498–501.
158 Wolffsohn JS, Hunt OA, Gilmartin B. Continuous measurement of accommodation in human factor applications. *Oph Phys Optics* 2002;22:380–4.
159 Alio JL, D'Oria F, Toto F, *et al*. Retinal image quality with multifocal, edof, and accommodative intraocular lenses as studied by pyramidal aberrometry. *Eye Vis (Lond)* 2021;8:37.
160 Bhatt UK, Sheppard AL, Shah S, *et al*. Design and validity of a miniaturized open-field aberrometer. *J Cataract Refract Surg* 2013;39:36–40.
161 Croft MA, McDonald JP, Nadkarni NV, *et al*. Age-Related changes in centripetal ciliary body movement relative to centripetal lens movement in monkeys. *Exp Eye Res* 2009;89:824–32.
162 Gibson GA, Cruickshank FE, Wolffsohn JS, *et al*. Optical coherence tomography reveals sigmoidal crystalline lens changes during accommodation. *Vision (Basel)* 2018;2:33.
163 Xie X, Sultan W, Corradetti G, *et al*. Assessing accommodative presbyopic biometric changes of the entire anterior segment using single swept-source OCT image acquisitions. *Eye (Lond)* 2022;36:119–28.
164 Nemeth G, Lipecz A, Szalai E, *et al*. Accommodation in phakic and pseudophakic eyes measured with subjective and objective methods. *J Cataract Refract Surg* 2013;39:1534–42.

165 Santodomingo-Rubido J, Mallen EAH, Gilmartin B, *et al*. A new non-contact optical device for ocular biometry. *Br J Ophthalmol* 2002;86:458–62.
166 Buckhurst PJ, Wolffsohn JS, Shah S, *et al*. A new optical low coherence reflectometry device for ocular biometry in cataract patients. *Br J Ophthalmol* 2009;93:949–53.
167 Sheppard AL, Evans CJ, Singh KD, *et al*. Three-Dimensional magnetic resonance imaging of the phakic crystalline lens during accommodation. *Invest Ophthalmol Vis Sci* 2011;52:3689–97.
168 Dong L, Agarwal AK, Beebe DJ, *et al*. Adaptive liquid microlenses activated by stimuli-responsive hydrogels. *Nature* 2006;442:551–4.
169 Zhang W, Aljasem K, Zappe H, *et al*. Completely integrated, thermo-pneumatically tunable microlens. *Opt Express* 2011;19:2347–62.
170 Ashtiani AO, Jiang H. Tunable microlens actuated via a thermoelectrically driven liquid heat engine. *Journal of Applied Physics* 2014;115:243103.
171 Liu H, Wang L, Jiang W, *et al*. Bio-Inspired eyes with eyeball-shaped lenses actuated by electro-hydrodynamic forces. *RSC Adv* 2016;6:23653–7.
172 Jin B, Lee J-H, Zhou Z, *et al*. Adaptive liquid lens driven by elastomer actuator. *Opt Eng* 2016;55:017107.
173 Lee SW, Lee SS. Focal tunable liquid lens integrated with an electromagnetic actuator. *Appl Phys Lett* 2007;90:121129.
174 Wang L, Li F, Liu H, *et al*. Graphene-based bioinspired compound eyes for programmable focusing and remote actuation. *ACS Appl Mater Interfaces* 2015;7:21416–22.
175 Galstian T, Asatryan K, Presniakov V, *et al*. Electrically variable liquid crystal lenses for ophthalmic distance accommodation. *Opt Express* 2019;27:18803–17.