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Presbyopia: Effectiveness of correction strategies

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ABSTRACT

Presbyopia is a global problem affecting over a billion people worldwide. The prevalence of unmanaged presbyopia is as high as 50% of those over 50 years of age in developing world populations, due to a lack of awareness and accessibility to affordable treatment, and is even as high as 34% in developed countries. Definitions of presbyopia are inconsistent and varied, so we propose a redefinition that states "*presbyopia occurs when the physiologically normal age-related reduction in the eye's 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*". Strategies for correcting presbyopia include separate optical devices located in front of the visual system (reading glasses) or a change in the direction of gaze to view through optical zones of different optical powers (bifocal, trifocal or progressive addition spectacle lenses), monovision (with contact lenses, intraocular lenses, laser refractive surgery and corneal collagen shrinkage), simultaneous images (with contact lenses, intraocular lenses and corneal inlays), pinhole depth of focus expansion (with intraocular lenses, corneal inlays and pharmaceuticals), crystalline lens softening (with lasers or pharmaceuticals) or restored dynamics (with 'accommodating' intraocular lenses, scleral expansion techniques and ciliary muscle electrostimulation); these strategies may be applied differently to the two eyes to optimise the range of clear focus for an individual's task requirements and minimise adverse visual effects. However, none fully overcome presbyopia in all patients. While the restoration of natural accommodation or an equivalent remains elusive, guidance is given on presbyopic correction evaluation techniques.

1. Introduction

Presbyopia is a global problem affecting over a billion people worldwide (Holden et al., 2008), with the number of presbyopes set to increase further against a backdrop of an ageing global population where the median age could reach 40 years by 2050 (note: the median age of the world population in 2015 was 29.6 years) (Portal, 2018). In the younger human eye, the accommodation mechanism acts to enable individuals to view targets clearly at various distances. Although there are ongoing debates as to the exact mechanism of accommodation (Schachar, 2006), the most compelling empirical data support Helmholtz's theory (Helmholtz, 1962) where, in a response to ciliary muscle contraction, crystalline lens thickness increases (Kasthurirangan et al., 2011; Richdale et al., 2013) lens diameter decreases (Hermans et al., 2009; Sheppard et al., 2011), and both the anterior and posterior curvature of the lens increase (Dubbelman et al., 2005; Rosales et al., 2006) resulting in an increase in lenticular power and, therefore, accommodation. Whilst the symptoms of presbyopia manifest in mid-life, it is important to note that the decline in accommodation response, which ultimately results in presbyopia, begins as early as the first decade of life (Donders, 1865). Indeed, data from Duane's (1922) early work on accommodative amplitude on over 4000 eyes, together with more contemporary studies, clearly show that accommodation is a condition of age rather than ageing (Gilmartin, 1995)(see Fig. 1). Despite the significance and ubiquity of presbyopia, and the resultant deleterious effect on near visual function, it is perhaps rather surprising that no one single effective optical, pharmaceutical or surgical method currently exists to restore dynamic accommodation to the ageing eye. Indeed, even the definition of presbyopia remains equivocal.

1.1. Presbyopia definition

Some definitions of presbyopia purely focus on near visual loss, but do not relate this to a visual requirement (Moshirfar et al., 2017; Zeri et al., 2018); hence many young visually impaired individuals could be considered presbyopic with such definitions. However, other definitions are more functional such as "*Presbyopia is a condition of age rather than ageing and as such is devolved from the lamentable situation where the*

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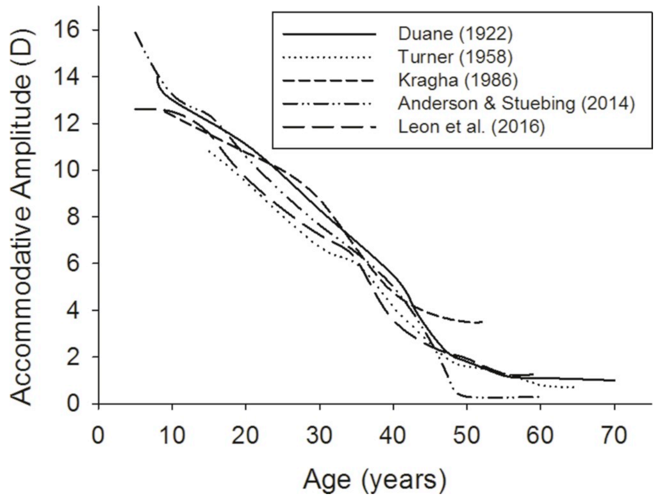

Fig. 1. Measures of monocular subjective amplitude of accommodation with age (Anderson and Stuebing, 2014; Duane, 1922; Kragha, 1986; Leon et al., 2016; Turner, 1958)). The techniques used to acquire these data vary between studies, but include the use of push-up and modified push-down methods.

normal age-related reduction in amplitude of accommodation reaches a point when the clarity of vision at near cannot be sustained for long enough to satisfy an individual's requirements" (Gilmartin, 1995) or Millodot in his *Dictionary of Optometry and Visual Science* who defines presbyopia as "*A refractive condition in which the accommodative ability of the eye is insufficient for near vision work, due to ageing*" (Millodot, 2007). Some articles do not define presbyopia at all, but refer to its onset, which, as the decline in accommodation is well described to commence in the teenage years, implies a functional definition (Charman, 2005).

Another approach to defining presbyopia has been to adopt a more physiological approach, describing presbyopia as an age-related progressive decline in the crystalline lens' ability to accommodate, resulting in the inability to focus on near objects (Abdelkader, 2015; Arines et al., 2017; Benozzi et al., 2012; Fedtke et al., 2017; Moarefi et al., 2017). While both objective(Anderson and Stuebing, 2014; Leon et al., 2016) and subjective measures(Cobb, 1964; Donders, 1865; Turner, 1958) of accommodation indicate that to the accommodative response starts to decrease in the early teens, there is only a concurrent drop in accommodative gain by the fifth decade, reducing near image quality and resulting in the apparent acceleration of symptoms in early presbyopes (Almutairi et al., 2017). Presbyopia has even been described as *causing* the loss of accommodation (Sha et al., 2016).

Holden and colleagues (Holden et al., 2008) identified two different presbyopia definitions in epidemiological studies of presbyopia: 1) functional presbyopia, defined as needing a significant optical correction added to the presenting distance refractive correction to achieve a near visual acuity absolute (such as N8 or J1) or relative (such as 1 line of acuity improvement) criteria; or 2) objective presbyopia, where the significant optical correction is defined (such as $\geq$1.00 D) and added to the best optical distance correction to achieve a defined near visual acuity. In more recent epidemiological studies, however, presbyopia is typically defined as a person aged greater or equal to 35 years who is unable to read binocularly N8 (or 6/12) at 40 cm or their habitual working distance, and additionally in some studies, limited to those whose near vision improves with additional lenses (Cheng et al., 2016; Girum et al., 2017; Kaphle et al., 2016; Muhit et al., 2018; Nsubuga et al., 2016).

1.1.1. *Revised definition*

The efficacy of a condition management option cannot be assessed if the condition is not defined. As presbyopia is derived from Ancient Greek πρέσβυς translated into Latin (présbus, "old man") and ὤψ (ṓps, "eye" or to "see like")(Gualdi et al., 2017),), a functional definition to fit this etymology would appear more appropriate, otherwise a new term for the condition should be adopted. Perhaps a more apposite definition would be that 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.

1.2. *Presbyopia correction*

Often regarded as the 'Holy Grail of vision correction' (Doane and Jackson, 2007; Mertens, 2010; Pepose et al., 2017a), the act of restoring true dynamic accommodation to the presbyopic eye is clearly an aspiration for many clinicians, researchers and patients alike. When exploring this notion, one must question exactly what would be the outcome characteristics of this accommodation restoration and, importantly, what physiological factors would need to persist in the ageing eye in order for this correction to be a viable method?

The 'ideal' presbyopia correction has been described as "*capable of restoring to pre-presbyopic levels the dioptric range within which accurate focus can be smoothly and rapidly achieved. It should also be able to maintain this range throughout the remaining decades of the life of the individual, without any further intervention, with the eye always being emmetropic at the lower end of the range*"(Charman, 2017b). In addition the correction should be invisible to the outside observer and changes in focus should occur 'naturally', in synchrony with convergence movements of the eyes, which implies that at least some natural accommodation systems should be utilised, such as innervation of the ciliary muscle (Charman, 2017b). It has been suggested that a minimum subjective amplitude of accommodation should be 5.0 D (Schor, 2012). However, the pre-presbyopic human accommodative system has been shown to be robust to fatigue even during intense and prolonged near work, allowing a greater proportion of an individual's amplitude of accommodation to be continuously exerted than previously suggested. Indeed, a study by Wolffsohn and colleagues demonstrated that when viewing a task at 40 cm, on average only a maximum amplitude of 2.6 D would be needed, but as much as 5.5 D depending on the individual (Wolffsohn et al., 2011b).

2. Anatomical structure of the accommodative system with ageing

2.1. *Crystalline lens*

The young crystalline lens is transparent, bi-convex and, when at rest, is responsible for approximately 30% of the eye's total refractive power (Bennett, 1988; Borja et al., 2008). The crystalline lens substrate can be broadly split into two distinct compartments, the nucleus and the cortex, which become delineated during the unique biphasic (prenatal and postnatal) growth profile of the structure (Augusteyn, 2010, 2018). The oldest fibres (including fibres present at birth) reside within the nucleus and the overlying fibres form the cortex (Dubbelman et al., 2003).

The crystalline lens continues to grow throughout life due to the addition of new lens epithelial cell fibres (Bassnett and Sikic, 2017), the result of which leads to an increase in lenticular axial thickness; this increase is between 0.019 and 0.031 mm/year of life (Atchison et al., 2008; Kasthurirangan et al., 2011; Richdale et al., 2013, 2016). The equatorial diameter of the crystalline lens also appears to increase with age (Kasthurirangan et al., 2011), whilst the surface radii of curvature decrease with age, becoming steeper (Richdale et al., 2016), with the greatest change observed across the anterior surface (Koretz et al., 2004). Throughout life, lens protein content increases (Chang et al., 2017). Overtime, as there is no breakdown of proteins in the fibre cells, the cellular protein concentration increases which leads to a corresponding increase in refractive index as the cells become more compacted. Consequently, older, more central cells exhibit a higher refractive index than surrounding cells, which, in turn, leads to a refractive index gradient (Augusteyn, 2008). Intuitively, one might imaging that with further compacting of lens cells throughout life, the refractive index of the lens centre would also continue to increase. In fact, the opposite occurs where central refractive index values plateau at about 1.418 (Jones et al., 2005; Khan et al., 2018).

With an increase in lenticular thickness and surface curvature throughout life one might expect a corresponding increase in optical power and thus a relatively myopic eye. In reality, however, due to further changes in the gradient refractive index of the crystalline lens with advancing age, the equivalent power of the crystalline lens actually decreases with age: a phenomenon termed the 'crystalline lens paradox' (Brown, 1974; Brown et al., 1999; Koretz and Handelman, 1988). Although the refractive index of the crystalline lens centre does not change significantly with age (Augusteyn, 2010), the nucleus increases in size with age, causing the gradient between high and low refractive indices to become steeper (Jones et al., 2005; Kasthurirangan et al., 2008), however, the exact shape and location of the gradient remains equivocal (Pierscionek and Regini, 2012). More recently, the gradient index (GRIN) model has been proposed as the most accurate way to represent the crystalline lens with a lamellar, shell-like structure (Giovanzana et al., 2017).

Perhaps one of the most significant changes to the crystalline lens with advancing age occurs to its flexibility. Here, more than a three-fold increase in the overall relative resistance of the *in vitro* human crystalline lens to compressive forces over the life-span has been observed (Glasser and Kaufman, 1999). Indeed, Glasser and Campbell (1998) found that older lenses did not undergo significant changes in focal length in response to simulated zonular tension and relaxation *in vitro*. The stiffness of the nucleus and cortex increase at different rates with age, becoming similar between the ages of 35–45 years (Weeber et al., 2007). The nucleus is stiffer than the cortex in old lenses, whereas the cortex is stiffer than the nucleus in young lenses (Heys et al., 2004). Indeed, for a 20 year old eye, Heys and colleagues' ex vivo study showed that crystalline lens stiffness (measured as log shear modulus) was approximately 1.5 Pa at the nucleus and 2.0 Pa at the cortex; this inverted in the older eye where a 70 year old lens would change to approximately 4.2 Pa at the nucleus and 3.2 Pa at the cortex. Increasing rigidity of the crystalline lens is, therefore, considered the main cause of presbyopia in humans (Burd et al., 2011; Laughton et al., 2017; Sheppard et al., 2011). That said, significant variability in data derived from such studies remains. Also, when considered alongside accommodative stimulus-response profiles in the ageing eye, changes in lenticular stiffness do not correlate. Indeed, despite a reduction in the amplitude of accommodation from the first decade of life (see Fig. 1), lenticular stiffness appears invariant up to approximately 30 years of age (Heys et al., 2004). Coupled with the destructive nature of ex vivo investigations of lens stiffness, further work is indicated.

In addition to increasing lenticular rigidity, presbyopia has also been attributed to the change in shape and size of the crystalline lens with age. The geometric theory suggests the axial increase in crystalline lens mass and reduction in the radii of curvature causes the zonular insertion area to widen around the lens equator, increasing the distance between the anterior and posterior zonules (Farnsworth and Shyne, 1979), pulling the ciliary muscle antero-inwards (Pardue and Sivak, 2000; Sheppard and Davies, 2011) and reducing the magnitude of the parallel vector force the zonules can impart on the crystalline lens equator. Therefore, contraction and relaxation of the zonules will gradually have less of an impact on crystalline lens shape with age (Koretz and Handelman, 1986). As indicated in Section 2.2, further *in vivo* research may also demonstrate a reduction in efficiency of zonular action with age (Croft et al., 2016).

In a previous *Progress in Retinal and Eye Research* review, Strenk and colleagues (Strenk et al., 2005) modified the geometric theory to consider the putative role of the uveal tract. Here, Strenk and colleagues suggested continuous anterior crystalline lens growth and movement pushes the pupillary margin forwards. The applied force travels down the iris root and across the rest of the uvea, causing an antero-inwards movement. The age-related reduction in circumlental space (the distance between the ciliary muscle inner apex and the crystalline lens equator) reduces zonular tension in the absence of accommodation, allowing the crystalline lens to take-up a thicker, more curved shape and therefore reducing the change in crystalline lens shape possible during accommodation. Indeed, the relocation of the anterior uveal tract to a more posterior position once the presbyopic crystalline lens has been removed seems to support this hypothesis (Strenk et al., 2010).

2.2. Zonules

The zonules connect the ciliary body to the crystalline lens, relaxing and contracting in response to ciliary muscle activation and relaxation (Charman, 2017b). The zonules are derived from loose bundles of fibres from the vitreous framework. They are tubular fibrils that form sheets of bundles arranged radially from the ciliary body (Raviola, 1971). The zonular plexus consists of fibres that are divided into anterior and posterior/vitreous zonules. The main anterior zonules are responsible for suspending the crystalline lens and are flexible enough to permit dynamic changes in crystalline lens size and shape. The main anterior zonular insertion sites are within the ciliary processes (non-pigmented ciliary epithelium) and the crystalline lens capsule, close to the crystalline lens epithelium (Rohen, 1979). The insertion sites of the main posterior/vitrous zonules are the ciliary processes and the *pars plana* (Glasser, 2008). More recent studies have also provided *in vivo* evidence for a new structure that extends from the posterior insertion zone of the vitreous zonule in a straight course directly to the posterior lens equator, without passing in proximity to the zonular plexus (termed PVZ INS-LE)(Croft et al., 2013a, 2013b). Moreover, together with the posterior/vitreous zonule, the PVZ INS-LE structure may dampen the accommodative lens shape change in the ageing eye (Croft et al., 2016).

2.3. Ciliary body

The ciliary body is part of the uveal tract, which forms embryonically from the mesenchyme surrounding the two vesicles that bud off the forebrain (Beebe, 1986; Nickla and Wallman, 2010). The ciliary body connects to the peripheral iris anteriorly and the choroid posteriorly, and runs continuously with the sclera from the scleral spur to the *ora serrata*. The anterior section of the ciliary body is the *pars plicata*, which consists of 70–80 highly-vascular folds of non-pigmented ciliary epithelium (ciliary processes), which are responsible for aqueous humour secretion (Cole, 1977). The posterior section of the ciliary body is the *pars plana*, which extends from the ciliary processes to the *ora serrata*. The ciliary body comprises six layers: the supraciliary lamina, ciliary muscle, stroma, basal lamina, epithelium and internal limiting membrane (Aiello et al., 1992). The ciliary muscle lies beneath the ciliary processes and constitutes approximately two-thirds of the ciliary body mass (Remington, 2005).

2.3.1. Ciliary muscle

The ciliary muscle is a multi-unit smooth muscle, made up of bundles of muscle cells surrounded by connective tissue cells (Ishikawa, 1962). The muscle bundles form three distinct fibre types: longitudinal, radial and circular. Longitudinal fibres run parallel to the sclera from the scleral spur to the posterior visible limit of the ciliary muscle. Radial fibres run perpendicular to longitudinal fibres and circular fibres encircle the ciliary muscle aperture and are the closest fibres to the crystalline lens (Pardue and Sivak, 2000). The radial fibre cells contain the most mitochondria organelles (Ishikawa, 1962), whereas the tips of the longitudinal fibre cells contain the fewest mitochondria and more myofibrils (Flugel et al., 1990), possibly facilitating faster contraction and providing greater stiffness than the rest of the fibres (Rohen, 1979).

The ciliary muscle connective tissue is mainly made up of collagen fibrils and fibroblasts (Ishikawa, 1962). The ciliary muscle is thicker temporally than nasally (Sheppard and Davies, 2010).

Contraction of the ciliary muscle during accommodation causes a centripetal (inwards, towards the centre of the eye) and anterior (towards the cornea) movement of ciliary muscle mass (Esteve-Taboada et al., 2017; Sheppard and Davies, 2010; Tamm et al., 1992). The longitudinal fibres are responsible for the anterior shift in muscle mass during contraction, whereas the radial and circular fibres are responsible for the inward movement of muscle mass during contraction, with the circular fibres acting as a sphincter (Pardue and Sivak, 2000), whilst the contractile response is thought to be greater temporally than nasally, possibly in order to align the lenticular axes during convergence (Sheppard and Davies, 2010).

3. Presbyopia social and economic impact

As highlighted previously, presbyopia has been estimated to affect 1.37 billion people worldwide by the year 2020 (Holden et al., 2008). While the impact of presbyopia can be minimised relatively easily by use of a visual correction, such as spectacles, contact lenses or refractive surgery (see Section 6), these corrections have a financial burden (Naidoo et al., 2016) and it is estimated that globally over 50% of adults > 50 years (over 50% in some developing world where there is a lack of awareness and accessibility to affordable treatment options (Cheng et al., 2016; Girum et al., 2017; Hookway et al., 2016; Muhit et al., 2018; Schellini et al., 2016) and up to 34% even in developed countries) do not have adequate near correction, impacting task performance and productivity (Frick et al., 2015; Holden et al., 2008; Kaphle et al., 2016; Man et al., 2016; Nsubuga et al., 2016; Zebardast et al., 2017). Even in developed countries, increasing digital demands are associated with asthenopia, perhaps due to latent accommodative dysfunction, in people in their thirties, which is a form of largely undiagnosed early onset presbyopia (Reindel et al., 2018).

Another aspect of presbyopia that has largely been overlooked by research is the correction habits of presbyopic patients and the impact of the combination of corretions utilised on their quality of vision and life. In a sample (unpublished) of 529 sequential presbyopic patients (> 45 years) attending 4 optometric practices for routine check-ups in diverse areas across London, over half (54.7%) managed without glasses at least some of the time, while distance, reading or progressive spectacles were used by between 30 and 40%. Those using Progressive Addition Lenses wore them on average over 80% of the time, while those wearing reading spectacles utilised them on average only approximately 25% of the time. Only ~5% had had a surgical correction for presbyopia (2.8% monovision in IOLs and 2.8% a multifocal IOL), but only 7 out of 30 were fully spectacle independent.

4. Presbyopic correction clinical evaluation techniques

Appropriate presbyopic evaluation techniques depend on the mode of correction, but could include visual function, adverse effects, lens and lens-eye combined aberrations, pupil size, subjective benefits, restoration of accommodation and safety aspects (Table 1).

4.1. Visual function

4.1.1. Visual acuity and defocus curves

Near visual acuity and near vision adequacy are the most common clinical evaluations of presbyopic corrections, but while these fits with a functional focus of the definition of presbyopia (see Section 1), often arbitrary distances are assessed such as 40 cm for near and 80 cm for intermediate, with no regard for the patients comfortable or habitual working distance (Gupta et al., 2008). Hence assessment of how visual acuity changes over a range of distances from distance to near are needed to better understand the potential of a presbyopic correction.

Table 1
Assessment techniques recommended to evaluate different forms of presbyopia treatment.

Presbyopic Management	Spectacles	Contact Lenses		Scleral Expansion	Intraocular Lenses			Inlays	Laser Refractive Surgery				Pharmacologic	Electro-stimulation
	Bifocal/ progressive	Monovision	Simultaneous images/ translation		Monovision	Multifocal	Accommodating		Corneal Monovision	Corneal Shrinkage	Corneal Multifocal	Lenticular 'softening'		
Visual acuity/defocus curves	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contrast sensitivity	X		X			X		X			X	X	X	
Reading	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stereopsis		X			X				X					
Straylight & glare			X			X		X		X	X	X	X	
Aberrations, pupil size & different illumination levels			X			X		X			X		X	
Subjective benefits	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Restoration of accommodation				X			X					X	X	X

Defocus curves provide greater granularity of how presbyopic corrections would perform for an individual and hence one could argue replace the need for distance corrected visual acuity measurements at discrete distances. Snellen charts have been the mainstay of distance visual acuity measurement for over 150 years, but their irregular separation between lines and letters and varying number of letters on lines makes them non-ideal for accurate measurement (Wolffsohn and Kingsnorth, 2016). The Bailey Lovie logMAR design principals overcome these issues increasing the repeatability of measurement (Chaikitmongkol et al., 2018), but the resulting large size of these charts has resulted in poor adoption in clinical practice (Bailey and Lovie, 1980). In the electronic age, computer monitors have the resolution to display logMAR charts with the advantage of features such as letter randomisation and letter isolation (Wolffsohn and Kingsnorth, 2016). Loss of visual acuity is also a key safety metric whether through ocular damage during surgery or compromised distance visual acuity through simultaneous multifocality.

If the correction restored accommodation, evaluation of the range of clear focus could be measured with the push-up/push-down test; an average of the combined methods repeated at least three times is recommended (Pointer, 2012), although the target for detecting blur is generally supra-threshold, leading to an overestimation of the capability of the correction. More universally a defocus curve can be plotted (Fig. 2). The patient should view a distance chart and their acuity scored from the logMAR letters read correctly with lenses inserted to change the focal distance of the chart typically from −3.00 D to +1.50 D in 0.50 D steps (Wolffsohn et al., 2013a). While another approach would be to move the target in real space, this required resizing of the chart at each distance and careful control of the illumination level, so is rarely performed. Either the order of the lenses should be randomised or the letters randomised for each lens (Gupta et al., 2007, 2008). The results at each level of focus should be adjusted for image minification/magnification induced by the lenses (Gupta et al., 2008). In terms of analysis, the direct comparison method involves statistical comparison of the visual acuity at each defocus level; the linked nature of repeated measurements needs to be accounted for statistically and the large number of comparisons can complicate clinical interpretation. Alternatively, the depth-of-focus method of analysis describes the dioptric range over which the subjects can sustain a specific absolute (such as 0.3 logMAR) or relative (such as 0.1 logMAR worse than the best corrected distance visual acuity) level of visual acuity. As the defocus curve of a simultaneous image correction can pass through the depth of focus criterion acuity several times across a range of focusing distances, an area of focus metric has been validated across far, intermediate and near distances to achieve a better comparison of these correction modalities (Fig. 2) (Buckhurst et al., 2012b).

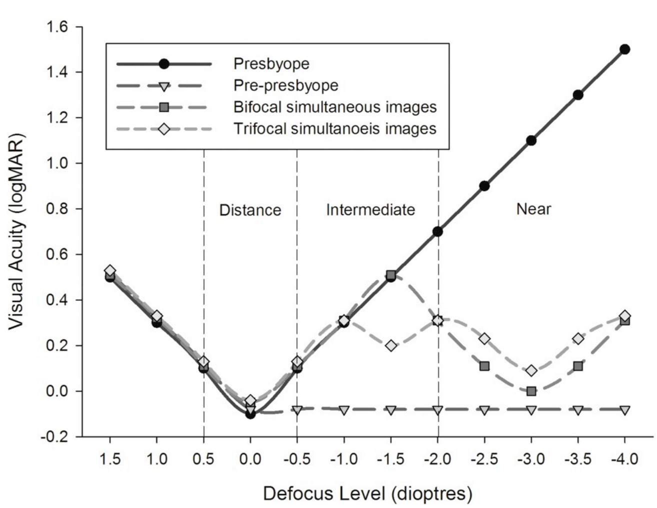

Fig. 2. Typical defocus curve (magnification corrected) for: a presbyope with no active accommodation (both positive and negative blur has a symmetrical effect of visual acuity loss); a pre-presbyope with at least 4.00 D of active accommodation; bifocal simultaneous image optics with a near addition of 3.00 D; and a trifocal with an intermediate addition of +1.50 D and near addition of +3.00 D (note the resulting compromises in distance for multifocal design and near for the trifocal).

4.1.2. Contrast sensitivity

Measurements of the contrast sensitivity function better characterise functional vision than high contrast visual acuity alone. Paper based clinical charts (such as the Pelli-Robson) are often limited in the number of stimuli they present, hence they only assess broad discrete steps of spatial frequency and contrast, and require the examiner to manually implement and respond to feedback from the patient (Maudgal et al., 1988); their reliability is also limited (Pesudovs et al., 2004; Reeves et al., 1991). Another popular choice for multifocal IOL studies, the CSV-1000, although testing four spatial frequencies, only requires a selection of the circle with the grating from the mean intensity grey circle so guessing can cause a significant error in the results (Kelly et al., 2012). Computerized contrast sensitivity testing equipment can render a multitude of grating stimuli of various frequencies and contrast and adopt complicated testing methods that render stimuli in response to patient feedback, such as staircase or adaptive two-alternate forced choice procedures (Lesmes et al., 2010). Despite a reduction in the contrast resolution available to tablet liquid crystal displays, innovative pixel dithering techniques (Tyler, 1997) have enabled gratings based testing on mobile tablets to be indistinguishable from traditional cathode ray tube lab setups (Dorr et al., 2013; Kollbaum et al., 2014). It is now possible to test all relevant spatial frequencies on a tablet in less than 1 min (Kingsnorth et al., 2016). It is also questionable whether distance contrast sensitivity should be measured as well as near as no cases have been identified where differences would be clinically relevant (Kingsnorth et al., 2016).

4.1.3. Reading speed

Reading is one of the most vital and common skills for engaging, communicating and interpreting ideas. Any visual loss that affects reading ability will have a disproportionate impact on a patient's quality of life and is often cited as a major factor in patients seeking professional help (Elliott et al., 1997) for eye related problems. Reading speed more closely aligns with task performance than visual acuity metrics (Gupta et al., 2009b). Current paper based reading (aloud) performance charts such as the MNRead and Radner charts (Radner et al., 1998; Subramanian and Pardhan, 2006) are generally cumbersome and time consuming to use, involving manual time measurement, sentence unveiling, and error recording which have to be undertaken simultaneously by the examiner. Additionally, reading performance metrics are determined by plotting reading performance data graphically, which is time consuming and the data can be noisy (Cheung et al., 2008). A reading speed desk has been introduced to try to automate some of the process (Dexl et al., 2010), but is not well suited to clinical practice. However, portable tablet technology now allows quick, efficient and reliable reading speed, critical print size (when the reading speed starts to slow down) and threshold near visual acuity determination testing, including working distance and screen tilt monitoring along with automated time, word error and metric generation (Kingsnorth and Wolffsohn, 2015).

4.1.4. Stereopsis

Stereopsis is generally assessed when comparing monovision to multifocal presbyopic correction. Random dot stereograms are thought to be a more robust clinical technique as the object seen if stereopsis is present cannot be determined from changes in head position and other monocular cues (Heron and Lages, 2012). Stereopsis is more precise at near and therefore is generally assessed at a close distance (Rodríguez-Vallejo et al., 2017).

4.2. Straylight and glare

Dysphotopsia is a disturbance of vision and includes light phenomena such as glare and haloes, the subjective perception of a bright ring around a light source. It occurs due to optical non-conformities in the optical path such as cataract or optical boundaries, for example following simultaneous image creating multifocal IOL implantation (Leyland and Zinicola, 2003; Wilkins et al., 2013). The majority of studies examining dysphotopsia use various subjective questioning in the form of verbal interviews (Jacobi et al., 2003; Marques and Ferreira, 2015), bespoke questionnaires (Kohnen et al., 2006), a validated questionnaire (Aslam et al., 2004a, 2004b) or through subject-initiated complaints (Shoji and Shimizu, 1996). An alternative method is to use graphics depicting visual demonstrations of different types of dysphotopsia allowing the subject to indicate which is most representative of what they perceive (Hunkeler et al., 2002; McAlinden et al., 2010).

Disability glare is usually quantified as the reduction in vision from a glare source present within the visual field, and is due to the spread of light (or straylight) across the retina (Vos, 2003). A psychophysical method to assess straylight has also been commercialised, but its ability to differentiate between multifocal IOLs is limited as dysphotopsia due to multifocal IOLs may primarily be the result of a second out of focus image being present on the retina (typically corresponding to angles smaller than one degree) rather than diffuse straylight over the retinal surface (scatter affecting an area much broader than one degree) as induced by conditions such as cataract (Epitropoulos et al., 2015; Hofmann et al., 2009). To measure the qualitatively described light surrounding the retinal blur circle or halo, halometers have been created and validated, which measure the size of the photopic scotoma created by a central glare source (Babizhayev et al., 2009; Buckhurst et al., 2015; Meikies et al., 2013). They have been found to be repeatable and discriminatory between different optical designs used to correct presbyopia (Buckhurst et al., 2017).

4.3. Aberrations, pupil size and different illumination levels

Most simultaneous image presbyopic corrections, other than large coverage diffractive lenses (see section 6.3.2.2), will alter their proportion of light focused at different distances due to the size of the pupil. Hence this is considered an important metric (see Section 6.2) and the true impact on an individual can be assessed by measuring metrics such as visual acuity and contrast sensitivity under photopic and mesopic lighting conditions. Only the aberration profile of the lens through which rays of light are not blocked by the pupil will be relevant to the visual outcomes of the presbyopic correction (Bradley et al., 2014; Legras and Rio, 2017). It is also often overlooked that the visual outcomes will be determined by the combination of the individual's natural optical aberrations in combination with the lens on-eye, not the lens in isolation (Sivardeen et al., 2016a).

4.4. Subjective benefits (quality of life)

Presbyopia reduces vision related quality-of-life and although this can be improved with corrections, it cannot currently be restored to pre-presbyopic states (McDonnell et al., 2003). Standardised vision-related questionnaires generally include few items to assess near visual activities, concentrate on spectacle dependence only, are targeted to measure another aspect of vision (McAlinden et al., 2010), or have not been appropriately validated (Alio and Mulet, 2005; Alio et al., 2004; Bakaraju et al., 2018; Diec et al., 2017; Kohnen et al., 2017; Walkow et al., 1997; Wang et al., 2005). There is only one validated questionnaire available which specifically assesses near visual ability (Buckhurst et al., 2012a) and this is being updated to make it relevant to modern intermediate and near vision tasks such as smartphone and tablet use.

4.5. Restoration of accommodative function

The 'ideal' presbyopia correction has been described as "*capable of restoring to pre-presbyopic levels the dioptric range within which accurate focus can be smoothly and rapidly achieved* …"(Charman, 2017b) Accommodation has been estimated from optical coherence tomography or ultrasound imaged lens movement to pharmacological stimulation (pilocarpine) (Fayed, 2017; Grzybowski et al., 2017, 2018; Shao et al., 2018). Ultrasound sound waves can partially pass through the pupil, but the technique has a lower resolution and is more invasive than optical coherence tomography. Only Magnetic Resonance Imaging avoids the distortions of the intervening media due to their physical properties (which are difficult to accurately correct for)(Khan et al., 2018; Richdale et al., 2016; Sheppard et al., 2011) but this is of lower spatial and temporal resolution although higher tesla devices are becoming available (Stahnke et al., 2016). Direct accommodation assessment requires measurement of changes of the optics of the eye which can be achieved objectively through autorefractors (Win-Hall et al., 2010; Wolffsohn et al., 2011a) or aberrometers (Bhatt et al., 2013; Glasser et al., 2017; Perez-Merino et al., 2014). These should be open-field not to stimulate instrument myopia and ideally should allow dynamic measurement so the latency, speed and amplitude of accommodation/disaccommodation can be quantified to determine how different this is to natural accommodation (Fig. 3)(Wolffsohn et al., 2002).

4.6. Other considerations

Other metrics which may be important to understand the impact and mechanism of presbyopic corrections include eye and head movement for spectacle lenses (Rifai and Wahl, 2016), contact lens movement for translating optics (Wolffsohn et al., 2013b), electrophysiology or functional magnetic resonance imaging to understand neural processing (Zeri et al., 2018), ocular health after surgery or with contact lens wear and 'real world' performance such as movement lab testing of mobility or driving assessment (Chu et al., 2009b, 2010). Objective measurement is generally more rapid and less fatiguing to the participant than subjective assessment of visual function at different distances, but requires high spatial resolution to assess optics designed to create simultaneous images.

5. Presbyopic correction strategies

Strategies for correcting presbyopia include separate optical devices located in front of the visual system or a change in the direction of gaze

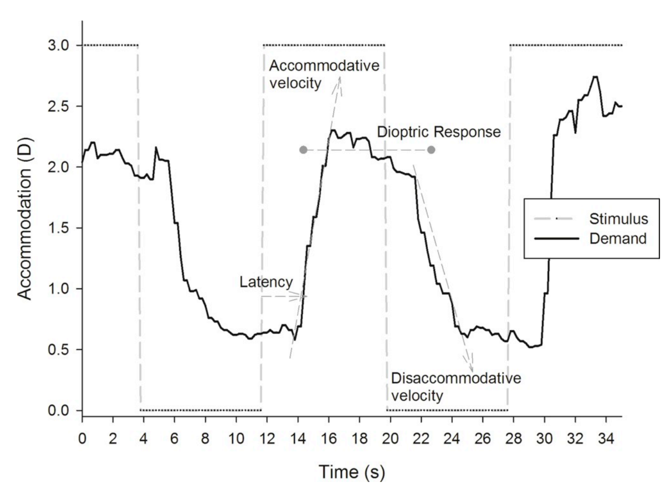

Fig. 3. Dynamic accommodative trace captured with a modified autorefractor (Mallen et al., 2015) demonstrating latency, accommodative/disaccommodative velocities and average dioptric response evaluation.

Table 2
Comparative studies of the correction of presbyopia with contact lenses from 2008 onwards. No adaptation indicates lenses not dispensed (generally a maximum of 10 min adaptation prior to testing). MF = multifocal; BF = Bifocal; SV = distance single vision contact lenses; DoF = Depth of focus; CLs = contact lenses; VA = Distance visual acuity; IVA = Intermediate visual acuity; NVA = Near visual acuity; CS = contrast sensitivity; photopic/mesopic indicates acuity testing under different luminance levels; Qs = subjective questionnaire.

Study	N°	Age (yrs)	Design	Lenses	Measurements
Novillo-Diaz et al., 2018	150	40–62	3 months, n-50 with each design	Distanza, Biofinity MF, Air Optix Aqua MF	Drop-out rate, Qs
Bakaraju et al., 2018	43	42–63	1wk Crossover	Air Optix Aqua MF, Acuvue Oasys MF, extended DoF CLs	VA, NVA + range, CS, stereopsis, Qs
Labuz et al., 2017	16	21–48	Contralateral - non dispensing	Proclear MF, Acuvue Oasys vs Air Optix	Straylight
Imbeau et al., 2017	13	45–60	3 wk Crossover	Biofinity MF, monovision CLs	VA, NVA, stereorsis, electrophysiology
Diec et al., 2017	55	52.0 ± 5.4	1 wk Crossover	Acuvue Oasys MF, Air Optix Aqua MF	VA, NVA, CS, stereopsis, Qs,
Fedtke et al., 2017	17	55.1 ± 6.9	Crossover - non dispensing	Air Optix Aqua MF, Proclear MF near/distance designs, Clariti 1 Day MF, Acuvue BF, PureVision MF, Air Optix Aqua SV	VA, NVA, CS, aberrations
Tilia et al., 2017	41	45–70	Crossover - non dispensing	Acuvue Oasys MF, extended DoF CLs	VA, NVA, CS, steropsis, Qs
Sha et al., 2016	42	45–70	Crossover - non dispensing	Acuvue Oasys MF, Air Optix Aqua MF, Air Optix Aqua SV	VA, CS, Stereopsis, Qs
Sivardeen et al., 2016b	50	42–65	1mth Crossover	Air Optix Aqua MF, PureVision 2, Acuvue Oasys MF, Biofinity MF, monovision CLs	VA, NVA, CS, defocus curves, aberrometry, stereopsis, reading speed, Qs, halometry
Woods et al., 2015	49	43–66	2wk Crossover	Air Optix Aqua MF vs monovision CLs	VA, IVA, NVA, stereopsis, Qs
Garcia-Lazaro et al., 2013	22	50–64	Contralateral – non dispensing	PureVision MF vs Pinhole	VA, NVA, CS, photopic/mesopic, defocus curves, stereopsis
Plainis et al., 2013a	12	22–29	Crossover – non dispensing	Air Optix Aqua MF low, medium & high add	VA, defocus curves, artificial pupil, aberrometry
Madrid-Costa et al., 2012	20	45–65	1mth Crossover	PureVision MF low add, Acuvue Oasys MF	VA, NVA, CS, photopic/mesopic, defocuscurves
Madrid-Costa et al., 2012	20	45–65	1mth Crossover	Proclear MF toric, Proclear toric, reading spectacles	VA, NVA, CS ± glare, photopic/mesopic, defocus curves, stereopsis
Llorente-Guillemot et al., 2012	20	41–60	1mth Crossover	PureVision MF high add, spectacles	VA, CS ± glare, photopic/mesopic
Ferrer-Blasco and Madrid-Costa, 2011	25	50–60	1mth Crossover	Proclear MF, SV, spectacles	VA, NVA, stereopsis
Ferrer-Blasco and Madrid-Costa, 2010	20	50–60	1mth Crossover	Proclear MF, SV, spectacles	VA, NVA, stereopsis
Chu et al., 2010	11	45–64	Crossover – non dispensing	PALs, BF spectacles, MF CLs	Driving metrics
Chu et al., 2009b	20	47–67	Crossover - non dispensing	PALs, BF spectacles, MF CLs	Driving Metrics
Woods et al., 2009	25	38–50	1wk Crossover	Focus MF, monovision CLs, Habitual correction, SV	VA, CS, stereopsis, reading speed, Qs
Chu et al., 2009a	255		Survey	Habitual	Survey
Papas et al., 2009	88	40–60	4day Crossover	Acuvue BF, Focus MF, Proclear MF, Soflens MF	VA, IVA, NVA, photopic/mesopic, steropsis, reading speed, Qs
Gupta et al., 2009a	20	49–67	1mth Crossover	PureVision MF vs monovision	VA, IVA, NVA, CS, reading speed, defocus curves, stereopsis, Qs

to view through optical zones of different optical powers (see Sections 6.1), monovision (see section 6.2.1; 6.3.1; 6.3.4.1; 6.3.4.2), simultaneous images (see sections 6.2.2; 6.3.2; 6.3.3), pinhole depth of focus expansion (see sections 6.3.2; 6.3.3; 6.4), crystalline lens softening (see Section 6.3.4.4; 6.4) or restored accommodative dynamics (see section 6.3.2.3; 6.3.1; 6.5). These strategies may be applied differently to the two eyes to optimise the range of clear focus for an individual's task requirements and minimise adverse visual effects (termed modified monovision).

Monovision is when an unbalanced correction between the two eyes corrects one more for far vision and the other for intermediate or near distances. Therefore monovision is a form of imposed anisometropia. Unlike simultaneous image designs that cause the superimposition of a more in-focus image with a more blurred image at any task distance, interocular suppression between the eyes in monovision can lead to clear vision when viewing binocularly at both the targeted optical vergences. However, a recent study suggests that interocular suppression is bimodal, with only approximately 40% of people having the required strong 'dominance' although the sample size was relatively small (Li et al., 2010). At a neural level, with monovision feed-forward activity in the primary visual area and feedback activity in extrastriate areas (C1 and N1) are reduced whereas, other brain activities in both extrastriate visual areas (the P1 component) and in the anterior insula (the pP1 component) are increased to compensate, suggesting fluid brain adaptation in visual and non-visual areas (Zeri et al., 2018). There is a deterioration of the binocular vision when inducing anisocoria causing a higher perception of halos, a lower contrast sensitivity and poorer binocular summation (astro et al., 2016). Recent research confirms that simulated anisometropia (as induced by monovision) reduces stereoacuity proportional to the intraocular difference in vergence and that the effect is equivalent whether induced in the dominant or non-dominant eye (Nabie et al., 2017), despite the fact that the near addition is traditionally added to the non-dominant eye. Sighting ocular dominance can change with both gaze angle and viewing distance (Ho et al., 2018; Quartley and Firth, 2004) and is fluid and adaptive (Evans, 2007), so its value in choosing which eye to assign to near (versus dominance strength perhaps aiding to predict tolerance to monovision) could be questionable. Adaptation with time does not seem to occur with monovision, whereas acuity improves and light disturbances decrease after initial fitting with simultaneous images multifocal contact lenses (Fernandes et al., 2013, 2018); however, subjective satisfaction does not seem to change with time with either modality (Woods et al., 2015).

6. Effectiveness of presbyopic correction modalities

While some previous reviews have focused on presbyopia corrections characterised by their mechanism (such as gaze relocation, simultaneous images or monovision) or anatomical location, clinically the modality is usually selected first (such as spectacles, contact lenses or intraocular lens implantation), hence this review is organised to reflect this approach.

6.1. Spectacles

Perhaps the most rudimentary method of ameliorating the symptoms of presbyopia is with the use of spectacle lenses (either single vision, bifocal/trifocal, or progressive power lenses). In the simplest of forms, near vision spectacle lenses, prescribed to optimise near vision at a defined distance and range, provides an effective means of correcting vision. For many years now (Jiang et al., 2012), additional designs in the form of bifocals, trifocals and progressive lenses have been available to restore some form of pseudo-dynamic 'accommodation' through gaze relocation through optical zones of different optical powers, with varying degrees of success (Charman, 2014a). As with so many presbyopia correction modalities, however, no spectacle lens is currently available capable of restoring the dynamic range of accommodation to the ageing eye. As a result, presbyopes continue to experience problems (Alvarez et al., 2017) particular in real-world environments (Konig et al., 2015), which can even result in secondary musculoskeletal symptoms (Weidling and Jaschinski, 2015) and falls (Elliott, 2014). Little research on progressive lens designs and their effectiveness in ameliorating presbyopia is published in the peer reviewed literature, with these mainly subjective trials of iterative design changes kept internal by the lens manufacturer.

6.2. Contact lenses

Table 2 summarises the methodology applied to contact lens for presbyopia studies conducted over the previous decade.

6.2.1. Monovision

Clinical results after an adaptation period to contact lens monovision in terms of the range of clear focus seem to be good, although contrast sensitivity and stereopsis is reduced (Gupta et al., 2009b; Imbeau et al., 2017; Sivardeen et al., 2016b; Woods et al., 2009, 2015). The optimum near addition for monovision seems to be ~+1.50 D, with lower levels not stimulating sufficient interocular summation and higher levels negatively impacting stereopsis (Hayashi et al., 2011).

6.2.2. Multifocal designs

While power profiles of soft multifocal contact lenses vary when measured in the laboratory, (Fedtke et al., 2017; Kim et al., 2017), the aberration differences when the lenses are in combination with those of the human eye are much less marked (except for centre distance / centre near designs worn contralaterally)(Fedtke et al., 2017; Sivardeen et al., 2016a); this could explain the similar performance (Sivardeen et al., 2016b) and lack of predictability of preference found clinically (Sivardeen et al., 2016a). Hitherto, all recent commercial contact lens multifocal designs have been refractive concentric designs, although a recent addition has off-set the near zone to try and benefit from near convergence in a form of translation. Unpublished data with this lens compared to traditional concentric designs on 31 presbyopes showed that after 1 h of adaptation, all the lenses were decentred temporally ($p < 0.001$) and this was generally increased (but only on average by ~0.6 mm) with binocular near viewing (Fig. 4), supporting the concept of an asymmetrical lens design to increase the proportion of light focused at near during near viewing and decreasing the proportion of light focused at near during distance viewing.

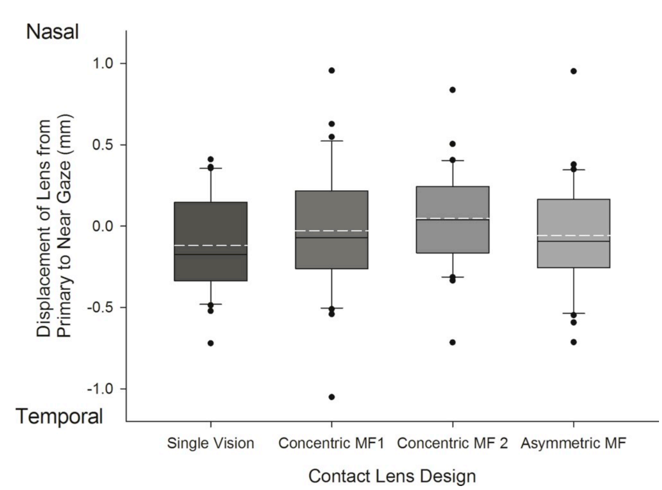

Fig. 4. Temporal displacement (median solid line, average dotted white line) of soft contact lenses on near viewing. Box extremes indicate SD, bars 95% confidence intervals and dots points outside the 95% confidence internal. N = 31.

Modelling indicates multiple refractive zone concentric rings are more robust in providing multifocality with a range of pupil sizes than two zone designs (Bradley et al., 2014; Legras and Rio, 2017; Rio et al., 2016). It has recently been emphasised that refractive error is associated with pupil size as well as age and luminance (together accounting for just over 70% of the variance in pupil diameter)(Guillon et al., 2016), with one lens manufacturer factoring this into their simultaneous-image multifocal contact lens design. However, while pupil size should make a difference in lens performance and hence preference (Charman, 2017a; Papadatou et al., 2017), this does not seem to be the case clinically (Sivardeen et al., 2016a).

Although anecdotally clinicians often state they are successful with fitting multifocal lenses as they carefully assess patients to identify the most suitable lens for them, research has demonstrated that prediction of which lens design will work best with different patients in terms of their environment, visual demands, natural ocular aberrations and pupil size is still beyond current clinical metrics (Sivardeen et al., 2016a; Woods et al., 2009). A recent paper examined electrophysiological as well as subjective visual metrics, but as no significant differences were found between a multifocal and monovision contact lens wear for acuity, stereopsis or electrophysiology, no predictive neural markers were identified. However, a significant correlation accounting for a third of the variance ($r = -0.58$) was found between the difference in stereopsis scores and the P100 latency evoked by the binocular pattern at T0, confirming it to be an indicator of binocular summation which is reduced in monovision (Imbeau et al., 2017). Interestingly, the main reason for discontinuation of contact lens wear in a presbyopic population is both vision and comfort (Rueff et al., 2016), hence comfort aspects need to be tackled as well as optimising the range of clear vision.

There is only one peer reviewed publication over the last decade on the use of multifocal rigid gas permeable (RGP) designs, showing the potential of fabricating an RGP with a diffractive pattern to extend its range of focus (Yaish et al., 2014). Due to the additional mobility of RGP lenses, these can work by creating alternating principally distance and near focused light through translation on near vision (concentric and stabilised asymmetric designs) as well as concentric simultaneous image designs (Bennett, 2008). Larger corneal and scleral/semi-scleral designs translate less and therefore multifocal approaches are simultaneous image designs.

6.2.3. *Modified monovision*

While ‘modified monovision’, such as prescribing a single vision lens in one eye and a simultaneous image design in the other, or a simultaneous image design in both eyes, but with different near addition powers or locations (centre distance versus centre near) is used clinically, little research has been conducted on this approach using contact lenses, although a commercial lens fitting guide which advocates a centre distance lens in one eye and centre near in the other outperformed other commercial lens designs which use the same design in both eye (Sivardeen et al., 2016b).

6.3. *Surgical approaches*

6.3.1. *Scleral expansion*

Predicated on an alternative theory of accommodation (Schachar, 1992; Schachar et al., 1993) based more on the work of Tscherning (1924) than Helmholtz (von Helmholtz, 1924), scleral expansion surgery purports to restore dynamic accommodation to the ageing eye by increasing the distance between the lens equator and the ciliary body. According to Schachar and colleagues' theory, on contraction of the ciliary muscle during accommodation, equatorial zonular tension increases, causing the central anterior crystalline lens surface to steepen (often likened to a mylar balloon). With age, however, weakened zonular tension, caused by equatorial growth of the crystalline lens, renders the zonules unable to impart enough force to drive a change in crystalline lens shape. Despite this controversial and widely unsupported theory, *in vivo* studies by independent laboratories have offered some surrogate evidence for a reduction in zonular tension by demonstrating a reduction in circumlental space/equatorial lens growth with advancing age (Kasthurirangan et al., 2011; Strenk et al., 1999). Rather than providing support for Schachar's theory, this reduction in circumlental space may, in fact, prevent the ageing eye from assuming its fully relaxed (or disaccommodated) shape. Further, although there is no *in vivo* evidence to support the concept of scleral expansion, Hunter and Campbell suggested that any subjective improvement in post-operative near vision might simply be due to an unintentional anterior displacement of the crystalline lens in combination with excess tilts and/or decentrations (Hunter and Campbell, 2006), however, the concept and clinical acceptance of scleral expansion remains unsubstantiated.

In initial iterations, the surgical procedure involved implanting a polymethylmethacrylate (PMMA) annulus into the sclera overlying the ciliary muscle to stretch the sclera radially outwards by 0.5–1.5 mm in order to restore zonular tension. Subsequently, this annulus was replaced with scleral expansion bands which consist of PMMA rods approximately 5 mm long and 0.7 mm in diameter (Charman, 2014b). The expansion surgery has been performed on bovine eyes (Schachar et al., 1993) and presbyopic humans (Schachar, 1992) where subjective amplitude of accommodation appeared to increase in all participants. Subsequent studies assessing accommodation changes have been unable to replicate these findings (Malecaze et al., 2001; Mathews, 1999; Qazi et al., 2002) and have brought into question the validity of the technique and underlying theory (Glasser and Kaufman, 1999).

Despite these mixed reports, the pursuit of a successful scleral expansion technique, and thus an increase in circumlental space, remains. The VisAbility Micro-Insert scleral implant (Refocus Group, Dallas, TX, USA), an updated version of the PresView (Refocus Group, Dallas, TX, USA), is now the only scleral implant with the CE mark and is currently undergoing FDA clinical trials (U.S. National Institutes of Health Clinical Trials, 2018), with the final data collection point having taken place in November 2017. Even if the early VisAbility clinical trial results seem promising, substantial risks remain for patients. Anterior segment ischemia due to mechanical vascular compression from the implant can occur; subconjunctival erosion, moderate to severe subconjunctival haemorrhage, implant infection, and endophthalmitis could all occur subsequent to implantation (Hipsley et al., 2018).

6.3.2. *Intraocular lenses (IOLs)*

Intraocular lenses are still commonly implanted with a delay between eyes, despite the low risk of endophthalmitis with modern pharmaceutical recommendations and cost/patient advantages (Leivo et al., 2011; Sarikkola et al., 2011). Compared to contact lens options, a mix and match approach, fitting the second eye with a different design to complement rather than mimic the first eye, seems more common. Few studies on this approach have a concurrent bilateral control group, but mix and match implantation of diffractive IOLs with different addition power has been shown to: provide a better binocular defocus curve and spectacle independence than bilateral implantation of the same power add IOLs, without compromising contrast sensitivity and stereopsis (Hayashi et al., 2015); increase the depth of focus if aspheric IOLs with different levels of spherical aberration are implanted (Tarfaoui et al., 2013); and bilateral trifocal IOLs have been shown to result in better visual acuity at all distances than mix and match bifocal implantation (one with a near add and the other with an intermediate add)(Bilbao-Calabuig et al., 2016).

6.3.2.1. Monovision with IOLs. Monovision can also be induced with intraocular lenses (IOLs). A recent systematic review and meta-analysis of randomised controlled trials of monovision versus multifocal IOLs (identifying 9 suitable trials), suggested while monovision achieved with IOLs was inferior in visual outcome to multifocal IOLs; laser induced monovision tended towards equivalence, but the data was limited and largely inconclusive (Kelava et al., 2017). Another review assessing a wider range of pseudophakic monovision for presbyopia correction similarly evaluated this form of correction to give a high rate of spectacles independence with minimal dysphotopsia side effects (Labiris et al., 2017).

6.3.2.2. Multifocal IOLs. Multifocal IOLs have been available from the late 1980s (Hansen et al., 1990; Keates et al., 1987). Early versions were refractive in design, having concentric rings of far and near focus or an aspheric profile, while more recently diffractive optics (largely pupil independent) have been added to some lenses or asymmetric refractive segments (Alio et al., 2017; Greenstein and Pineda, 2017).

Initial multifocal IOL optics created two fixed focal points with an aim of delivering a sharp image on the patient's retina at distance and at a closer working distance. Reasonable levels of spectacle independence were reported, but bifocals (Hutz et al., 2008) and monovision (Greenstein and Pineda, 2017) resulted in poorer focus for intermediate distance tasks such as viewing computer monitors. Hence trifocal diffractive IOLS were developed overlaying two diffractive eschelet patterns on the lens surface, one with a second principal plane at near (~3.0 D) and the other with the second principal plane at half that optical power (~1.5 D) for intermediate vision, with the third optical plane adding to the light focusing at the near distance of the other pattern (Fig. 5)(Sheppard et al., 2013). Hence these lenses boast less light loss (~16% vs 18%, although unlikely to be clinically significant) than single spacing/height diffractive patterns. Trifocals have been shown to provide better visual acuity than biofocal IOLs at intermediate distances (de Medeiros et al., 2017; Vilar et al., 2017). The most recent iteration is a quadrifocal optic (diffractive step heights giving focal planes at 40 cm, 60 cm, and 120 cm), although it is stated as acting as a trifocal IOL (Kohnen, 2015; Kohnen et al., 2017). The term 'pan-focal' has been applied to these lenses, but whether everything in an image, from the foreground to the background, is in focus depends on the definition of the term and as the natural human accommodation can focus all the light received through the pupil to a single optical plane, even quadrifocal lenses do not achieve this extent of image clarity across the focal range.

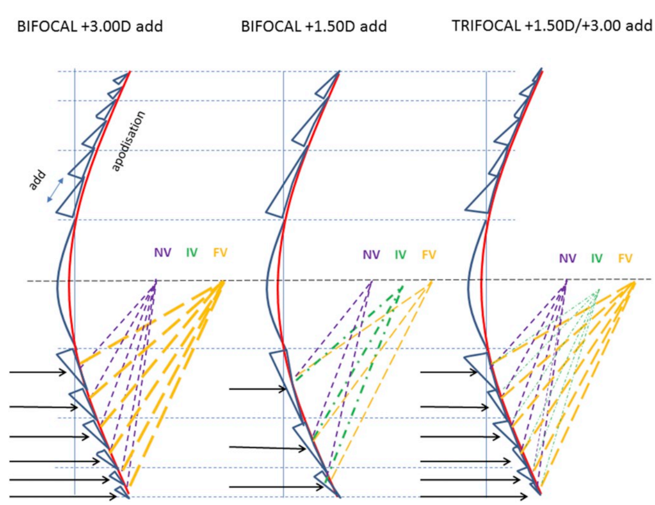

Fig. 5. A schematic illustration of +3.00 D near addition (NV) and +1.50 D intermediate addition (IV) bifocal diffractive designs (width of the steps govern the addition) and their combination with alternating height steps to create a trifocal design. Note: the wider the eschelet, the lower the near addition; the diffractive zero order allow the majority of the light to focus for far vision (FV); as the intermediate adds 2nd order is twice the add of the 1st order, it contributes to a typical near focal distance. Weighting of the displayed rays indicative of the proportion of light focused at each distance. Apodisation is changing the shape of the mathematical shape to distribute more light to near vision when a patient's pupil is small, and to distance when their pupil is larger.

Asymmetric IOL designs have also been more recently introduced and provide good vision from distance to near, with contrast sensitivity clinically equivalent to monofocal IOL implantation, generally with less dysphotopsia than similar near powered concentric multifocal IOL designs (Moore et al., 2017; Venter et al., 2014). Smaller pupils have been demonstrated to have a significant negative impact on subjectively reported quality of vision with asymmetric IOLs (Pazo et al., 2017). The orientation of the segment has been shown with adaptive optics simulation to be optimised when aligned relative to the optical aberrations of the eye it is implanted in (Radhakrishnan et al., 2016).

Near addition powers were initially high (typically 3.0 to 4.0 D), but due to adverse effects such as dysphotopsia and a reduction in contrast sensitivity, newer designs tend to have a lower add (Rojas and Yeu, 2016). An extension to this trend are IOL described as 'Extended Depth of Focus' (EDOF). Designs include a low near addition (+1.75 D) (Gatinel and Loicq, 2016) diffractive IOL (Millan and Vega, 2017; Weeber et al., 2015) and an asymmetric (+1.50 D) IOL (Pedrotti et al., 2018). The studies hitherto suggest this approach provides visual benefits across all distances after cataract surgery, with a minimal level of disturbing photic phenomena and high levels of patient satisfaction (Cochener and Concerto Study, 2016; Kaymak et al., 2016). Compared to modern diffractive trifocal IOLs, however, it provides generally an equivalent or slightly better visual acuity at distance, but a reduced level of vision at near and only equivalent contrast sensitivity and (low) levels of dysphotopsia (de Medeiros et al., 2017; Monaco et al., 2017; Pedrotti et al., 2016; Ruiz-Mesa et al., 2017a, 2017b).

An alternative IOL design classified as EDOF is an aspheric IOL with positive spherical aberration in the central 2 mm zone and negative spherical aberration in the pericentral 1 mm annulus (Bellucci and Curatolo, 2017; Dominguez-Vicent et al., 2016), although to date there is no peer reviewed published clinical assessment on this IOL. Alterations to the light adjustable IOL once implanted in the eye through UV radiation patterns can also create an EDOF effect (Villegas et al., 2014). There is also a pinhole iris-fixated IOL specifically designed to reduce dysphotopsia and photophobia (Munoz et al., 2015), which will extend the depth of focus as will any aspheric design (Steinwender et al., 2017). Hence, in 2016, the American Academy of Ophthalmology Task Force Consensus Statement on EDOF IOLs was published to provide minimum performance criteria to evaluate a device as having an EDOF performance under photopic, mesopic, and glare conditions based on testing vision at far and intermediate distances as well as defocus curve testing (MacRae et al., 2017). Unfortunately, the statement is unreferenced and elements such as 0.25D defocus curve steps between ± 0.5 D and at least 50% of eyes monocular distance corrected intermediate visual acuity of better than or equal to logMAR 0.2 (20/32) at 66 cm are not evidence based.

How to select patients who will gain maximum benefit from multifocal IOLs and how patients will adapt to them is largely based on clinical intuition, with a lack of publication on this topic; whereas there is more evidence to support appropriate management of complications (Alio et al., 2017). Interestingly, a small study (with 49 consecutive patients) of dissatisfaction after largely multifocal and some pseudo accommodation IOL implantation, identified residual refractive error and dry eye as the principal factors (Gibbons et al., 2016).

6.3.2.3. 'Accommodating' IOLs. Restoring function similar to the biological solution for the young eye is still the 'holy grail' of presbyopia correction. The ciliary muscle retains some contractility even in an aged eye, giving hope that implanting a suitably flexible IOL into the excavated lens capsule following cataract surgery could restore accommodation (Tabernero et al., 2016). However, the surgery itself alters the anatomy of the anterior chamber, resulting in a decrease in lens thickness, which has been shown to increase ciliary body movement and altered the ciliary body shape through iris posterior displacement (Fayed, 2017), which needs to be taken into account. An 'accommodating' IOL needs to restore a controllable dynamic increase in dioptric power to change clear focus from distance viewing through intermediate to near. Few studies, however, actually measure accommodation, with most: assessing lens shift (Leng et al., 2017) often using pharmacological stimulation with pilocarpine (Li et al., 2016) rather than physiologically driven accommodative demand; assessing the range of clear focus subjectively (Sadoughi et al., 2015); or measures of vision such as acuity at a limited range of distances, together with contrast sensitivity and questionnaires on subjective impressions (Lan et al., 2017). Early designs showed a small amount of presumed ciliary muscle driven 'accommodation' (Leng et al., 2017), but only for a short period before it is presumed lens fibrosis and capsular shrinkage reduced the lens flexibility (Wolffsohn et al., 2006a, 2006b). Others seem to achieve an increased level of spectacle independence, but principally from pseudoaccommodative mechanisms such as multifocality, rather than a change in optical power (Pepose et al., 2017a). Newer designs (few that have been clinically tested) include dual optics, shape changing optics and refractive index changing optics (Ben-Nun and Alio, 2005; DeBoer et al., 2016; McCafferty and Schwiegerling, 2015; Tomas-Juan and Murueta-Goyena Larranaga, 2015). The latter research on possible future advances in 'accommodating' implants is discussed in Section 8. In conjunction prevention and/or treatment of capsular contraction to allow the lens mechanisms to continue to function have been explored (Pepose et al., 2017b). It is noteworthy that the number of peer-reviewed publications on these IOLs has reduced significantly over the last decade and are now generally reviews or evaluations of older IOL designs.

6.3.3. Inlays

Currently marketed corneal inlays have either a pinhole design to extend depth-of-focus (Dexl et al., 2015), a thin 'lens' which reshapes the anterior corneal surface creating negative spherical aberrations (Whang et al., 2017; Whitman et al., 2016a, 2016b) or attempts to create corneal multifocality (distance vision through a plano central zone surrounded by rings of varying additional power; Table 3). Previous large and impermeable inlays disrupted the cornea's natural state by hindering natural metabolic functions, hence modern inlays are thin, of small diameter and are made of biocompatible materials that have high fluid and nutrient permeability (Moarefi et al., 2017). These characteristics allow them to be implanted relatively deep in a femtosecond laser cut flap or pocket, the latter preserving more nerves and, therefore, theoretically having less impact on corneal sensitivity and the homeostasis of the tear film (Moarefi et al., 2017). Increased pocket depth seems to be associated with better postoperative visual acuity outcomes (Moshirfar et al., 2016a). Some femtosecond laser platforms are unable to construct a conventional pocket within a lamellar, instead creating a conventional flap, but with the hinge width extended to ~330°, leaving only a small rim cut (termed a flocket). No difference was found in early wound healing and refractive responses between pocket and flocket enabled presbyopic inlay implantation in rabbits, but the largest (8 mm) incision showed the least keratocyte activation (Konstantopoulos et al., 2017).

Unlike traditional laser refractive surgery, inlays do not remove any tissue and therefore can be removed/reversed with little consequence if there have been no complications. The surgical placement of a corneal meniscus shaped inlay beneath a corneal flap alters the stroma anterior to the inlay to adopt predominately the inlay's shape (Lang et al., 2016). The epithelium remodels within a zone approximately twice the inlay diameter (Lang et al., 2016), with ~19 μm of central (~1 mm radius) central thinning regardless of the refractive error treated (Steinert et al., 2017). One disadvantage of the monocular approach of implanting inlays to increase the depth of focus of the visual system, is that the resulting anisocoria creates an imbalance in the retinal illuminances between the two eyes. Intraocular latency differences have been shown to occur with reduced aperture monovision (a Pulfrich effect, leading to distortions in the perception of relative movement)(Plainis et al., 2013b), but the inlay aperture does not seem to interfere with the field of view, presumably as oblique rays enter the pupil around the opaque area (Atchison et al., 2016). A safety comparison based on the USA regulatory submission of the corneal inlay clinical trials to date (Moshirfar et al., 2017) suggests both inlay types are safe, but secondary surgical intervention was required in 12% of thin lens inlays within 3 years of implantation; a drop in corrected visual acuity of ≥2 acuity lines was more common in pinhole inlays (3.4% vs 1.0%). However, clinical studies suggest that when implanted monocularly in the non-dominant eye, meniscus shaped inlays cause only minimal distance visual acuity compromise in the implanted eye and provide good near acuity, stereopsis and contrast sensitivity (Igras et al., 2016a; b; Jalali et al., 2016; Lin et al., 2016; Linn et al., 2017). They can be implanted safely with similar outcomes before or after traditional or femtosecond laser-assisted cataract surgery (Ibarz et al., 2017; Stojanovic et al., 2016) and with simultaneous photorefractive keratectomy (PRK)(Moshirfar et al., 2016b). More recently diffractive corneal inlays have been conceived and simulated showing an improved performance compared to the small aperture thin lens corneal inlays (Furlan et al., 2017).

6.3.4. Laser refractive

6.3.4.1. Corneal monovision. Analogous to the contact lens/IOL modality of the same name (see Section 6.2.1/6.3.2.1), perhaps the most rudimentary method to address presbyopia with corneal laser vision correction is monovision (Gil-Cazorla et al., 2016). Normally, an excimer laser is used to reshape the cornea to correct the dominant eye for distance vision and the contralateral eye for near. Studies have shown that the success rate can reach 90% (Jain et al., 2001; Levinger et al., 2013; Miranda and Krueger, 2004); however, there are some associated disadvantages including an impairment of mid-range vision; reduced scotopic/mesopic visual acuity; attenuation of contrast sensitivity; and reduction of stereopsis (Jain et al., 2001; Levinger et al., 2013; Richdale et al., 2006).

Table 3
Current commercially available corneal inlay designs. Adapted from Moarefi et al. (2017).

	Thickness	Diameter	Implantation Depth	Centration	Material	Mechanism of Action
Raindrop	32 μm	2 mm	120–200 μm	Central over light constricted pupil	Hydrogel	Increases central radius of curvature of overlying cornea
Flexivue microlens	15–20 μm	3 mm	280–300 μm	Over 1st Purkinje image	Hydroxyethyl methacrylate & methyl methacrylate + UV blocker	Distance vision through plano central zone surrounded by rings of add power 1.25 to 3.50D in 0.25D steps
KAMRA	5 μm	3.8 mm (1.6 mm central aperture)	200–250 μm	Over 1st Purkinje image	Poly-vinylidene Fluoride	Increases depth of focus through pinhole

6.3.4.2. Corneal collagen shrinkage. Conductive Keratoplasty (CK) is a non-invasive technique that uses radiofrequency energy (in the order of 350–400 kHz) to raise the temperature of *in vivo* corneal tissue to approximately 65°, causing the corneal collagen fibrils to dehydrate, retract and, therefore, shrink within the peripheral stroma (Aquavella et al., 1976; Brinkmann et al., 2000). A probe is inserted to a depth of 450–500 μm in the peripheral cornea at a series of spots forming concentric rings with diameters of 6, 7 and 8 mm (Stahl, 2007). The process leads to a corresponding change to the mid-peripheral tissue and a steepening of the central cornea to crease an aspheric surface (Charman, 2014b), thus increasing the refractive power of the eye and providing correction for presbyopia. Correction of astigmatism, or refinements to residual refractive errors following laser in-situ keratomileusis (LASIK), can also be achieved by modifying the pattern of the treatment spots. Whilst studies have demonstrated that the technique is safe (McDonald et al., 2004), data also suggest that there is a relatively high rate of refractive regression, rendering the technique unpopular with patients and surgeons alike (Gil-Cazorla et al., 2016); this has resulted in a decline in its use in recent years.

A further method adopted to modify corneal curvature through collagen shrinkage is the intrastromal femtosecond laser-based procedure (INTRACOR). This technique employs a focused laser beam with a wavelength of 1.043 μm to reconfigure the corneal profile. Long-term follow-up studies analysing the visual outcomes of patients who have undergone the surgery over a 3-year period have seen positive results in uncorrected near visual acuity in the treated eye, with a median increase from 0.7 logMAR to 0.1 logMAR over the 36 month period. However, the studies also revealed a corresponding reduction in corrected distance acuity of approximately one line of letters or 0.10 logMAR (Khoramnia et al., 2015; Thomas et al., 2016).

6.3.4.3. Multifocal corneal laser profile. Corneal multifocality created by excimer laser ablation, often termed presbyLASIK, produces a multifocal corneal ablation profile, against a trade-off of increased corneal aberrations. The technique can be further subdivided into central (where the central cornea power is optimised for near vision) (Alio et al., 2006), peripheral (where the peripheral cornea power is optimised for near vision)(El Danasoury et al., 2009), or blended (where a modified version of monovision laser vision correction is applied)(Reinstein et al., 2009, 2011, 2012). Despite generally good optical outcomes for patients, they are typically dissatisfied with the compromise to their vision, particularly the deleterious effect on distance acuity (Luger et al., 2013). Table 4 outlines prospective studies that have examined the vision performance of a range of corneal laser vision correction techniques.

6.3.4.4. Lenticular 'softening'. In a similar way to the INTRACOR technique, described previously (Section 6.3.4.2), to modify the corneal stroma, a further viable use of the femtosecond laser could be to restore the ageing crystalline lens to its pre-presbyopic, malleable form by disrupting the rigid structure of the lens substrate whilst maintaining its optical clarity. In essence, coherent light from a pulsing femtosecond laser can be focused accurately and precisely within the crystalline lens to induce local photodisruption (Zhang et al., 2013). Typically, a femtosecond laser pulse focused within the crystalline lens will ablate the surrounding material within a spheroid with an axial length of about 20 μm (parallel with the lens axis) and a equatorial diameter of approximately 5 μm (Stachs et al., 2009). The material within this ablation zone is immediately vaporised, which results in the formation of a gas vacuole. Over time, the gas is absorbed into the surrounding tissue. By creating a series of these internal lenticular micro-incisions, lamellar-type plates can be formed which act as 'gliding planes' (Lubatschowski et al., 2010) and allow the lens to deform on accommodation (Schumacher et al., 2008). The pattern and position of these systematic lenticular micro-incisions vary and can take the form annular, cylindrical, radial, conical and 'waffle' cleavage patterns (Charman, 2014b). The central portion of the lens is preserved, as changes in lenticular composition along the visual axis would impair vision. *In vitro* studies on human donor (Krueger et al., 2001; Schumacher et al., 2009) and porcine (Hahn et al., 2015; Ripken et al., 2008; Zhang et al., 2013) lenses have shown promise, with improvements in lens malleability and little or no change in central lens transparency. Further *in vivo* studies on rabbit (Krueger et al., 2005; Lubatschowski et al., 2010) and monkey (Reggiani Mello and Krueger, 2011) eyes were also unable to show any significant cataract formation over study periods ranging from 3 months to 4 years. Whilst some pilot *in vivo* human work has been undertaken on pre-cataract extraction patients, further consideration should be given to computational finite element models (Burd and Wilde, 2016) to mimic and optimise the laser cleavage patterns before full human studies on presbyopic patients are conducted.

6.4. Pharmaceuticals

Pharmaceutical treatments for presbyopia include stimulating the contraction of the ciliary muscles in the presence of different miotics (Abdelkader, 2015; Abdelkader and Kaufman, 2016; Renna et al., 2016) and nonsteroidal anti-inflammatory drugs (Benozzi et al., 2012). However, the studies are generally poorly conduced with no measurement of the range of clear focus (defocus curve) or objective accommodation measurement (Table 5). Potential new approaches include lipoic acid treatment which in mice leads to a concentration-dependent decrease in lens protein disulfides concurrent with an increase in lens elasticity (Garner and Garner, 2016). EV06 (Novartis) is a prodrug comprised of lipoic acid choline ester 1.5%. EV06 aims to restore and maintain accommodative amplitude (lens softening) by reducing crystalline protein disulfide bonding between crystalline proteins within lens fibre cells, which causes the crystalline lens to become stiff, inducing presbyopia (Babizhaev et al., 1990). A clinical study (NCT02516306) in presbyopes demonstrated improvement in distance corrected near vision acuity over a 90 day, twice a day (after day 7) dosing compared to a control. A follow-up 7 months after cessation of the drops in 34 patients compared to 18 controls indicated the visual benefit was maintained for 5–7 months after the last dose of EV06 (Fig. 6)(Stein et al., 2017). A phase 2 clinical trial of AGN-199201 ophthalmic solution (Oxymetazoline, a alpha adrenoceptor agonist, Allergan)(2018) showed up to 70% of patients had at least a 2 line improvement in uncorrected near visual acuity.

6.5. Ciliary muscle electrostimulation

A single recent study reported on the bilateral pulsed electrostimulation of the ciliary muscle on 4 occasions at 2 week intervals using a polycarbonate scleral contact lens equipped with four microelectrodes at the four cardinal points positioned 3.5 mm outside the limbal area (corresponding to the ciliary body region) to stimulate the ciliary muscle (Gualdi et al., 2017). However the examination of whether any accommodation was restored (acuity and reading speed tests and ultrasonography on a sub-set of 7 of the 27 patients) was limited and the study was not masked or randomised.

7. Impact of prescribing a presbyopic correction

It has been shown that prescribing a presbyopic correction (in the form of single vision near spectacles) causes a statistically significant reduction in the amplitude of accommodation which surprisingly was maintained following 2 months cessation of the near correction. This may suggest that a near correction should be delayed for as long as possible, although the reduction seems to be < 0.50D and therefore may not be clinically significant (Vedamurthy et al., 2009). Clearly further work is needed in this area to understand the dynamic characteristics of the oculomotor system based on the timing of the near

Table 4
Studies examining the efficacy of corneal laser vision correction techniques to correct presbyopia. DCNVA – Distance corrected near visual acuity; UDVA - uncorrected distance visual acuity; UNVA – uncorrected near visual acuity; CDVA – corrected distance visual acuity.

Study	Participants (eyes)	Technique	Post-op data point	Results
Alio et al., 2006	25 (50)	PresbyLASIK in an open-label, prospective, non-comparative pilot study	6 months	• After 6 months, 16 (64%) patients achieved UDVA of ≥20/20 and 18 (72%) patients achieved a near UCVA of > or = 20/40.
Uthoff et al., 2012	30 (60)	Femto-Lasik using the PresbyMAX software in hypermentropes, emmetropes, and myopes	6 months	• Mean binocular uncorrected vision was reduced in myopes but increased in hyperopes and emmetropes. The mean binocular UNVA increased in the hyperopic and emmetropic groups, but decreased in myopes
Luger et al., 2013	33 (66)	PresbyMAX for hyperopia and myopia	12 months	• Postoperative mean spherical equivalent refraction was −0.47 ± 0.44 D. • 70% of patients achieved UDVA 0.1 logMAR or better, 84% patients obtained UNVA 0.1 logRAD or better, and 83% of eyes were within 0.75 D of defocus.
Ryan and O'Keefe, 2013	23 (46)	Bilateral LASIK using a multifocal corneal ablation profile was performed on hyperopic presbyopic patients (+1.00 to +3.25 D)	6 months	• Mean binocular UDVA was 0.07 logMAR ± 0.12 (SD); 91% had a binocular UDVA of 0.2 logMAR or better. • 91% had an uncorrected reading ability of N8 or better, and 93% were fully independent of reading glasses.
Baudu et al., 2013	358 (716)	PresbyMAX biaspheric multifocal ablation	6 months	• Postoperative mean spherical equivalent was −0.17 ± 0.34 D. • 76% of patients achieved a UDVA of 0.1 logMAR, 91% of patients obtained a UNVA of 0.1 logRAD or better. • 96% of patients achieved a UDVA of 0.2 logMAR or better, and a UNVA of 0.2 logRAD or better. • Mean binocular corrected distance visual acuity degraded from 0.00 ± 0.01 logMAR to a UDVA of 0.09 ± 0.07 logMAR. • Mean binocular corrected near visual acuity degraded from 0.02 ± 0.01 logRAD to a UNVA of 0.07 ± 0.07 logRAD.
Pinelli et al., 2008	22 (44)	PresbyLASIK (Peripheral Multifocal LASIK ablation pattern) on hyperopic patients	6 months	• Mean postoperative spherical equivalent refraction was −0.42 D (range: −1.12 to +0.87 D). • Mean binocular UCVA was 1.06 ± 0.13 for distance and 0.84 ± 0.14 for near.
Uy and Go, 2009	Participant numbers not defined. 195 myopic eyes; 119 hyperopic or emmetropic eyes	Pseudoaccommodative cornea (PAC) treatment	3 months	• Mean postoperative spherical equivalent refraction was −0.40 ± 0.77 D for myopic presbyopia and +0.15 ± 0.62 D for hyperopic or emmetropic presbyopia. • Functional vision, defined as 20/30 or better UDVA combined with J3 or better UNVA, was achieved in 162 (83%) eyes with myopic presbyopia and 103 (87%) eyes with hyperopic or emmetropic presbyopia
El Danasoury et al., 2009	34 (68) hyperopes; and 39 (78) myopes	LASIK with a centre far, peripheral near ablation algorithm	12 months	• The mean postoperative spherical equivalent refraction was −0.10 ± 0.55 D in hyperopes and −0.48 ± 0.51 D in myopes. • 2% of eyes in each group lost two lines of CDVA. DCNVA 20/40 or achieved in 33% of hyperopes and 36% of myopes. • 54% of hyperopes and 48% of myopes were satisfied or very satisfied with their postoperative DCNVA.
Epstein and Gurgos, 2009	103 (monocular)	Peripheral presbyLASIK on the non-dominant eye with distance-directed monofocal refractive surgery	1.1–3.9 years (mean 27.4 months)	At final follow-up, • 91.3% (94/103) of all patients, 89% (25/28) of hyperopes, and 92% (69/75) of myopes reported complete spectacle independence and 7.8% (8/103) used spectacles for less than 1 h per week. • UDVA was at least 20/20 in 67.9% (19/28) of hyperopes and 70.7% (53/75) of myopes, at least 20/20 at 80 cm in 85.7% (24/28) of hyperopes and 84% (63/75) of myopes, and at least 20/20 at 40 cm in 71.4% (20/28) of hyperopes and 65.3% (49/75) of myopes.

Table 5
All published peer reviewed studies on the use of pharmaceuticals to minimise the effects of presbyopia.

Study	N°	Age (yrs)	Design	Pharmaceuticals	Efficacy/Mechanism Measurements	Findings
Abdelkader and Kaufman, 2016	10	42–58	Single dose in non-dominant eye Crossover	3% carbachol & 0.2% brimonidine combined and separate forms	Pupil size, distance & near visual acuities at 1, 2, 4 & 8 h	Pupil size decreased and NVA improved more with combined treatment
Abdelkader, 2015	48	43–56	Once daily for 3 months in non-dominant eye	N = 30 2.25% carbachol plus 0.2% brimonidine eye drops. N = 18 placebo drop controls	Pupil size, distance & near visual acuities at 1, 2, 4, 8 & 10h	Pupil size decreased and NVA improved with treatment and effect maintained over 3 months
Renna et al., 2016	14	41–55	Single dose binocularly	0.247%, phenylephrine 0.78%, polyethyleneglycol 0.09%, nepafenac 0.023%, pheniramine 0.034% & naphazoline 0.003%	Pupil size, Distance & near visual acuities and auto-refraction 0.5, 1, 2, 3, 4, and 5 h, 1 wk & 1 month	Pupil size initially decreased and NVA improved up to 5h
Benozzi et al., 2012	200	45–50	Single dose at 6h intervals binocularly over 5 yrs	pilocarpine 1% & 0.1% diclofenac	Accommodation (method unstated) yearly	Doubling of accommodation maintained over 5yrs

vision intervention. Little is known about how an individual adapts to the presbyopic correction. This may drive acceptance rates based on costs (spectacle lenses cannot easily be trialled before purchase) and ease of removal (which perhaps explains why contact lens generated monovision is less ‘successful’ than that achieved with IOLs) (Evans, 2007; Gil-Cazorla et al., 2016).

8. Conclusions and future directions

Presbyopia is a global problem affecting over a billion people worldwide (Holden et al., 2015). The prevalence of unmanaged presbyopia is high due to a lack of awareness and accessibility to affordable treatment in the developing world, but is also reported to be high in some developed countries. There is a lack of consistency in quoted definitions of presbyopia so we propose a new, unifying definition that states “*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*”. Some forms of refractive correction such as IOLs have been more innovative towards the amelioration of presbyopia symptoms, adopting diffractive as well as refractive optics and asymmetrical designs, whereas others, such as contact lenses, have been more conservative (almost exclusively concentric simultaneous image designs); hence it is not surprising the latter are hard to differentiate between (Sivardeen et al., 2016a; b). The approach that seem to work best is using different designs in each eye (such as the centre of the lens focusing at distance for one eye and focusing at near for the other eye (Sivardeen et al., 2016a) or mixing bifocal and trifocal designs(de Gracia, 2016) biasing the non-dominant eye to near with a small amount of monovision).

It would seem from the recent reduction in publications concerning ‘accommodating’ IOLs that the quest for an unpowered crystalline lens to restore natural accommodation has reached some significant barriers. Controlled electrical charge applied to liquid crystals (LCs) changes the orientation of the crystals, altering their refractive index due to their inherent birefringence. Hence LCs in the form of fresnel lens layers (Srivastava et al., 2015; Wang et al., 2014), flat gradient index lenses (Naumov et al., 1999; Ye et al., 2004), diffractive lenses (Li et al., 2006; Valley et al., 2010) and flat lenses using inhomogeneous electric fields (Lin et al., 2005) can be used to create a switchable lens of varying focal power, such as by embedding LCs in a PMMA contact lens (Milton et al., 2014). New materials such as graphene have been proposed as the electrodes to LC stimulation due to its high electrical conductivity, transparency, flexibility and elasticity properties (Kaur

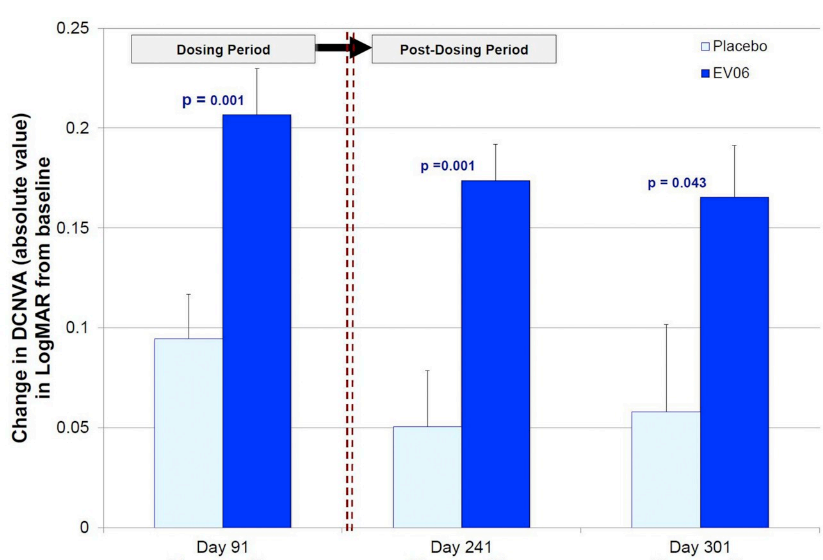

Fig. 6. Effects of bilaterally dosed (after day 7) topical lipoic acid choline ester eye drops twice a day for 90 days for the treatment of presbyopia and followed up for 7 months post cessation in distance corrected near visual acuity (DCNVA) compared to a control.

et al., 2016). LC lenses to correct for presbyopia can also be combined with a second lens to correct for overlaid image registration in augmented reality (Wang et al., 2017b).

Other forms of optoelectronic adjustable lens technologies with a potentially wider optical power range include: electro-wetting lenses which modulate the wetting angle of fluid droplet(s) suspended within an annular electrode to change power, both by surface affinity and/or a change in surface tension in the presence of an electric field - their size is limited by inertial effects on the droplet; Alvarez-Lohmann lenses are formed of a substantially complimentary, mostly-cubic waveform on two lens elements whose combined power equates to a uniform field which varies as a function of the relative overlap of the two elements; and fluid lenses consist of a rigid frame holding an elastic membrane filled with a transparent refracting fluid (Stevens et al., 2017). Providing the power required to stimulate these lenses as well as the physiological trigger are still major challenges for this form of presbyopic correction, with suggestions for the pupil size to act as the physiological trigger (Park et al., 2016) even though pupil size can be affected by many factors unrelated to the required focusing distance.

Another approach to presbyopia correction is to negate the need for optical correction by using waveguides to project images, such as holograms, onto the retina with gaze tracking to alter the effective focal power of the virtual image (Dunn et al., 2017; Wu et al., 2017).

Optical methods to increase the depth of focus of lenses could include cubic phase masks to provide an optical transfer function that is virtually insensitive to defocus, allowing the brain to adapt to the image which is equally blurred for different object distances (Arines et al., 2017; Mira-Agudelo et al., 2016). While pinhole inlays and IOLs have already been commercialised and papers describing pinhole contact lenses exist as early as 1952, there is more recent interest (Garcia-Lazaro et al., 2012, 2013) and a 2016 completed industry funded clinical trial (ClinicalTrials.gov Identifier: NCT02612584).

High intensity focused ultrasound has been demonstrated in rabbits to be able to increase the curvature of the cornea due to shrinkage of the corneal stromal collagen, with little disturbance to the epithelium, and this has been suggested as a technique that could correct presbyopia through a refractrive index change of the corneal tissue (Du et al., 2016; Wang et al., 2017a). However, the safety aspects in live animals and the clinical efficacy in humans has not been tested.

As optical methods to extend the depth of the focus of the eye work in combination with the aberrations of the individual's own eyes, prediction of which approach will work best for them with current clinical metrics is challenging. Many recent studies have used adaptive optics to neutralise the observer's optical aberrations and to test the simulated aberrations of different multifocal designs, such as using temporal multiplexing to simulate simultaneous image designs, to determine the optimum design (Akondi et al., 2017; Dorronsoro et al., 2016; Papadatou et al., 2016; Vinas et al., 2017). However, the adaptation time is generally minimal, the field of view restricted and the targets generally artificial, so the promise to allow optimum prescribing of presbyopic corrections for an individual have yet to be convincingly demonstrated.

Finally, neural approaches to overcoming presbyopia such as ‘perceptual learning’ which is presumed to improve stimulus processing by the brain, still lack convincing evidence, despite continued interest (Heinrich, 2017; Liu et al., 2016; Sterkin et al., 2017). Hence multidisciplinary approaches to effectively and safely overcoming the effects of presbyopia are still much needed.

In summary, given the accessibility of corrective devices, the optimal correction of presbyopia is often overlooked in developed countries. Despite this, given the ubiquity and inevitability of presbyopia, there is a clear and pressing need for further research to understand better the physiological changes to the ageing eye that are, in turn, likely to inform the future development of ‘smart’ technologies capable of restoring ‘true’ dynamic accommodation to presbyopes.

Competing interests

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