Special Issue

IMI—Interventions for Controlling Myopia Onset and Progression 2025

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Myopia is recognized as a significant public health problem, particularly in East and Southeast Asia. This has led to the development and evaluation of a range of interventions to slow its progression and delay its onset. Since the publication of the 2019 International Myopia Institute's review of interventions for controlling myopia onset and progression, treatment options have continued to grow in number. This article reviews the efficacy of such interventions under five categories: optical, pharmacological, environmental (behavioral), colored light, and surgical. In summarizing the efficacy of mature technologies, only randomized controlled trials were considered, although such data are very limited for emerging treatments. The overall conclusion is that there are multiple effective interventions in most categories. Further research should aim to understand the mechanisms underlying myopia progression and the modalities that slow its progression in order to develop more effective treatments.

Keywords: myopia, myopia control, myopia prevention, optical, pharmacological, behavioral, surgical, children, axial length

Six years ago, the first series of white papers from the International Myopia Institute was published in a special issue of *Investigative Ophthalmology and Visual Science*, including a review of interventions for controlling myopia onset and progression.[1] Two years later, a short update was provided.[2] Since this time, the range of myopia control interventions has expanded, the underlying technology has advanced, and outcome data have been strengthened. Following the same general organization as the previous review, occupying prime position are the two most widely used interventions: optical and pharmacological, followed by behavioral modifications (and monitoring), along with surgical interventions which aim to stabilize highly myopic eyes. Two new additions are colored light therapies and combination treatments—primarily optical and pharmacological in the latter case—reflecting the growing evidence base. Finally, interventions to delay myopia onset in non-myopic children are discussed. Although the efficacy of interventions for controlling myopia onset and progression is the primary focus of this paper, some attention is given to practical considerations, including compliance and safety. Furthermore, there have been meaningful developments in how data from myopia clinical trials can and should be presented. Thus, these issues are discussed first to set the stage for evaluating the various treatment modalities.

Measuring Efficacy

The efficacy of any myopia control intervention may be based on measures of axial length, refractive error, or both. Changes in axial length and refractive error in myopic children are well correlated, with myopia progression in children due almost exclusively to axial elongation.[3]

Axial elongation is a normal feature of childhood eye development in emmetropic eyes, with more rapid growth in early childhood and stabilization in the mid-teens.[4] However, besides age, axial length is also influenced by gender and height.[5] In myopic eyes, there is an acceleration in axial elongation that precedes myopia onset by several years.[6,7] In modern clinical trials, axial length is measured almost exclusively using optical coherence interferometry methods.[8] The technique is non-contact, safe, very repeatable, and does not require cycloplegia,[9] although measurements from different instruments may show small discrepancies and thus may not be considered interchangeable.[8,10,11] The cost of these optical biometers has limited their uptake in clinical practice. The alternative, ultrasonography, requires topical anesthesia, contact with the cornea, a higher degree of patient cooperation, and has poorer repeatability.[12,13]

Refractive error is typically expressed as the spherical equivalent, that is, sphere + half cylindrical power and is influenced not only by axial length but also by the power and relative location of the cornea and crystalline lens. Data derived from large population-based childhood studies show that corneal curvature changes little beyond 2 years of age.[14,15] The flattening of the crystalline lens partially compensates for axial elongation in the progressing myope in the first 10 years of life.[16] The ratio of myopia progression to axial elongation will thus be lower in young children with myopia, with 1 mm corresponding to approximately 2 diopter (D).[16] Refractive error can be assessed by subjective refraction or autorefraction; and with and without cycloplegia.[8,17] Cycloplegic autorefraction is more repeatable than subjective refraction[18] and less subject to examiner bias. Non-cycloplegic autorefraction usually overestimates myopia, particularly with closed-field instrumentation. Cycloplegia improves the repeatability of auto-refraction but measurements remain far less repeatable than optical biometry.[8,19] Variation in the degree of cycloplegia achieved may account for some of this variability[20] and not all eyecare professionals may have access to cycloplegia.

It can been argued that axial elongation is the preferred metric for evaluating myopia control modalities (although not necessarily predicting onset), as it can be measured more precisely and without cycloplegia.[19] Some studies of inter-

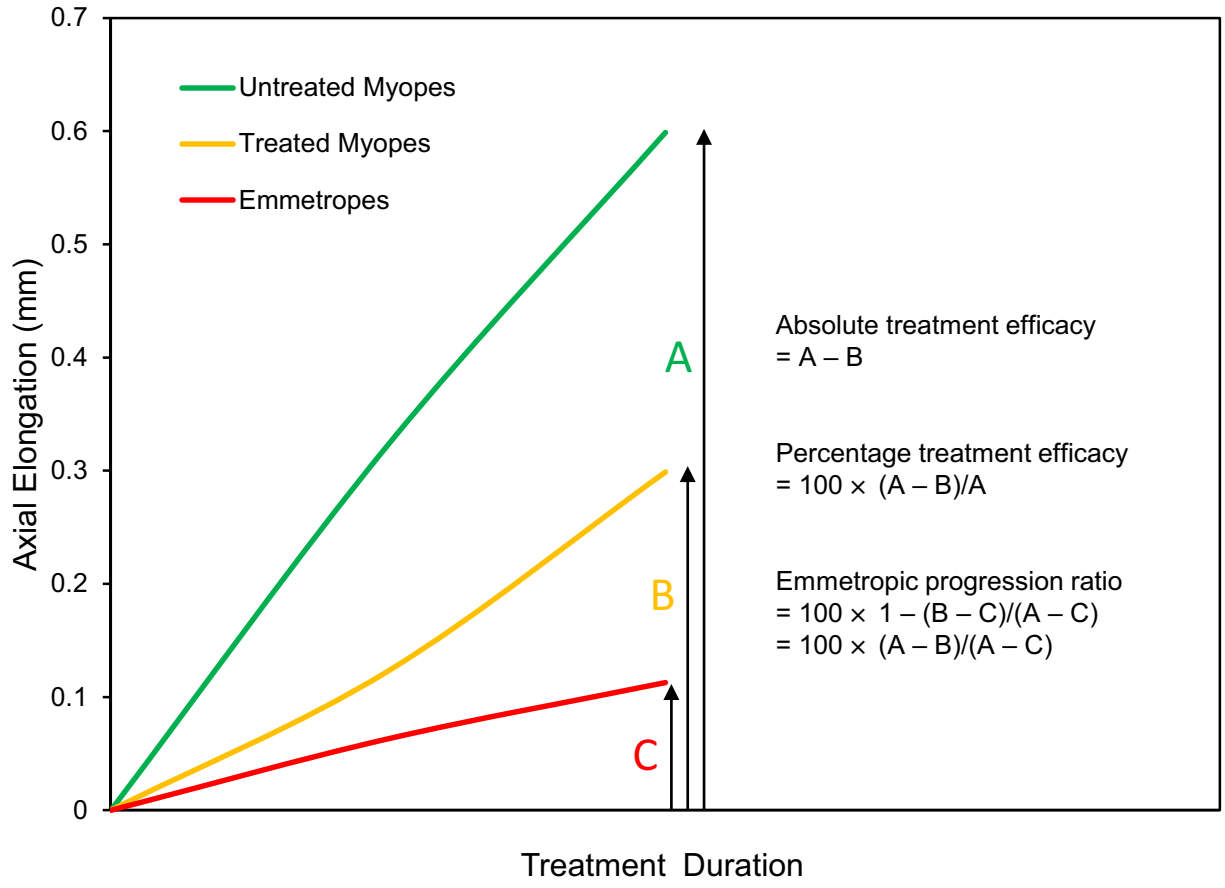

Figure 1. Hypothetical axial elongation in groups of untreated patients with myopia (**A**), treated patients with myopia (**B**), and patients with emmetropia (**C**). Formulae are shown for the calculation of absolute treatment efficacy, percentage treatment efficacy, and emmetropic progression ratio.

ventions, notably overnight orthokeratology, can only report efficacy in terms of axial length.[21]

Definitions of Efficacy

Critical to comparing myopia control intervention is an understanding of treatment efficacy. As background, the alternative approaches to characterizing the efficacy of a myopia control intervention are examined and their strengths and weaknesses discussed. The different approaches are illustrated in Figure 1.

Myopia Progression and Axial Elongation. Efficacy is most commonly portrayed as the difference in axial elongation and myopia progression between treated and control groups. The advantage of this simple approach is that the values are easily interpreted and presented in the same units as the underlying measurements. Furthermore, these absolute measures of efficacy for a given treatment modality appear to be constant regardless of the underlying progression rate and thus across age and race.[19,22] There is an initial boost of efficacy in the first few months of treatment, such that absolute measures are time dependent and must be considered in terms of study duration.[3] It should be noted that systematic reviews and meta-analyses only use absolute measures of axial elongation and myopia progression in their analyses.[23,24]

Alternatively, efficacy can be expressed as a percentage where the difference in progression between the treated and control groups is divided by progression in the control group. While these percentages are easy for the general public to understand, they vary dramatically with underlying progression rate. For example, in the Low-Concentration Atropine for Myopia Progression (LAMP) study: the 1-year efficacy of 0.05% atropine was 0.54 D and varied little with age.[25] When expressed as a percentage, however, this translated to 40% efficacy in the youngest children, but 130% in the oldest participants.[19] With the slowing of efficacy over time added to the mix, percentage efficacy projections are unrealistic, misleading, and overly optimistic for those at high risk of fast progression.[19]

Another approach to evaluating the efficacy of myopia control interventions compares axial elongation in treated children with myopia to that of age-matched children with emmetropia.[26] This is usually accomplished graphically.[27] An Emmetropic Progression Ratio (EPR) may be defined as (1 – ((elongation with treatment – elongation in emmetropes)/(elongation without treatment – elongation in emmetropes))) × 100% (Ohlendorf A, et al. IOVS 2024;65:ARVO E-Abstract 127). Values closer to 100% approach emmetropic eye growth, that is, greater efficacy. Most published models of emmetropic eye growth show consistent patterns in different populations,[4,28–30] although there are outliers.[28] However, as axial elongation in East Asian children with myopia is approximately 40% faster than in their white counterparts,[31] achieving emmetropic eye growth will be more difficult in this demographic.

Treatment Response or Failure. The distribution of axial elongation and myopia progression is commonly shown in bar-charts for both treated and untreated children. This can provide rich data about the distribution within each group, which usually have similar standard deviations.[19] Definitions of success and failure in a clinical trial can also be predetermined based on the expected distribution of progression. Success may be expressed by a specific value of myopia progression or axial elongation in any particular cohort, for example, less than −0.50 D or 0.2 mm.[32] Statistically, categorizing results in a loss of information decreases the power of an analysis.[33,34] However, these rates are easy to understand and may be helpful when counseling parents and setting appropriate expectations.

Success of a treatment could also be evaluated by identifying when progression or elongation has reached a particular threshold. The threshold could be onset of myopia (incident myopia in pre-myopic children) or high myopia, a percentage reaching threshold at a set time, or slowing in the time taken to progress by a certain amount.[35] For example, an analysis of children wearing dual-focus soft contact lenses for 6 years showed a mean axial elongation of 0.48 mm over a 6-year period, whereas the control group reached this value after approximately 2 years, thus representing a saving of 4 years of progression.[36]

Scope of This White Paper

The following sections summarize the efficacy of various myopia control interventions based on peer-reviewed publications through the end of 2024. For mature technologies, the evidence is limited to randomized clinical trials which both included a concurrent control group and reported axial length. An additional requirement was at least 12 months of follow-up, to account for seasonal variability in myopia progression[37,38] and treatment efficacy (Boatman M, et al. IOVS 2024;65:E-Abstract 165). Due to the heterogeneity in the study data, no meta-analyses were undertaken. Where treatments across different clinical trials were considered similar, for example, orthokeratology, 0.01% atropine, and their combination, median (and interquartile range [IQR]) were derived. For spectacles and soft contact lenses, the optical designs were considered to be sufficiently diverse that median efficacy is not reported.

In the interest of ensuring that the narrative is readable, standard deviations, confidence intervals, and results of statistical analyses are not given in the text. Unless otherwise stated, readers should assume that the described effect of an intervention reached statistical significance. Where a critical mass of clinical trials have been published a comprehensive table summarizing the key features of each clinical trial is included. Mean myopia progression and axial elongation are reported for treated and control patients along with the absolute efficacy in millimeters (mm) and D. Figure 2 shows the relation between treatment efficacy and study duration for six categories of interventions. All values in the tables are for the duration of the trials which vary between 1 and 5 years.

Optical Interventions

The current dominant hypothesis regarding the mechanisms by which optical interventions impact myopic eye growth focuses on the role of peripheral retinal defocus in refractive development. This hypothesis suggests that even with a clear foveal image, the nature and type of blur affecting the peripheral retina are critical in shaping refractive development.[39–41] The initial observations in animal models were later validated by clinical trials in children,[42] which consistently demonstrate that optical myopia control strategies that involve inducing myopic defocus on the peripheral retina are effective.[43] However, the exact mechanism by which these lenses are exerting their effect is not fully understood, and recent data suggest a role for altering contrast as a method to slow myopia progression in children.[44–47]

Spectacle Lenses

The use of spectacle lenses for slowing myopia progression offers several attractive features. Spectacles are easy to fit, generally well accepted and tolerated, and minimally invasive alongside correcting the myopic refractive error. Approaches to myopia control using spectacle lenses include customized single vision designs, peripheral defocus lenses, and contrast altering designs, as well as bifocal and progressive lenses. The development of spectacle lens interventions to slow myopia progression has been guided by various theoretical frameworks. Early hypotheses theorized that myopia resulted from excessive or prolonged accommodation,[48] leading to a permanent increase in the thickness and curvature of the crystalline lens inducing excessive ocular power and myopia. Subsequent evidence incorporated the potential roles of intraocular pressure (IOP) and the action of extraocular muscles.[49,50] This mechanical theory of myopia was later replaced by an adaptive hypothesis, supported by findings from animal models.[39] These studies demonstrated that when young animals from a number of species wore minus lenses that imposed hyperopic defocus, they developed myopia. It was further observed that humans, particularly children with myopia, may exhibit underaccommodation when viewing near objects, with a pronounced accommodative lag.[51] This gave rise to the accommodative lag theory, which proposed that errors in accommodation during near vision cause retinal defocus that acts as a driver of myopia progression. Based on this theory, bifocal and progressive addition spectacles for myopia control were evaluated in several studies. Although these interventions have shown statistically significant effects, they have largely shown limited clinical value.[52]

Table 1 shows results from randomized controlled trials on children using different designs of spectacle lenses with single vision spectacles as the control. Data for undercorrection, progressive addition lenses, and bifocal lenses are not shown but are discussed below.

Undercorrection of Myopia. The practice of undercorrection to slow myopia progression started many years ago, albeit with limited evidence.[53–55] Undercorrection of myopia was initially thought to work by reducing accommodative demand and subsequently by reducing accommodative lag during near tasks.[56] Additionally, evidence from animal studies showing slowed eye growth in response to experimentally induced myopic defocus, sparked comparisons with the myopic defocus experienced during distance viewing with undercorrection, fueling speculation about its potential benefits.[57] Three well-designed, randomized controlled trials investigated undercorrection for distance by 0.50 to 0.75 D in children over 1.5 to 2.0 years.[55,57,58] These studies suggest that this strategy has no benefit and may increase myopia progression compared with fully corrected single vision spectacle wearers.[59–61] One possible, although unproven, explanation is that undercorrection affects chil-

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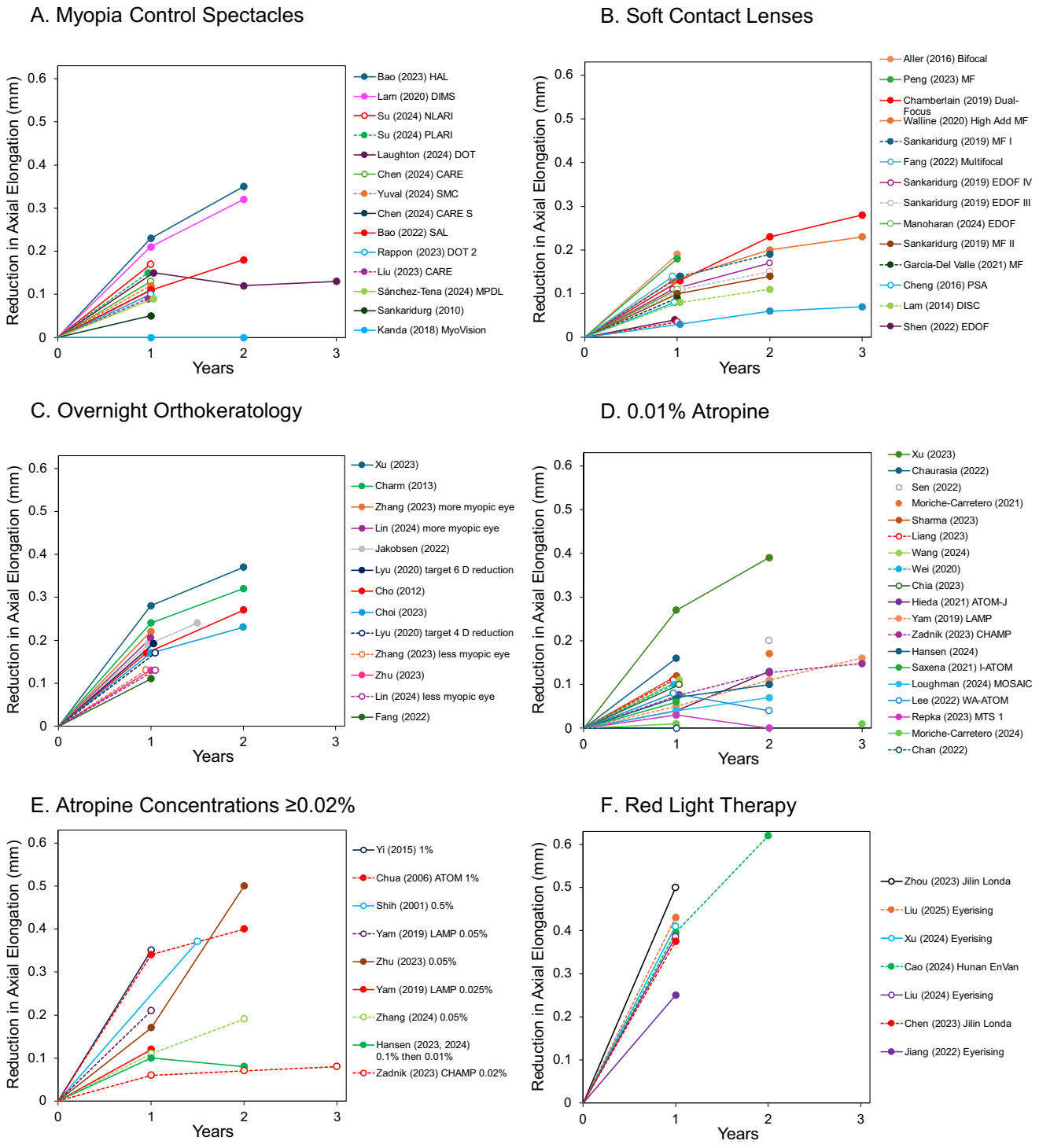

Figure 2. (**A**) Myopia control spectacles; (**B**) SoV contact lenses; (**C**) Overnight orthokeratology; (**D**) 0.01% atropine; (**E**) Atropine concentrations ≥0.02%; (**F**) Red light therapy. Reduction of axial elongation relative to untreated control children as a function of treatment duration for different myopia control interventions. For each panel, the legend is arranged by approximate treatment efficacy, not date. ATOM, Atropine for the Treatment of Myopia; ATOM-J, Atropine for the Treatment of Myopia - Japan; CARE, cylindrical annular refractive elements; CHAMP, Childhood Atropine for Myopia Progression; DIMS, defocus incorporated multiple segments; DISC, defocus incorporated soft contact; DOT, diffusion optics technology; EDOF, extended depth of focus; HAL, highly aspherical lenslets; I-ATOM, India - Atropine for the Treatment of Myopia; LAMP, Low-Concentration Atropine for Myopia Progression; MF, multifocal; MOSAIC, Myopia Outcome Study of Atropine in Children; MPDL, myopic peripheral defocus; MTS-1, Myopia Treatment Study-1; NLARI, negative power lenslets; PLARI, positive power lenslets; PSA, positive spherical aberration; SAL, slightly aspherical lenslets; SMC, Shamir myopia control; WA-ATOM, Western Australia - Atropine for the Treatment of Myopia. See Supplementary Figures S1–S6 for individual plots.

Investigative Ophthalmology & Visual Science

Table 1. Characteristics and Outcomes of Randomized Clinical Trials of the Efficacy of Novel Spectacle Lens Technologies for Myopia Control

Author (Country)	Duration, Y	Treatment	Baseline Age Range, Y	Baseline Myopia Range, D	*N* (Complete/ Enrolled)		Myopia Progression, D			Axial Elongation, mm		
					Treated	Control	Treated	Control	Efficacy, D	Treated	Control	Efficacy, mm
Peripheral defocus												
Sankaridurg (China)[72]	1	Reduce relative peripheral hyperopia Type I	6 to 16	−0.75 to −3.50	48/50	49/50	−0.81	−0.78	**−0.03**	0.36	0.36	**0.00**
		Type II	6 to 16	−0.75 to −3.50	58/60	49/50	−0.81	−0.78	**−0.03**	0.35	0.36	**0.01**
		Type III	6 to 16	−0.75 to −3.50	46/50	49/50	−0.66	−0.78	**0.12**	0.31	0.36	**0.05**
Kanda (China)[73]	2	Reduce relative peripheral hyperopia	6 to 12	−1.50 to −4.50	102/105	101/102	−1.43	−1.39	**−0.04**	0.73	0.69	**−0.04**
Lam (Hong Kong)[74]	2	DIMS	8 to 13	−1.00 to −5.00	79/93	81/90	−0.38	−0.93	**0.55**	0.21	0.53	**0.32**
Bao (China)[75]	2	HAL	8 to 13	−0.75 to −4.75	54/58	50/55	−0.66	−1.46	**0.80**	0.34	0.69	**0.35**
	2	SAL	8 to 13	−0.75 to −4.75	53/57	50/55	−1.04	−1.46	**0.42**	0.51	0.69	**0.18**
Liu (China)[76]	1	CARE	8 to 12	−1.00 to −4.00	52/61	44/57	−0.56	−0.71	**0.15**	0.25	0.36	**0.11**
Chen (China)[77]	1	CARE	6 to 13	−0.75 to −5.00	78/80	77/80	−0.65	−0.35	**0.30**	0.19	0.32	**0.13**
	1	CARE S	6 to 13	−0.75 to −5.00	78/80	77/80	−0.65	−0.36	**0.29**	0.21	0.32	**0.11**
Yuval (Israel)[78]	1	SMC	6 to 13	−0.50 to −6.25	56/65	43/61	−0.48	−0.64	**0.16**	0.21	0.32	**0.11**
Su (China)[47]	1	NLARI	6 to 12	−1.00 to −4.00	77/80	78/80	−0.21	−0.66	**0.45**	0.17	0.34	**0.17**
	1	PLARI	6 to 12	−1.00 to −4.00	76/80	78/80	−0.30	−0.66	**0.36**	0.19	0.34	**0.15**
Sanchez-Tena (Spain)[79]	1	MPDL	5 to 12	At least −0.50	42/46	41/46	–	–	–	0.14	0.23	**0.09**
Laughton (United States)[46]	3	DOT 1	6 to 10	−0.75 to −4.50	71/88	83/95	−0.83	−1.16	**0.33**	0.59	0.72	**0.13**
		DOT 2	6 to 10	−0.75 to −4.50	46/80	83/95	−1.19	−1.16	**−0.03**	0.67	0.72	**0.04**

CARE, cylindrical annular refractive elements; DIMS, defocus incorporated multiple segments; DOT, diffusion optics technology; HAL, highly aspherical lenslets; MPDL, myopic peripheral defocus; NLARI, negative power lenslets; PLARI, positive power lenslets; SAL, slightly aspherical lenslets; SMC, Shamir myopia control.

The values for myopia progression, axial elongation, and efficacy are for the entire study duration.

dren's willingness to engage in outdoor activities, thereby indirectly influencing progression.

Progressive Addition Lenses. A nonrandomized study suggested that progressive addition lenses (PALs) could slow myopia progression by 0.50 D or more over 2 years.[62] However, several randomized clinical trials involving over 1000 children collectively disproved this initial finding.[52,63–67] The Correction of Myopia Evaluation Trial (COMET),[52] a US-based study, found a modest 3-year slowing of myopia progression (0.20 D) and axial elongation (0.11 mm) among children wearing PALs compared with those wearing single vision spectacle lenses. Almost all the effect occurred within the first year. A corresponding 2-year study in Hong Kong found no significant difference in progression or axial elongation between PAL and single vision lens wearers, with no significant difference in myopia progression (0.14 D) or axial elongation (0.02 mm), respectively.[63] Similarly, a randomized clinical trial in Japan using PALs versus single vision spectacles in a crossover design over 3 years also found minimal impact on slowing myopia progression.[64] Collectively, these findings indicate that PALs are largely ineffective as a myopia control strategy.

There was a suggestion from a subgroup analysis of COMET[52] that children with higher lags of accommodation and near esophoria had the largest effect, but this was refuted in the COMET 2 and Study of Theories about Myopia Progression (STAMP) clinical trials that only enrolled children with myopia with a high lag and near esophoria.[67,68] Whereas statistically significant, the 3-year slowing of progression in COMET 2 (0.28 D) was clinically negligible (axial length was not measured). The adjusted 1-year differences in STAMP of 0.18 D and 0.08 mm were also significant, but not clinically important. Additionally, a trial of flat-top bifocals compared with single vision lenses in 82 children, with esophoria at near, found only a small slowing of myopia progression (0.25 D) and axial elongation (0.09 mm) over 30 months.[69]

Bifocal Lenses. Executive bifocal lenses have been shown to be more effective than PALs. In an unmasked study in 135 Chinese Canadian children aged 8 to 13 years, participants were randomized into 1 of 3 groups: single vision lenses, +1.50 D executive bifocals, or +1.50 D executive bifocals with 3-Δ base-in prism in the near segment.[70] Over 3 years, mean myopia progression was −2.06, −1.25, and −1.01 D, respectively, with corresponding axial elongation of 0.82, 0.57, and 0.54 mm. These findings suggest executive bifocals are an effective myopia control intervention, particularly when prism is incorporated. However, an earlier US-based 3-year trial involving 207 children, aged 6 to 15 years, randomized to single vision lenses or executive bifocals with either +1.00 or +2.00 D additions, found contradictory results with no significant difference among the groups, with annual progression rates of −0.34, −0.36, and −0.34 D, respectively.[71] The contrasting results between these two studies remain unexplained, however the demographics of the participating populations were different, the more recent study enrolled only progressing myopes, and the earlier study reported a 40% loss to follow-up.

Interestingly, the aforementioned executive bifocal study reported that treatment efficacy was largely independent of near phoria status, with prism bifocals showing slightly greater efficacy in children with lower accommodative lag.[70] This raises the possibility that the increased effectiveness of executive bifocals compared to PALs may stem from their design: bifocals expose a larger portion of the visual field to positive power, whereas PALs confine the effect to a smaller area.

Novel Spectacle Lens Technologies. Although early myopia control efforts using spectacle lenses only had a very modest impact, recent advancements in lens designs for myopia control demonstrate significant potential. These innovations mark a shift toward effective, evidence-based interventions that leverage insights from peripheral defocus and altering contrast, which are thought to drive myopia progression. Ten randomized clinical trials greater than 6 months in duration and including a single vision control group were identified, the first published in 2010, but the majority since 2022. The main design characteristics and outcomes of these clinical trials are shown in Table 1.[46,47,72–79] Reductions in axial elongation as a function of treatment duration are shown in Figure 2A.

Peripheral Hyperopic Defocus Designs. Early attempts to reduce peripheral hyperopic defocus used a form of concentric PAL-like designs. A 12-month pilot study randomized 210 Chinese children, aged 6 to 16 years, to 1 of 3 experimental lens designs or to single vision lenses.[72] No significant differences in progression were observed, although one design showed potential benefit in younger children who had one parent with myopia. This design was evaluated in a subsequent clinical trial of 207 children with myopia aged 6 to 12 years with at least one myopic parent, who were randomized to the test lens or a single vison lens.[73] Over 2 years, myopia progression and axial elongation in the treated group were no different from those in the control group (mean difference = 0.04 D and 0.04 mm).

Defocus Incorporated Multiple Segments. Defocus Incorporated Multiple Segments (DIMS) lenses have a 9-mm clear central optical zone surrounded by a 33-mm annular zone with multiple 1-mm segments providing +3.50 D of relative positive power, creating a peripheral myopic defocus.[74] In a randomized trial involving 183 Chinese children, aged 8 to 13 years, the 2-year myopia progression was −0.41 D in the DIMS group compared to −0.85 D in the single vision control group, a slowing of 0.44 D.[74] Likewise, axial elongation was slowed by 0.34 mm in the DIMS group (0.21 mm versus 0.55 mm). In a third year, the myopia control effect was sustained in children who had worn the DIMS spectacles in the previous 2 years and was also observed in children who were switched from single vision to DIMS lenses.[80]

Highly Aspherical Lenslet Technology. Highly Aspherical Lenslet (HAL) technology incorporates aspheric lenslets that also generate myopic defocus. The lenses have a 9-mm clear central zone surrounded by 11 concentric rings of contiguous lenslets. A 2-year randomized trial in China, involving 157 children aged 8 to 13 years, found that HAL lenses slowed myopia progression by 0.80 D and axial elongation by 0.35 mm compared to single vision lenses. In contrast, slightly aspherical lenses (SAL) demonstrated lower efficacy (0.42 D and 0.18 mm).[75]

Both the DIMS and HAL lens technologies impart peripheral defocus concentrically. Another lens design induces defocus using a U-shape pattern that creates a clear central vertical canal and a continuous defocus toward the periphery.[78] This design aims to minimize disturbance of vision in the vertical plane while still imposing sufficient peripheral defocus. The relative power increased from 0.5 D at the end of the canal to 3 D horizontally and 1.50 D in inferior meridian. In a 2-year clinical trial involving 126 Israeli children aged 6 to 13 years, the participants were randomized to

Investigative Ophthalmology & Visual Science

either the test lens or single vision lenses. One-year interim data show a slowing of myopia progression by 0.16 D and axial elongation by 0.11 mm in the treated group.[78]

Cylindrical Annular Refractive Elements Technology. Cylindrical Annular Refractive Elements (CARE) Technology spectacle lenses are currently in clinical trials. The CARE lenses utilize microcylinders to generate high-order aberrations in the peripheral retina to slow myopia progression. One-year interim data have been reported from two separate trials using slightly different designs of spectacle lenses. Two different designs, one with a 7-mm central clear zone and a relative positive power of the cylindrical elements of +4.6 D (CARE) and the other lens design with a 9-mm central zone and +3.8 D relative positive power (CARE S), were tested in 240 Chinese children aged 6 to 13 years, randomly assigned to wear one of the test lenses or single vision spectacles.[81] The difference in myopia progression and axial elongation between children wearing the test lenses and single vision spectacles at 12 months was 0.30 D and 0.13 mm for CARE, and 0.29 D and 0.11 mm for CARE S. Another trial that also used cylindrical annular elements found differences of 0.14 D and 0.09 mm between the test and single vision group,[76] however, this study used a larger central aperture of 9.4 mm and the spectacle lenses differed in the power of the cylindrical elements and their spacing.

Asymmetric Lens Design. An asymmetric myopic defocus ophthalmic lens design has been evaluated in children in Spain.[79] The myopic peripheral defocus lens (MPDL) comprised an ovoidal, blur-free central area with a horizontal size of 7 mm and a peripheral treatment area consisting of an asymmetrical horizontal myopic defocus with a relative power of +1.50 D at 25 mm nasally and +1.80 D at 25 mm temporally. Additionally, the lens also featured a +2.00 D myopic defocus inferiorly. Ninety-two children aged 5 to 12 years, were randomly assigned to either the test lens or a single vision lens. After 1 year of treatment, there was 0.09 mm less axial elongation and 0.25 D less myopia progression in the treated group.[79]

Contrast Modifying Spectacle Lenses. The diffusion optics technology (DOT) lenses were developed[45] based on the theory that "environmental factors that produce abnormal contrast between adjacent cones is a signal for axial elongation."[82] The lenses incorporate microscopic diffusers outside a central 5-mm clear zone, with the intended goal of lowering retinal contrast. A trial with 256 North American children, aged 6 to 10 years, randomized them to 1 of 2 different DOT lens densities or to a single vision control group.[46] The test lenses differed in the density of the microscopic diffusers. The difference between the lower density and single vision was 0.33 D and 0.13 mm over 3 years, with the majority of the treatment benefit occurring in year 1. The authors postulate that this was due to the coronavirus disease 2019 (COVID-19) pandemic public health restrictions and school closures that coincided with this study period. The researchers present data for a fourth year that shows continued benefit of the DOT lenses.[46]

Other Approaches. Most designs have used relative positive power to induce myopic defocus. An interesting study has used both relative positive and relative negatively powered lenses to explore impact on myopia control.[47] The rationale for the study was that the underlying mechanism for myopia control may not be limited to peripheral myopic defocus, a rationale which aligns with the DOT lens technology.[46] Interestingly, the DIMS and HAL lenses have not been found to produce significant peripheral myopic defocus.[83] The Lenslet-ARray-Integrated (LARI) spectacle lenses have a clear central optical zone for correcting distance vision and a control zone of noncoaxial lenslet arrays arranged in a hexagonal pattern. Two designs were evaluated: either with lenslets of +3.00 D additional power (positive LARI [PLARI]) or with lenslets of −3.00 D additional power (negative LARI [NLARI]). Both designs provide the wearer with a clear central visual field while altering the higher-order wavefront aberration profile to produce similar image blur on the retina. A clinical trial randomized 240 children aged 6 to 12 years in China, to wear PLARI, NLARI, or single vision spectacle lenses.[47] The 1-year myopia progression and axial elongation were significantly less in the PLARI and NLARI groups compared with those in the single vision group (−0.30, −0.24, and −0.66 D, respectively; and 0.19, 0.17, and 0.34 mm, respectively), but with no difference between the PLARI and NLARI groups.

Summary and Long-Term Findings. Notably, the efficacy of some novel peripheral designs for myopia control, including DIMS and HAL lenses, has been demonstrated to persist beyond the first year of use, distinguishing them from PALs. The DOT lens study faced interruptions due to public health restrictions, but the 4-year data provide insights into the potential long-term treatment effects.[46] Emerging longer-term data from alternative study designs suggest that spectacle lenses for myopia control offer a viable and effective strategy for managing myopia progression in children over extended periods despite the mechanisms of action not being fully understood.[84,85]

Soft Contact Lenses

Multifocal soft contact lenses (i.e. lenses with more than one focal power) are a commonly studied modality in randomized clinical trials with several designs being used in an attempt to slow eye growth and myopia progression in children. Published randomized clinical trials to date have only investigated center-distance designs in which the center of the lens optics corrects distance vision with plus power incorporated in a variety of ways away from the central distance zone. Center-distance multifocal optical designs studied in randomized clinical trials include concentric ring designs, designs that progressively increase in plus power away from the center of the lens (including positive spherical aberration), extended depth of focus (EDOF) designs, other novel designs that incorporate a combination of these design principles to create unique optical profiles, and decentered bifocal designs. Whereas some of the center-distance multifocal lens designs studied in clinical trials were originally developed for use by patients with presbyopia,[86,87] numerous novel optical designs have been investigated in more recent clinical trials to determine their ability to slow the progression of myopia.

There have been 14 published randomized clinical trials that were at least 10 months in duration and included either a control group or used the participant's contralateral eye as a control. The main design characteristics and outcomes of these clinical trials are shown in Table 2.[86–99] Of these clinical trials, 9 were 1 year or less in duration,[86,90,91,95–99] 3 were 2 years in length,[89,92,93] and 2 were 3-year clinical trials.[87,94] Some of these trials continued to follow participants after the randomized portion of the study ended in order to assess rebound in eye growth and will be discussed later.

Of the randomized clinical trials that met the criteria for inclusion in the present summary, 12 had a concurrent control group, whereas 2 utilized a contralateral eye design

Table 2. Characteristics and Outcomes of Randomized Clinical Trials of the Efficacy of Soft Contact Lenses for Myopia Control

Author (Country)	Duration, Y	Treatment	Baseline Age Range, Y	Baseline Myopia Range, D	N (Complete/Enrolled)		Myopia Progression, D			Axial Elongation, mm		
					Treated	Control	Treated	Control	Efficacy, D	Treated	Control	Efficacy, mm
Anstice (New Zealand)[*,88]	0.83	Dual-Focus	11 to 14	−1.25 to −4.50	35/40	35/40	−0.44	−0.69	**0.25**	0.11	0.22	**0.11**
Aller (United States)[86]	1	Distance center bifocal	8 to 18	−0.50 to −6.00	40/??	39/??	−0.22	−0.79	**0.57**	0.05	0.24	**0.19**
Lam (Hong Kong)[89]	2	DISC—Defocus incorporated	8 to 13	−1.00 to −5.00	65/111	63/110	−0.59	−0.79	**0.20**	0.25	0.37	**0.11**
Fujikado (Japan)[90]	1	Decentered aspheric	10 to 16	−0.75 to −3.50	11/11	9/9	−0.62	−0.84	**0.22**	0.15	0.20	**0.05**
Cheng (United States)[91]	1	PSA	8 to 11	−0.75 to −4.00	52/64	57/63	–	–	**0.28**	–	–	**0.08**
Ruiz-Pomeda (Spain)[92]	2	Dual-Focus	8 to 12	−0.75 to −4.00	41/46	33/33	−0.45	−0.74	**0.29**	0.28	0.45	**0.16**
Sankaridurg (China)[93]	2	Multifocal I	8 to 13	−0.75 to −3.50	47/103	47/104	−0.87	−1.15	**0.28**	0.41	0.60	**0.19**
	2	Multifocal II	8 to 13	−0.75 to −3.50	45/101	47/104	−0.88	−1.15	**0.27**	0.46	0.60	**0.14**
	2	EDOF III	8 to 13	−0.75 to −3.50	45/98	47/104	−0.78	−1.15	**0.37**	0.45	0.60	**0.15**
	2	EDOF IV	8 to 13	−0.75 to −3.50	47/104	47/104	−0.85	−1.15	**0.30**	0.43	0.60	**0.17**
Chamberlain (Canada, Portugal, Singapore, UK)[94]	3	Dual-Focus	8 to 12	−0.75 to −4.00	53/65	56/70	−0.65	−1.31	**0.67**	0.34	0.62	**0.28**
Walline (United States)[87]	3	Distance center high add	7 to 11	−0.75 to −5.00	97/98	97/98	−0.60	−1.05	**0.46**	0.42	0.66	**0.23**
	3	Distance center medium add	7 to 11	−0.75 to −5.00	98/98	97/98	−0.89	−1.05	**0.16**	0.58	0.66	**0.07**
Garcia-Del Valle (Spain)[95]	1	Peripheral defocus	7 to 15	−0.50 to −8.75	32/36	26/34	−0.28	−0.57	**0.29**	0.13	0.22	**0.09**
Fang (China)[96]	1	Aspheric	7 to 15	−1.00 to −8.00	22/26	24/26	−0.63	−1.00	**0.37**	0.31	0.45	**0.14**
Shen (Taiwan)[*,97]	1	EDOF	9 to 14	−1.00 to −8.00	68/72	68/72	−0.70	−0.88	**0.18**	0.34	0.38	**0.04**
Peng (China)[98]	1	DISC—Defocus incorporated	7 to 12	−1.00 to −5.00	17/??	15/??	−0.69	−1.45	**0.67**	0.25	0.43	**0.18**
Manoharan (India)[99]	1	EDOF	7 to 15	−0.50 to −10.00	31/48	38/56	−0.20	−0.48	**0.28**	0.11	0.22	**0.11**

DISC, defocus incorporated soft contact; EDOF, extended depth of focus; PSA, positive spherical aberration.
The values for myopia progression, axial elongation, and efficacy are for the entire study duration.
[*] Contralateral control.

where 1 eye wore the multifocal contact lens, and the other eye wore a single vision control contact lens. The subjects in the control groups in these studies mostly wore single vision contact lenses, although single vision spectacles were worn in three studies, thereby eliminating the potential for participant masking to the assigned treatment. The participants' ages at the time of enrollment in these clinical trials ranged from 6 to 18 years, with only 5 studies including children older than 14 years.[86,90,95,96,99] Of these studies, only 2 clinical trials included children older than 15 years,[86,90] and the mean age of children enrolled in each of the clinical trials included ranged from 9 to 14 years. Losses to follow-up in each study ranged from none to as high as 54%,[93] with a mean of 17%. Overall, across all studies combined, 73% of participants completed the clinical trials.

The slowing of axial elongation by year is shown in Figure 2B. Across all clinical trials, the range of slowing of axial elongation by the test lenses ranged from 0.03 to 0.19 mm after 1 year, 0.06 to 0.23 mm after 2 years, and 0.07 to 0.28 mm after 3 years. In studies of 2 or 3 years, treatment effect continued to accrue, although generally less than in the first year. When considering myopia progression across all clinical trials, the slowing ranged from 0.08 to 0.67 D after 1 year, 0.09 to 0.52 D after 2 years, and 0.16 to 0.66 D after 3 years. Of note, the 2 clinical trials that followed children and maintained randomization with a control group for 3 years both found a significant slowing of axial elongation after 3 years compared to the control group (0.28 mm and 0.23 mm, respectively).[87,94] Whereas the clinical trials in this summary studied a variety of lens designs, two studies evaluated more than one add power in the same clinical trial. One evaluated two different designs (peripheral plus and EDOF) each with a mid and high add power and did not find a significant difference in efficacy among the four multifocal contact lenses. The study experienced a 54% loss to follow-up, with roughly half of the discontinuations occurring after receiving contact lenses prior to the 1-month visit and a significant number later due to one of the clinical sites closing.[93] The BLINK Study also evaluated both a medium add and a high add multifocal contact lens and found that after 3 years, the high add multifocal design significantly slowed axial elongation and myopia progression, whereas the medium add multifocal did not compared to the single vision control contact lens.

The prevailing hypothesis regarding the mechanism by which multifocal soft contact lenses slow myopia progression is based on numerous studies in animal models in which myopic retinal defocus slows eye growth.[100] Although previous nonrandomized studies reported significant, although clinically small, associations between either peripheral refractive error while wearing contact lenses and myopia progression[93] or relative peripheral refractive error and axial elongation,[101] only one of the randomized controlled clinical trials concurrently measured peripheral defocus while wearing study lenses to evaluate this hypothesis. The BLINK Study failed to find a clinically meaningful association between peripheral defocus in children wearing their assigned study contact lenses and the slowing of eye growth that resulted from wearing high-add multifocal soft contact lenses, suggesting an optical signal other than defocus may be responsible for the treatment effect.[102]

Two recently published studies that did not meet the criteria for inclusion in this summary are mentioned for their approach. A 6-month randomized controlled clinical trial evaluated the efficacy of 2 versions of a novel non-coaxial ring focus design compared to a dual focus design and a single vision control lens.[103] A 1-year randomized clinical trial compared a new contact lens design for myopia control to an existing myopia control contact lens design rather than to a single vision control; however, rather than conduct a non-inferiority analysis, the authors conducted a standard test comparing progression between the two groups.[104]

Overnight Orthokeratology

Overnight orthokeratology was introduced over 25 years ago for the temporary reduction of myopia but was serendipitously found to also slow axial elongation.[21] The term is shortened to orthokeratology, but the discussion refers exclusively to overnight wear. Orthokeratology lenses are corneal rigid contact lenses, designed to transiently reshape the cornea during night-time wear. The effectiveness of orthokeratology in slowing axial elongation is largely attributed to its impact on corneal topography. The lenses flatten the central cornea and steepen the mid-periphery, thereby generating a myopic defocus on the peripheral retina. These topographical changes also increase central higher-order aberrations.[105]

Orthokeratology has emerged as an efficacious intervention for myopia control. Because of the purposely induced changes in refractive error, only axial elongation outcomes are presented. Table 3 summarizes 10 randomized clinical trials of orthokeratology.[96,106–114] Five were 1-year trials,[96,108,112–114] one lasted 18 months,[109] and 4 were 2 years in duration.[106,107,110,111] The median (IQR) 1-year efficacy is 0.17 mm (0.13 to 0.20) and the median two-year efficacy is 0.30 mm (0.26 to 0.33). As can be seen from Figure 2C, orthokeratology is among the most effective myopia control modalities, while also providing freedom from optical correction during the day.

The Impact of Orthokeratology Lens Design. Higher levels of myopia require greater central flattening, which in turn induces greater variation in power across the cornea, thereby resulting in greater relative peripheral myopia. Higher addition power in a distance-center multifocal soft lens is associated with less axial elongation.[87] It might be hypothesized, therefore, that patients with higher myopia undergoing orthokeratology will experience a higher "add power" and thus show less axial elongation than patients with less myopia also undergoing orthokeratology. The data support this hypothesis; in an early, nonrandomized study of orthokeratology, patients with higher levels of myopia showed substantially less 2-year axial elongation than those with lower myopia.[115] More recently, 2 studies of patients with approximately 1.5 D of anisomyopia clearly demonstrate that the 1-year axial elongation was 0.1 mm lower in the more myopic eye than in the less myopic eye (see Fig. 2).[112,114]

Several studies have identified an intrinsic relationship between corneal refractive change and the efficacy of myopia control by orthokeratology. First, a negative correlation was observed between changes in corneal refractive power along the nasal, temporal, and inferior quadrants with 2-year axial elongation.[116] This was corroborated by a second study that found that the area, height, and volume of corneal refractive change after orthokeratology were all negatively correlated with axial elongation.[117] Collectively,

Table 3. Characteristics and Outcomes of Randomized Clinical Trials of the Efficacy of Orthokeratology for Myopia Control

Author (Country)	Duration, Y	Baseline Age Range, Y	Baseline Myopia Range, D	N (Complete/ Enrolled)		Axial Elongation, mm		Efficacy, mm
				Treated	Control	Treated	Control	
Cho (Hong Kong)[106]	2	6 to 15	Up to −4.00	37/51	41/51	0.36	0.63	**0.27**
Charm (Hong Kong)[107]	2	6 to 15	−5.75 or worse, partial correction	12/26	16/26	0.19	0.51	**0.32**
Lyu (China) target reduction −6 D[108]	1	8 to 15	−6.00 to −8.75, partial correction	29/34	31/34	0.10	0.29	**0.19**
Lyu (China) target reduction −4 D[108]				30/34	31/34	0.12	0.29	**0.17**
Fang (China)[96]	1	7 to 15	−1.00 to −8.00	20/26	24/26	0.34	0.45	**0.11**
Jakobsen (Denmark)[109]	1.5	6 to 12	Up to −4.75	19/30	28/30	0.17	0.41	**0.24**
Choi (Hong Kong)[110]	2	8 to 12	Up to −4.00	43/52	28/39	0.37	0.60	**0.23**
Xu (China)[111]	2	8 to 12	−1.00 to −6.00	34/40	30/40	0.42	0.81	**0.38**
Zhang (China) more myopic eye[112]	1	8 to 14	−0.75 to −5.00	28/30	30/30	0.13	0.36	**0.23**
Zhang (China) less myopic eye[112]						0.24	0.37	**0.13**
Zhu (China)[113]	1	8 to 12	−1.00 to −5.00	137/154	142/154	0.22	0.35	**0.13**
Lin (China) more myopic eye[114]	1	8 to 14	−0.75 to −5.00	??/61	??/41	0.06	0.26	**0.20**
Lin (China) less myopic eye[114]						0.15	0.28	**0.13**

Only axial length was measured and reported. The values for axial elongation and efficacy are for the entire study duration.

these studies indicate that the modulation of corneal refractive power distribution may be the primary mechanism through which orthokeratology lenses slow myopia progression.

The use of orthokeratology lenses with smaller back surface optical zones appears more effective at slowing axial elongation. A 2-year randomized clinical trial demonstrated that orthokeratology lenses with a 5-mm optical zone produced a smaller treatment zone, as shown by corneal topography, and showed significantly less axial elongation (0.15 mm) compared to a 6-mm optical zone (0.35 mm).[118] Other randomized clinical trials have also shown that a smaller optical zone more effectively slows axial elongation,[119,120] likely due to increased peripheral myopic defocus.[120] It should be noted that optical zone is not an independent variable in orthokeratology lens design; factors such as base curve asphericity, and the radius and width of the reverse curve, are also adjusted to maintain consistent sagittal depth. A smaller optical zone will result in a smaller treatment zone, as observed by corneal topography, however, other factors, notably higher baseline myopia, are also associated with a smaller treatment zone.[121,122]

The compression factor—also known as the Jessen Factor—refers to the extra dioptric power that is added to the patient's refractive correction in order to achieve an overcorrection to compensate for some regression during the day after lens removal. Orthokeratology lenses with higher compression factors (1.25 to 1.75 D) have been shown to expedite full refractive correction and enhance myopia control. In a prospective randomized clinical trial, the mean annual axial elongation in the 1.75 D compression factor group (0.17 mm) was significantly lower than in the 0.75 D group (0.25 mm).[120] Nonetheless, higher compression factors may increase ocular higher-order aberrations, potentially degrading visual quality.[123]

Decentration is common for all types of contact lenses and orthokeratology is no exception. This results in a decentered treatment zone, a factor that has been consistently shown to influence axial elongation. Although not intended, greater decentration relative to the pupil center is associated with less axial elongation.[124–132] Decentration is predominantly inferior and temporal, with between 50% and 67% of all locations lying in the Inferotemporal quadrant.[128,130,132] Whereas a decentered lens may have greater myopia control efficacy, in some patients, it may decrease visual performance. Therefore, it may be advisable to control the degree of decentration to maximize visual quality.

Summary. In summary, converging evidence from clinical trials demonstrates that orthokeratology is among the most effective myopia control modalities with relatively consistent results across studies (see Fig. 2C). Future research should focus on identifying baseline patient characteristics to refine treatment indications, discovering biomarkers for treatment responsiveness, and optimizing lens design to enhance efficacy.[133]

Pharmacological Control of Myopia

Atropine

Atropine is a muscarinic antagonist with a history of myopia control dating back 2 centuries.[134] The application of atropine in myopia management began with the hypothesis that excessive accommodation was a major factor in myopia development.[135] Early research in humans that goes back to the 19th century suggested that atropine could slow down or prevent the progression of myopia, attributed to paralyzing the ciliary muscle and thereby reducing the accommodative effort.[136] However, further studies demonstrated that atropine effectively slows myopia progression through non-accommodative mechanisms, redirecting the focus of

Investigative Ophthalmology & Visual Science

research toward understanding these pathways.[137] Atropine may impact myopia development through several mechanisms. For example, it modulates retinal neurotransmitters, notably inhibiting the downregulation of ZENK mRNA and to potentially restoring depleted retinal dopamine levels, both which have been linked to form deprivation myopia.[138] The possible involvement of off-target interaction with retinal GABA receptors, the serotonergic pathway, or both, can also not be ruled out.[139–141] Beyond the retina, both the choroid and sclera represent further potential sites of action, based on the presence of muscarinic receptors. Atropine also induces choroidal thickening, as with myopia control optical interventions,[140] while a direct scleral effect remains under debate.[142]

In the last 25 years, rigorous clinical trials have consistently demonstrated atropine's potential to slow myopia progression and axial elongation, with its efficacy dependent on the concentration used.[143] Although higher concentrations, notably 0.5% and 1%, significantly slow myopia, the associated chronic mydriasis and cycloplegia may result in photophobia and near vision difficulties, requiring the use of multifocal and photochromic spectacles.[144] In addition, rebound with these concentrations following treatment cessation appears to be more pronounced than found with any other myopia control modalities,[145] with the possible exception of red light therapy (see below).[146] These drawbacks prompted the exploration of lower concentrations.[147]

Two of the most influential clinical trials of atropine control for myopia were the Atropine for the Treatment of Myopia (ATOM) study[148] and its successor ATOM2.[149] The ATOM study randomized 400 children with myopia to receive either nightly unilateral 1% atropine or a placebo. The unilateral approach was chosen to avoid the potential confounding effect of multifocal spectacles. There was a pronounced slowing of axial elongation and myopia progression in the first year (see Fig. 2E)—the magnitude of which has yet to be approached by optical methods. In the second year, there was a much smaller treatment effect.

ATOM2 randomized 400 children with myopia to receive bilateral 0.5%, 0.1%, or 0.01% atropine in a 2:2:1 ratio for 2 years.[149] There was no control group, so the 2-year changes were compared to the ATOM study, although different axial length measurement technology was used and the trials were separated by approximately 6 years. A significant dose–response was observed, with lower atropine doses showing less efficacy in comparison to the untreated children from the original ATOM study, although differences among concentrations were small. Curiously, there was no slowing of axial elongation in those treated with 0.01% atropine compared to the ATOM control group, a feature of the data that has often been overlooked.[150,151] Nonetheless, the slowing of myopia progression led to a proliferation of randomized clinical trials of 0.01% atropine. Table 4 lists 21 clinical trials, all of which have been published since 2019, including 16 since 2022.[32,111,152–169] Over half of these trials were 1 year in duration, with 8 trials lasting 2 years, along with a 3-year and 5-year clinical trial. Ten of the studies were conducted in East or Southeast Asia, with four each performed in India and Europe. The median (IQR) 1-year efficacy was 0.08 mm (0.05 to 0.12) and the median 2-year efficacy was 0.12 mm (0.08 to 0.16). Thus, the year 2 efficacy is approximately half that of year 1 (see Fig. 2D).[170] As shown in Table 4, a few studies report values far outside of these ranges.[111,154,167] Two of these clinical trials report unusually high 1-year axial elongation in their control group and are thus not plotted in Figure 2D.[111,154]

The efficacy of 0.01% atropine has been questioned for some time,[171] prompting researchers to explore a broader range of concentrations. A smaller number of randomized clinical trials have evaluated atropine concentrations other than 0.01%. Nine such trials were identified and are listed in Table 5, by decreasing concentration and plotted in Figure 2E.[32,148,152,164,172–175] All studies of concentrations greater than 0.05% were conducted prior to 2019, whereas those evaluating concentrations of 0.05% and lower were published since then. As shown in Table 5, in general, efficacy decreases in a dose dependent fashion, although one study of 0.05% atropine reported the highest efficacy.[174] As seen in Figure 2E, the reduction in axial elongation in year 1 of this trial is consistent with other studies of 0.05% atropine (0.17 mm), but there is an atypical increase in efficacy in year 2 (0.33 mm).

A few other findings are worthy of comment. The largest clinical trial to date evaluated 2 concentrations, 0.01% and 0.02%.[32] Surprisingly, the children who received the lower concentration exhibited greater slowing of axial elongation (see Tables 4, 5; Figs. 2D, 2E). In contrast, the LAMP study[152] reported a dose dependent relationship for concentrations of 0.01%, 0.025%, and 0.05% that was maintained beyond the first year.[176,177] As described previously, the ATOM2 study found a slowing of myopia progression with 0.01% atropine,[149] but no slowing of axial elongation, albeit in reference to a previous control group.[148] A similar disconnect was observed in the one 5-year clinical trial of 0.01% atropine[166] that began recruitment prior to publication of the ATOM2 findings.[149] Although not shown graphically in the paper,[166] the data indicate that all of the slowing of myopia progression occurred in the first year, with a small reduction in efficacy thereafter. Conversely, there was no slowing of axial elongation until after the third year of treatment.[166]

Long-Term Efficacy, Tapering, and Rebound Management. To mitigate the risk of rebound following atropine treatment,[145,146] some authors have discussed tapering strategies, in which the concentration of atropine is gradually reduced before discontinuation,[178] but there is no published evidence for such protocols. Furthermore, rebound appears to be minimal with concentrations below 0.1%.[146]

The recently published Atropine Treatment Long-Term Assessment Study (ATLAS) study[179] represents long-term follow-up of the children previously treated in ATOM and ATOM2.[148,149] Of the original 400 ATOM participants,[148] 71 returned as adults (18%) with a mean age of 30.5 years, approximately 18 years after their previous year 3 visit.[145] There was no difference in myopia progression or axial elongation from the original baseline between the atropine-treated eyes (−2.38 D, 1.13 mm) and either the untreated contralateral eyes (−2.17 D, 1.00 mm) or the placebo-treated eyes (−2.62 D, 1.16 mm).[179] Importantly, there was relatively little difference among these groups when they were last examined at the year 3 visit.[145] After the 2 years of original treatment with 1% atropine, treated eyes showed significantly less progression and elongation than the untreated contralateral eyes and the placebo-treated eyes. After the third washout year, the differences in myopia progression had dissipated to nonsignificant values of less than 0.2 D.[145] With respect to axial elongation, there was no significant difference after 3 years between the treated eyes and the untreated contralateral eyes. In contrast, there was still a

Table 4. Characteristics and Outcomes of Randomized Clinical Trials of the Efficacy of 0.01% Atropine for Myopia Control

Author (Country)	Duration, Y	Baseline Age Range, Y	Baseline Myopia Range, D	N (Complete/Enrolled)		Myopia Progression, D			Axial Elongation, mm		
				Treated	Control	Treated	Control	Efficacy, D	Treated	Control	Efficacy, mm
Yam (Hong Kong)[152]	1	4 to 12	At least −0.50	97/110	93/111	−0.59	−0.81	**0.22**	0.36	0.41	**0.05**
Wei (China)[153]	1	6 to 12	−1.00 to −6.00	76/110	83/110	−0.49	−0.76	**0.26**	0.32	0.41	**0.09**
Zhao (China)[154]	1	5 to 14	−1.00 to −6.00	20/20	20/20	−0.34	−1.30	**0.96**	0.24	0.72	**0.48**
Hieda (Japan)[155]	2	6 to 12	−1.00 to −6.00	78/85	80/86	−1.26	−1.48	**0.22**	0.63	0.77	**0.14**
Moriche-Carretero (Spain)[156]	2	5 to 11	At least −0.50	163/171	165/168	−0.51	−0.76	**0.25**	0.20	0.37	**0.17**
Saxena (India)	1	6 to 14	−0.50 to −6.00	47/50	45/50	−0.16	−0.35	**0.19**	0.22	0.28	**0.06**
Chan (Hong Kong)[157]	1	7 to 10	−0.50 to −5.00	34/36	27/35	−0.70	−0.66	**−0.04**	0.32	0.30	**−0.02**
Lee (Australia)[158]	2	6 to 16	At least −1.50	94/104	37/49	−0.64	−0.78	**0.14**	0.34	0.38	**0.05**
Sen (India)[159]	2	5 to 15	At least −0.50	72/75	73/75	−0.30	−0.88	**0.58**	0.12	0.32	**0.20**
Chaurasia (India)[160]	1	6 to 16	−1.00 to −7.00	40/43	40/43[*]	−0.26	−0.72	**0.46**	0.20	0.36	**0.16**
Sharma (India)[161]	1	5 to 12	−0.50 to −10.00	50/NA	50/NA	−0.31	−0.80	**0.49**	0.11	0.23	**0.12**
Zadnik (United States)[32]	3	3 to 17	−0.50 to −6.00	133/164	144/165	−1.04	−1.28	**0.24**	0.68	0.81	**0.13**
Chia (Singapore)[162]	1	6 to 11	−1.00 to −6.00	25/26	26/26	−0.35	−0.60	**0.25**	0.25	0.36	**0.11**
Liang (China)[163]	1	6 to 12	−1.00 to −6.00	76/110	83/110	−0.50	−0.73	**0.23**	0.30	0.41	**0.11**
Hansen (Denmark)[164]	2	6 to 12	At least −1.00[†]	32/32	28/32	−0.92	−1.18	**0.26**	0.47	0.57	**0.10**
Repka (United States)[165]	2	5 to 12	−1.00 to −6.00	119/125	58/62	−0.82	−0.80	**−0.02**	0.44	0.45	**0.01**
Moriche-Carretero (Spain)[166]	5	Mean = 6.7	−1.00 to −4.00	NA/184	NA/177	−0.63	−0.92	**0.25**	0.26	0.49	**0.23**
Xia (China)[167]	1	6 to 16	–	82/82	82/82	−0.39	−0.75	**0.36**	0.79	1.14	**0.35**
Xu (China)[111]	2	8 to 12	−1.00 to −6.00	31/42	30/42	–	–	**—**	0.42	0.81	**0.39**
Loughman (Ireland)[168]	2	6 to 16	At least −0.50	136/167	68/83	−0.53	−0.63	**0.12**	0.33	0.40	**0.07**
Wang (China)[169]	1	6 to 12	−0.50 to −6.00[‡]	171/200	76/100	−0.51	−0.75	**0.24**	0.31	0.42	**0.11**

NA, not available.
The values for myopia progression, axial elongation, and efficacy are for the entire study duration.
[*] Contralateral control.
[†] At least −2.00 in 9- to 12-year-old children.
[‡] Intermittent exotropia.

Table 5. Characteristics and Outcomes of Randomized Clinical Trials of the Efficacy of Atropine at Concentrations of 0.02% or Greater for Myopia Control

Author (Country)	%	Duration, Y	Baseline Age Range, Y	Baseline Myopia Range, D	N (Complete/Enrolled)		Myopia Progression, (D)		Efficacy, D	Axial Elongation, mm		Efficacy, mm
					Treated	Control	Treated	Control		Treated	Control	
Chua (Singapore)[148]	1%	2	6 to 12	−1.00 to −6.00	166/200	190/200	−0.28	−1.20	**0.92**	−0.02	0.38	**0.40**
Yi (China)[172]	1%	1	7 to 12	−0.50 to −2.00	68/70	64/70	0.32	−0.85	**1.17**	−0.03	0.32	**0.35**
Shih (Taiwan)[173]	0.5%	1.5	6 to 13	Mean = −3.37	66/76	61/76	−0.42	−1.40	**0.98**	0.22	0.59	**0.37**
Yam (Hong Kong)[152]	0.05%	1	4 to 12	At least −0.50	102/109	93/111	−0.27	−0.81	**0.54**	0.29	0.41	**0.12**
Zhu (China)[174]	0.05%	2	7 to 12	−1.00 to −6.00	72/88	70/88	−0.46	−1.72	**1.26**	0.26	0.76	**0.50**
Zhang (China)[175]	0.05%	2	6 to 12	−1.00 to −6.00	212/213	209/211	−0.31	−0.92	**0.61**	0.23	0.42	**0.19**
Yam (Hong Kong)[152]	0.025%	1	4 to 12	At least −0.50	91/108	93/111	−0.46	−0.81	**0.35**	0.20	0.41	**0.21**
Zadnik (United States)[32]	0.02%	3	3 to 17	−0.50 to −6.00	212/247	144/165	−1.18	−1.28	**0.10**	0.73	0.81	**0.08**
Hansen (Denmark)[164]	0.1% then 0.01%	2	6 to 12	At least −1.00*	32/33	28/32	−1.06	−1.18	**0.12**	0.49	0.57	**0.08**

The values for myopia progression, axial elongation, and efficacy are for the entire study duration.
*At least −2.00 in 9- to 12-year-old children.

significant difference of 0.23 mm remained between the treated eyes and the placebo eyes. These differences dissipated to zero over the subsequent 18 years. This is, perhaps, the most interesting feature of the long-term data and the dramatic post-treatment acceleration seen in the third, untreated year may have continued in subsequent years. Thus, the unilateral treatment in ATOM may have exaggerated these pronounced rebound effects. Similar changes have been observed in other unilateral treatment studies.[180]

Of the original 400 original ATOM2 participants, 158 returned as adults (39%) with a mean age of 24.5 years.[179] Of these, 148 were included in the analysis, comprising 28, 61, and 59 individuals from the original 0.01%, 0.1%, and 0.05% atropine treatment groups, respectively. At the adult follow-up visit, there was similar myopia progression and axial elongation since the original baseline among the 0.01% group (−1.90 D, 1.06 mm), the 0.1% group (−2.32 D, 1.22 mm), and the 0.5% group (−2.57 D, 1.27 mm).[179] These small, nonsignificant differences were also present at the end of the original 5-year study. Between the age of 14 and 24 years, all groups progressed by approximately only 0.50 D, lower than anticipated. One possible explanation is that parents, having had their children enrolled in a clinical trial, sought out myopia control options. The absence of a control group and the retreatment of some participants limits the ramifications of the follow-up of the ATOM2 participants. Other limitations of the ATLAS study are discussed elsewhere.[181]

Summary. In summary, atropine is an important tool for managing myopia, with the 0.05% concentration emerging as the most effective among lower dosages. Concentration atropine shows greater efficacy, in a dose-dependent fashion, although long-term rebound and methodological concerns in some studies warrant caution. Nonetheless, the long-term efficacy of atropine is still uncertain.[177,179]

7-Methylxanthine and Caffeine

Oral 7-methylxanthine (7-mx), a nonselective adenosine antagonist, has been licensed for myopia control in Denmark since 2009, following a randomized clinical trial,[182] however, the 1-year treatment effect was both relatively small and statistically nonsignificant (0.03 mm and 0.07 D).

Interestingly, topical caffeine, another xanthine derivative, was found to be as effective as oral 7-mx in inhibiting the development of myopia in a primate defocus model of myopia.[183] Caffeine both slowed vitreous chamber elongation and increased choroidal thickness. These results along with data from an earlier human study[184] demonstrated that topical caffeine ophthalmic solution is safe and well-tolerated, supporting the rationale for its investigation as a myopia control treatment in children. Nonetheless, a 12 month clinical trial involving 2% caffeine eye drops and Vietnamese children with myopia failed to show any positive impact on myopia progression,[185] although interestingly, when combined with topical atropine alone, caffeine reduced the mydriatic effect of 0.02% atropine, as measured under photopic conditions (0.8 mm with the combination treatment compared to 1.2 mm in the atropine alone), without affecting the efficacy of atropine.[185]

Hypotensive Eye Drops

An early randomized controlled trial included three treatment groups: a single vision control group (n = 49), a

bifocal spectacles group (n = 51), and a timolol group (n = 45).[186] The mean age of participants was approximately 11 years in all groups. The timolol group received 0.25% timolol maleate administered twice daily. Children were monitored for 2 years, with follow-up examinations conducted for an additional year thereafter. Although timolol significantly reduced IOP by approximately 3 mm Hg, with the greatest effect observed in those with initially high IOP, the 2-year myopia progression in the timolol group was no different compared than the control and bifocal groups (−0.59 D per year in the timolol group, −0.57 D per year in the control group, and −0.48 D in the bifocal lens group). Interestingly, higher myopia progression rates were linked to higher IOP in the control group, with this relationship being statistically significant among female patients, and a similar but nonsignificant trend observed in male patients.

The risks of significant side effects such as bronchospasm in susceptible individuals necessitates caution when using timolol.[187] In the above trial, side effects led to the timolol treatment being discontinued in six children. For five of the children, symptoms were ocular in nature, involving stinging, itching, and foreign body sensations, possibly related to the formulation rather than the timolol itself.[186]

Whereas other ocular hypotensive drugs have been assessed in nonrandomized clinical trials,[188] there is insufficient evidence to support the hypothesis that reducing IOP can slow myopia progression. Some IOP-related eye drops may be candidates for myopia control, but their evaluation has been limited to animal experiments.[189–191] Ocular hypotensive drugs have also been proposed as a therapy for adults with myopia, although data from clinical trials have yet to be reported.[192,193]

Combination Therapies

Combining optical and pharmacological treatments have the potential to offer additive or synergistic effects. To date, robust evidence is limited to the combination of overnight orthokeratology and 0.01% atropine.

Atropine and Orthokeratology. The enhanced efficacy of combining orthokeratology lenses with 0.01% atropine has been confirmed in multiple randomized clinical trials (Table 6).[111,194–197] Two-year trials have found that axial elongation in the combination group was significantly lower than in the orthokeratology monotherapy group (median = 0.12 mm),[111,194,196] whereas a 2-year randomized crossover trial demonstrated that combination therapy significantly slowed axial elongation in both the first and second years, by 0.10 mm and 0.09 mm, respectively.[195] Interestingly, the median 2-year benefit (0.12 mm) of adding 0.01% atropine to orthokeratology (see Table 6) is the same as the median 2-year efficacy of 0.01% atropine monotherapy (see Table 4).

Two of the three studies that continued the same treatments through 2 years found that the impact of atropine decreased over time. One showed a 0.09 mm benefit of the atropine in the first year, but only 0.02 mm in the second year.[194] A second found 0.11 mm and 0.06 mm slower elongation with atropine in the first and second years, respectively.[196] In contrast, a third study found a slightly greater benefit of atropine in the second year.[111] The impact of adding atropine to orthokeratology may be greater at lower

Table 6. Characteristics and Outcomes of Randomized Clinical Trials of the Efficacy of Combining Orthokeratology and 0.01% Atropine for Myopia Control Compared With Orthokeratology Alone

Author (Country)	Duration, Y	Baseline Age Range, Y	Baseline Myopia Range, D	N (Complete/Enrolled)		Axial Elongation, mm		Additional Efficacy, mm
				Combination	Orthokeratology	Combination	Orthokeratology	
Kinoshita (Japan)[194]	2	8 to 12	−1.00 to −6.00	38/43	35/37	0.29	0.40	**0.11**
Yu (China)[197]	1	8 to 12	−1.00 to −4.00	27/30	26/30	0.10	0.20	**0.10**
Tan (China)[196]	2	6 to 11	−1.00 to −4.00	34/48	35/48	0.17	0.34	**0.17**
Xu (China)[111]	2	8 to 12	−1.00 to −6.00	34/42	31/42	0.31	0.43	**0.12**
Li (China)[195]	1*	8 to 12	−1.00 to −4.00	26/30	26/30	0.10	0.20	**0.10**

Only axial length was measured and reported. The values for axial elongation and efficacy are for the entire study duration.
*Two-year crossover study. Results from first year presented.

levels of myopia. Consistent with previous studies,[112,114,115] one combination study found that axial elongation in their orthokeratology group was significantly lower in patients with higher myopia, but that no such relationship existed for the combination group.[194]

The improved efficacy observed with combination treatment is speculated to be due to the mydriatic effect of atropine enhancing the efficacy of orthokeratology lenses,[196,198] and the concurrent alteration to peripheral aberrations.[199] In recent years, several studies have highlighted the pupil diameter as an important factor influencing the effectiveness of orthokeratology in controlling myopia. A 2-year study found that axial elongation was lower in orthokeratology wearers with larger baseline pupil diameters compared with those with smaller pupils, but no relation was found in the spectacle wearers.[198]

Atropine and Other Optical Treatments. No randomized clinical trials have evaluated atropine in combination with other optical myopia control therapies, although retrospective and nonrandomized prospective studies have reported largely encouraging results for 0.01% atropine combined with myopia control soft contact lenses[200,201] and myopia control spectacles.[202–204] Of note was a 3-year prospective study of 46 children who wore multifocal soft contact lenses and administered 0.01% atropine nightly. The cohort was compared to an age-matched group from the BLINK Study who wore the same lenses.[87] There was no significant difference in myopia progression between the two groups (0.03 D), although the difference in axial elongation bordered on significance (0.08 mm, $P = 0.05$).

Summary

Randomized clinical trials have shown that combination therapy slows axial elongation more effectively than orthokeratology alone.[111,194–196] For individuals with suboptimal myopia control results with monotherapy, combination therapy can be considered.[205] Myopia progression and axial elongation can be influenced by multiple factors, including age, severity of myopia, parental myopia, and treatment duration.[111,194,206–208] In clinical trials that have investigated monotherapy, efficacy is typically adjusted for these factors. Future studies investigating efficacy of combination treatment on myopia should consider baseline factors to better understand the additive effect of combining treatment strategies.

To date, the only randomized clinical trials have evaluated the combination of orthokeratology and 0.01% atropine. Future studies should rigorously explore the combination of atropine other optical therapies. Likewise, trials of combination therapy have only evaluated 0.01% atropine, which has modest efficacy. Thus, future work should explore higher concentrations.

Light-Based Therapies

Several light-based therapies have been proposed for slowing myopia progression, including red light, blue light, and ultraviolet light. The evidence on how various characteristics of light may affect refractive development via image- and non-image-forming pathways is reviewed comprehensively in a companion paper.[209]

Red Light Therapy

Red light therapy has been used for over 3 decades in China as an alternative treatment for amblyopia, although evidence of its efficacy is limited.[210,211] It has recently been repurposed for myopia control. Support for its use for myopia control comes from the finding that red light rearing slows the development of experimental myopia in rhesus monkeys and tree shrews.[212,213] Published studies evaluating the efficacy of red light therapy for myopia control have generally used desktop devices used at home, with typical treatment schedules of 3 minutes of exposure twice a day, separated by a minimum of 4 hours, for 5 to 7 days per week. Most of the devices used in these studies incorporated a red laser light (635−650 nm) stimulating a retinal area of approximately 0.075 mm^2,[214] with differences in device power and stimulus intensity representing additional variables. Red light therapy gained generally wide acceptance in China as a myopia control therapy, with recent adoption and approval in some other countries, yet there are also growing concerns over its safety (see below).

Photobiomodulation as a Possible Mechanism of Action for Red Light Therapy Effect. In a variety of non-ocular tissues and cell types, exposure to long-wavelength light, as used in photobiomodulation (PBM), has been shown to improve mitochondrial function by increasing adenosine triphosphate production and reducing reactive oxygen species.[215,216] Nonetheless, the mechanism and site of action of red light therapy remain unclear. There is evidence linking PBM with increased levels and availability of nitric oxide in non-ocular tissues,[217,218] and nitric oxide has also been shown to play key roles in regulating eye growth[219] and choroidal thickness modulation.[220] Assuming that such changes are linked to increased choroidal blood flow,[221,222] they would serve to reduce scleral hypoxia, which may be linked to the development and progression of myopia.[221,222] Furthermore, increased cell proliferation and collagen synthesis, as observed in cultured human fibroblasts exposed to PBM,[223] could plausibly contribute to slowing myopia progression; this assumes that scleral fibroblasts respond similarly to red light therapy, although increased transdifferentiation of cultured fibroblasts into myofibroblasts, as observed with PBM,[224] is in the opposite direction to that expected for slowed scleral remodeling, with increases in myofibroblasts reported in the myopic sclera[225–227] rather than the reverse.[221,228]

Efficacy. Details of published randomized controlled trials of red light therapy as a myopia-control therapy are summarized in Table 7.[210,229–234] As seen in Figure 2F, the 1-year efficacy of red light therapy is greater than any other treatment. The median (IQR) reduction in axial elongation is 0.40 mm (0.38 to 0.42 mm) and is remarkably consistent across studies using a range of devices. Red light therapy has also been shown to outperform low-dose atropine[235] and orthokeratology.[236] Nonetheless, few trials meet the previously published International Myopia Institute (IMI) recommendations for minimum study duration and washout.[237] One study reported incomplete 2-year outcomes, and these are plotted in Figure 2F. Furthermore, only one study used a sham red light therapy device as control,[238] hence, most trials have been either single-masked or unmasked.[238] Moreover, to date, all trials have been conducted in China.

Some, although not all, red light therapy devices include systems for monitoring treatment compliance, with one such system being a linked online management system that allows

Investigative Ophthalmology & Visual Science

Table 7. Characteristics and Outcomes of Randomized Clinical Trials of the Efficacy of Red Light Therapy for Myopia Control

Author	Duration, Y	Device	Baseline Age Range, Y	Baseline Myopia Range, D	N (Complete/Enrolled)		Myopia Progression, D		Efficacy, D	Axial Elongation, mm		Efficacy, mm
					Treated	Control	Treated	Control		Treated	Control	
Jiang[210]	1	Eyerising	8 to 13	−1.00 to −5.00	111/119	114/145	−0.20	−0.79	**0.59**	0.13	0.38	**0.25**
Zhou[229]	1	LD-A	8 to 12	−0.50 to −8.00	20/25	15/25	0.28	−0.97	**1.25**	−0.02	0.48	**0.50**
Chen[230]	1	Longda	6 to 13	−0.75 to −6.00	46/51	40/51	0.05	−0.64	**0.69**	0.01	0.39	**0.38**
Liu[231]	1	Eyerising	8 to 13	−1.00 to −6.00	32/40	36/40	−0.08	−0.86	**0.78**	0.03	0.41	**0.38**
Cao[232]	1	Hunan EnVan	6 to 12	Up to −6.00	??/112	??/112	0.26	−0.71	**0.97**	−0.12	0.27	**0.39**
Xu[233]	1	Eyerising	6 to 16	At least −4.00	96/97	92/95	0.10	−0.75	**0.86**	−0.06	0.34	**0.41**
Liu[234]	1	Eyerising	7 to 12	At least −6.00	130/132	68/70	0.18	−0.80	**0.98**	−0.11	0.32	**0.43**

All the trials were conducted in China.

the number of therapy sessions completed each day to be monitored,[235] as well as the number and frequency of treatments to be controlled. Interestingly, one study[239] found that compliance was not significantly correlated with 1-year axial elongation.

Assessments of Safety. Given the young age of the patients being repeatedly exposed to a laser-based device, there are legitimate safety concerns. Despite regular assertions that red light therapy is safe,[231,238] decreases in foveal cone density have been documented[214] along with a report of a 12-year-old patient experiencing bilateral vision loss after 5 months of red light therapy.[240] Optical coherence tomography (OCT) imaging in this case revealed bilateral foveal photoreceptor and retinal pigment epithelium damage, with visual acuities decreased from 20/20 to 20/30 in both eyes. The adequacy of protocols for detecting adverse events in clinical studies of red light warrants scrutiny, often assessed via questionnaires, combined with the measurement of high contrast visual acuity, with some, but not all, studies also using OCT imaging. The output of red light devices may be directly measured and compared against published safety standards. One such study[241] found that two commonly available devices approached or exceeded the maximum permissible exposure based on American National Standards Institute (ANSI) standards.[242] It is also worth noting that such standards are primarily designed for intermittent retinal exposure and may not adequately account for therapeutic uses in which patients are required to fixate the laser source. The China National Medical Products Administration recently introduced significant regulatory changes affecting the manufacture and sale of red light devices,[211] with all now required to meet laser class III certification, with extensive safety studies, including on nonhuman primates.[243] Currently, none of the available red light devices meet the class III certification requirements.

Summary. Red light therapy significantly slows myopia progression, but there are safety concerns and treatment cessation is associated with significant rebound (see below).[230,244]

Optic Nerve Head Stimulation With Blue Light for Myopia Control

Intrinsically Photosensitive Retinal Ganglion Cells, Melanopsin, and Rationale for Photic Stimulation of the Optic Nerve Head for Myopia Control. Although the optic nerve head (ONH) is void of classical photoreceptors, that is, rods and cones, it does relay the axons of retinal ganglion cells to higher visual processing centers in the brain. Of relevance to the targeting of the optic nerve head for light stimulation is the presence in the inner retina of intrinsically photosensitive retinal ganglion cells (ipRGCs), which express the photopigment melanopsin,[245,246] thereby conferring them with an intrinsic sensitivity to light, specifically in the short wavelength (blue) region of the visible spectrum ($\lambda_{max} \sim 480$ nm).[247–249] Importantly, melanopsin is not confined to the somas of ipRGCs but is also present in their dendrites and axons,[249] thereby in the latter case, conferring light sensitivity on the ONH. Whereas the roles of ipRGCs are yet to be fully understood, they are known to drive a variety of non-image-forming responses to light, including circadian entrainment, melatonin suppression,[250,251] and the pupil-

lary light reflex,[248,252] with other studies showing effects on vision, including enhanced contrast sensitivity and alterations in brightness perception following blue light stimulation of the blind spot.[253,254] See a companion paper for a review.[209]

In relation to a potential role of ipRGCs and melanopsin in emmetropization and refractive error development, there are accumulating experimental data, mostly from studies in mice, although the underlying mechanism or mechanisms are unclear.[255,256] For example, ipRGC ablation was found to reduce axial elongation and myopic shift in mice,[256] and mice lacking functional ipRGCs showed increased susceptibility to myopia.[255] The potential impact of ipRGCs on refractive error development may reflect their modulatory influence via dopaminergic amacrine cells on retinal dopamine, a neurotransmitter involved in ocular growth modulation.[257,258] Although light regulation of dopamine can also occur independently of melanopsin,[259] a study in rabbits reported significantly increased dopamine concentrations in the aqueous humor and vitreous body after stimulation of the ONH with blue light (470 nm), likely due to enhanced dopamine release in the retina.[260] Nonetheless, the possibility of light scattering by the ONH could not be ruled out and no evidence supporting melanopsin expression in the ONH was provided in this study.

The effect of direct stimulation of the ONH with blue light on myopia development or progression has not been directly examined in any myopia animal model to date. Whereas one clinical trial (NCT04967287; $n = 124$) of ONH stimulation with blue light for myopia control was completed at the end of 2024, results had not been published at the time this review was submitted.

Gaps in Knowledge and Future Directions. In addition to the issues related to the descriptions of the stimulus used in these studies, there are issues related to understanding how scatter at or beyond the ONH may affect the responses of the retina. In addition, the rationale for choosing a peak wavelength that lies between the peak sensitivities of the human cyanopic (S cone) and melanopic (ipRGC) pigments, as in the cited studies,[261,262] is not clear. Additionally, it is unknown how differences in axial length, pupil sizes,[263] and crystalline lens characteristics, all of which are known to be altered in myopic eyes,[264] affect the intensity of light reaching the ONH. For example, longer eyes and radially stretched lenses, as in myopic eyes, and larger pupils and more transparent media, as in children[263,265,266] may be expected to result in larger areas, intensity of stimulation, or both.

In the single ongoing clinical trial, there are no details on the stimulus conditions given except that children in the treatment arm should use the device for direct stimulation of the ONH with short-wavelength light twice daily (at home) for 12 months. In future clinical trials, two key aspects warrant consideration and reporting. First, the safety of using "invisible" blue light stimulation must be ensured. This requires strict adherence to photobiological safety standards and close monitoring for any potential photochemical damage to the ONH or other retinal regions. Second, given that blue light is highly effective in phase-shifting the circadian timing system and suppressing melatonin secretion,[250,267] the timing of the intervention must be given careful consideration, with evening interventions avoided, if disruption of the normal melatonin rhythm is to be avoided.

Ultraviolet Light for Myopia Control

Reduced exposure to ultraviolet light (UV-A: 360–400 nm), which is deficient in our indoor environments, has been proposed as a potential myopiagenic factor, with studies in animal models, and retrospective observations in humans, suggesting that UV-A light exposure may be used a therapy to inhibit axial elongation.[268,269] At the molecular level, UV-A light exposure has been linked with the upregulation of early growth response-1 (EGR-1), a gene linked to myopia suppression,[268] with experiments in the retina-specific Opn5 knockout mice model further suggesting the involvement of retinal opsin 5 (Neuropsin or OPN5).[269]

To date, the effect of UV-A therapy on myopia progression has been investigated in two independent clinical studies, using UV-A-transmitting spectacles[270] and UV-A-emitting spectacle frames.[271] Notably, no significant differences in axial elongation or myopia progression between intervention and control groups were found in either study. Implementation challenges included high loss-to-follow-up rates (19%), due to unspecified family issues, as well as spectacle frame breakages, with one of the two trials being suspended for frame redesign. These data suggest a need for improved implementation strategies for this UV-A therapy.[272] Although compliance tracking methods were described, adherence rates were not reported. In relation to potential adverse effects, exposure to UV-radiation in the 370 to 400 nm range is known to cause damage to both the skin and the crystalline lens.[273–276] Nonetheless, neither of the two studies reported any adverse effects linked to the UV-A therapy, although notably overall daily UV-A light exposure was very limited, with enrolled children spending less than 1 hours outdoors per day.

Modifying and Monitoring Behavior

Behavioral Approaches to Myopia Control

Behavioral and environmental influences are widely recognized as key drivers of myopia prevalence.[277] The rapid rise in myopia prevalence coincides with the shift to modern, indoors-centric lifestyles. High levels of educational engagement, extended years of schooling, high academic pressures, and intense near visual activities have become defining features of contemporary life. Technology-driven distractions have also emerged, competing with traditional outdoor activities for leisure time.[278] Taken together, children today live in an increasingly myopiagenic world and adopt lifestyles that significantly heighten their risk of developing myopia.[279,280]

The dominance of these environmental and lifestyle factors as driving forces in the myopia pandemic parallel those implicated in other chronic diseases, where interventions targeting behavior change have proven effective.[281] This suggests that similar strategies could be adapted to address the increasing prevalence of myopia. The most consistently observed protective factor against myopia onset is increased outdoor time, which provides protection through multiple interrelated factors that are largely absent in indoor environments. Natural daylight provides high light intensity and a broad spectral composition,[282,283] and outdoor environments offer rich visuo-spatial stimuli with high spatial frequencies and reduced accommodative demands.[284,285] Conversely, education, with increased near work, is associated with a higher risk of myopia,[286,287]

Investigative Ophthalmology & Visual Science

although the available evidence remains inconsistent regarding the impact of different types of near work[286] and the underlying mechanisms potentially driving this near work effect.[288] A framework for tackling the myopia epidemic has previously been proposed, which emphasized the importance of targeting these two factors, with increased outdoor time highlighted as an immediate priority, and educational reform to reduce myopiagenic pressures as a longer term focus.[289]

Taiwan and Singapore have undertaken some of the most comprehensive public health strategies aimed at myopia prevention and control. These efforts include promoting outdoor time during school hours, regulating near work and screen usage, improving classroom environments, and conducting educational campaigns. For example, Taiwan's "Tien Tien 120" program, mandating 2 hours of daily outdoor activity,[290] and Singapore's National Myopia Prevention Programme, which integrates public education and school-based initiatives,[291] have demonstrated measurable reductions in myopia incidence and prevalence. Similarly, China and Hong Kong have developed initiatives targeting outdoor exposure, classroom design, academic burdens, and parental awareness. It is clear that school-based initiatives to increase outdoor time can help prevent myopia,[292,293] and possibly slow its progression,[293–295] with the greatest benefits observed in children who have not yet developed myopia.[296–298]

Smart Devices for Monitoring Myopia Risk Factors and Behavioral Interventions

Smart devices have recently been introduced to support monitoring of myopia-related environmental factors. They are generally categorized as wrist-worn devices, head-mounted devices, and software or Apps for digital smart devices. Concurrently, novel biomarkers have also been developed to quantify outdoor exposure. The use of these tools has largely been confined to clinical trials and research studies, and do not form part of mainstream clinical practice.

Wrist-Wearable Devices. The Actiwatch, a device designed to measure light intensity, light spectrum, and physical activity, was the first wrist-worn device applied to estimate outdoor time.[299] Based on this, the FitSight was developed, a wrist-wearable device, to monitor outdoor time, by measuring the ambient light intensity.[300,301] Another wrist-worn device, the Mumu, has been developed, which records light intensity, UV intensity, and the geographic coordinates.[301] By combining all of these data, the Mumu provides a more nuanced estimation of outdoor time. Although the Actiwatch is no longer commercially available, there are a number of other wrist-worn light sensing devices that are available, for example, Geneactive (https://activinsights.com/digital-health-technologies/professional-wearables/geneactiv/) and ActLumus (https://condorinst.com/en/actlumus-actigraph-nova/).

Head-Mounted Devices. Head-mounted devices can solely record viewing distance, or measure both viewing distance and ambient light intensity. For the former category, ultrasonic technology mounted on a headband has been used,[302] whereas the RangeLife has similar functionality, but is smaller in size.[303] For the latter category, primary devices include Clouclip and Vivior, both of which are mounted to the temples of the spectacle frames.[304,305] The Clouclip has been used to monitor spectacle wearing time in at least one clinical trial.[306] Recently, a smart spectacles prototype has been developed, that is able to monitor viewing distance, light intensity, and spectral composition.[307] The Visual Environment Evaluation Tool (VEET), a similar device developed by Meta Reality Research Labs, was also developed (https://projectveet.com). Other head-mounted devices allow eye and viewing distance tracking.[308,309]

Device-Based Software Applications. Over the last 2 decades, computers and smart phones have become a routine part of daily life, with digital devices integrated into schooling in many countries. The need for objective measures of screen time has been highlighted.[310] In this context, a smartphone application (Myopia app; Innovattic) was developed to objectively measure smartphone use and face-to-screen distance.[311]

Biomarkers for Behavior. In addition to the aforementioned smart devices, some researchers have explored the use of biomarkers to objectively assess outdoor exposure time. Conjunctival ultraviolet autofluorescence (CUVAF) agrees strongly with survey-based assessment of time spent outdoors and that CUVAF is negatively associated with myopia in adults.[312,313] Additionally, numerous studies indicate that the blood vitamin D status is a surrogate marker for time outdoors and that blood 25(OH)D level may be a confounder rather than an intermediary between time outdoors and myopia.[314]

Gaps in Knowledge and Future Directions

Smart devices present exciting opportunities to revolutionize preventive and behavioral aspects of myopia management by enabling real-time monitoring, advanced data analysis, and behavior modification. Future devices could offer more precise tracking of risk factor exposure, such as eye-level light intensity, which may provide deeper insights into how outdoor time protects against myopia.[298,315] With improvements in wearable technology, these devices could capture critical environmental and behavioral data, allowing for a more personalized approach to myopia prevention and treatment.

Perhaps the most transformative opportunity lies in real-time intervention capabilities. A wearable device that provides real-time alerts for prolonged near work, close proximity, head tilt, or inadequate lighting has been leveraged in a randomized trial of Chinese children.[306] With continued innovation and interdisciplinary collaboration, the technology has the potential to become an integral tool in myopia prevention, progression monitoring, and personalized treatment strategies.

Interventions to Delay Myopia Onset

There is a well-documented relationship between the age of myopia onset in childhood and the magnitude of myopia reached in adulthood, with earlier age of onset associated with higher myopia in adulthood.[316–328] For example, the risk of high myopia (–6 D or worse) in adulthood in a Chinese cohort increased from less than 5% when myopia onset at 12 years or older, to more than 50% when myopia was present at 7 or 8 years of age.[316] It has been determined that for each year of delay in myopia onset, a saving of –0.75 D or more in the final magnitude of myopia recorded could be attained.[328] A more modest impact was determined from non-East Asian data. Nonetheless, final myopia magni-

tude may be constrained more effectively through delaying onset than through slowing myopia once it is manifest by the myopia management interventions currently on offer.[328] Hence, it is important to identify effective prophylactic interventions and implement them in emmetropic children who are at risk of developing myopia.

Several studies to date have explored the potential of prophylactic interventions applied to non-myopic children to prevent or delay myopia onset, including pharmacological, optical, and light-based and behavioral approaches.

Light-Based and Behavioral Interventions

The most well-established of the light-based and behavioral approaches is the value of time spent outdoors as an effective method to delay myopia onset, although the mechanisms are not entirely understood,[277,294,295,298,329,330] but are discussed in a companion review.[209] A number of randomized controlled trials of interventions to increase daily outdoor time in schools have shown that such interventions significantly reduce incident myopia (up to a 9% absolute reduction in myopia incidence compared to healthy controls),[277,295,298,329–331] with more recent studies also reporting significant associations between the protective effects of outdoor time on myopia onset and the duration and intensity of objectively measured light exposure.[294,298] The effectiveness of outdoor interventions in significantly reducing myopia onset has also been demonstrated in selected populations of "pre-myopic" (spherical equivalent >-0.50 D and $\leq+0.75$ D) children.[332]

Recent studies have explored whether parental education delivered via social media[333] or text messaging,[334] aiming to increase their children's outdoor time[334] and to limit digital screen time,[333] has an impact upon myopia development. These interventions impacted children's behaviors, with some evidence of increased outdoor time, particularly on weekends,[334] and small reductions in myopia incidence and myopic shifts in refraction.[333,334]

Other behavioral interventions have utilized wearable devices to provide real-time monitoring of near working behaviors and light exposure. In a randomized trial of 413 Chinese children aged 7 to 11 years, participants wore a head-mounted device that objectively measured near working distance, ambient light exposure, and head posture.[306] Children were randomized to one of three groups. One group received real-time vibration reminders from the device if engaged in continuous near work (working distance of 10–60 cm) for 20 minutes or more, near work closer than 33 cm for 15 seconds or more, near work with a head tilt of 10 degrees or more, or near work under ambient illumination of less than 300 lux. The other group received the same real-time device vibration reminders, along with feedback from the device (and positive reinforcement from their teacher, school, and parents) regarding their daily near work behaviors, and the third group was a control group with no reminders or feedback. At the end of the 1-year intervention period, there was a significantly lower incidence of myopia (13% and 22% vs. 28%,) and myopic shift in refraction (0.52 D and 0.59 D vs. 0.73 D) in the 2 intervention groups compared to the control group. Participants were followed for a further year with no intervention, after which there was no significant difference in myopia incidence among the three groups. Analyses of near-work behaviors revealed a lower duration of near work, longer working distance, and higher light intensity associated with the intervention, which returned to baseline levels once the intervention ceased. This study highlights the potential for behavioral interventions to impact myopia development, but emphasizes the need for a sustained intervention to maintain effects.

An alternative approach to increasing time spent outdoors, has been to alter the light exposure profile of indoor settings, particularly in schools. Researchers suspended T5 fluorescent lamps with white louvres in the intervention classrooms to achieve consistently greater luminance than originally present.[292] Over the subsequent year, significantly fewer children became myopic in these intervention classrooms with higher ambient light levels than in the traditionally lit rooms (4% vs. 10%). The corresponding axial elongation in the 2 groups was 0.13 and 0.18 mm. It is worth noting that the luminance in the original classrooms was 74 lux, significantly lower than the 500 lux advocated for general classroom activities in European lighting standards.[335] The study's suspended lighting intervention increased the ambient light levels to an average of 558 lux, bringing the illumination in line with European standards.

The value of artificially synthesized natural light, whose spectrum aligns more closely to the natural spectrum of outdoor light than traditional indoor light sources, on myopia incidence over 3 years in Chinese children aged 7 to 9 years has also been explored.[336] Compared with classrooms whose overall ambient luminance was similar (standard classroom 491 lux; artificially synthesized natural light classroom 512 lux), a significantly lower incidence of myopia was observed, albeit based on non-cycloplegic refraction and visual acuity (26% vs. 21%). Three-year axial elongation was also significantly lower in the artificially synthesized natural light group (0.72 mm) than in the control group (0.77 mm). It is unclear whether these outcomes are replicable in other cohorts or indeed if the modest reduction in 3-year incidence could be enhanced with modification of the artificially synthesized natural light lamps.

Other researchers have introduced alternative modifications to classroom designs as methods to potentially prevent myopia, including a glass-constructed "bright classroom" that aims to allow exposure to greater levels of natural light in the classroom,[337] and a classroom with custom made wallpaper and desk coverings with images of outdoor scenes to try to replicate the spatial frequency content of outdoor environments.[338] Although these modified classrooms have been reported to be generally well accepted by teachers and students, their effects on myopia development have yet to be reported.[337,338]

The safe and relatively straightforward procedure of exchanging traditional lamps and lighting design to improve or modify the classroom light profile is an attractive option for large-scale implementation in populations at high risk of myopia and further research is warranted in this area. Whereas classroom-based lighting solutions show relatively modest reductions in incidence of myopia compared with studies investigating the application of other prophylactic anti-myopia interventions, this may be at least in part attributed to the less selective nature of the inclusion criteria in classroom-based lighting trials. The participants in these trials were not selected for increased risk of myopia other than the risk conveyed by their ethnicity and environment.

The influence of red light therapy (described above) on myopia onset was evaluated in 278 Chinese children aged 6 to 11 years with refractive errors from -0.50 D to $+0.50$ D inclusive and at least one myopic parent.[339] Children were

randomized to either two 3-minute sessions of red light therapy (EyeRising device) per day 5 days each week or no treatment. The 1-year incidence of myopia in the red light group (49/120, 41%) was significantly lower than in the control group (68/111, 61%). Furthermore, axial elongation and myopic shift were lower in the red light group than in the control group: 0.30 vs. 0.47 mm and −0.35 vs. −0.76 D. These differences were greater in children whose baseline refractive error was between 0.00 and +0.50 D than those between 0.00 and −0.50 D. A second, smaller trial also evaluated the impact of the same treatment protocol and device in a group enriched for their potential to become myopic.[231] Children aged 8 to 13 years with refractive errors ≤+0.75 to >−0.50 D and at least one parent with myopia were assigned to either receive red light therapy or not. The 1-year incidence of myopia was higher (7/36, 19%) in the control group than in the red light group (1/40, 2.5%). Axial elongation and myopic shift were again lower in the red light group than in the control group: 0.15 vs. 0.29 mm and −0.18 vs. −0.52 D. Longer term follow-up of non-myopic children would be helpful to determine whether delayed myopia onset results in lower myopia and if growth accelerates after cessation of treatment, thereby negating benefits of early intervention, particularly given evidence of marked rebound in myopic children.[146,244]

Pharmacological Interventions. Several authors have evaluated the efficacy of low dose atropine in delaying myopia onset.[340–343] The largest and longest trial to date compared the incidence of myopia after 2 years in children aged 4 to 9 years with cycloplegic refractive errors from 0.00 to +1.00 D and at least one myopic parent.[341] The children were prescribed nightly administration of 0.05% atropine, 0.01% atropine, or a placebo eye drop and myopia defined as −0.50 D or worse in either eye. The results showed that children receiving 0.05% atropine were significantly less likely to become myopic (28.4%, 33/116) than those in the placebo (53.0%, 61/115) or 0.01% atropine (45.9%, 56/122) groups. The 2-year axial elongation was 0.48 mm in the 0.05% atropine group, 0.63 mm in the 0.01% atropine group, and 0.70 mm in the placebo group. The corresponding changes in refractive error were −0.46 D, −0.84 D, and −1.01 D, respectively. Low dose atropine as a preventive measure to delay myopia onset appears to be relatively well tolerated by children at risk for myopia,[340–343] with a low level of adverse events.[344] Photophobia and blurred near vision are the most commonly reported adverse effects,[345] but it is currently unclear, as with the other delaying strategies discussed, whether delaying myopia onset with low dose atropine results in lower long-term magnitudes of myopia.

Optical Interventions. Non-myopic children who are not habitually wearing an optical correction and do not gain significant visual benefit from contact lenses or spectacles, may be reluctant to wear their correction. Despite these potential challenges, a randomized controlled trial examined the impact of HAL spectacles on refractive error and eye growth in Chinese children aged 6 to 10 years, with low levels of hyperopia (0.00 to +2.00 D).[346] No significant differences in the 1-year change in refraction or axial length were found between the treatment and control groups.

Gaps in Knowledge and Future Directions. It is relatively straightforward for increased outdoor time to be safely initiated from a young age, whereas optical and pharmacological treatments may need to identify at risk children. Algorithms incorporating age, refractive status, and other demographic variables to identify children at risk of myopia onset have been developed and will continue to be refined.[347–351] Outdoor activity for children between 3 and 9 years of age is associated with reduced myopia incidence between 10 and 15 years, which suggests that interventions in the earlier childhood years may be beneficial.[352] The association between early age of onset of myopia and higher levels of myopia in adulthood,[316–328] further suggests that earlier intervention has the potential to provide the most benefit. The duration required for such treatments to achieve the best outcomes in terms of myopia prevention is currently not clear. Myopia onset can occur through adolescence,[322–326,353] so prolonged treatment may be required to achieve true prevention. Nonetheless, even delaying the onset of myopia by 12 months is likely to have a meaningful effect on the final level of myopia.[328] Furthermore, in addition to potentially delaying myopia onset, encouraging outdoor activity has beneficial impacts on general health.

Surgical Management of High Myopia

Surgical interventions for stabilizing the sclera and thus controlling further myopia progression have a long history, with interest revitalized due to the increase in the global prevalence of high myopia. Against a background of progressive thinning and increasing biomechanical instability of the sclera, there is continued axial elongation.[354,355] The biomechanically weak sclera[39,356] is therefore the primary treatment target for pharmacological intervention, for example, injection-based scleral strengthening, and collagen cross-linking.[357–365] However, the possibility of inadvertently compromising nearby structures, including the optic nerve, ocular vasculature, and retina, remains an unresolved obstacle to widespread clinical adoption.[366] Thus, surgical procedures remain the only treatment options in current use. In the case of children, the goal of posterior scleral reinforcement (PSR) is to prevent the onset of vision-threatening degenerative lesions, and in the case of adults, macular buckling (MB) is applied to address existing pathological complications and visual impairment, and slow further deterioration in vision.

Posterior Scleral Reinforcement

Despite the nearly 100-year-old history of posterior scleral reinforcement, it remains the only method for preventing the uncontrolled axial elongation of malignant high myopia in clinical use. Shevelev was the first to recognize the need to intervene at the level of the sclera, as early as 1930, with PSR surgery subsequently being introduced and later refined by others.[367–370] The main goal is to stabilize the weakened posterior pole sclera and so prevent further ocular elongation before vision threatening degenerative lesions develop. The suggested indication for PSR in children is progressive early onset high myopia, with or without incipient pathological alterations at the posterior pole and associated unilateral high myopia (or significant myopic anisometropia) represents a further indication. In adults, the stabilization of the myopic refractive errors with PSR also has merit beyond halting further expansion of the eye, when cataract or refractive surgery is being considered.

PSR involves the surgical implantation of graft strips, inserted under the extraocular muscles and ultimately over the macular region under general anesthesia. The allograft and xenograft materials used for scleral reinforcement include human sclera, including pre-treated,

crosslinked[371–379] dura-,[380,381] and fascia-lata,[382] and bovine pericardium.[383,384] Human sclera is now the most popular material,[371–378] despite the challenges of harvesting and a potential future shortage. Furthermore, whereas the use of human fascia lata[367,370] have been proposed and largely restricted to early surgeries, lyophilized and sterilized cadaver fascia lata preparations offer a convenient and safe option, with minimal risk of infection and comparable performance.[382]

While initially popularized in the former Soviet Union, and subsequently in parts of the United States and central Europe, the epicenter for the surgical approach subsequently shifted to East Asia. Its relatively limited use elsewhere is likely attributable, at least in part, to the unfortunate history associated with its introduction in the United States, where two different versions of the same surgery led to very different outcomes. Thus whereas the Snyder-Thompson single vertical strip procedure proved to be safe and effective in clinical practice, based on experience on the US West Coast,[369] an X-shape method developed by Curtin proved to be both ineffective and unsafe.[367] In the United States, the latter negative outcomes continue to impact the reputation of the surgery, while an improved and simplified version of the Snyder-Thompson's procedure has been widely adopted by ophthalmic surgeons outside the United States.[385]

Table 8 shows the characteristics of more recent studies of PSR from 2000 to 2024 with follow-up of up to 5 years.[371–384,386] All but two were conducted in China,[372–381,383,384,386] with one each from the United States[371] and Hungary.[382] Most studies enrolled children and used a version of the Snyder-Thompson's procedure technique. The majority included a comparison group—either fellow eyes or myopia-matched patients—but only one was a randomized clinical trial.[374] Outcomes were generally positive, not only in terms of myopia progression and axial elongation, but also in relation to best-corrected visual acuity. Among the 12 studies with a comparison group (see Table 8), the median (IQR) annual slowing of axial elongation is 0.19 mm (0.10 to 0.28), comparable with the best interventions in Figure 2, albeit in a very different patient population.

Regarding safety, conjunctival congestion, and chemosis are a consistent consequence rather than a complication of surgeries applying limbal peritomy.[372,377,378,382,383] The second most frequently reported, transient complication is diplopia, due to extraocular muscle motility restriction.[371,375,382] Other complications are detailed in reviews and meta-analyses,[387–389] with the most recent involving pediatric cohorts and the Snyder-Thompson procedure concluding that the surgery is safe and effective.[389] This conclusion contrasts with the conclusion of the 2020 meta-analysis which included outcomes from Curtin's X-shape procedure.[388]

Macular Buckling Surgery

Myopic tractional maculopathy includes foveoschisis, foveal detachment, macular hole, and macular hole retinal detachment. Currently, the primary surgical approach is vitrectomy to resolve intraocular preretinal pathologic changes, including tangential force from epiretinal membranes and centripetal force from posterior vitreous traction. Nonetheless, vitrectomy cannot alleviate continued eye elongation, which is often localized, and linked to progression of posterior staphyloma. Therefore, there has been a resurgence of interest in MB surgery, either alone, or combined with vitrectomy, in accordance with a myopic tractional maculopathy staging system.[390] In contrast to PSR, which aims to strengthen scleral tissue to prevent or decrease further elongation, MB aims to change the curvature of the posterior staphyloma and even invert it and so diminish the stretching forces on the nearby retina. Although prevention of eye elongation is not the primary purpose of MB, it may be a beneficial side effect. Nonetheless, due to the very localized nature of the intervention, under the macular region, and the possible need for indentation, the MB procedure is both more difficult and riskier than PSR. For this reason, although recently garnering more interest from retinal surgeons, it remains an unpopular surgery, reserved for cases of myopic tractional maculopathy with loss of vision or vision-threatening changes, such as foveal or macular detachment.

A variety of buckle elements, designs, and surgical maneuvers fall under the umbrella of MB,[391] which can be classified into direct suture, L-shape, T-shape, and sling types. Among the materials used are silicone sponges with or without wire or titanium plate, silicone bands, Gore-Tex vascular graft, and donor sclera,[391,392] with most MB elements localized using the encircling buckles, or in a manner as fashioned by the surgeon, due to the limited number of available commercial designs. Separation of the extraocular muscles and even disinsertion of the lateral rectus or superior oblique muscles may be necessary to allow for suitable placement and suturing of the MB,[393–395] with isolation of the inferior oblique muscle also necessary for T-shape and sling but not L-shape MBs. Appropriate placement of the MB in the macular area is achieved under visual guidance, with direct microscopy, indirect ophthalmoscopy during indentation, light pipe lighting in the macular area, and intraoperative OCT among the methods used. The final step involves suturing the element directly to the sclera in the macular area, for which a risk of ocular perforation cannot be avoided.

Potential intraoperative and postoperative side effects and complications are wide-ranging. An unavoidable consequence of MB is macular indentation, resulting in a reduction in axial length and a hyperopic shift. However, optic nerve compression, globe perforation (which can occur during the suturing process), choroidal detachment, and intraocular hemorrhage (suprachoroidal, chorioretinal, or macular) represent more sight-threatening intraoperative complications. Together, they emphasize the need for gentle and limited ocular indentation and manipulation during such surgeries, with special precautions taken to avoid injury to the intraorbital vortex veins and ciliary vessels, which can lead to choroidal detachment, suprachoroidal hemorrhage, or lacquer cracks with hemorrhage. Among post-surgical complications are choroidal neovascularization, motility restrictions, buckle infection, malposition, and/or extrusion, with choroidal atrophy also reported in one long-term (15 year) follow-up case, confined to the indentation created by a sponge strip.[395]

Gaps in Knowledge and Future Directions

That PSR is largely a preventive procedure may be one of the reasons for its limited uptake. More convincing evidence of its long-term efficacy in slowing myopia progression, from longitudinal studies with a broader geographic representation is needed. For MB, methods to improve the surgical

Investigative Ophthalmology & Visual Science

Table 8. Recent Studies of PSR

Source	Study Design	Controls	Surgical Technique	Material	Eyes (PSR)	Age, Y	Follow-Up, Y	Baseline AL	Myopia, D	ΔAL, ΔSE/ Y PSR Vs. Control	ΔBCVA (logMAR)	Adverse Events (Most Transient)
Ward (United States)[371]	NR controlled	Fellow eyes	S-T single wide strip	Human sclera	59	39 (18 to 68)	4	27.8 to 34.6	(9 to 22)	0.01 vs. 0.18 mm	Individual cases only	Diplopia, ↑IOP, choroidal effusion
Chen (China)[380]	NR controlled	Myopia matched	S-T single wide strip	Human dura	64	6.5 (2 to 16)	5	26.55	10.31 (7 to 15)	0.25 vs. 0.41 mm* 0.3 vs. 0.6 D*	0.44 vs. 0.35*	NS, conjunctival chemosis
Zhu (China)[372]	NR controlled	Fellow eyes	S-T single wide strip + PIOL	Human sclera	11	13.2 (3 to 17)	3	30.9	17.57 (11 to 26)	0.08 vs. 0.37 mm*	Pre- postop ΔBCVA: 0.36*	–
Xue (China)[373]	NR controlled	Fellow eyes	S-T single wide strip	Human sclera	35	7.5 (4 to 15)	2.5	26.2	9.72	0.3 vs. 0.37 mm* 0.45 vs. 0.72 D*	0.09 vs. 0.08	–
Shen (China)[374]	RCT	Randomized control	S-T single wide strip	Human sclera	16	4.94	3	26.96	12.3	0.14 vs. 0.44 mm* 0.43 vs. 0.99 D*	1.28 vs. 0.94	NS
Li (China)[375]	NR controlled	Myopia matched	S-T single wide strip + scleral buckle	Human sclera	52	41.3	5	29.49	16.12	0.06 vs. 0.27 mm* 0.14 vs. 0.64 D*	0.01 vs. 0.11	NS, ↑IOP, diplopia
Hu (China)[383]	NR controlled	Myopia matched	S-T single wide strip	Bovine pericardium	32	8.21	1	27.1	11.35	0.13 vs. 0.75 mm* 0.11 vs. 0.24	0.16 vs. 0.19*	–
Xue (China)[386]	NR controlled	Fellow eyes	PSCR	XL human sclera	40	10 (3 to 17)	3	27.6	11.7	0.02 vs. 0.22 mm* 0.29 vs. 0.52 D*	0.06 vs. 0.03	Conjunctival chemosis, ↑IOP, visual distort
Peng (China)[376]	NR controlled	Myopia matched	S-T single wide strip	Human sclera	38	37.36	3	29.42	15.22	0.06 vs. 0.34 mm* 0.23 vs. 1.04 D*	0.02 vs. 0.1*	No new PM alteration in PSR
Miao (China)[377]	Single-arm	–	Modified S-T with bivalve scleral buckle	Human sclera	85	6.3 (3 to 15)	1.8	25.77	9	0.26 mm*	ΔBCVA: 0.69*	NS, conjunctival chemosis
Dong (China)[378]	NR controlled	Myopia matched	Modified S-T with round scleral patch	Human sclera	72	7.28 (3 to 17)	3	26.72	9.05	0.09 vs. 0.27 mm* 0.1 vs. 0.75 D*	0.22 vs. 0.02*	NS, conjunctival chemosis
Széll (Hungary) [382]	NR controlled	Myopia matched	S-T single wide strip	Human fascia lata	38	11.5 (6 to 18)	3.5	26.79	9.18	0.21 vs. 0.49 mm* 0.18 vs. 0.29 D*	Decimal 0.15 vs. 0.01	NS, conjunctival chemosis, diplopia
Gao (China)[384]	Single-arm	–	S-T single wide strip	Bovine pericardium	33	4.9 (2 to 10)	2	25.92	10.54	pre- vs. postop 0.61 vs. 0.42 mm −2.14 vs. −0.21 D	0.24	–
Wang (China)[379]	NR controlled	Myopia matched	Modified S-T	Human sclera	35	6.5 (2 to 14)	1.48	24.57 to 29.29	6.5 to 17.25	0.38 vs. 0.42 mm	0.50 vs. 0.5	–
Ye (China)[381]	Single-arm	–	Modified S-T with double quarter implant	Dura mater	112	8.83 (5 to 14)	0.7 (0.25 to 2)	26.78 (25.04 to 29.78)	10.17	−0.68 mm* 0.67 D	0.04 improvement	–

AL, axial length; BCVA, best corrected visual acuity; BL, baseline; FU, follow-up; logMAR, logarithm of the minimum angle of resolution; NR, non-randomized; NS, no serious; PIOL, phakic intraocular lens; PSCR, posterior scleral contraction reinforcement; RCT, randomized controlled trial; SE, spherical equivalent; S-T, Snyder-Thompson; XL, cross-linked.

* Statistically significant difference.

localization of the scleral implant over the posterior pole and so to improve surgical outcomes are needed. More consideration to the implant materials used in the surgery is also needed, for example, to avoid the risk of infection with cadaver grafts, use of suitable synthetic implants,[392] or lyophilized and sterilized allo- or xenograft preparations, which are at the same time reasonably economical and also more accessible than cadaver grafts. Although MB carries the potential benefit of at least partly reversing the excessive eye elongation and possibly preventing further axial elongation, this surgical technique in its various forms remains challenging and there is no one ideal approach at this time. Further research into safer and technically easier surgeries is warranted. Whereas most studies show the appearance of inverted dome-shaped macular contours after surgery, definitive supporting data, including the extent of axial shortening are generally lacking, yet much needed.

Discussion

This comprehensive review illustrates the increase in myopia control clinical trials since previous IMI papers.[1,2] Indeed, over 70% of the clinical trials used to construct Figure 2 were published since 2020, demonstrating a massive proliferation of research on interventions to slow myopia progression. Other recent reviews provide a complementary narrative on the state of the field.[396,397] Figure 2 is unique in that it provides a comprehensive summary, demonstrating how efficacy varies within and across modalities and as a function of treatment duration in a mostly nonlinear fashion. Likewise, the tables provide important summary information that allows comparison of the characteristics of different randomized clinical trials. We have been judicious about averaging the results within a given modality, in contrast to meta-analyses that have inappropriately grouped all atropine concentrations 0.05% and lower and averaged efficacy across spectacle and soft contact lenses with different add powers and diverse designs.[23,398]

This review limited the summaries of efficacy (see Fig. 2; Tables 1–7) for optical, atropine, and red light therapies to randomized clinical trials for at least 1 year in duration, with an untreated control group, and published no later than December 2024. In general, these clinical trials were well conducted, although a more rigorous critique of issues such as the potential for bias can be found elsewhere.[23] Of note, the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement provides guidelines for randomized clinical trials to ensure the transparent and uniform reporting of results and has been adopted by most journals.[399] Nonetheless, some of the clinical trials reported here do not contain all of the required items on the CONSORT checklist, limiting direct comparisons among published trials. In several instances, neither intention-to-treat analyses nor masking were conducted.

The variation in the optical design of myopia control spectacles and contact lenses is reflected in their wide range of efficacy (see Fig. 2). In contrast, clinical trials of overnight orthokeratology, 0.01% atropine, and most notably red light therapy demonstrate more consistent results. Regardless, most categories of myopia control interventions include designs or concentrations that slow myopia progression by a clinically meaningful extent, although access to some modalities varies across the world. Nonetheless, in general, clinicians are able to prescribe based on a child's lifestyle and parent preference, with adherence (compliance) being a critical determinant of efficacy for any myopia control strategy.[400] Of course, access to interventions may be limited by regulatory approval or scope of practice. Adherence to using the prescribed intervention is a critical factor in the efficacy of any myopia control strategy. This is particularly relevant for myopia control spectacles, as children can easily remove their spectacles for some activities. Unfortunately, data on wearing times are usually gathered through subjective questionnaires or direct questioning, making them susceptible to bias. That the interventions themselves may also influence behavior is a relatively unexplored area. While the development of objective methods to accurately track behavior and wearing times for optical appliances is an area of increasing research activity, increased deployment of the same, ideally implemented without influencing the child's behavior, may help fully evaluate future outcomes.

Safety of Myopia Control. Although the primary focus of most clinical trials is the efficacy of the treatment, it is also important to consider the safety of myopia control treatments. Some of the potential safety issues for emerging technologies have been discussed earlier. For established technologies such as spectacles, contact lenses, and atropine, these issues have been quantified. For atropine, pupil dilation, loss of accommodation, and allergic reactions are short-term concerns.[149,152,401] Atropine use appears to have few long-term consequences.[179] Studies of myopia control spectacle lenses do not report any serious adverse events,[45,74,75] although small reductions in visual acuity, contrast sensitivity, and other functional measures when viewing through the peripheral, treatment zones of the lenses have been reported.[402–404] The most serious potential complication of contact lens wear is microbial keratitis. The risk has been extensively studied in adults, establishing that the incidence is the order of 1 to 3 per 10,000 patient years of wear but increases by 10-fold with overnight wear.[405] The risk of complications with daily wear is no higher in children and may be lower.[406,407] The incidence of microbial keratitis is higher with overnight orthokeratology, but less than with extended wear contact lenses.[408,409]

Rebound: Excessive Progression After Cessation of Myopia Control. A valid concern is whether the slowing of myopia progression and axial elongation is maintained after stopping treatment with myopia control interventions. Although it is reasonable to expect progression to increase following cessation of treatment compared to during treatment, the question remains: does it return to the expected untreated rates based on the child's age and race, or does it accelerate further?[146] The IMI defines rebound in the context of myopia control as a faster axial elongation and myopia progression upon cessation of myopia control treatment than that expected in a matched group.[410] Thus, the comparator should be the rate of progression in age-matched untreated myopic eyes, not the previous rate of progression during treatment.

A recent comprehensive review identified 19 studies, comprising 24 treatment groups where rebound could be estimated.[146] No evidence of rebound was found for myopia control spectacles and soft contact lenses, echoing previous statements.[411,412] Conversely, five of the six highest rebound values (≥0.14 mm) were reported in studies of atropine or red light therapy. For example, during the third year of the ATOM study, after the 2-year treatment was ceased, the mean axial elongation was 0.35 and 0.15 mm in the

Investigative Ophthalmology & Visual Science

atropine and placebo groups, respectively, a difference of 0.20 mm.[145] Likewise, in the second year of a 1-year randomized clinical trial of red light therapy, axial elongation in the previously treated children was 0.42 mm compared with 0.28 mm in the untreated control group.[244] The absence of rebound following long-term treatment with myopia control soft contact lenses has been confirmed in two recent publications.[413,414]

Finally, studies evaluating rebound should, when possible, account for the impact of myopia control therapies on choroidal thickness. Effective interventions typically induce slight thickening of the choroid, leading to a temporary shortening of axial length, both of which dissipate when treatment is stopped. The dynamics of the choroid will influence estimates of rebound, albeit to a very small extent.[146]

The Future of Clinical Trials of Myopia Control. Clinical trials have contributed to knowledge of myopia progression and axial elongation in untreated children, leading to models of untreated children that can provide an important reference for practitioners.[31,415] In this regard, the field of myopia control may be at a pivot point and there may be fewer clinical trials with untreated control groups conducted in the coming years. With the increased availability of effective treatments and enhanced understanding of the long-term consequences of myopia on visual impairment,[416] withholding treatment from children with myopia for multiple years may no longer be considered ethical,[412] although it continues to be required by some regulatory agencies. Ethical concerns, along with pressure to publish, may explain the predominance of 1-year studies in Figure 2. Furthermore, recruitment may be challenging and there may be contamination or withdrawal among the control group, thus biasing estimates of efficacy.[158,417] Such concerns have led researchers to propose alternative study designs,[170] for example, the treatment under investigation could be compared to an established or predicate drug or device. In this design, participants would be randomized to one of two or more treatments, thereby avoiding the ethical and recruitment challenges associated with an untreated group of children.

An alternative is to initially randomize children to treatment and control groups but initiate treatment in the control group after a year or 2.[170] This approach has additional merit in allowing long term efficacy to be estimated by extrapolating the myopia progression and axial elongation in the control group for the untreated years to subsequent years,[31] and has already been used to quantify the long-term efficacy of low dose atropine,[176,177] dual focus contact lenses,[36] and myopia control spectacle lenses.[35] Inspection of Figure 2 demonstrates that 2- and 3-year efficacy estimates generally reflect the 1-year data, especially so in the case of multifocal soft contact lenses and overnight orthokeratology. Alternatively, participants could still be randomized to treatment and control groups, but the primary outcome measure is time to treatment failure, with rescue treatment administered as soon as a predetermined progression or elongation is reached.[93]

A further possibility involves the use of virtual control groups[170] or historical controls matching for race and age.[31,418] Unfortunately, untreated cohorts recruited from the same population can show large variations in progression rate,[62,80,89] due to evolving socio-economic factors, the changing availability of myopia control treatments, and other sources of recruitment bias.

Surrogate Markers for Treatment Responsiveness. Evaluation of new myopia control options could benefit by identifying short-term ocular changes that reflect long-term efficacy. One such parameter that has received some attention is choroidal thickness.[419] Effective myopia control therapies, on average, produce an increase in choroidal thickness of up to 20 µm, which is reflected in a corresponding reduction in axial length of up to 0.02 mm.[420] Increased choroidal blood flow was also reported in a recent related prospective cohort study involving orthokeratology, with the changes in the first month of treatment being predictive of slowed axial elongation at 1 year.[421] Short-term (1 week to 1 month) choroidal thickness changes after beginning treatment with orthokeratology,[419] atropine,[422] and red light therapy[423] have also been found to be associated with longer term (6 to 12 months) changes in axial elongation associated with treatment.

The BLINK Study reported an average increase in choroidal thickness of 8 µm, 2 weeks after initiating contact lens wear in their high-add MFCL group that was sustained for the duration of the 3-year study.[424] The authors found an association between increased choroidal area 2 weeks after initiating high-add multifocal contact lens wear and slower axial elongation after controlling for factors including age and sex, although the choroidal changes only accounted for a portion (29%) of the treatment effect. Nonetheless, the high within-group variability in these choroidal changes (participants within the treatment had both choroidal thickening and thinning), limits the clinical use of choroidal changes as a predictor of future efficacy on an individual basis.[424] Results from the LAMP Study also found choroidal thickening, on average, of about 20 µm in children using 0.05% atropine, but again, there was high within-group variability (SD of $\sim$ 30 µm), indicating that there was both thickening and thinning within this group.[425] These changes in choroidal thickness accounted for approximately 19% of the effect on spherical equivalent myopia progression in a mediation analysis.

One major challenge in using choroidal responses as surrogate markers is the ability to distinguish small treatment-related changes from confounding factors, such as diurnal variations, physical activity, and dietary or medication influences on the cardiovascular system and thus choroidal blood flow. Additionally, the comparability between changes in choroidal thickness measured by OCT B-scans and axial length measured by A-scans has not been fully validated, limiting widespread clinical application. A lack of validated, automated choroidal segmentation methods incorporated into clinical OCT devices is a further limiting factor. Despite these challenges, short-term alterations in choroidal thickness and blood flow warrant further examination as potential biomarkers for predicting long-term treatment outcomes of new treatment options.

Gaps in Knowledge and Future Directions. The majority of clinical trials of myopia control spectacles, overnight orthokeratology, and combination therapy have been conducted in China and surrounding countries, along with all studies of red light therapy. The extent to which these results translate to Western populations is unclear. Forthcoming multicenter clinical trial results of optical interventions from North America are expected to provide important information. While myopia progresses more rapidly in East Asian children,[31] some have argued that efficacy is not dependent on ethnicity.[22] Inspection of Figure 2D and Table 4 suggests that 0.01% may be more effective

Investigative Ophthalmology & Visual Science

in East Asian children, although differences in treatment adherence cannot be ruled out as an alternative explanation. Nonetheless, slower progression rates in European children may necessitate larger sample sizes to detect treatment effects, particularly for lower-potency interventions, such as low-dose atropine. Future trials might consider stratified recruitment or adaptive designs to account for regional and baseline differences in myopia progression.

The mechanisms by which many optical devices slow myopia progression remains unclear. Whereas some interventions that manipulate peripheral refraction are supported by animal studies, this is not true in all cases.[42] For example, spectacle lenses that contain either positive or negative lenslets both slow progression, and to similar degrees.[47] Likewise, reducing spatial contrast in the peripheral visual field slows progression,[45] opposite to predictions from animal studies. Further investigations into, and improved understanding of, the mechanisms underlying myopia development and progression may provide key insights into these unresolved issues and potentially also lead to enhanced myopia control spectacle lens and contact lens designs. Likewise, successful resolution of the mechanisms by which atropine slows axial elongation could lead to more targeted therapeutic formulations.[138,141,142]

In summary, this review represents a time capsule, chronicling the efficacy of currently available myopia control interventions. The coming years will, undoubtedly, see the development of more new technologies, additional clinical trial results, and enhanced management of myopia.

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