Optical and pharmacological strategies of myopia control

Pauline Kang PhD BOptom (Hons) FAAO
School of Optometry and Vision Science, The University of New South Wales, Sydney, New South Wales, Australia
E-mail: p.kang@unsw.edu.au

Submitted: 6 July 2017
Revised: 21 November 2017
Accepted for publication: 4 January 2018

Key words: contact lenses, multifocal spectacles, myopia control, optical, orthokeratology, pharmacology

Normal eye growth during childhood is regulated by a unique homeostatic process known as emmetropisation, where the focal lengths of all optical elements grow to match the length of the eye without significant accommodation. Interruption of this highly coordinated growth results in refractive error. Myopia occurs due to a mismatch between the refractive and axial components of the eye. It can develop when a single or a combination of ocular refractive elements have too high a power relative to the eye’s focal length and is termed refractive myopia. More commonly, myopia results when the axial length of the eye exceeds the focal length formed by its optical components and is known as axial myopia. This excessive axial elongation is usually due to increase in vitreous chamber depth. Myopia was once considered a mere refractive error with little or no long-term consequences, but is now recognised as one of the most significant causes of blindness worldwide. Traditional classifications have divided myopia as low ‘physiological’ and high ‘pathological’ myopia. This arbitrary binary divide has created a long-standing perception that only individuals with high myopia (greater than −5.00 D or −6.00 D) are at risk of developing potentially blinding ocular conditions such as retinal detachments and maculopathies. However, recent re-evaluation of extensive literature has revealed that even low degrees of myopic refractive error increase the lifelong risk of these complications when compared to emmetropes. Consequently, the dramatic increases in global myopia prevalence rates have contributed to myopia becoming a significant worldwide public health issue.

The highest prevalence rates for myopia are reported from East Asia and South-East Asia, and there is evidence of increasing rates in Europe and the USA. With projections that almost five billion individuals of the world’s population will suffer from myopia by 2050, there is strong motivation to develop effective means to slow or stop the progression of myopia in children to reduce the lifelong risk of developing the associated, potentially blinding ocular diseases. Optical, pharmacological and behavioural interventions that serve this purpose are collectively termed myopia control. The impact of this research has been significant as the growing evidence from high-quality clinical trials of effective myopia control strategies in children has resulted in myopia management increasingly becoming a part of routine clinical practice.

This review will discuss investigations of various optical and pharmaceutical interventions of myopia control in children and will conclude with a discussion of potential future myopia control research directions.

OPTICAL STRATEGIES OF MYOPIA CONTROL

Landmark animal studies have revealed that eye growth involves constant visual feedback and that manipulating the visual experience has a profound impact on eye growth. This has stimulated the development of numerous optical strategies of myopia control which will be described in detail below. It should be noted that in myopia control treatment studies, investigated interventions are typically compared to conventional single vision corrections and the efficacy of treatment is generally quantified by differences in refractive error (spherical equivalent) or axial length changes.

Single vision spectacles and contact lenses

Single vision spectacle or contact lens corrections are typically the first treatment offered to children with myopia as they carry minimal side effects while correcting their myopic refractive error. Early studies have suggested myopia control with single vision rigid contact lenses, and it was hypothesised that better retinal image
quality with rigid contact lens wear may be responsible for these effects. A more recent two year randomised clinical trial involving six- to 12-year-old Singaporean children found rigid gas-permeable (RGP) lenses had no effect on axial length elongation or myopia progression compared to single vision spectacle lens correction.29 These results are supported by similar results from the Contact Lens And Myopia Progression (CLAMP) study29 which compared myopia progression in children randomly fitted with either RGP or disposable soft contact lenses (SCLs). Although refractive data suggested greater myopia progression in children wearing RGP lenses, axial length growth was similar between the two treatment groups. Currently, single vision spectacle and contact lenses are not prescribed for myopia control and are typically allocated as control treatments in myopia control studies.30

**Under-correction**

The rationale for deliberate under-correction of distance refractive error correction as a means of myopia control is to induce myopic retinal defocus during distance viewing and/or to reduce accommodative demand and response during near viewing.31 One theory is supported by studies which have provided evidence that myopic retinal defocus slows down or stops myopia progression in animal models.2 The second theory stems from the proposal that under-correction will reduce accommodative demand as well as accommodative error during near viewing, in alignment with the theory under which multifocal spectacles are prescribed for myopia control as described below. Under this treatment paradigm, under-correction by 0.50 to 0.75 D is typically prescribed as it will maintain an acceptable level of distance vision.

Recent investigations suggest that under-correction may enhance rather than slow down myopia progression in children. Chung et al.32 monitored a group of children who were randomly assigned to wear spectacle lenses that were under-corrected to achieve distance vision of 6/12 (approximately 0.75 D under-correction) compared to a control group wearing full distance correction single vision spectacle lenses. The under-correction group experienced greater myopia progression (−1.00 D) compared to the control group (−0.77 D) by the end of the two-year study period. These results were confirmed by a subsequent study which also reported a slight increase in myopia progression of 0.17 D in a group of children who were under-corrected by 0.50 D compared to a full correction group, over an 18-month period.33 A recent retrospective analysis of a private optometric practice’s clinical data further supports the notion that under-correction results in greater myopia progression compared to full correction. Authors reported a significant positive correlation, with greater amounts of under-correction resulting in greater myopic progression.31

In contrast, recent reports from the Anyang Childhood Eye study proposed that under-correction may not enhance myopia progression.34 Myopia progression rates in a group of progressive myopic children wearing full correction were compared to myopic children who were wearing no correction. Interestingly, after two years, children with no correction progressed less in myopia (adjusted difference of 0.27 D). It must be noted that there was a significant difference in baseline cycloplegic refractive error (full correction: −3.05 ± 1.13 D; no correction: −1.31 ± 0.60 D) and axial length (full correction: 24.70 ± 0.75 mm; no correction: 23.88 ± 0.76 mm) between the two groups which may influence the reported myopia progression rates.34 Further studies are required to better understand the effects of under or no correction of distance refractive error on myopia progression in children compared to those in full correction.

**Multifocal spectacle lenses**

Multifocal spectacles in the form of bifocal or progressive addition lenses (PALs) with near additions varying between +1.00 to +2.00 D have been prescribed for myopia control.27,30 under the premise that the near addition correction reduces accommodative demand as well as accommodative error during near viewing35-37 or induces changes in peripheral retinal blur which may remove the stimulus for myopic progression.35,38

Accommodative error is measured clinically as accommodative lead or lag when viewing near targets and a previous study measured a reduction in accommodative lag of 0.39 D per dioptre of increase in positive lens power.39 Myopic children generally display insufficient accommodation with larger lags of accommodation compared to emmetropic children, even before the development of myopia.40-43 The resultant larger retinal hyperopic defocus has been hypothesised to encourage axial length elongation, although contrasting data has been reported in the literature with some studies showing no association between increased accommodative lag and myopia progression.44,45

In studies which do report an association, myopic children with larger lags of accommodation have been found to experience faster myopia progression46 and excessive periods of accommodation have also been implicated as a potential cause of myopia progression owing to associations between myopia and near work. Time spent reading is often used as a surrogate for near work and children who spent more time reading were more likely to be myopic.47,49 Children who read continuously for more than 30 minutes are reportedly more likely to develop myopia than those who read for shorter durations. Additionally, children with closer reading distances (<30 cm) are 2.5 times more likely to be myopic than those with longer working distances, suggesting that the intensity as well as duration of near work may be factors associated with myopia development.50

The Correction of Myopia Evaluation Trial (COMET) was the largest randomised, multi-centre clinical trial investigating PALs for myopia control. Four hundred and sixty-nine children aged 6–11 years were recruited and randomised to wear either PALs (with +2.00 D addition) or single vision lenses. Of the 462 children who completed the trial, a three-year difference in refractive error and axial length changes between the PAL and control groups of 0.29 ± 0.08 D and 0.11 ± 0.03 mm, respectively, were reported (Figure 1). Interestingly, the treatment effect appeared to occur only during the first year. Although the difference in myopia progression between the PAL and single vision groups was statistically significant after three years of treatment, it was deemed to be clinically insignificant.46

Further analysis of the COMET study data indicated a greater myopia control effect in children with higher lags of accommodation in combination with near esophoria or lower amounts of baseline myopic refractive error.49 This prompted a follow-up study (COMET2), to reinvestigate the effect of PAL correction on myopia progression. One hundred and eighteen children aged eight to <12 years were
recruited with the inclusion criteria requiring all subjects to have high lags of accommodation (initially defined as at least 0.50 D then later changed to 1.00 D), near esophoria of ≥2 prism dioptre (PD) and lower baseline myopia between −0.75 to −2.50 D. Children were randomised to wear either PAL (with +2.00 D addition) or single vision lens corrections. After three years of treatment, 110 children completed the study and a clinically small difference in myopia progression of 0.28 D was reported between the PAL and single vision control groups (Figure 1). Follow-up studies in Asia and the USA similarly reported small myopia control effects of PALs of questionable significance.

Earlier studies exploring the influence of bifocal spectacle lenses on myopia progression in children similarly reported minimal impact on myopia progression compared to single vision correction. However, a recent trial of bifocal and prismatic bifocal lenses have demonstrated one of the greatest myopia control effects. This three-year randomised clinical trial required children to be assigned to one of three treatments: single vision distance correction lenses, executive bifocal lenses with +1.50 D near addition or executive prismatic bifocals with a 3 PD base-in correction incorporated into +1.50 D near addition segment of both lenses. After three years of treatment, bifocal lenses reduced myopia progression by approximately 50 per cent compared to the single vision control group. Mean difference in myopia progression between the single vision group and bifocal and prismatic bifocal groups were −0.81 and −1.05 D, respectively (Figure 1).

Correspondingly, reduction in axial length elongation of 0.25 mm and 0.28 mm was measured in the bifocal and prismatic bifocal groups compared to the control group, respectively. Standard and prismatic bifocals exhibited similar myopia control effects in children with high lags of accommodation (>1.00 D) whereas prismatic bifocal lenses produced greater benefits in children with low lags of accommodation (≤1.00 D). Authors proposed that the apparent enhanced myopia control effect with prismatic bifocal lenses may be due to reduced convergence and lens-induced exophoria with prism correction. However, this study was not without some limitations; treatment was not randomised or masked, and further studies supporting the promising myopia control effects of prismatic bifocal lenses are required.

Bernsten et al. reported myopia progression in 84 children fitted with PALs (with +2.00 D near addition) over a one-year study period. Authors measured peripheral retinal defocus changes and reported that PALs induced significant myopic shifts in peripheral retinal defocus compared to single vision lenses, with the greatest shift occurring in the superior retina corresponding to the PAL near addition corridor. The adjusted central myopia progression rates in children who experienced absolute superior myopic defocus was −0.38 D while children who experienced absolute superior hyperopic retinal defocus progressed by −0.65 D. It was proposed that changes in peripheral retinal defocus, particularly in the superior retina may in some part be responsible for the modest myopia control effects reported with PALs.

One of the major limitations in clinical studies investigating the effect of multifocal spectacle lenses for myopia control is the simplified ‘one size fits all’ approach of prescribing the same near addition power, which typically varies between +1.00 to +2.00 D, to all children in the study. Although the intention of the near addition in multifocal corrections is to reduce accommodative demand and error, there is significant individual variability in response to the near addition and some children may even experience over-accommodation. Thus, the near addition selected for a particular study may not be suitable for some of the recruited children. Additionally, it has been recently shown that not only the amount of addition but the distribution of optical power through the near vision zone of PALs can also influence accommodative responses.

**Novel multifocal spectacles and contact lenses**

As central vision provides the highest visual acuity, the impact of optical defocus and compensatory eye growth changes have been studied extensively at the central retina. Interestingly, recent studies have demonstrated that contrary to traditional beliefs, visual signals deriving from the peripheral retina supersede those originating from the central retina, bringing to light a new understanding of the dominance of visual cues deriving from the peripheral visual field. Optical blur experienced on the peripheral retina appears to govern overall ocular growth; peripheral hyperopic blur stimulates excessive ocular growth while the opposite effect is demonstrated with peripheral myopic blur. The visual experience in the peripheral visual field plays a critical role in the regulation of ocular growth or refractive error development and peripheral myopic defocus has been proposed to counteract the stimulus for axial elongation. Consequently, this has sparked the interest of researchers and industry, resulting in the development of various novel multifocal spectacles and contact lenses with the aim of manipulating...
reported modest myopia control effects.\textsuperscript{27} Indicated by a dagger in Table 1, tifocal SCLs that included these studies explored and a recent meta-analysis of multiple studies reporting in the literature are summarised in Table 1.

Further details of various investigational lens designs reported in the literature are summarised in Table 1.

The myopia control effects of most of the aforementioned lens designs have been explored and a recent meta-analysis of multifocal SCLs that included these studies (indicated by a dagger in Table 1) reported modest myopia control effects.\textsuperscript{27} Compared to the control group, mean annual reduction in myopic refractive error progression and axial length elongation of 0.22 D and 0.10 mm were reported with progressive power design lenses and a slightly larger effect of 0.31 D and 0.12 mm with concentric design lenses. This translated to approximately 30–50 per cent reduction in myopia progression compared to single vision correction over two years.\textsuperscript{27} However, the main limitations of studies exploring the efficacy of novel contact lenses are the short treatment period which was typically one year and high subject drop-out rates.

A handful of commercially available multifocal SCLs that were originally designed for presbyopia correction have been used for off-label myopia control treatment owing to studies that have shown that these multifocal lenses induce relative peripheral myopic defocus.\textsuperscript{77–79} A two-year study involving 8–11-year-old children investigated the effects of CooperVision Proclear Mutifocal (centre D design) on myopia progression.\textsuperscript{80} Although this study experienced a high drop-out rate, myopic refractive error progressions of $\sim1.03 \pm 0.06$ D and $\sim0.56 \pm 0.06$ were found in the control single vision and multifocal contact lens groups, respectively. Similar changes in axial length elongation were reported ($0.41 \pm 0.03$ mm in the control group compared to $0.29 \pm 0.03$ mm in the multifocal SCL group) indicating a 50 per cent reduction in myopic refractive error progression and 29 per cent reduction in axial length elongation.\textsuperscript{80}

The Control Of Nearsightedness-Trial Of Lenses (CONTROL) study investigated myopia progression in children aged 8–18 years with eso-fixation disparities fitted with distance centre concentric ring design multifocal SCLs (Vistakon Acuvue Bifocal) compared to single vision lenses (Vistakon Acuvue 2).\textsuperscript{81} The unique feature of this randomised, double-masked study was the individualised selection of near addition of the SCLs in the treatment group. The minimum add power required to neutralise or reduce near eso-fixation disparity while maintaining acceptable vision was selected for each child. After 12 months of treatment a 72 per cent reduction in myopic cycloplegic refractive error progression and 80 per cent reduction in axial length elongation were reported in children wearing the concentric ring design SCLs compared to the single vision control group. This study has reported one of the greatest myopia control effects with the authors attributing this to the individualised refinement of near addition selected for each subject compared to standardised near additions used in other studies.\textsuperscript{81}

**Orthokeratology**

Orthokeratology (OK) involves the overnight wear of specialised rigid contact lenses. Temporary lens-induced changes in corneal topography acts to correct mild to moderate degrees of ametropia, most commonly myopia.\textsuperscript{82} Although myopic OK was first prescribed for the correction of myopia, numerous studies have repeatedly demonstrated myopia control effects.\textsuperscript{83–87}

Thus, OK is increasingly used for myopia control. It is currently considered to be one of the most efficacious optical strategies of myopia control with the added benefit of providing clear unaided vision during waking hours.\textsuperscript{88} Myopia control effects of OK have been attributed to induction of peripheral myopic defocus along both the horizontal and vertical meridians after OK lens wear.\textsuperscript{89–91}

Following anecdotal reports of myopia control with OK,\textsuperscript{92,93} a study was conducted by Cho et al. to determine the influence of OK on myopia progression.\textsuperscript{97} This landmark two-year prospective pilot study included 35 children aged 7–12 years and compared axial length changes to a historical single vision spectacle lens control group. Axial length elongation was 0.23 ± 0.25 mm in the OK group compared to 0.48 ± 0.26 mm in the control group, which is equivalent to approximately 50 per cent reduction in myopia progression during two years of OK treatment.\textsuperscript{97} Subsequent prospective studies conducted from various parts of the world have consistently demonstrated myopia control with OK compared to single vision correction.\textsuperscript{83–86,94} Recent meta-analyses of OK have reported an overall reduction in

![Figure 2. A: Concentric ring and B: progressive power multifocal lens designs where white represents distance correction and black represents the plus power treatment zone](image-url)
Study | Correction type | Investigational lens description
--- | --- | ---
Sankaridurg et al. (2010) | Spectacle lens Type 1 investigational lens: rotationally symmetrical design with a 20 mm clear central aperture and a progressively ramped zone of increasing positive power (a maximum SER of +1.00 D relative peripheral power) surrounding the central aperture achieved 25 mm from its axis. 
Type 2 investigational lens: rotationally symmetrical design with a clear central aperture of 14 mm diameter with a steeper zone of increasing positive power in comparison to Type 1. A maximum SER of +2.00 D relative peripheral power was achieved 25 mm from its axis.
Type 3 investigational lens: asymmetric design with a clear central aperture extended approximately 10 mm on either side of the centre along the horizontal meridian and a similar distance inferiorly. A positive additional relative peripheral power of 1.9 D 25 mm from the axis in that meridian was incorporated.
Sankaridurg et al. (2011†) | Progressive power design soft contact lenses Silicone hydrogel soft contact lenses (lotrafilcon B) with an 8.6 mm base curve and 14.2 mm total diameter. The lens has a clear central 1.5 mm semi-chord for distance correction surrounded by a progressively increasing relative positive power to reach a relative positive power of +1.00 D at 2 mm semi-chord and +2.00 D at the edge of the peripheral treatment zone. Total treatment zone was 9.00 mm.
Anstice et al. (2011†) | Concentric design soft contact lenses (Dual-Focus [DF] lens) Hydrogel soft contact lenses (hioxifilcon A) with a base curve of 8.5 mm and total lens diameter of 14.2 mm. The lens has a central correction zone with a diameter of 3.36 mm surrounded by alternating rings of treatment (relative +2.00 D) and distance correction zones. Total treatment zone diameter was 11.66 mm.
Lam et al. (2014†) | Concentric design soft contact lenses (Defocus Incorporated Soft Contact [DISC] lens) A concentric design HEMA soft contact lens with base curves between 8.0 to 8.9 mm and total lens diameter of 13.5 or 14.0 mm. The lens has a distance correction zone in the centre surrounded by a series of alternating rings of distance and treatment zones having a proportion of 50:50. The treatment zones have a relative power of 2.50 D.
Fujikado et al. (2014†) | Progressive power design soft contact lens A progressive power hydrogel soft contact lens with a base curve of 8.6 mm and total lens diameter of 14.5 mm. The lens has a central zone 3.25 mm in diameter for distance correction beyond which the power progressively changes to the edge of the treatment zone (8 mm chord diameter) where a relative +0.50 D is achieved. The optic zone is deliberately decentred 0.5 mm in the nasal direction from the geometric centre of the soft contact lens.
Paune et al. (2014, 2015†) | Progressive power design soft contact lens (Soft Radial Refractive Gradient [SRRG] lens) A concentric design HEMA soft contact lens (hioxifilcon B) with base curves between 8.0 to 8.9 mm and total lens diameter of 14.0 to 15.0 mm. The lens included an 8 mm optic zone with a progressive power design with an aspheric front curve and spherical back curve that reached +6.00 D of addition plus power at the edge of the optical zone (8 mm chord diameter).
Paune et al. (2014, 2015†) | Rigid contact lens A rigid contact lens made from Boston XO 2 (hexafocon B) material with base curves between 7.50 to 8.20 mm and an optic zone diameter of 9.0 mm and a total lens diameter of 10.5 mm. The optic zone consists of an aspheric front curvature, spherical back curvature resulting in a +1.50 D relative addition at 2 mm from centre (4 mm chord diameter) and approximately +6.50 D at the edge of the optic zone (9 mm chord diameter).
Cheng et al. (2016†) | Progressive power design soft contact lens A progressive power design soft contact lens (etafilcon A) with a base curve of 8.5 mm and a total lens diameter of 14.0 mm. The front aspheric surface incorporated 0.175 μm of positive spherical aberration in the lenses optic zone (for a 5 mm diameter aperture).

SER: spherical equivalent refraction.
†Indicates lens designs that were included in a recent meta-analysis of multifocal SCLs for myopia control.27

Table 1. Description of investigational multifocal spectacles and soft and rigid contact lenses developed for myopia control
Myopia control Kang

Figure 3. Axial length elongation from baseline in A: Hiraoka et al.99 and B: DOEE (Cho and Cheung101) studies (adapted from Hiraoka et al.99 and Cho and Cheung101). Error bars represent standard deviation of the mean.

myopia progression ranging 41–45 per cent.95,96

Traditional OK lenses are typically fitted on children with mild to moderate degrees of myopia with minimal astigmatism. With improvements in lens designs and instrumentation, the application of OK lenses are expanding to correct for astigmatic and highly myopic individuals. A previous study investigated the myopia control effects of toric OK lenses fitted on children with the-rule refractive astigmatism of 1.25 to 3.50 D. At the end of the two-year treatment period, reduction of myopia progression in the OK group of approximately 50 per cent compared to the control group was reported, although this non-randomised study did suffer from a high dropout rate.97

The same research group also investigated the effects of partial correction in high myopes.98 Children with myopia greater than 6.00 D were fitted with OK lenses that had a target correction of −4.00 D and spectacle lenses were prescribed to correct for residual refractive errors. Increases in axial length after two years of treatment were 0.19 ± 0.21 mm in the partially corrected OK group compared to 0.51 ± 0.32 mm in the control group, indicating a significant myopic control effect. However, this study also suffered from high attrition rates. Although further studies are required to confirm the results, these studies provide promising preliminary data of the potential for OK as a means of myopia control for children who have high myopia and astigmatism.

Many studies investigating the myopia control effects of OK have been limited to two-year treatment periods. Hiraoka et al.99 followed 22 children aged 8–12 years who were fitted with OK for myopia control for five years. Authors found a significant difference in myopia progression rates during the first two years of treatment; myopia progression almost halved in children in the OK compared to single vision spectacle lens group during the first year of treatment and by approximately 21 per cent during the second year. The difference in myopia progression between the two treatment groups reduced over the subsequent years. Although the eyes of children undergoing OK treatment had overall shorter axial lengths compared to children in the control group, interestingly, no significant difference in myopia progression rates was found after three years of treatment, suggesting an attenuation of myopia control effects with longer duration of treatment (Figure 3A). However, as axial elongation slows with age, it is more difficult to detect significant differences in myopia progression rates between groups with longer treatment periods.99

A retrospective analysis of data derived from a clinical setting provided greater insight into the longer-term myopia control effects of OK.100 Data from 26 patients who were treated with OK for an average of 4.90 ± 0.35 years were analysed. Although axial length or vitreous chamber depth measurements were not taken and myopia progression was determined by manifest refractive error changes, authors claimed an apparent stabilisation of myopic refractive error in 64 per cent of investigated eyes.

Another area of significance is the effect of discontinuation of treatment. One study, the Discontinuation of Orthokeratology of Eyeball Elongation (DOEE) study, has explored the effects of six months discontinuation of OK on myopia progression.101 This study involved children who were a part of two previous studies exploring myopia control with OK.86,97 There were three treatment groups (control, continuous OK and discontinued OK) and two study phases. During the first phase (Phase I; initial seven months), the control group wore habitual spectacles, the continuous group wore OK lenses and the discontinued OK group stopped lens wear and were instructed to wear spectacle correction. During the second phase (Phase II; following seven months), the control group continued to wear spectacles and both the continuous and discontinued OK groups wore OK lenses. Axial length changes during the second phase of the study are shown in Table 2 and Figure 3B. In Phase I, there was a significant difference in myopia progression rates; during discontinuation, axial length increased in the discontinued OK
group at a faster rate compared to both the control and continuous OK groups. After re-initiation of OK treatment in the discontinued OK group, increase in axial length was similar between all groups.

An interesting observation from this study is the similarity in axial length elongation rates between all three groups during Phase II. Although axial lengths were overall shorter in children fitted with OK, there does not seem to be a significant myopia control effect after the first two years of treatment, in agreement with reports by Hiraoka et al.99 as shown in Figure 3A. This suggests that there may be an attenuation of myopia control effects after two years of OK treatment. Nonetheless, authors recommend against premature termination of OK treatment in children 14 years or younger, and in the case of discontinuation and myopia progression, children can be refitted and resume OK myopia control treatment.101 Further, studies with greater periods of discontinuation and in older children is required to better understand and develop recommendations regarding the schedule and length of OK treatment for myopia control.

There are currently two proposed theories of the mechanisms of myopia control with OK. The first is the peripheral myopic defocus theory; OK lenses have been found to inadvertently induce peripheral myopic defocus along both the horizontal and vertical meridians and this has been proposed as a potential underlying mechanism.96–99 The same premise under which novel multifocal SCLs are believed to induce myopia control effects. However, there is ongoing debate regarding the potential causative link between peripheral hyperopic retinal defocus and the development of central myopia, with evidence suggesting that relative retinal hyperopic defocus may be a consequence rather than a cause of myopia development and progression.102–105

The second and more recent theory relates to binocular visual function. Returning to the original theory of accommodative dysfunction and myopia development, anecdotal evidence has suggested improvements in accommodative vergence function subsequent to OK may play a role in myopia control. Reduction in accommodative lag, and hence hyperopic retinal defocus and improvements in accommodative facility have been reported.106–108 This is an area that warrants further investigation.

### PHARMACOLOGICAL STRATEGIES OF MYOPIA CONTROL

There are two topical pharmaceutical agents, atropine and pirenzepine, which have been recently investigated for myopia control. Currently no pharmaceutical agents have been approved by the Australian Therapeutic Goods Administration or US Food and Drug Administration for myopia control treatment. Thus, the use of these agents for myopia control is considered off-label.

### Atropine

Atropine is a non-selective anti-muscarinic agent that has a high affinity to M1-M5 receptors in the pupillary sphincter and ciliary muscle resulting in mydriasis and cycloplegia. Since the early trials in the 1970s,109–112 numerous studies have explored the effect of atropine on myopia progression and atropine is currently the most extensively studied pharmaceutical agent for myopia control. Various clinical trials that have repeatedly shown that atropine eye-drop treatment combined with distance and near correction, typically in the form of PALs, can control the progression of myopia in children.120,121,122

Although atropine was initially prescribed due to its effect on accommodation, the exact mechanism by which it induces myopia control is not well understood. Animal studies, particularly those involving the chick eye, have provided evidence that atropine may work via a non-accommodative mechanism; experimental myopia results despite various methods to prevent accommodation in chicks.111,112,113,114 Additionally, atropine, which has no effect on accommodation in the chick eye due to the absence of muscarinic receptors in the chick ciliary muscle, resulted in the reduction of eye enlargement and experimentally induced myopia, further supporting the notion that atropine induces myopia control effects via a non-accommodative mechanism.118

The wide distribution of muscarinic receptors in ocular tissue creates further difficulties in identifying the site of action of atropine in myopia control.115–117 The retina, choroid and sclera all contain muscarinic receptors and have been identified as possible sites of action.118 Despite this, atropine is increasingly used in clinical practice for myopia control owing to numerous studies that have repeatedly demonstrated significant myopia control effects with its application.122

The Atropine for the Treatment of Myopia (ATOM) was a landmark study which propelled the use of atropine for myopia control around the world.123 This

| Atropine concentration (%) | SER change (D) | Axial length change (mm) |
|----------------------------|----------------|--------------------------|
| 1% (ATOM1)                 | −0.28 ± 0.92   | −0.02 ± 0.35             |
| 0.5% (ATOM2)               | −0.30 ± 0.60   | +0.27 ± 0.25             |
| 0.1% (ATOM2)               | −0.38 ± 0.60   | +0.28 ± 0.28             |
| 0.01% (ATOM1)              | −0.49 ± 0.63   | +0.41 ± 0.32             |
| Control (ATOM1)            | −1.20 ± 0.69   | +0.38 ± 0.38             |

Table 3. Change (mean ± SD) in spherical equivalent refractive error (SER; D) and axial length (mm) after two years of atropine treatment (Phase I)

© 2018 Optometry Australia
randomised clinical trial involved 346 Singaporean children aged 6–12 years. During Phase 1, children were randomly selected to be treated daily with one per cent atropine or a vehicle eye drop in one eye for two years. By the end of the treatment period, the eye receiving atropine exhibited a small increase in myopic refraction (−0.28 ± 0.92 D) and no increase in axial length (−0.02 ± 0.35 mm). The placebo-treated eyes increased in myopic refractive error and axial length by −1.20 ± 0.69 D and 0.38 ± 0.38 mm, respectively (Table 3). Of note is the use of PALs or bifocal lenses in combination with atropine eye-drops due to accommodative side effects. As previously discussed, these optical corrections alone have been found to induce myopia control effect. The interaction of these two treatments, and whether it produces a synergistic effect, is unknown.135

The unintended consequences or side effects of atropine have often discouraged clinicians from adopting atropine for myopia control. The most frequently experienced side effects include photophobia and blurred vision due to miosis and cycloplegic effects of atropine. Premature presbyopia, and potential retinal and lens phototoxicity effects are other longer-term concerns.124 Furthermore, allergies to atropine or preservatives in eye-drops have also been reported from clinical trials.123,125 These limitations motivated investigations into lower doses of atropine, in the hope that myopia control can be preserved while minimising visual side effects.

The Atropine for the Treatment of Myopia 2 (ATOM2) study was conducted as a follow-up to the first ATOM1 study, which characterised the myopia control effects of three lower atropine concentrations of 0.5 per cent, 0.1 per cent and 0.01 per cent. Myopia progression rates were compared to the ATOM1 study control group. Atropine was administered daily in both eyes for two years (Phase 1) and confirming a previous report,120 a dose-dependent relationship was found with higher concentrations of atropine resulting in greater myopia control (Table 3). Interestingly, 0.01 per cent atropine, which was assumed to have minimal effects and chosen to act as an active control for the study, was also found to induce clinically significant myopia control effects.

After two years of treatment, eyes receiving daily administration of 0.01 per cent atropine progressed in myopic refractive error by 0.49 ± 0.63 D and increased in axial length by 0.41 ± 0.32 mm. Although refractive data suggests less myopia progression compared to the control group, interestingly, axial length elongation appears to be similar between the two groups. A recent retrospective analysis127 reported less myopic refractive error progression in children receiving 0.01 per cent atropine (−0.10 ± 0.60 D) compared to matched controls (−0.60 ± 0.40 D) after approximately a year of treatment, supporting results of the ATOM2 study. Although the effects of 0.01 per cent atropine on axial length elongation needs to be further elucidated, the encouraging reports of myopia control with lower concentrations have caused a change in prescribing habits among clinicians, with a shift away from prescribing higher (0.5 per cent and one per cent) to now lower concentrations of atropine.122

To determine the stability of atropine treatment, changes in refractive error and axial length were monitored in children who were a part of the ATOM1 and ATOM2 studies for a year after cessation of atropine (Phase 2).129,129 Eyes that originally received atropine experienced significant rebound and accelerated eye growth after cessation of treatment compared to the untreated controls and a dose-related relationship was also noted: the higher the concentration of atropine, the greater the rebound effect. The rate of myopia progression during the year of not receiving one per cent atropine treatment was greater than twice that of the fellow untreated eye and eyes receiving placebo treatment, and less dramatic changes were reported with lower concentrations of atropine.128,129 Cessation of 0.01 per cent atropine resulted in minimal rebound effect, suggesting a more sustained myopia control effect.129

A third phase was initiated in the ATOM2 study and involved children who had experienced myopia progression of 0.50 D or greater in at least one eye during the one-year discontinuation period restarting 0.01 per cent treatment for another two subsequent years.130 During this second treatment (Phase 3), myopia progression was similar to that measured in the group receiving 0.01 per cent atropine treatment during the first two years of the ATOM2 study (Phase 1). Fewer children who were originally treated with 0.01 per cent atropine required retreatment due to fewer rebound effects. These results led authors to conclude that retreatment is as effective as primary treatment of 0.01 per cent atropine and that clinicians can cease and re-initiate treatment as appropriate for the individual child.130

All concentrations of atropine will result in some side effects. Cooper et al.131 explored various concentrations of atropine and reported 0.02 per cent was the highest concentration that resulted in a clinically acceptable level of pupillary dilatation and loss of accommodation with no subjective symptoms. The ATOM2 study reported 0.01 per cent atropine increased pupil diameter in myopic children by approximately 1 mm under both scotopic and photopic conditions, and mean accommodative amplitude reduced by approximately 4.50 D over the two years of treatment (Phase 1).

Another study was conducted to determine the visual impact of low-dose atropine in a group of 14 young adults after five days of daily 0.01 per cent atropine instillation. Subjects were reported to have a 1.31 mm and 1.08 mm increase in photopic pupil size in the right and left eyes, respectively, and an 11 per cent reduction in binocular accommodative amplitude over the study period. Visual function represented by reading speed remained unchanged and subjects reported that 0.01 per cent atropine was acceptable/tolerable and allowed continuation of normal visual-related activities.132 Minimal side effects and acceptance of treatment further supports the use of low-dose atropine for myopia control.123,131,132

**Pirenzepine**

Pirenzepine is a selective anti-muscarinic agent with a high affinity for the M1 and M4 receptors. A distinct benefit of pirenzepine compared to the non-selective anti-muscarinic atropine is that it is less likely to cause cycloplegia and mydriasis and was therefore considered as an alternative myopia control treatment. Pirenzepine has been reported to reduce form deprivation myopia and eye enlargement in the animal model133,134 and there have been a handful of clinical trials which have demonstrated myopia control effects of pirenzepine in children.135–137 A two-year randomised clinical trial involved children 8–12 years receiving two per cent pirenzepine gel applied twice daily for two years. At the
end of the treatment period, a reduction in myopia progression was measured in children who were treated with pirenzepine compared to the placebo-treated group (Table 4).

Subjects undergoing pirenzepine treatment experienced adverse effects of accommodative dysfunction and medication residue. The most frequently experienced ocular side effect was papillae/follicles. Although one of the main benefits of pirenzepine is the minimal effect it has on pupil size and accommodation, it is no longer studied for myopia control use, which is likely attributed to reduced efficacy compared to atropine and a twice daily treatment schedule. Cur- rently pirenzepine cannot be commercially sourced which further restricts its use as a myopia control treatment.

### FUTURE RESEARCH

Despite the plethora of studies in myopia control, there remain many unanswered questions. Currently no treatment is considered to be 100 per cent effective and our limited understanding in the aetiology of myopia presents as a major hurdle. Myopia is a complex and multifactorial condition, thus the optical and pharmacological treatments discussed in this review are based on different causative theories. Some areas of future research based on unanswered questions relating to myopia control are discussed below.

### Individualised treatment

To overcome the ‘one size fits all’ approach in myopia control, there have been efforts to individualise treatment in the hope of improving the efficacy of various myopia control treatments. For example, the CONTROL study individually selected the minimum near add power required to neutralise or reduce the near associated esophoria while maintaining acceptable vision for each child. There have also been efforts to modify OK lens designs to induce specified changes in corneal topography and consequently peripheral refraction. It has also been suggested that children with higher degrees of myopic refractive error may benefit most from OK. PALs for myopia control have been shown to induce greater myopia control effects in those with esophoria while prismatic bifocal lenses produced greater benefits in children with low accommodation lag (≤ 1.00 D) compared to standard bifocal lenses.

Additionally, there are limited studies on the influence of ethnicity on treatments. A recent study suggested atropine has a greater effect on myopia control in children of Asian compared to European ethnicity. Studies involving atropine have typically included children with ages ranging 6–12 years. Future research into identifying those children who are most likely to benefit from different types of treatment is required.

### Combination treatment

Various optical and pharmacological treatments have been investigated as potential myopia control treatment options and many have shown promising effects. In the hopes of improving the efficacy of current myopia control treatments, the impact of combining two treatments options are being explored, including combining OK with atropine eye-drops.

### Schedule of treatment

Various myopia control treatments are prescribed on a daily basis and the impact of modifying the schedule of treatment is an area which has not been explored. Some treatments such as OK may be required to be worn on a daily basis to maintain the refractive error correction. Other treatments such as multifocal contact lenses or glasses, and atropine eye-drops, may not need to be administered every day to experience myopia control, although potential issues with compliance need to be taken into consideration. Currently, studies investigating variations in dosing regimens of 0.01 per cent and 0.05 per cent atropine on pupil dilation and accommodation, as a measure of the level of active drug in the eye, are underway to better understand the effect of schedule of atropine treatment on myopia control.

### CONCLUSION

Myopia is recognised as a global health issue and myopia control management is increasingly becoming a part of mainstream clinical practice. Various optical and pharmacological treatments have demonstrated beneficial myopia control effects as detailed in this review. Research into questions relating to the aetiology of myopia and its management continues with the goal of developing not only a method to slow down or stop myopia progression, but to ultimately discover a means to prevent the development of myopia in children.

### ACKNOWLEDGEMENTS

The author sincerely thanks Mr Andrew Nho and Dr Alex Hui for their assistance with writing this review. The author is a scientific consultant to CooperVision Inc, USA.

### REFERENCES

1. Flitcroft DI. Is myopia a failure of homeostasis? Exp Eye Res 2013; 114: 16–24.
2. Wallman J, Winawer J. Homeostasis of eye growth and the question of myopia. Neuron 2004; 43: 447–468.
3. Xie R, Zhou XT, Lu F et al. Correlation between myopia and major biometric parameters of the eye: a retrospective clinical study. Optom Vis Sci 2009; 86: E503–E508.
4. McBrien NA, Adams DW. A longitudinal investigation of adult-onset and adult-progression of myopia in an occupational group. Refractive and biometric findings. Invest Ophthalmol Vis Sci 1997; 38: 321–333.
5. Kinge B, Midelfart A, Jacobsen G et al. Biometric changes in the eyes of Norwegian university students—a three-year longitudinal study. Acta Ophthalmol Scand 1999; 77: 648–652.

---

**Table 4. Change (mean ± SD) in spherical equivalent refractive error (SER; D) and axial length (mm) after two years of pirenzepine gel treatment**

| Treatment group | SER change (D) | Axial length change (mm) |
|-----------------|---------------|--------------------------|
| 2% pirenzepine gel | −0.58 ± 0.53 | 0.28 ± 0.37 |
| Placebo (control) | −0.99 ± 0.68 | 0.40 ± 0.34 |

© 2018 Optometry Australia Clinical and Experimental Optometry 101.3 May 2018
Myopia control
Kang

6. Saw SM, Chua WH, Gazzard G et al. Eye growth changes in myopic children in Singapore. Br J Ophthalmol 2005; 89: 1489–1494.

7. Fan DS, Cheung EY, Lai RV et al. Myopia progression among preschool Chinese children in Hong Kong. Ann Acad Med Singapore 2004; 33: 39–43.

8. Saw SM. How blinding is pathological myopia? Br J Ophthalmol 2009; 93: 525–526.

9. Saw SM, Gazzard G, Shi-Yen EC et al. Myopia and associated pathological complications. Ophthalmic Physiol Opt 2005; 25: 381–391.

10. Fricke TR, Wilson DA et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. Ophthalmology 2016; 123: 1036–1042.

11. Smith EL III. Optical treatment strategies to slow myopia progression: effects of the visual extent of the optical treatment zone. Exp Eye Res 2015; 114: 27–37.

12. Girard P, Girard KL. The future of myopia control contact lenses. Optom Vis Sci 2016; 93: 336–343.

13. Smith EL III. Prentice award lecture 2010: a case for peripheral optical treatment strategies for myopia. Exp Eye Res 2011; 88: 1029–1044.

14. Sankaridurg P. Contact lenses to slow progression of myopia. Clin Exp Optom 2017; 100: 432–437.

15. Li SM, Kang MT, Wu SS et al. Studies using concentric ring bifocal and peripheral add multifocal contact lenses to slow myopia progression in school-aged children: a meta-analysis. Ophthalmic Physiol Opt 2017; 37: 51–59.

16. Katz J, Schein OD, Levy B et al. A randomized trial of rigid gas permeable contact lenses to reduce progression of children’s myopia. Am J Ophthalmol 2003; 136: 82–90.

17. Walline JJ, Jones LA, Mutti DO et al. A randomized trial of the effects of rigid contact lenses on myopia progression. Arch Ophthalmol 2004; 122: 1760–1766.

18. Walline JJ, Lindsley K, Vedula SS et al. Interventions to slow progression of myopia in children. Cochrane Database Syst Rev 2011; CD004916.

19. Vasudevan B, Esposito C, Peterson C et al. Under-correction of human myopia—is it myopicopic?: a retrospective analysis of clinical refraction data. J Optometry 2014; 7: 147–152.

20. Cheng D, Drobe B et al. Effect of bifocal contact lenses on myopia progression. Vision Res 2002; 42: 2555–2559.

21. Adler D, Millodot M. The possible effect of undercorrection on myopic progression in children. Clin Exp Optom 2006; 89: 315–321.

22. Sun YJ, Li SM, Li SY et al. Effect of undercorrection versus full correction on myopia progression in 12-year-old children. Graefe’s Arch Clin Exp Ophthalmol 2017; 255: 189–195.

23. Cheng D, Woo GC, Schmid KL. Bifocal lens control of myopic progression in children. Clin Exp Optom 2011; 94: 24–32.

24. Gwiazda J, Hyman L, Hussein M et al. Randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. Invest Ophthalmol Vis Sci 2003; 44: 1492–1500.

25. Correction of Myopia Evaluation Trial 2 Study Group for the Pediatric Eye Disease Investigator Group. Progressive addition lenses versus single vision lenses for slowing progression of myopia in children with high accommodative lag and near esophoria. Invest Ophthalmol Vis Sci 2011; 52: 2749–2757.

26. Berntsen DA, Sinnott LT, Mutti DO et al. A randomized trial using progressive addition lenses to evaluate theories of myopia progression in children with a high lag of accommodation. Invest Ophthalmol Vis Sci 2012; 53: 640–649.

27. Cheng D, Schmid KL, Woo GC. The effect of positive-lens addition and base-in prism on accommodation accuracy and near horizontal phoria in Chinese myopic children. Ophthalmic Physiol Opt 2008; 28: 225–237.

28. Gwiazda J, Thorn F, Bauer J et al. Myopic children show insufficient accommodative response to blur. Invest Ophthalmol Vis Sci 1993; 34: 690–694.

29. Gwiazda J, Bauer J, Thorn F et al. A dynamic relationship between myopia and blur-driven accommodation in school-aged children. Vision Res 1995; 35: 1299–1304.

30. Mutti DO, Mitchell GL, Hayes JR et al. Accommodative lag before and after the onset of myopia. Invest Ophthalmol Vis Sci 2006; 47: 837–846.

31. Fricke TR, Wilson DA, Sinnott LT, Mutti DO et al. Accommodative lag and juvenile-onset myopia progression in children wearing refractive correction. Vision Res 2011; 51: 1039–1046.

32. Koomson NY, Amedo AO, Opoku-Boah H et al. Relationship between reduced accommodative lag and myopia progression. Optom Vis Sci 2016; 93: 685–691.

33. Williams KM, Bertelsen G, Cumberland P et al. Increasing prevalence of myopia in Europe and the impact of education. Ophthalmology 2015; 122: 1489–1497.

34. Koh V, Yang A, Saw SM et al. Differences in prevalence of refractive errors in young Asian males in Singapore between 1996-1997 and 2006-2007. Ophthalmic Epidemiol 2014; 21: 247–255.

35. Dolgin E. The myopia boom. Nature 2015; 519: 276–278.

36. Sun J, Zhou J, Zhao P et al. High prevalence of myopia and high hyperopia in 5060 Chinese university students in Shanghai. Invest Ophthalmol Vis Sci 2012; 53: 7594–7599.

37. Jung SK, Lee JH, Kakizaki H et al. Prevalence of myopia and its association with body stature and educational level in 19-year-old male conscripts in Seoul, South Korea. Invest Ophthalmol Vis Sci 2012; 53: 5579–5583.

38. Holden BA, Fricke TR, Wilson DA et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. Ophthalmology 2016; 123: 1036–1042.

39. Smith EL III. Optical treatment strategies to slow myopia progression: effects of the visual extent of the optical treatment zone. Exp Eye Res 2015; 114: 27–37.

40. Girard P, Girard KL. The future of myopia control contact lenses. Optom Vis Sci 2016; 93: 336–343.

41. Smith EL III. Prentice award lecture 2010: a case for peripheral optical treatment strategies for myopia. Exp Eye Res 2011; 88: 1029–1044.

42. Sankaridurg P. Contact lenses to slow progression of myopia. Clin Exp Optom 2017; 100: 432–437.

43. Li SM, Kang MT, Wu SS et al. Studies using concentric ring bifocal and peripheral add multifocal contact lenses to slow myopia progression in school-aged children: a meta-analysis. Ophthalmic Physiol Opt 2017; 37: 51–59.

44. Katz J, Schein OD, Levy B et al. A randomized trial of rigid gas permeable contact lenses to reduce progression of children’s myopia. Am J Ophthalmol 2003; 136: 82–90.

45. Walline JJ, Jones LA, Mutti DO et al. A randomized trial of the effects of rigid contact lenses on myopia progression. Arch Ophthalmol 2004; 122: 1760–1766.

46. Walline JJ, Lindsley K, Vedula SS et al. Interventions to slow progression of myopia in children. Cochrane Database Syst Rev 2011; CD004916.

47. Vasudevan B, Esposito C, Peterson C et al. Under-correction of human myopia—is it myopicopic?: a retrospective analysis of clinical refraction data. J Optometry 2014; 7: 147–152.

48. Cheng D, Drobe B et al. Effect of undercorrection versus full correction on myopia progression in 12-year-old children. Graefe’s Arch Clin Exp Ophthalmol 2017; 255: 189–195.

49. Cheng D, Woo GC, Schmid KL. Bifocal lens control of myopic progression in children. Clin Exp Optom 2011; 94: 24–32.

50. Gwiazda J, Hyman L, Hussein M et al. Randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. Invest Ophthalmol Vis Sci 2003; 44: 1492–1500.

51. Correction of Myopia Evaluation Trial 2 Study Group for the Pediatric Eye Disease Investigator Group. Progressive addition lenses versus single vision lenses for slowing progression of myopia in children with high accommodative lag and near esophoria. Invest Ophthalmol Vis Sci 2011; 52: 2749–2757.

52. Berntsen DA, Sinnott LT, Mutti DO et al. A randomized trial using progressive addition lenses to evaluate theories of myopia progression in children with a high lag of accommodation. Invest Ophthalmol Vis Sci 2012; 53: 640–649.

53. Cheng D, Schmid KL, Woo GC. The effect of positive-lens addition and base-in prism on accommodation accuracy and near horizontal phoria in Chinese myopic children. Ophthalmic Physiol Opt 2008; 28: 225–237.

54. Gwiazda J, Thorn F, Bauer J et al. Myopic children show insufficient accommodative response to blur. Invest Ophthalmol Vis Sci 1993; 34: 690–694.

55. Gwiazda J, Bauer J, Thorn F et al. A dynamic relationship between myopia and blur-driven accommodation in school-aged children. Vision Res 1995; 35: 1299–1304.

56. Smith EL III, Lee JS, Ramamirtham R et al. Peripheral vision can influence eye growth
and refractive development in infant monkeys. *Invest Ophthalmol Vis Sci* 2005; 46: 3965–3972.

60. Smith EL III, Ramanatham R, Qiao-Grider Y et al. Effects of foveal ablation on emmetropiza-
tion and form-deprivation myopia. *Invest Ophthalmol Vis Sci* 2007; 48: 3914–3922.

61. Smith EL III, Hung LF, Huang J. Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. *Vision Res* 2009; 49: 2586–2592.

62. Benavente-Perez A, Nour A, Troilo D. Axial eye growth and refractive error development can be modified by exposing the peripheral retina to relative myopic or hyperopic defocus. *Invest Ophthalmol Vis Sci* 2014; 54: 6765–6773.

63. Liu Y, Wildsoet C. The effect of two-zone concentric bifocal spectacle lenses on refractive error development and eye growth in young chicks. *Invest Ophthalmol Vis Sci* 2011; 52: 1078–1086.

64. Liu Y, Wildsoet C. The effective add inherent in 2-zone negative lenses inhibits eye growth in myopic young chicks. *Invest Ophthalmol Vis Sci* 2012; 53: 5083–5093.

65. Tepelus TC, Vazquez D, Seidemann A et al. Effects of lenses with different power profiles on eye shape in chickens. *Vision Res* 2012; 54: 12–19.

66. Charman WN, Radhakrishnan H. Peripheral refraction and the development of refractive error: a review. *Optometric Physical Opt J* 2010; 39: 321–338.

67. Sankaridurg P, Donovan I, Varnas S et al. Spectacle lenses designed to reduce progression of myopia: 12-month results. *Optom Vis Sci* 2010; 87: 651–661.

68. Tabernero J, Vazquez D, Seidemann A et al. Effects of myopic spectacle correction and radial refractive gradient spectacles on peripheral refraction. *Vision Res* 2009; 49: 2176–2186.

69. Sankaridurg P, Holden B, Smith E 3rd et al. Decrease in rate of myopia progression with a contact lens designed to reduce relative peripheral hyperopia: one-year results. *Invest Ophthalmol Vis Sci* 2011; 52: 9362–9367.

70. Paule J, Queiros A, Lopes-Ferreira D et al. Efficacy of a gas permeable contact lens to induce peripheral myopic defocus. *Optom Vis Sci* 2015; 92: 596–603.

71. Ts C, Tang WC, Tse DV et al. Defocus Incorporated Soft Contact (DISC) lens slows myopia progression in Hong Kong Chinese schoolchildren: a 2-year randomised clinical trial. *Br J Ophthalmol* 2014; 98: 40–45.

72. Paule J, Morales H, Armengol J et al. Myopia control with a novel peripheral gradient soft lens and orthokeratology: a 2-year clinical trial. *Biomol Res Int* 2015; 2015: 507572.

73. Cheng X, Xu J, Chehab K et al. Soft contact lenses with positive spherical aberration for myopia control. *Optom Vis Sci* 2016; 93: 533–366.

74. Paule J, Queiros A, Quevedo L et al. Peripheral myopization and visual performance with experi-
mental rigid gas permeable and soft contact lens design. *Cont Lens Anterior Eye* 2014; 37: 455–460.

75. Anstice NS, Phillips JR. Effect of dual-focus soft contact lens wear on axial myopia progression in children. *Ophthalmology* 2011; 118: 1152–1161.

76. Fujikado T, Ninomiya S, Kobayashi T et al. Effect of low-addition soft contact lenses with a peripheral optical design on myopia pro-
gression in children: a pilot study. *Clin Ophthalmol* 2014; 8: 1947–1956.
117. Schwahn HN, Schaeffel F. Chick eyes under cycloplegia compensate for spectacle lenses despite six-hydroxy dopamine treatment. Invest Ophthalmol Vis Sci 1994; 35: 5516–5524.
118. McBrien NA, Moghaddam HO, Reeder AP. Atropine reduces experimental myopia and eye enlargement via a nonaccommodative mechanism. Invest Ophthalmol Vis Sci 1993; 34: 205–215.
119. Liu S, Li J, Tan DT et al. Expression and function of muscarinic receptor subtypes on human cornea and conjunctiva. Invest Ophthalmol Vis Sci 2007; 48: 2987–2996.
120. Collison DJ, Coleman RA, James RS et al. Characterization of muscarinic receptors in human lens cells by pharmacologic and molecular techniques. Invest Ophthalmol Vis Sci 2009; 41: 2633–2641.
121. Qiu J, Zhou X, Xie R et al. The presence of m1 to m5 receptors in human sclera: evidence of the sclera as a potential site of action for muscarinic receptor antagonists. Curr Eye Res 2006; 31: 587–597.
122. Fang YT, Chou YJ, Pu C et al. Prescription of atropine eye drops among children diagnosed with myopia in Taiwan from 2000 to 2007: a nationwide study. Eye (Lond) 2013; 27: 418–424.
123. Chua WH, Balakrishnan V, Chan YH et al. Atropine for the treatment of childhood myopia. Ophthalmology 2006; 113: 2286–2291.
124. Song YI, Wang H, Wang BS et al. Atropine in ameliorating the progression of myopia in children with mild to moderate myopia: a meta-analysis of controlled clinical trials. J Ocular Pharmacol Ther 2011; 27: 361–368.
125. Chia A, Chua WH, Cheung YB et al. Atropine for the treatment of childhood myopia: safety and efficacy of 0.5 per cent, 0.1 per cent, and 0.01 per cent doses (Atropine for the Treatment of Myopia 2). Ophthalmology 2012; 119: 347–354.
126. Shih YF, Chen CH, Chou AC et al. Effects of different concentrations of atropine on controlling myopia in myopic children. J Ocular Pharmacol Ther 1999; 15: 85–90.
127. Clark TY, Clark RA. Atropine 0.01 per cent eye drops significantly reduce the progression of myopia. J Ocular Pharmacol Ther 2015; 31: 541–545.
128. Chia A, Chua WH, Wen L et al. Atropine for the treatment of childhood myopia: changes after stopping atropine 0.01%, 0.1% and 0.5%. Am J Ophthalmol 2014; 157: 451–457.e1.
129. Tong I, Huang XL, Koh AL et al. Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. Ophthalmology 2009; 116: 572–579.
130. Chia A, Lu QS, Koh AL et al. Maximization of therapeutic benefits and safety of 0.01% atropine for myopia control. Ophthalmology 2016; 123: 391–399.
131. Cooper J, Eisenberg N, Schulman E et al. Maximum atropine dose without clinical signs or symptoms. Optom Vis Sci 2015; 92: 1467–1472.
132. Loughman J, Flitcroft D. The acceptability and visual impact of 0.01 per cent atropine in a Caucasian population. Br J Ophthalmol 2016; 100: 1525–1529.
133. Cottriall CL, McBrien NA. The M1 muscarinic antagonist pirenzepine reduces myopia and eye enlargement in the tree shrew. Invest Ophthalmol Vis Sci 1996; 37: 1568–1579.
134. Leech EM, Cottriall CL, McBrien NA. Pirenzepine prevents form deprivation myopia in a dose dependent manner. Ophthalmic Physiol Opt 1995; 15: 351–356.
135. Tan DT, Lam DS, Chua WH et al. One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2 per cent pirenzepine ophthalmic gel in children with myopia. Ophthalmology 2005; 112: 84–91.
136. Siatkowski RM, Cotter SA, Crockett RS et al. Two-year multicenter, randomized, double-masked, placebo-controlled, parallel safety and efficacy study of 2 per cent pirenzepine ophthalmic gel in children with myopia. J AAPOS 2008; 12: 332–339.
137. Siatkowski RM, Cotter S, Miller JM et al. Safety and efficacy of 2 per cent pirenzepine ophthalmic gel in children with myopia: a 1-year, multicenter, double-masked, placebo-controlled parallel study. Arch Ophthalmol 2004; 122: 1667–1674.
138. Kang P, Gifford P, Swarbrick H. Can manipulation of orthokeratology lens parameters modify peripheral refraction? Optom Vis Sci 2013; 90: 1237–1248.
139. Li SM, Wu SS, Kang MT et al. Atropine slows myopia progression more in Asian than white children by meta-analysis. Optom Vis Sci 2014; 91: 342–350.