Special Issue

IMI – Interventions for Controlling Myopia Onset and Progression Report

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Myopia has been predicted to affect approximately 50% of the world's population based on trending myopia prevalence figures. Critical to minimizing the associated adverse visual consequences of complicating ocular pathologies are interventions to prevent or delay the onset of myopia, slow its progression, and to address the problem of mechanical instability of highly myopic eyes. Although treatment approaches are growing in number, evidence of treatment efficacy is variable. This article reviews research behind such interventions under four categories: optical, pharmacological, environmental (behavioral), and surgical. In summarizing the evidence of efficacy, results from randomized controlled trials have been given most weight, although such data are very limited for some treatments. The overall conclusion of this review is that there are multiple avenues for intervention worthy of exploration in all categories, although in the case of optical, pharmacological, and behavioral interventions for preventing or slowing progression of myopia, treatment efficacy at an individual level appears quite variable, with no one treatment being 100% effective in all patients. Further research is critical to understanding the factors underlying such variability and underlying mechanisms, to guide recommendations for combined treatments. There is also room for research into novel treatment options.

Keywords: myopia control, optical, pharmacological, behavioral, surgical

1. General Introduction

This article encompasses various interventions in current use for controlling myopia progression in children, organized under three broad categories: optical, pharmacological and environmental (behavioral). Surgical interventions aimed at stabilizing highly myopic eyes are also covered as a fourth topic. In each case, current treatments, as well as those in limited use and/or subjected to clinical trial, are considered. The still climbing myopia prevalence figures worldwide, including of high myopia, and the association between high myopia and sight-threatening ocular pathologies, provides strong motivation for research into underlying mechanisms and effective therapies that can limit ocular elongation, with the hope that the incidence of such pathologies also may be limited. Other articles in this special issue of *Investigative Ophthalmology and Visual Science* offer comprehensive coverage of the experimental animal model literature and approaches for monitoring progression, with best practice recommendations in relation to assessing treatment outcomes (see accompanying IMI – Clinical Management Guidelines Report).[1] Thus in this article, coverage has been limited to a brief background overview of the treatments themselves, evidence for efficacy, with emphasis on high-quality randomized clinical trials, adverse effects, and future directions for research.

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2. Optical Interventions for Myopia Management

2.1 Introduction

Optical interventions for controlling myopia have an extensive history, with early clinical studies largely based around spectacles aimed at altering the near visual experience. Clinical studies involving contact lens–based treatments are largely limited to the 21st century, with studies demonstrating optical defocus-driven regulation of eye growth in animal models helping to reawaken interest in, and drive new optical approaches to myopia control. Specifically, as demonstrated first in young chicks, imposed myopic defocus is known to slow eye growth, whereas the converse is true for hyperopic defocus (i.e., eye growth accelerates).[2] This report summarizes the results from clinical studies using spectacles, contact lenses, and orthokeratology (OK). The evidence contained in relevant published studies has been evaluated and recommendations for using optical strategies for myopia control provided, based on the quality of reported results and the evidence.

2.2 Spectacles

The utility of using spectacle lenses for slowing myopia progression has many advantages over other forms of myopia management, as they are easy to fit, are mostly well accepted and tolerated, are affordable by most, and are minimally invasive. The various spectacle lens–based approaches aimed at slowing the progression of myopia include both standard and customized single-vision (SV) lens designs, as well as bifocal and progressive spectacle lenses.

There is equivocal evidence concerning whether full correction with SV spectacles causes faster myopic progression than full correction with soft contact lenses.[3–7] The evidence would suggest that if that is the case then the difference is likely clinically irrelevant.

2.2.1 Undercorrection With Spectacles. Undercorrection to slow the progression of myopia has been in practice for many years and was originally considered to slow the progression of myopia by reducing the accommodative demand during near tasks. The accumulating reports of slowed eye growth in response to experimentally imposed myopic defocus in animal models,[2,8] also led to parallels being drawn with the myopic defocus experienced during distance tasks with undercorrection, and thus speculation about this potential additional benefit.

An early nonrandomized trial of undercorrection, conducted in 1960s,[9] found this treatment to slow the progression of myopia. More recently (since 2000), well-designed, randomized controlled trials (RCTs) examining undercorrection for distance (by +0.50 to +0.75 diopters [D]) over 1.5 to 2.0 years found this treatment to either increase myopia progression or have no benefit, when compared with myopia progression in fully corrected SV spectacle wearers (Table 1).[10–12] Although all trials involved relatively young children at an age when progression is common, the trials were only small to moderate in size. However, the latter weakness does not explain the consistent trend of faster progression in undercorrected eyes observed in some studies. Nonetheless, although another larger, albeit nonrandomized trial also found no significant difference between comparable treatment groups, curiously, myopia progression significantly decreased with increasing undercorrection.[13] The latter trend is also consistent with results from a recent study comparing myopia progression in uncorrected and fully corrected 12-year-old children; this study found slower progression in the former group, the latter effect increasing with the amount of undercorrection.[14] The possibility that the lack of sharp distance vision with undercorrection strategies may lead to behavioral changes, such as reduced outdoor activities in some children, thereby favoring myopia progression, warrants investigation, although the contrasting study outcomes suggest additional factors are at play.

2.2.2 SV Peripheral Defocus-Correcting Lenses. Findings from animal studies,[2] including monkeys,[29] offer strong evidence for contributions by the peripheral retina to eye growth regulation and refractive development (see accompanying IMI – Report on Experimental Models of Emmetropization and Myopia).[30] In addition, a number of studies have reported relative peripheral hyperopia in myopic eyes when fully corrected with SV spectacles.[31–33] Thus, it has been hypothesized that the hyperopic defocus experienced by the retinal periphery may drive further axial elongation.

Three novel spectacle lens designs aimed at reducing the relative peripheral defocus were tested in an RCT designed to evaluate this notion.[27] The results were generally disappointing, with no significant differences in myopia progression between the groups observed. In subgroup analysis, one of the lens designs (Type III) that was specific to right and left eyes demonstrated a small benefit (of 0.25 D), compared with SV spectacles in younger children with parental myopia. Likewise, a recent trial involving Japanese children found no benefit of the MyoVision lens, a positively aspherized design,[34] and in a further test of this treatment approach, no benefit was found by combining a peripheral defocus correction with a progressive addition zone for near work.[28]

2.2.3 Bifocal Spectacles. Traditional rationales for prescribing bifocal spectacles for myopia control include reducing or eliminating lags of accommodation during extended near work, lags being a potential source of hyperopic defocus. Reducing accommodative demand is another, with the associated reduction in ciliary muscle tension potentially reducing stress on the overlying sclera. All multifocal (MF) lens designs, including bifocal lens designs, also induce relative myopic shifts in peripheral refractive errors, at least in superior retinal field.[31] Many of the bifocal spectacle trials, with the exception of a single trial involving executive bifocal lenses,[26] were conducted before 2000, and mostly in 1980s.

There have been a number of RCTs involving bifocal spectacle lenses. One such study,[15] which involved children with near point esophoria followed over 2.5 years, reported a modest (0.25 D), albeit statistically significant, reduction in progression with a 28-mm flat top bifocal lens compared with SV spectacles. Vitreous chamber growth was also significantly reduced, although the change in axial length (AL) was not. However, in a previous 3-year trial, mean rates of progression were less for SV spectacles worn on a continuous basis compared with bifocal spectacles or SV spectacles for distance only (−1.46 D, continuous SV versus −1.58 D, bifocal (+1.75 D, straight top), versus −1.88 D, SV spectacles for distance only).[17] Similarly, no significant differences in myopia progression were observed in the Houston Myopia study,[18] between groups wearing either of two executive bifocal lens designs (+1.00 or +2.00 D add) or SV lenses. Retrospective analysis of longitudinal data from three optometry practices also found no significant differences in myopia progression between those wearing SV spectacles and bifocal spectacles.[16]

The above results stand in sharp contrast to those of a relatively recent RCT involving two high-set executive bifocal lens designs (+1.50 D add alone and +1.50 D add with 3Δ base-in prism), both of which significantly reduced myopia progression in children older than 3 years compared with SV spectacles (−1.25 D [bifocals] versus −1.01 D, [prismatic bifocals] versus −2.06 D [SV]), in children with progressing

Table 1. A Summary of Results From Previous Spectacle Myopia Control Studies Reported in the Peer-Reviewed Literature

Study (Country)	Sample Size [Age Range, y]	Control	Study Design [Duration, y]	% Loss to Follow-Up	% Slowing Myopia Progression	% Slowing Axial Elongation	Baseline Age, y	Myopia Range, D	Average Myopia, D
Undercorrection									
Li et al., 2015[13] (China)	253 [10–16]	FC specs	Nonrandomized, observational [1]	NA	5.8	0	FC: 12.7 ± 0.4 UC: 12.7 ± 0.5	NP	FC: −3.75 ± 1.23 UC: −3.12 ± 1.29
Adler and Millodot, 2006[12] (UK)	48 [6–15]	FC specs	Randomized [1.5]	22.5	Worse with UC: 20.7	NC	FC: 10.2 ± 2.2 UC: 9.9 ± 2.7	FC: 1.06 to −4.50 UC: −1.37 to −5.30	FC: −2.82 ± 1.06 −2.95 ± 1.25
Chung et al., 2002[10] (Malaysia)	94 [9–14]	FC specs	Randomized [2]	NP	Worse with UC: 29.8	NP	FC: 11.5 ± 1.5 UC: 11.6 ± 1.5	Greater than −0.50	FC: −2.68 ± 1.17 −2.68 ± 1.41
Koomson et al., 2016[11] (Ghana)	150 [10–15]	FC specs	Randomized [2]	0.6	7.4	12.5	FC: 12.4 ± 1.2 UC: 12.4 ± 1.4	−1.25 to −4.00	FC: −1.96 ± 0.57 −2.02 ± 0.54
Bifocals									
Fulk et al., 2000[15] (USA)	82 [6–13]	SV specs	Randomized [2.5]	8.5	20.2	18.4	BF: 10.7 ± 1.3 SV: 10.8 ± 1.4	Greater than −0.50 and near point Esophoria	BF: −2.12 ± 1.16 −2.52 ± 1.40
Goss et al., 1986[16] (USA)	112 NP	SV specs	Nonrandomized [NP]	NA	15.9	NA	NP	NP	NP
Pärssinen et al., 1989[17] (Finland)	240 [9–11]	SV specs-distant SV specs-continuous	Randomized [variable]	NP	20.2 vs. SV* 8.2 worse vs. SV cont*	NA	SV Distant: 10.9 SV Cont: 10.9 BF: 10.9	NP	SV Distant: LE: −1.3 SV Cont: LE: −1.5 BF: LE: −1.5
Grosvenor et al.,1987[18] (USA)	207 [6–15]	SV specs	Randomized [3]	40.1	+1.00 Add: worse 5.8 +2.00 Add: 5.8	NA	NP	Greater than −0.25	NP
Cheng et al., 2014[26] (Canada)	135 [8–13]	SV specs	Randomized [3]	5.2	ΔBF: 51.0 BF: 39.3	ΔBF: 34.1 BF: 30.5	ΔBF: 10.4 ± 0.3 BF: 10.1 ± 0.3 SV: 10.3 ± 0.3	−1.00 or more with ≥ 0.5D progression in preceding year	ΔBF: −3.27 ± 0.16 BF: −3.03 ± 0.16 SV: −2.92 ± 0.19
Progressive addition spectacles									
Leung et al., 1999[19] (Hong Kong)	80 [9–12]	SV specs	Nonrandomized [2]	15.0	PAL +1.50: 38.2 PAL +2.00: 46.3	PAL+1.50: 33.7 PAL +2.00: 44.5	PAL +1.50: 10.5 PAL +2.00: 10.2 SV: 10.4	−1.00 to −5.00	PAL +1.50: −3.73 ± 1.13 PAL +2.00: −3.67 ± 0.97 SV: −3.67 ± 1.15
Edwards et al., 2002[20] (Hong Kong)	298 [7–10.5]	SV specs	Randomized [2]	14.7	11.1	3.1	PAL: 9.2 SV: 8.9	−1.25 to −4.50	PAL: −2.82 ± 0.99 SV: −2.92 ± 0.99
Yang et al., 2009[21] (China)	178 [7–13]	SV specs	Randomized [2]	16.3	17.3	15.7	All: 11.0 ± 1.6	−0.50 to −3.00	PAL: −1.60 ± 0.63 SV: −1.78 ± 0.68
Gwiazda et al., 2003[22] (USA)	469 [6–11]	SV specs	Randomized [3]	1.5	13.5	14.6	PAL: 9.3 ± 1.3 SV: 9.4 ± 1.3	−1.25 to −4.50	PAL: −2.40 ± 0.75 SV: −2.37 ± 0.84

Table 1. Continued

Study (Country)	Sample Size [Age Range, y]	Control	Study Design [Duration, y]	% Loss to Follow-Up	% Slowing Myopia Progression	% Slowing Axial Elongation	Baseline Age, y	Myopia Range, D	Average Myopia, D
Hasebe et al., 2008[23] (Japan)	92 [6–12]	SV specs	Randomized crossover [1.5]	7.0	25.8 (phase I)	NA	PAL: 10.0 SV: 9.7	−1.25 to −6.00	PAL: −3.17 SV: −3.31
COMET 2011[24] (USA)	118 [8–12]	SV specs	Randomized [3]	7.0	24.3	NA	PAL: 10.2 ± 1.1 SV: 10.0 ± 1.1	−0.75 to −2.50	PAL: −1.50 ± 0.45 SV: −1.45 ± 0.47
Berntsen et al., 2012[25] (USA)	85 [6–11]	SV specs	Randomized [1]	1.1	34.6	28.5	PAL: 9.6 ± 1.2 SV: 10.1 ± 1.5	−0.75 to −4.50	PAL: −1.95 ± 0.64 SV: −2.04 ± 0.91
Peripheral defocus management									
Sankaridurg et al., 2010[27] (China)	210 [6–16]	SV specs	Randomized [1]	4.4	Type I: Worse 3.8 Type II: Worse 3.8 Type III: 15.4	Type I: 0 Type II: 2.8 3.8 Type III: 13.9	Type I: −10.7 ± 2.4 Type II: −11.1 ± 2.2 Type III: −11.4 ± 2.3 SV: 10.8 ± 2.5	−0.75 to −3.50; cyl ≤ 1.50	Type I: −1.82 ± 0.62 Type II: −1.81 ± 0.67 Type III: −1.82 ± 0.66 SV: −1.87 ± 0.68
Hasebe et al., 2014[28] (China/ Japan)	197 [6–12]	SV specs	Randomized [2]	14.3	PA-PAL +1.0: 13.7 PA-PAL +1.5: 20	PA-PAL +1.0: 7.3 PA-PAL +1.5: 11.7	PA-PAL +1.0: 10.6 ± 1.5 PA-PAL +1.5: 10.0 ± 1.5 SV: 10.4 ± 1.2	−0.50 to −4.50	PA-PAL +1.0: −2.52 ± 1.01 PA-PAL +1.5: −2.80 ± 1.02 SV: −2.61 ± 1.00

BF, bifocal; FC, full correction; NA, not applicable; NP, not provided; PA-PAL, peripheral aspherized PAL; Specs, spectacles; UC, undercorrection; NC, no change; cont, continuous wear.
* Left eye rather than average across both eyes compared.

myopia). Overall, the magnitude of change was similar between the two bifocal groups, except for children with low lags of accommodation, for whom the prismatic bifocal lenses had a greater benefit.[26] The investigators speculated that for children with low lags, both convergence and lens-induced exophoria were reduced by the base-in prism; the latter effects presumably led to improved compliance.

2.2.4 Progressive Addition Spectacles (PALs). Of all the spectacle interventions assessed for their efficacy in slowing the progression of myopia, PALs have been the most studied. As with bifocal spectacles, the rationale for their use has been to reduce the accommodative demand and/or reduce accommodative lag during near tasks.

Leung and Brown[19] proposed the use of PALs as an alternative to bifocal lenses, which were considered to not adequately control defocus for all distances. Their clinical trial, which compared myopia progression with +1.50 and +2.00 D PALs and SV lenses over 2 years, found significantly reduced myopia progression relative to that with SV lenses with both +1.50 D (0.47 D difference) and +2.00 D PAL (0.57 D difference).[19] However, this study was not fully randomized and later RCTs conducted in the United States, Hong Kong, China, and Japan (using either +1.50 or +2.00 D add power compared with SV lenses), found that although PALs significantly reduced myopia progression, often the difference from progression with SV lenses was <0.25 D and not considered clinically significant.[20–23] Larger treatment effects were observed with the +2.00 D PALs used in children with both high accommodative lag and near esophoria (of 0.28 D over 3 years) but here again, they were not deemed to be clinically useful.[24] Likewise, the results from a shorter (1-year) study, which specifically targeted children with high accommodative lag and/or near esophoria, indicated a positive, but clinically questionable treatment effect with PALs (0.18 D after 1 year of lens wear), although a relationship between superior retinal defocus and the change in on-axis refractive error was noted, with superior myopic defocus associated with less central myopia progression.[25,31]

2.3 Contact Lenses

2.3.1 SV Soft Contact Lenses. Most soft lenses with spherical surfaces have negative spherical aberration in negative powers.[35] At first glance, this might appear to produce a hyperopic shift in the peripheral refraction, which could encourage axial growth of the eye, compared with, for example, an SV spectacle lens that has little spherical aberration.[36] However, Atchison[37] has shown with optical modeling that spherical contact lenses will produce more peripheral myopic shift than spherically surfaced spectacle lenses. As a result, one may hypothesize that if a myopic peripheral refraction retards myopia progression, then SV soft contact lenses may be protective against myopia progression compared with SV spectacles.

In a retrospective chart review, Andreo[5] examined the effects of soft contact lenses on myopia in patients aged 14 to 19 years over a 13-month period. There was no statistically significant difference in the rate of myopia progression between those who wore contact lenses full-time and those wearing spectacles. To-date, there have been two prospective, randomized studies comparing the rate of myopia progression between contact lens and spectacles wearers. Horner et al.[4] examined 175 adolescents between the ages of 11 and 14 years and found no difference in mean spherical equivalent refractive errors, between spectacle and soft contact lens wearers after 3 years. Walline and coworkers[3] examined myopia progression over 3 years in 484 children aged between 8 and 11 years and concluded "soft contact lens wear by children does not cause a clinically relevant increase in AL, corneal curvature, or myopia relative to spectacle lens wear."

Fulk and colleagues[6] permitted a small cohort of subjects to choose either soft contact lenses or spectacles to wear after a clinical trial of bifocal spectacles for myopia control treatment. They found that myopia progressed at an age-adjusted average rate of 0.74 D in 19 children who switched to soft contact lenses compared with 0.25 D for 24 children remaining in spectacles ($P < 0.0001$), some of which was accounted for by steepening of the corneal curvature in the contact lens wearers. Marsh-Tootle et al.[7] reported on 286 participants from the COMET study who wore their original spectacle lenses for 6 years ($n = 199$), or wore soft contact lenses most or all the time between the 5- and 6-year visits ($n = 87$). The two-year myopia progression was evaluated in a subset of 183 participants who wore the same lens type for an additional year. Mean (± SD) myopia progression after 1 year was significantly higher ($P = 0.003$) in the contact lens group (–0.28 ± 0.33 D) than in the spectacle group (–0.14 ± 0.36 D), and remained higher after 2 years in the two subsets (–0.52 ± 0.46 D versus –0.25 ± 0.39 D, $P < 0.0001$). Corneal curvature remained unchanged in both groups. They concluded that children switching from spectacles to contact lenses experienced a small, statistically significant but clinically inconsequential increase in myopia progression over this time.[7]

Low oxygen transmissibility (Dk/t) lenses, worn under extended wear conditions have also been linked to greater myopic progression compared with high Dk/t lenses worn under the same conditions.[38,39] However, the higher Dk/t lenses were manufactured from a higher modulus (silicone-based) material and caused corneal flattening; as the lenses also have minimal spherical aberration, it is not clear which factors may have influenced myopia progression in this study.[38]

In conclusion, there is no substantial evidence in the literature that conventional soft contact lens wear leads to either slower or faster myopia progression than spectacle wear.

2.3.2 Gas-Permeable Contact Lenses (GP). There have been suggestions over several decades that alignment-fit GPs (not OK design), can slow myopia progression in children.[40–42] However, most of these studies have important limitations in their study design.[43,44] More recent, well-conducted studies showed that the use of these lenses did not impact axial elongation and that the apparent control of myopia progression observed with GPs was most likely induced by corneal flattening.[44,45]

2.3.3 Soft Multifocal (MF) Contact Lenses. Soft MF contact lenses are increasingly used for controlling myopia progression in children, although some designs were originally intended for use by presbyopes and are used off-label. Although they come in many designs, only center-distance designs have been formally investigated in the context of myopia control. In these designs, the peripheral region of the lens has relatively more positive (plus) power, incorporated as a gradual increase toward the periphery (progressive design) or presented in distinct zones (concentric ring design). The lens design is reflected in the labeling: bifocal, MF, gradient, progressive, or positive spherical aberration–inducing lenses. In most cases, the lenses are intended to provide clear distance vision, while imposing myopic defocus on the more peripheral retina as a putative stimulus to slow eye growth. However, higher-order aberrations, including spherical aberration, are an inherent feature of most MF lens designs, with potential benefits to near vision in presbyopes; these aberrations likely also contribute to the myopia control effect of these lenses.[46]

To-date, results from nine soft MF contact lens trials have been published.[47–55] The main features of these trials are summarized in Table 2. In brief, the trials include five RCTs with bilateral contact lens treatments[47,49–51,55] and one

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Table 2. A Summary of Results From Previous Soft Multifocal Contact Lens Myopia Control Studies Reported in the Peer-Reviewed Literature and Comparison of Baseline Variables to the BLINK Study

Study (Country)	Sample Size [Age Range, y]	Control Treatment	Study Design [Duration, y]	% Loss to Follow-Up	% Slowing Myopia Progression	% Slowing Axial Elongation	Baseline Age, y	Myopia Range, D	Average Myopia, D
Anstice et al., 2011[48] (New Zealand)	70 [11–14]	Contact lens	Contralateral [0.8]	12.5	36.2	50.0	Unknown	−1.25 to −4.50	−2.71 ± 1.10
Sankaridurg et al., 2011[53] (China)	82 [7–14]	Spectacles	Prospective [1]	18.0	35.7	38.5	MF: 11.6 ± 1.5 Spec: 10.8 ± 1.9	−0.75 to −3.50	MF: −2.24 ± 0.79 Spec: −1.99 ± 0.62
Walline et al., 2013[54] (USA)	54 [8–11]	Contact lens	Historical control [2]	19.4	50.5	29.3	MF: 10.8 ± 1.0 SV: 10.8 ± 0.7	−1.00 to −6.00	MF: −2.24 ± 1.02 SV: −2.35 ± 1.05
Fujikado et al., 2014[50] (Japan)	24 [10–16]	Contact lens	Randomized crossover [2]	0	26.2	25.0	MF: 14.3 ± 1.3 SV: 13.1 ± 1.9	−0.75 to −3.50	MF: −2.52 ± 1.69 SV: −3.61 ± 0.98
Lam et al., 2014[51] (Hong Kong)	128 [8–13]	Contact lens	Randomized [2]	42.1	25.3	32.4	MF: 11.1 ± 1.6 SV: 10.9 ± 1.7	−1.00 to −5.00	MF: −2.90 ± 1.05 SV: −2.08 ± 1.03
Paune et al., 2015[52] (Spain)	40 [9–16]	Spectacles	Prospective [2]	43.7	42.9	26.9	MF: 13.3 ± 2.0 Spec: 13.1 ± 2.8	−0.75 to −7.00	MF: −2.44 ± 0.91 Spec: −2.64 ± 1.1
Aller et al., 2016[47] (USA)	79 [8–18]	Contact lens	Randomized [1]	8.1	77.2	79.2	MF: 13.0 ± 2.5 SV: 13.5 ± 2.2	−0.50 to −6.00	MF: −2.57 ± 1.34 SV: −2.81 ± 1.46
Cheng et al., 2016[49] (USA)	109 [8–11]	Contact lens	Randomized [1]	14.2	20.6	38.9	MF: 9.7 ± 1.1 SV: 9.7 ± 1.1	−0.75 to −4.00	MF: −2.44 ± 0.91 SV: −2.52 ± 1.46
Ruiz-Pomeda et al., 2018[55] (Spain)	89 [8–13]	Spectacles	Randomized [2]	16.9	39.32	36.04	MF: 11.0 ± 1.2 Spec: 10.1 ± 1.3	−0.75 to −4.00	MF: −2.16 ± 0.94 Spec: −1.75 ± 0.94

BLINK, Bifocal Lenses in Nearsighted Kids; MF, multifocal contact lens; Spec, single-vision spectacle; SV, single-vision contact lens.

contralateral control RCT.[48] Only three of the trials[47,55,56] used commercially available contact lenses. Three trials used concentric ring designs, with the other six trials using progressive power designs. Five of the studies followed subjects for 2 years,[50–52,54,55] with one of them involving a crossover design.[50] SV contact lenses were used as control treatments for most of the studies (7 of 9), with the remaining two studies using SV spectacles. All studies had similar boundary conditions for recruited subjects; ages ranged from 7 to 18 years, with low to moderate myopia (average SE: approximately −2 D; range: –0.50 to –6.00 D) (Table 2). Across all studies combined, 76% of subjects completed the trials.

Based on sample size–weighted averages, the eight trials published over the 2011 to 2016 period showed a 38.0% slowing of myopia progression and a 37.9% slowing of axial elongation with MF soft contact lens interventions (see Figure). Some studies showed greater apparent slowing of myopia progression than of axial elongation,[52,54] and others, greater apparent slowing of axial elongation than of myopia progression,[48,49] and some, approximately matched slowing of myopia progression and axial elongation.[47,50,51,53,55] Interestingly, concentric ring designs showed better control over axial elongation than progressive designs (44.4% versus 31.6%), whereas their effects on myopia progression were similar (36.3% versus 36.4%). The most recently published comprehensive data for the MiSight lens are from a randomized controlled but not masked trial.[55] Reductions in myopia progression and axial elongation at the end of a 2-year trial period, of 39% and 38% respectively, are similar to the group averages reported above, although the efficacy of the MiSight lens could have been slightly overestimated as the subjects in the treatment arm were slightly older (by approximately 1 year). Nonetheless, significant reductions in myopia progression were also observed at 1-, 2-, and 3-year visits in a larger, 3-year RCT of the same lens.[57] The dropout rates for the MiSight and SV (control) lenses over 3 years in the latter study were similar, 26% and 24%, respectively.[58]

Only two of the eight trials examined the potential influence of peripheral refractive errors on myopia progression.[52,53] Noteworthy, both trials used SV spectacle lenses as opposed to SV contact lenses as controls. Sankaridurg et al.[53] reported a significant correlation between the relative peripheral hyperopia at 30 and 40 degrees nasal and 40 degrees temporal, measured with correcting lenses in place, and myopia progression. Likewise, Paune et al.[52] reported a significant correlation between the relative peripheral refractive errors at 30 degrees nasal and temporal and axial elongation over the first year of treatment. In the crossover "contralateral control" trial of Anstice and Phillips,[48] the eyes wearing the MF soft contact lenses showed slower myopia progression and axial elongation relative to their fellows, in both phases of the trial. Furthermore, under the monocular MF lens condition of this study, accommodative responses to near tasks were consistent with accommodation being driven by the center-distance zone of the MF lenses, the implication being that accommodative lags would have been minimally affected. However, two other studies reported positive benefits on accommodative errors in the presence of MF soft contact lenses (i.e., decreased accommodative lags[46] and accommodative leads[59]). An increase in higher-order aberrations and a relative decrease in peripheral hyperopia through the MF contact lenses were also reported in the study of Paune and colleagues,[46] who speculated on the potential positive benefits for myopia control of both of these optical effects.

2.3.4 Orthokeratology. OK, also known as corneal reshaping therapy, involves reshaping of the cornea to reduce myopic refractive errors.[60–63] The development of specially

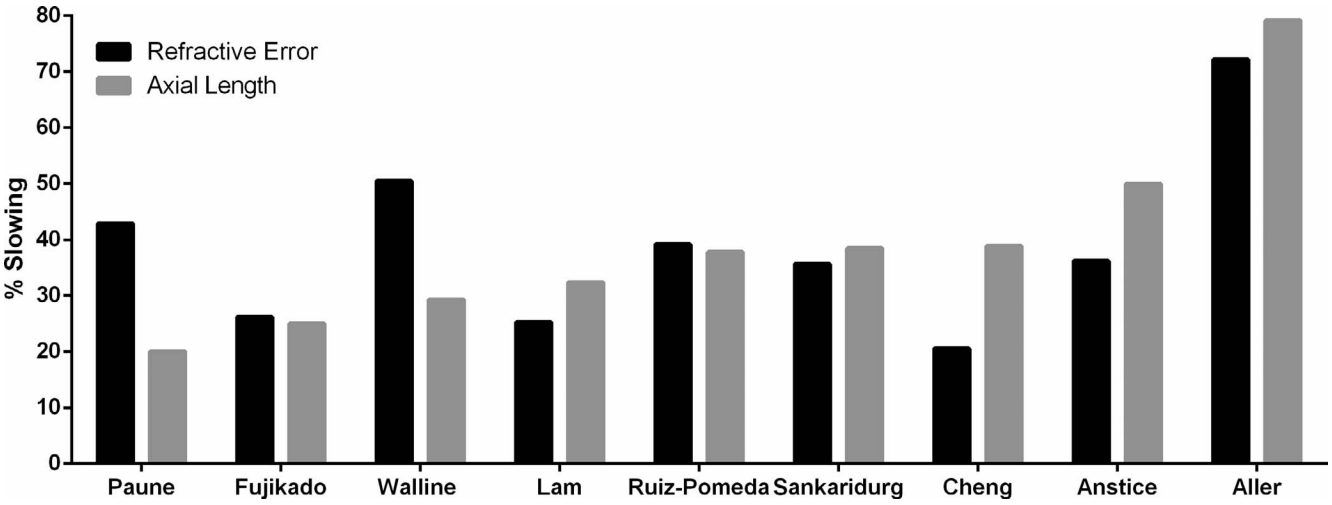

FIGURE. Percent slowing of change in refractive error and axial elongation for soft MF contact lens myopia control studies published in the peer-reviewed literature.

designed reverse geometry rigid GP lenses has revolutionized OK, by allowing sufficient reshaping of the cornea to be achieved with overnight wear. The reshaping is believed to be due to a redistribution of corneal epithelial cells following initial compression.[64] Although the initial goal of such therapies was to eliminate the need for daytime optical corrections, OK has proven to be effective in slowing myopia progression. OK also has been shown to induce relative myopic shifts in peripheral refractive errors in all meridians,[65] consistent with the most popular hypothesis for this myopia control effect,[66] although a role for altered higher-order aberrations cannot be excluded.[67,68]

Most studies on the effectiveness and reliability of OK for myopia control have focused on children,[60,69–75] with only limited reports on effects in adults.[63] They include two RCTs in children,[60,72] one randomized crossover trial,[61] and several longitudinal nonrandomized clinical trials. Details of these studies are summarized in Table 3.

In the earliest of these trials, the Longitudinal Orthokeratology Research in Children (LORIC) study,[69] 35 children aged 7 to 12 years and undergoing OK treatment, were monitored over 24 months. Comparative data were obtained from 35 historical controls (age-, sex-, and initial-spherical equivalent refractive error–matched children wearing SV spectacles).[20] Axial elongation in the OK group over the 2-year trial period was approximately half that in the control group (0.29 vs. 0.54 mm), with the respective increases in vitreous chamber depth largely accounting for this difference (0.23 vs. 0.48 mm). Following the LORIC study, other quasi-experimental studies on children with low to moderate myopia were conducted with similarly positive outcomes[70,71,74,75]; reported levels of control ranged from 32% to 55%, when changes were compared against those in children wearing either SV spectacles or SV soft contact lenses.

Results from the two published RCTs provided further evidence for the efficacy of OK as a myopia control treatment. In the first trial, the Retardation of Myopia in Orthokeratology (ROMIO) study,[72] axial elongation was reported to be slowed by an average of 43%, with treatment effects being proportionately larger in younger, more rapidly progressing myopic children (7–8 years: 20% versus 65% [control]) than in older children (9–10 years: 9% versus 13% [control]). Higher myopes (–5.75 D or above) were recruited into a second trial, the High Myopia–Partial Reduction Orthokeratology (HM-PRO) study[60] and randomly assigned into partial reduction (PR) OK and SV spectacles groups. As the PR OK treatment targeted a 4.00-D reduction only, treated subjects needed to wear SV spectacles to correct residual refractive errors during the day. Nonetheless, here also, axial elongation in the PR OK group was 63% less than that of the control group.

In a more recent study, the effect on "myopia progression" of OK was compared against conventional GP lenses using a novel experimental design,[61] in which one eye of each subject wore an OK lens and the other eye, a GP lens, each for two 6-month periods, with the lens type worn by each eye switched at the end of the first 6 months after a washout period of 2 weeks. The eye wearing GP lenses thus acted as a "self" control. The subjects were of East Asian ethnicity, aged 8 to 16 years. No increases in AL over either the first or second 6-month period were recorded for eyes subjected to OK, compared with increases of 0.04 and 0.09 mm respectively in eyes wearing the GP lenses. Note, however, that even the latter changes are small relative to changes recorded with control treatments in other studies.

All of the above studies used spherical design OK lenses and thus were confined to children with low astigmatism. However, a subsequent 2-year trial, the Toric Orthokeratology Slowing Eye Elongation (TO-SEE) study, involving children with moderate to high astigmatism and OK lenses with toric peripheries,[73] reported axial elongation to be 52% less than in their control group who wore SV spectacles.

Two relevant meta-analyses by Si et al.[76] and Sun et al.[77] have confirmed the effectiveness of OK for myopia control, although Si et al.[76] recommended further research, given that five of the seven studies included in their meta-analysis were from Asia.

A few studies suggest that early termination of OK treatment might lead to a greater increase in axial elongation and myopia in children,[61,78,79] although this has not been found to be the case in university students with adult-onset, progressive myopia.[80] Some studies also suggest that relative treatment efficacy may decrease with time.[75,81,82] Reduced treatment efficacy has been linked to lower baseline myopia,[69,82–84] although there may be confounding factors not accounted for. The magnitude of the treatment-induced power change has also been reported to impact myopia control, independently of baseline myopia,[85] although not in all studies.[71,72,75,86,87] On the other hand, larger pupil diameters, deeper anterior chambers, and steeper, more prolate corneas

Table 3. Summary of Results From Published Studies of Orthokeratology for Myopia Control

Study (Country)	Sample Size [Age Range, y]	Control Treatment	Study Design [Duration, y]	Loss to Follow-Up, %	Axial Elongation, mm	Slowing in Axial Elongation, %	Baseline Age, y	Baseline Myopia [SER, D]
Cho et al., 2005[69] (Hong Kong)	43 [+35 historical controls] 7–12	SV specs	Historical control [2]	19.0	OK: 0.29 ± 0.27 C: 0.54 ± 0.27	46	OK: 9.6 ± 1.5 C: 9.6 ± 0.69	OK: [−2.27 ± 1.09] C: [−2.55 ± 0.98]
Walline et al., 2009[70] (United States)	40 [+28 historical controls] 8–11	SCL	Historical control [2]	30.0	OK: 0.25 ± 0.27 C: 0.57 ± 0.27	55	OK: 10.5 ± 1.1 C: 10.5 ± 1.0	Unknown
Kakita et al., 2011[74] (Japan)	105 8–16	SV specs	Nonrandomized [2]	12.4	OK: 0.39 ± 0.27 C: 0.61 ± 0.24	36	OK: 12.1 ± 2.6 C: 11.9 ± 2.1	OK: [−2.55 ± 1.82] C: [−2.59 ± 1.66]
Hiraoka et al., 2012[75] (Japan)	59 ≤12	SV specs	Nonrandomized [5]	27.1	OK: 0.99 ± 0.47 C: 1.41 ± 0.68	30	OK: 10.04 ± 1.43 C: 9.95 ± 1.59	OK: [−1.89 ± 0.82] C: [−1.83 ± 1.06]
Santodomingo et al., 2012[71] (Spain)	61 6–12	SV specs	Nonrandomized [2]	13.1	OK: 0.47 C: 0.69	32	OK: 9.9 ± 1.6 C: 9.9 ± 1.9	OK: −2.15 ± 1.12 C: −2.08 ± 1.23
Cho and Cheung, 2012[72] (Hong Kong)	102 6–10	SV specs	Randomized [2]	23.5	OK: 0.36 ± 0.24 C: 0.63 ± 0.26	43	OK: 9.4 ± 1.4 C: 8.9 ± 1.6	OK: −2.05 ± 0.72 C: −2.23 ± 0.84
Chen et al., 2013[73] (Hong Kong)	80 6–12	SV specs	NR [2]	27.5	OK: 0.31 ± 0.27 C: 0.64 ± 0.31	52	OK: 9.4 ± 1.4 C: 8.9 ± 1.6	OK: −2.46 ± 1.32 C: −2.04 ± 1.09
Charm and Cho, 2013[89] (Hong Kong)	52 8–11	SV specs	Randomized [2]	46.2	OK: 0.19 ± 0.21 C: 0.51 ± 0.32	63	OK: Median 10, range 9.0–11.0 C: Median 10, range 8.0–11.0	OK: Median 6.50, range 6.0–8.30 C: Median 6.13, range 5.0–8.30
Swarbrick et al., 2015[61] (Australia)	32 8–16	GP	Contralateral eye Randomized crossover [1]	25	Phase 1 OK: −0.02 ± 0.05 C: 0.04 ± 0.06 Phase 2 OK: −0.04 ± 0.08 C: 0.09 ± 0.09	–	13.4 ± 1.9	Phase 1 OK: −2.43 ± 0.98 GP: −2.39 ± 0.93 Phase 2 OK: −2.60 ± 1.21 GP: −2.22 ± 1.10
Paune et al., 2015[52] (Spain)	70 9–16	SV specs	Nonrandomized [2]	44.3	OK: 0.32 ± 0.20 C: 0.52 ± 0.22	38	OK: 12.27 ± 1.76 C: 13.09 ± 2.79	OK: [−3.51 ± 2.13] C: [−3.61 ± 0.98]

SCL, soft contact lenses; SER, spherical equivalent refraction; C, control group; GP, gas-permeable rigid contact lenses.

are among ocular parameters that have been linked to slower axial elongation in children.[88]

2.3.5 Visual and Ocular Side Effects. Vision-related complaints tend to be defocus-related in origin across all optical interventions, and correctible with appropriate adjustment to prescriptions, although substantial changes to resolve the such complaints also may lessen the likelihood of adequate myopia control. Significant ocular side effects are largely limited to contact lenses used for myopia control. In OK wearers, pigmented ring formation[60,90] and altered corneal nerve pattern (fibrillary lines)[91,92] have been reported, although none of these changes appear to have adverse clinical ramifications. A number of cases of microbial keratitis associated with OK have been reported in the literature, more frequently encountered in the early years of OK,[93,94] with contact lens storage cases being one potential source of contamination.[95] Nonetheless, Bullimore and colleagues[96] compared the incidence of microbial keratitis associated with OK in children and adults and concluded that, within the limits of their study, there is no difference in the risk of microbial keratitis with OK and other overnight contact lens modalities, although the risk is higher for overnight compared with daily wear.

3. Pharmacological Control of Myopia

3.1 Introduction

In relation to pharmacological control of myopia progression, to-date topical atropine has dominated both clinical trials and clinical practice, where it is now used widely as either an approved product or off-label. Atropine is a nonselective irreversible antimuscarinic antagonist, with a long history of use in ophthalmology as a potent and long-acting mydriatic and cycloplegic agent. Clinically, it is used as a diagnostic aid in the assessment of refractive errors in very young children,[97] to penalize the preferred eye in therapy for amblyopia,[98] and to immobilize the iris and ciliary muscles as a component of therapy for uveal inflammatory conditions such as iritis.[99] Its use to treat myopia dates back to the 1960s.[100–103]

The earliest cohort studies involving topical atropine were published in the 1970s.[100–103] Since that time, numerous retrospective and cohort studies have been published.[104–112] The first randomized controlled trials (RCTs) to be published are those by Yen et al. (1989)[113] and Shih et al. (1999).[114] More recently, two large, back-to-back trials were undertaken in Singapore: the Atropine for Treatment Of Myopia studies (ATOM1 and 2),[115–119] followed by two smaller studies in China by Yi et al. (2015)[120] and Wang et al. (2017),[121] and a very recent larger trial in Hong Kong.[122] Table 4 summarizes details of these seven trials, including the tested atropine concentrations, which vary widely, from as low as 0.01% to 1.0%. Two other antimuscarinic drugs appear in these studies: tropicamide, which is a short-acting drug and was used as a control treatment, and cyclopentolate, which has an intermediate duration of action and was tested for its efficacy as a myopia control agent.

Other pharmacological approaches trialed for myopia control include topical timolol, a nonselective beta-adrenergic antagonist, and oral 7-methylxanthine (7-MX), an adenosine antagonist. The latter was approved for use in Denmark, as pharmacy-compounded tablets, with reimbursement from the Danish National Health Insurance for patients up to 18 years of age, after a small clinical trial of 7-MX in that country[123]; 7-MX is also generated by metabolism in the body from caffeine and theobromine, which are both ingredients of dark chocolate. To-date there have been no follow-up trials in other countries, although it remains a drug of interest, with related on-going studies in the monkey myopia model.[124]

Although recommendations for the use of ocular hypotensive drugs for myopia control appear in a number of early publications, including that by Curtin (1985),[125] well-described clinical trials of these agents are limited, although there are reports of positive treatment outcomes for epinephrine,[126,127] labetolol,[128] a combination of pilocarpine and timolol,[129] and timolol alone.[128] Denmark was the site of the largest RCT of twice-daily topical 0.25% timolol for myopia control, by Jensen (1991).[130] The driving principle for this approach is biomechanical (i.e., to lower IOP as a method of slowing ocular elongation). Topical timolol is widely available in many countries as a topical ophthalmic drug, approved for the treatment of open angle glaucoma.

Reviews covering pharmacological interventions for myopia control include one focused on primary research,[131] a Cochrane review,[56] and a more recent one focused on atropine.[132] In this article, results of relevant meta-analyses are also presented.

3.2 Atropine

3.2.1 Changes in Spherical Equivalent Refractive Error as an Outcome Measure. Based on changes in spherical equivalent refractive error as the outcome measure all studies have shown that atropine slows myopia progression. Bedrossian (1971)[100] in an early study of 150 children aged 7 to 13 years reported no myopia progression in 75% of eyes treated daily with 1% atropine over a 1-year period compared with only 3% of controls. Similarly another early study by Gimbel (1973)[103] in which 279 children received 1% atropine over 3 years reported a 66% reduction in myopia progression compared with that of 572 controls (–0.41 vs. –1.22 D).

The first two randomized controlled trials of atropine, both published in the 1990s, also reported very good control over myopia progression in children, with reductions exceeding 60% reported for the highest, 1% concentration. In the first randomized controlled trial by Yen and colleagues (1989),[113] 247 children aged 6 to 14 years received either topical 1% atropine, 1% cyclopentolate, or saline drops over a 1-year period. They reported 76% and 36% reductions in myopia progression in the groups treated with atropine and cyclopentolate, respectively, compared with the group treated with saline, although unfortunately, there was a large loss to follow-up (61%). In the second randomized controlled trial by Shih and colleagues (1999),[114] 200 children aged 6 to 13 years were treated with 0.5%, 0.25%, or 0.1% atropine over a 2-year period; reported reductions in myopia progression were 61%, 49%, and 42%, respectively, compared with children treated with 0.5% tropicamide as the control treatment.

The ATOM1 and 2 studies, which were performed between 1996 and 2013, involved 400 children, aged 6 to 12 years, randomized in each case, to atropine 1% and placebo in a 1:1 ratio in ATOM1, and to 0.5%, 0.1%, and 0.01% atropine in a 2:2:1 ratio in ATOM2.[115–119] Both trials involved a 2-year treatment period. On entering the studies, children had low to moderate myopia; baseline spherical equivalent refractive errors ranged between –1.0 and –6.0 D in ATOM1, and between –2.0 and –6.0 D in ATOM2. Overall, the profiles of the participants in these two trials were very similar, although slightly younger, with lower myopia in the first compared with the second trial (9.2 vs. 9.6 years; –3.4 vs. –4.7 D).[116,118] The reported mean progression rates for these trials were –0.2, –0.3, –0.4, and –0.5 D for the four atropine groups (1%, 0.5%, 0.1%, and 0.01%) compared with –1.2 D in the placebo group,[115–119] amounting to reductions in myopia progression compared with the latter group of approximately 80%, 75%,

Table 4. Summary of Design and Key Results From Randomized Trials Involving Topical Atropine for Myopia Control

Study (Country)	Size; Duration, y	Treatments	Age Range, y	Baseline Age, y*	Myopia Range, D	Average Myopia, D*	Change in SER*#	Change in AL, mm*#	Loss to Follow-Up, %
Yen et al. (1989)[113] (Taiwan)	247; 1	A 1% and Cyclo 1%	6, 14	10.5	−0.5, −4	−1.5 (0.9)	−0.2 D (76%)	-	61
				10.0		−1.4 (0.8)	−0.6 D (37%)		
		vs. Saline		10.4		−1.6 (0.9)	−0.9 D		
Shih et al. (1999)[114] (Taiwan)	200; 2	A 0.5%	6, 13	9.8	−0.5, −7	−4.9 (2.1)	−0.04 D/y (61%)	-	7
		A 0.25%		9.7		−4.2 (1.7)	−0.45 D/y (49%)		
		A 0.1%		8.9		−4.1 (1.5)	−0.47 D/y (42%)		
		vs. Trop 0.5%		8.3		−4.5 (1.8)	−0.61 D/y		
Chua et al. (2006)[118] (Singapore)	400; 2	A 1%	6, 12	9.2	−1, −6	−3.6 (1.2)	−0.3 (0.9) (77%)	−0.02 (0.35) (105%)	13
		vs. Placebo		9.2		−3.4 (1.4)	−1.2 (0.7)	0.38 (0.38)	
Chia et al. (2016)[119] (Singapore)	400; 2	A 0.5%	6, 12	9.5 (1.5)	−2, −6	−4.5 (1.5)	−0.3 (0.6) (75%)	0.27 (0.25)	11
		A 0.1%		9.7 (1.6)		−4.8 (1.5)	−0.4 (0.6) (67%)	0.28 (0.28)	
		A 0.01%		9.7 (1.5)		−4.7 (1.8)	−0.5 (0.6) (58%)	0.41 (0.32)	
Wang et al. (2017)[121] (China)	126; 1	A 0.5%	5, 10	9.1 (1.4)	−0.5, −2	−1.3 (0.4)	−0.8 (160%)	−1.1 (300%)	13
		vs. Placebo		8.7 (1.5)		−1.2 (0.3)	−2.0	+0.50	
Yi et al. (2015)[120] (China)	140; 1	A 1%	7, 12	9.9 (1.4)	−0.5, −2	−1.2 (0.3)	+0.3 (0.2) (138%)	−0.03 (0.07) (109%)	6
		vs. Placebo		9.7 (1.4)		−1.2 (0.3)	−0.9 (0.5)	0.32 (0.15)	
Yam et al. (2018)[122] (Hong Kong)	438; 1	A 0.05%	4, 12	8.45 (1.81)	−1 (min)	−3.98 (1.69)	−0.27 (0.61)	0.20 (0.25)	12
		A 0.025%		8.54 (1.71)		−3.71 (1.85)	−0.46 (0.45)	0.29 (0.20)	
		A 0.01%		8.23 (1.83)		−3.77 (1.85)	−0.59 (0.61)	0.36 (0.29)	
		vs. Placebo		8.42 (1.72)		−3.85 (1.95)	−0.81 (0.53)	0.41 (0.22)	

Cyclo, cyclopentolate; min, minimum; Trop, tropicamide.
* Standard deviations in brackets.
# Percent change from placebo.

67%, and 58%, respectively. Loss to follow-up over the 2-year treatment periods was 13% and 11% for ATOM1 and ATOM2, respectively.

Analysis of the changes in the ATOM1 study, year by year, revealed a hyperopic shift in the 1% atropine group of +0.03 versus −0.79 D in the control arm.[118] The comparable values for the 0.5%, 0.1%, and 0.01% atropine treatment groups included in ATOM2 are −0.17, −0.31, and −0.43 D respectively.[116] Thus, myopia progression rates appear to directly reflect the atropine concentration used, decreasing with increasing concentration. However, dose-dependent differences were not apparent over the second year of the trial, with all three concentrations achieving similar slowing of myopia progression. The net increases in myopia over the 2-year trial period were −0.49, −0.38, and −0.30 D for the 0.01%, 0.1%, and 0.5% concentrations, respectively.[116]

Two of three more recent RCTs involved relatively high concentrations of atropine, being 1% ($n = 126$) and 0.5 % ($n = 132$) in the studies by Yi et al. (2015)[120] and Wang et al. (2017),[121] respectively. Both reported hyperopic shifts in the atropine-treated groups, presumably reflecting, at least in part, the enduring strong cycloplegic action of this treatment, while continued progression in control groups over the same period of time was observed (i.e., +0.3 vs. −0.9 D and +0.5 vs. −0.8 D). Three lower concentrations of atropine, 0.01%, 0.025%, and 0.05%, were tested in the most recent of these studies, by Yam et al. (2018) ($n = 438$),[122] who reported a concentration-dependent reduction in myopia progression, with the highest concentration approximately halving the rate of axial elongation, as compared with the placebo control. All concentrations were well tolerated.

Although retrospective studies typically lack the same level of control of key study design variables as RCTs, overall their results are consistent with those of the RCTs just described. Several retrospective, cohort studies have tested higher, 0.5% to 1.0% concentrations of atropine, reporting treatment effects ranging from 70% to 100%.[104–106,108,109] In one of four studies involving lower concentrations of atropine, children treated with 0.025% atropine over 22 months were reported to progress by an average of −0.28 D per year, compared with −0.75 D in untreated children (a reduction of 63%).[107] Similarly, Fang and colleagues (2010),[111] using the same 0.025% atropine concentration with "premyopic" children (spherical equivalent refractive error: +1 to −1 D), reported a reduction in incident myopia and reduced progression compared with controls (21% versus 54%, −0.14 vs. −0.58 D). Wu and colleagues[110] also noted reduced progression with atropine treatments, although interpretation of their study findings is complicated by the variation in atropine concentrations used to treat individual patients over the 4.5-year monitoring period, between 0.05% and 0.1%; the overall mean progression was −0.23 D per year, compared with −0.86 D per year in historical "controls." A surprisingly low average myopia progression of −0.1 D per year was reported for 0.01% atropine in the only retrospective study involving this concentration, referenced against a control rate of −0.6 D per year,[112] although interestingly, this study included children of both Asian and Caucasian ethnicity.

3.2.2 Changes in AL as an Outcome Measure. Fewer studies have included AL as an outcome measure although arguably it more accurately reflects the treatment effect, being free from the confounding effect of cycloplegia, which affects refractive error data (see accompanying IMI – Clinical Myopia Control Trials and Instrumentation Report).[133] Notably, cycloplegic agents, by reducing ciliary muscle tone, reduce manifest myopia. Indeed, the latter effect likely accounts for, at least in part, the more promising results of lower concentrations of atropine, when expressed in refractive error terms, as compared with AL changes, given that the ciliary muscle is readily accessible to topically applied drugs. It can be further argued that AL changes are more clinically relevant, given that many of the pathological complications of myopia are by-products of excessive eye elongation (see accompanying IMI – Defining and Classifying Myopia Report).[134]

In the ATOM1 study, in which AL was measured using A-scan ultrasonography, changes in AL at the end of years 1 and 2 of −0.14 and −0.02 mm, respectively, were reported for children treated with 1% atropine compared with 0.20 and 0.38 mm in the placebo group.[118]

In the ATOM2 study, in which ALs were measured using a noncontact method (IOL Master; Zeiss, Oberkochen, Germany), changes in AL over the first year were 0.11, 0.13, and 0.24 mm in the 0.5%, 0.1%, and 0.01% atropine concentrations respectively.[116] Equivalent values for the total 2-year study period were 0.27, 0.28, and 0.41 mm. Without a control group, the true effect of lower doses of atropine on axial elongation is difficult to evaluate, given that there was also no difference between changes in the group treated with 0.01% atropine and historical controls in the ATOM1 study.[118] However, although AL increases with the lowest, 0.01% concentration was greatest over the first year in the ATOM2 study, the changes with the 0.5%, 0.1%, and 0.01% concentrations were more similar over the second year of the study (0.16, 0.15, and 0.17 mm, respectively).[116]

Of the two more recent RCTs, one also used A-scan ultrasonography, as in ATOM1; over the 1-year of this study, the mean change in AL was −0.03 mm in the 1% atropine treatment group, compared with 0.32 mm in the control group.[120] In the second RCT, which involved 0.5% atropine, AL data are not provided in an easily accessible form, although there appears to be a surprising reduction over the 1-year study period in AL of approximately 0.4 mm in the treated children compared with an increase of 0.5 mm in the control group.[121]

3.2.3 Poor and Nonresponders to Atropine and Time-Dependent Reductions in Efficacy. Although the studies just described confirm the efficacy of topical atropine as a myopia control treatment, the range of responses within treatment groups also implies that some individuals respond less well and there is also evidence that treatment efficacy may change over time.

In the early studies by Bedrossian,[100,101] 5% to 25% of children treated with 1% atropine for 1 year were reported to exhibit continued myopia progression. Likewise, for the same treatment regimen, progression of more than −0.5 D was reported in 22% of children in the Yen et al. study[113] and 12% of children in the ATOM1 study.[135] Nonetheless, results from the Shih et al. study[114] imply a related dose-dependence, with 4%, 17%, and 33% of children showing myopic progression >1.0 D, with 0.5%, 0.25%, and 0.1% atropine, respectively, after 1 year of treatment (compared with 44% of those treated with 0.5% tropicamide). Likewise, for the ATOM1 and ATOM2 studies, 4%, 7%, 11%, and 18% of children recorded progression rates of >1 D after 1 year of treatment with 1.0%, 0.5%, 0.1%, and 0.01%, respectively. Poor responders, as identified through multivariate analysis, tend to be younger, to be more myopic at baseline, to start wearing spectacles at a younger age, and to have myopic parents.[135] Note, however, that the trends evident after year 1 in the ATOM1 and ATOM2 studies were not sustained over the total 2-year treatment period due to loss of efficacy with the higher doses over the second year of treatment; thus, after 2 years, progression of >1 D was reported in 14%, 15%, 17%, and 17% of children treated with 1.0%, 0.5%, 0.1%, and 0.01% atropine, respectively.[116,118] Nonetheless, although the results of the ATOM studies point to some loss of treatment efficacy with time, at least with the higher concentrations of atropine, those from the study by Wu and colleagues,[110] which involved concentrations between 0.05% and 0.1%, suggest that treatment effects can be maintained for up to 4.5 years.

3.2.4 Rebound Effects After Termination of Atropine Treatment. The first evidence of apparent rebound effects on myopia progression after the termination of atropine treatment comes from the study of Bedrossian (1979),[101] which involved monocular 1% atropine, with treatment being alternated between right and left eyes on a yearly basis for 4 years; progression rates for eyes under treatment ranged from 0.17 to 0.29 D, substantially lower than those in fellow, untreated eyes of 0.81 to 0.91 D. However, it is not possible to judge whether these values represent exaggerated progression, due to the lack of an untreated control group. For 33 children reviewed 1 and 3 years after stopping atropine, myopia progression eventually slowed to an annualized rate of 0.06 D per year, presumably reflecting at least in part, the normal age-related decline in myopia progression.

In the ATOM studies, concentration- and age-related rebound in myopia progression was observed in children followed for a year after termination of atropine treatment.[115,117,119] Measured in refractive error terms, this rebound effect is likely to reflect, at least in part, the recovery of ciliary muscle tone, which will have been most strongly inhibited by the highest concentration. However, pharmacodynamic mechanisms are also likely to be at play; specifically, continuous long-term exposure to pharmacological antagonists is well known to cause upregulation of receptors, resulting in a loss of efficacy (tolerance) to the applied drug over time, and exaggerated symptoms when treatment is terminated.[131] Younger children and those previously treated with higher concentrations of atropine proved most at risk in these ATOM studies. Specifically, over a 1-year washout period following 2 years of treatment, progression of >0.5 D was observed in 68% and 59% of children treated with 0.5% and 0.1% atropine compared with 24% for 0.01% atropine. For 0.01% atropine, progression of >0.5 D was observed in 62%, 27%, and 8% of children who were 8 to 10, 10 to 12, and 12 to 14 years old, respectively, when the treatment was terminated.[119] Interestingly, children who recorded almost no myopia progression (<0.05 D/y) in the year before the termination of treatment were less likely to show a rebound effect, compared with those showing residual progression (0.12–0.24 D/y).[119] Note also that at the end of the washout period, eyes previously treated with the highest, 1% atropine concentration were shorter than the other groups, despite an increase in the rate of elongation relative to treatment values.[115]

3.2.5 Side Effects of Topical Atropine Treatment. The primary ocular side effects of topical atropine reflect the inhibitory actions of atropine on the iris sphincter and ciliary muscles, resulting in mydriasis and reduced accommodation and symptoms of glare and blur at near. Such side effects may lead to poor compliance on the part of users, as suggested in some studies.[114] That they can also be effectively addressed together through the prescription of tinted (photochromatic), progressive spectacles is reflected in the relatively low loss to follow-up rate (13.5% at 2 years) in the ATOM1 study, which applied this strategy.[118] As expected, the severity of these side effects was concentration-dependent; they also may be ethnicity-dependent. With 0.5% and 0.1% concentrations, pupil dilatation by 3.5 and 2.3 mm, respectively, and loss of accommodation by up to 10 to 11 D were documented in the ATOM studies, with much smaller changes of approximately 1 mm and 4 D with 0.01% atropine.[116,118] Consistent with these results, only 7% of subjects treated with 0.01% atropine took up the offer of photochromatic progressive spectacles, compared with 60% to 70% treated with the higher 0.1% and 0.5% concentrations.[116] Fang and colleagues[111] noted similar findings of glare with 0.025% atropine, with 16% complaining, although none reported near blur. A very low incidence of side effects was also reported in the study of Caucasian children by Clark et al.,[112] in which only 2 (4%) of 49 children using 0.01% atropine reported intermittent blur and glare. The trends just described are also consistent with

results of a meta-analysis by Gong et al.,[136] who reported photophobia rates of 6.5%, 17.5%, and 43.1% for low (0.01%), moderate (0.01%–0.5%), and high (1%) concentrations. They also noted less near vision symptoms with the low, compared with moderate and high concentrations of atropine (2.3%, 11.9%, and 11.6%, respectively; Table 5).

Allergic reactions represent the other, most common ocular side effect of atropine, with symptoms ranging from mild itch to follicular reactions and lid erythema, and reported incidences ranging from 0% to 4%.[108,114,118–120,136] More severe forms of allergic keratoconjunctivitis and lid erythema and rashes also can occur, and on occasion, may be sufficiently severe as to preclude continued use of atropine.

Concerns over the possibility of adverse effects on IOP, lens, and retina secondary to pupil dilation appear not to be justified.[102] In one study involving 1% atropine, IOPs remained within 5.5 mm Hg of baseline values.[118] Likewise, Wu and colleagues[137] and Lee and colleagues[138] reported no significant changes in IOP over a range of atropine concentrations. To-date there also has not been any report of lenticular changes linked to chronic topical atropine therapy applied for 2 to 3 years.[117,137] Studies of retinal effects of chronic topical atropine are limited to MF electroretinogram (mfERG) and full-field electroretinogram (ffERG) recordings as part of the ATOM studies. In ATOM1, no significant differences in mfERG amplitude and implicit times between treatment and placebo groups for posterior pole responses were found after 2 years of treatment.[139] In the ATOM2 study, ffERG recordings revealed a reduction in cone function over time (i.e., after 24 and 32 months), but the changes appeared tied to AL changes, with no significant atropine concentration–related differences.[140]

Systemic adverse effects of topical atropine eye drops are also possible, with the risk of systemic toxicity being higher in younger patients, due to their smaller body size. Possible side effects include dry skin, mouth, and throat, drowsiness, restlessness, irritability, delirium, tachycardia, and flushing of the face or neck.[141] Nonetheless, in two of the largest clinical trials of topical atropine, the ATOM1 and ATOM2 studies,[115–119] none of the reported adverse events were thought to be associated with atropine, and there have been no reports of significant adverse systemic side effects in other studies using topical atropine for myopia progression (i.e., in children older than 6 years).[140] However, practitioners using atropine need to be aware of these side effects, as some children may be hypersensitive to atropine.[142]

3.3 Pirenzepine

3.3.1 Effects on Myopia Progression. Pirenzepine, an M1 muscarinic receptor antagonist, has shown promising effects in reducing myopia progression in children.[145–147] A double-masked, placebo-controlled, randomized study in an Asian population used 2% pirenzepine gel administered twice daily and found myopic progression was reduced by 44% and axial elongation by 39% compared with the control group over 12 months.[146] A US-based, two year multisite clinical trial yielded a similar reduction in myopia progression with 2% pirenzepine compared to the placebo treatment, at 41% (0.58 vs. 0.99 D respectively).[147] However, the difference in axial elongation between the groups (0.28 vs. 0.40 mm) did not reach statistical significance. At this point in time, pirenzepine is not currently available as a treatment option and appears not to be targeted by industry for development.

3.3.2 Side Effects of Pirenzepine. Numerous side effects were noted with 2% pirenzepine gel administered twice daily over 12 months in one RCT involving an Asian cohort,[146] whereas in contrast, 2-year results from the multisite US-based clinical trial found the drug to have a clinically acceptable safety profile.

Table 5. Summary of Design of Meta-Analyses Covering Trials Involving Topical Atropine for Myopia Control

Studies and Design Features	Key Findings
Huang et al. (2016)[143] 4 RCT studies	0.5−1.0% atropine: 0.68 D/y and −0.21 mm/y 0.1% atropine: 0.53 D/y and −0.21 mm/y 0.01% atropine: 0.53D/y and −0.15 mm/y
Li et al. (2014)[144] 4 RCT and 7 cohort studies	Asian children: 0.54 D/y White children: 0.35 D/y Odds ratio: 4.47 (95% CI 0.91−21.94)
Gong et al. (2017)[136] 7 RCT and 9 cohort studies	0.57−0.62 D/y and 0.27 mm/y (higher doses) Pooled effect sizes RCTs: 2.67 (95% CI 1.46−3.88) Cohort studies: 1.30 (95% CI 0.61−1.98) Higher doses: 3.67 (95% CI 1.85−5.50) Lower doses: 0.68 (95% CI 0.08−1.27)

3.4 7-Methylxanthine

The study of oral 7-MX, an adenosine antagonist, in human subjects has been limited to Denmark. In relation to myopia control, it has been the subject of a number of animal studies (see accompanying IMI – Report on Experimental Models of Emmetropization and Myopia).[30] An initial small ($n = 68$) 12-month RCT tested 400 mg of 7-MX once per day in myopic children aged 8 to 13 years and included a placebo control.[123] The study was extended for a further 12 months over which all subjects were treated with 7-MX, either as a once or twice per day treatment, before treatment was terminated in all subjects. Although slowing of axial elongation and slowing of myopia progression were both recorded in this trial, treatment effects were relatively small. Efficacy was apparently tied to pretreatment (baseline) rates of eye growth and myopia progression. Thus, for those classified as having moderate and high axial growth rates, the differences between 7-MX and placebo groups were –0.055 mm/y (95% confidence interval [CI] –0.114 to +0.005 mm/y, $P = 0.073$), and –0.031 mm/y (95% CI –0.150 to +0.087 mm/y, $P = 0.593$), respectively. The matching refractive error differences were –0.108 and +0.070 D/y, with neither difference reaching statistical significance. Interpretation of the 2-year data collected from this study is challenging, as all subjects at this time had been treated for at least 12 months with 7-MX, with the only placebo data being that contained in the initial 12-month data set. Overall, a reduction in eye elongation appears to be achievable in children with moderate baseline axial growth rates, although it may not be achievable in children with high baseline axial growth rates. As a currently nonregistered compounded drug in Denmark, dosage decisions for 7-MX remain the responsibility of the prescribing doctor.

3.4.1 Side Effects of 7-MX. The treatment appears to be safe. In the above clinical trial, both participants and their parents were subject to structured interviews about gastrointestinal, cardiopulmonary, and central nervous system–related side effects. No ocular or systemic side effects were reported.[123]

3.5 Timolol

3.5.1. Effects on Myopia Progression. The RCT by Jensen[130] had three treatment arms: SV spectacles ($n = 51$), bifocal spectacles ($n = 57$), and SV spectacles + timolol ($n = 51$). The timolol arm used 0.25% timolol maleate, twice a day. Children were followed for 2 years, with additional examinations 1 year after completion of the trial. The results were generally disappointing, with mean myopia progression over the 2-year study period in the control and timolol groups being almost identical (1.14 vs. 1.18 D, respectively), and not significantly different from each other. This was despite confirmation that timolol lowered IOP significantly, by approximately 3 mm Hg, with those with high IOP showing the largest treatment effect. Also, although there appeared to be a trend toward increasing noncompliance over time, progression rates did not appear to reflect compliance. Curiously, higher progression rates appeared associated with higher IOP in the control group, with this relationship reaching statistical significance for the girls, with a similar but not significant trend for boys.

3.5.2. Side Effects of Timolol. In the above trial, side effects resulted in timolol treatment being discontinued in six children. For five of the children, symptoms were ocular in nature, involving stinging, itching, and foreign body sensations, these symptoms being possibly related to the formulation rather than to timolol per se.[130] Although reports of changes in ciliary muscle tone with timolol have been reported,[148] this effect tends to be small in magnitude and unlikely to explain the disturbance to vision reported for two subjects. More serious systemic side effects of headaches and difficulty in breathing were reported in only one subject, although these are well-known side effects of beta-blockers.[148]

4. Environmental Influences and the Role of Time Outdoors for Myopia Prevention and Control Over Progression

4.1 Introduction

> "*A robust child, well fed, enjoying a maximum of outdoor life, is less likely to get tired eyes and subsequent stretching of the coats of the eyeball and myopia than is a child that is cooped up indoors all day, sitting over lessons, and never joining in vigorous outdoor games.*"

This advice from Harman (1916),[149] a century ago, was based on his observations that myopic children tended to engage in more indoor, near-viewing tasks than their emmetropic peers, coupled with the obvious point that, at any moment in time, a child could be only either indoors or outdoors.

The above example reflects much early interest in environmental influences on ocular development. The first rigorous scientific evaluation of the relationship between time spent outdoors and myopia was reported in 1989 by Pärssinen et al.[150] In a clinical trial testing whether bifocal spectacles slowed myopia progression, 237 myopic children were asked to complete a questionnaire detailing, among other things, the time they spent engaged in outdoor activities. Self-reported time outdoors was found to correlate with the child's myopia progression over 3 years ($r = 0.17$, $P = 0.004$). On further analysis, the association was found to be largely restricted to boys.[151] The authors surmised that the correlation with time outdoors might be attributable "simply to being away from reading and close work." Perhaps because other myopia researchers also made the very plausible assumption that near work and outdoor play were inversely correlated, investigation of the link between time outdoors and myopia stalled for another decade, until the publication of a series of influential studies that stressed the potential importance of time outdoors or time engaged in sports/outdoor activities as being protective against myopia.[152–157] It has been hypothesized that the increased intensity of visible light outdoors may be one factor playing a critical role in these protective effects.[155] Data from animal studies indicating that bright light exposure during the day protects against the development of experimental form-deprivation myopia (findings are less consistent for lens-induced myopia)[158,159] support this notion, although other factors such as differences in the patterns of retinal image blur exposure associated with the outdoor environment also may play roles.[160,161] Achieving light levels indoors comparable with those typical of the outdoor environment would be challenging, even with high-efficiency light emitting diode (LED) sources.

4.2 Outdoor Studies

In the past decade, the relationship between time outdoors and myopia has been extensively studied.[162–166] Although several cross-sectional[152,155,167–170] and cohort studies[154,171–175] have addressed the issue of the protective role of increased outdoor time on myopia prevention, randomized controlled community-based trials are limited to four studies.[176–179] Because the evidence linking time outdoors to the prevention of incident myopia is stronger than that linking it to slowing the progression of existing myopia,[164] with potential implications for the ocular health management strategies for children, these two lines of enquiry are reviewed separately. The key features of the randomized controlled trials are summarized in Table 6 and of other relevant studies in Table 7.

4.2.1 Outdoors Studies and Myopia Onset. A recent randomized controlled trial among Chinese elementary school children in Guangzhou (GOAL),[177] reported a 9.1% reduction in the myopia incidence rate among children participating in an outdoor program that included a 40-minute-long, compulsory outdoor sports class at the end of each school day compared with the control group (i.e., 30.4% compared with 39.5% [$P < 0.01$]). Similar protection was reported in an earlier, albeit much smaller, intervention study involving Taiwanese primary school children; the myopia incidence rates were 8.4% and 17.7% for the intervention and control groups, respectively (9.2% reduction, $P = 0.001$).[176] A third large-scale trial of primary school children, also based in China, reported a reduction in the myopia incidence rate by 4.8% in the intervention group compared with the control group (3.7% versus 8.5%).[178] Most recently, an intervention trial in Taiwan involving grade 1 school children exposed to increased outdoor time during school hours (approximately 40 minutes per day), coupled with encouragement of greater outdoor time outside of school hours, reported a modest intervention-related reduction in the myopia incidence rate (14.5% versus 17.4%, $P = 0.054$).[179] The smaller reduction in myopia incidence in this study compared with the previous Taiwan-based intervention study[176] may reflect the greater daily outdoor time of the intervention (80 minutes) in the earlier study, coupled with the recent introduction of the "Tien-Tien 120" policy designed to promote 120 minutes of outdoor time per day in Taiwanese schools, which would have increased the outdoor time of all participants in the trial.

The association between increased time spent outdoors and protection against myopia in children and adolescents has been summarized in a recent meta-analysis,[162] which linked every additional 1 hour of outdoor time per week with a reduction in the risk of myopia by 2% (odds ratio 0.98; $P < 0.001$). This pooled estimate equates to an odds ratio of 0.87 for every additional 1 hour of outdoor time per day.[162] One

Table 6. Outdoor Intervention Studies for Myopia Prevention and Progression

Author (Year), Study Location, Study Design	Type of Intervention	Age at Baseline, Refraction	Main Findings
He et al. (2015)[177] China School-based, randomized clinical trial (GOAL study); $N = 1848$	Intervention group: One additional 40-minute class of outdoor activities on each school day. Control group: No additional class. 3-year RCT	6–7 y, Cycloplegic auto-refraction	Myopia incidence rate: Intervention group: 30.4%; Control group: 39.5%; Diff: −9.1 (95% CI −14.1 to −4.1); $P < 0.001$) after 3 y Myopia progression rates: Intervention group: −1.42 D (95% CI −1.58 to −1.27 D); Control group: −1.59 D (95% CI −1.76 to −1.43 D) Diff: 0.17 D (95% CI 0.01 to 0.33 D); $P = 0.04$ after 3 y Lost to follow-up: 4.7%
Jin et al. (2015)[178] China School-based, prospective, interventional study; $N = 3051$	Intervention group: Two additional 20-minute ROC programs, in the morning and afternoon. Control group: No program. 1-year RCT	6–14 y, Cycloplegic auto-refraction	Myopia incidence rate: Intervention group: 3.7%; Control group: 8.5%; Diff: 4.8% ($P = 0.048$) after 1 year Myopia progression rate: Intervention group: −0.10 ± 0.65 D; Control group: −0.27 ± 0.52 D; Diff: 0.17 D ($P = 0.005$) after 1 year Lost to follow-up rate: 10.7%
Wu et al. (2013)[176] Taiwan School-based, interventional trial; $N = 571$	Intervention group: Two additional 40-minute ROC programs, in the morning and afternoon. Control group: No program 1-year RCT	7–11 y, Cycloplegic auto-refraction	Myopia incidence rate: Intervention group: 8.41%; Control group: 17.65%; Diff: 9.24% ($P = 0.001$) after 1 year Myopia progression rate: Intervention group: −0.25 ± 0.68 D; Control group: −0.38 ± 0.69 D; Diff: 0.13 D ($P = 0.029$) after 1 y
Wu et al. (2018)[179] Taiwan School-based interventional trial; $N = 693$	Intervention group: 40-minute ROC in morning and encouragement to undertake 4 additional outdoor leisure activity programs; in addition to 120 min/d outdoors during school hours ("Tien-Tien 120"), 150 min/wk outdoor sports ("Sport and Health 150"). Control group: 120 min/d outdoors during school hours ("Tien-Tien 120"), 150 min/wk outdoor sports ("Sport and Health 150"). 1-year RCT	6–7 y, Cycloplegic auto-refraction	Myopia incidence: Intervention group: 14.5%; Control group: 17.4%; Diff: 2.9% ($P = 0.054$) after 1 year Myopia progression: Intervention group: −0.35 ± 0.58 D; Control group: −0.47 ± 0.74 D; Diff: 0.12 D (95% CI 0.05 to 0.19; $P = 0.002$) after 1 year

GOAL, Guangzhou Outdoor Activity Longitudinal study; ROC, Recess Outside the Classroom; Diff, Difference.

surprising outcome from epidemiology studies in children has been the consistent finding that the time children spend engaged in near work outside of school is not, in fact, related to the time spent outdoors; instead of the expected inverse relationship, most investigations have found no correlation between time engaged in near work and time outdoors,[154,155,167,172,174,180] although there have been exceptions in which an inverse correlation has been reported.[181] Thus, certain children seem to spend relatively long times, both outdoors and indoors, engaged in reading or studying, whereas other children spend little time doing either. However, it must also be recognized that most such studies have relied on subjective reporting of time spent in such activities.

4.2.2 Outdoor Studies and Myopia Progression. The evidence for outdoor time being protective against myopia progression is mixed.[174] In two of the four randomized studies referred to above, the effect of increased outdoor exposure on myopia progression was weaker than that on incident myopia. In the first Taiwanese study, mean progression rates in intervention versus control groups differed by 0.12 D ($P = 0.18$) in myopic children and by 0.18 D ($P = 0.02$) in nonmyopic children, with an overall difference of 0.13 D ($P = 0.029$; Table 6). Similarly, in the more recent intervention study in Taiwan, an overall 0.12 D difference in progression was observed (–0.35 vs. –0.47 D, $P = 0.002$), with significant effects on progression rates observed in both myopic and nonmyopic children. In this study, children spending greater time exposed to bright outdoor light conditions (>1000 lux) each day at school, as measured by wearable sensors, also exhibited significantly slower myopia progression (0.14 D, $P = 0.02$). Substantial differences in myopia progression rates between the two China-based studies (e.g., −1.59 vs. −0.27 D; control groups), are also reflected in differences in the statistical significance of the difference between intervention and control groups, which was 0.17 D for both groups (−1.42 vs. −1.59 D, $P = 0.04$; –0.10 vs. –0.27 D, $P = 0.005$).

Seasonal trends in myopia progression have been interpreted as indirect evidence of outdoor effects on myopia

Table 7. Outdoor Studies for Myopia Prevention and Progression

Author (Year) Study Location, Study Design	Age at Baseline, Refraction	Main Findings
Prevention		
Jones et al. (2007)[154] USA (OLSM), cohort study; $N = 514$	8–9 y, cycloplegic auto-refraction	Time outdoors (h/wk) and incident myopia (SER ≤ -0.75 D): OR = 0.91 (0.87 to 0.95); $P < 0.0001$
Guggenheim et al. (2012)[172] UK, cohort study (ALSPAC); $N = 7747$	7 y, noncycloplegic auto-refraction	Time outdoors (h/wk) and incident myopia (SER ≤ -1.00 D): HR = 0.76 (95% CI 0.60–0.96); $P = 0.02$; Lost to follow-up: 37.6%
French et al. (2013)[164] Australia, (SAVES), cohort study; $N = 2103$; 5–6-y follow-up	6 and 12 y, cycloplegic auto-refraction	Time outdoors (h/wk) and incident myopia (SER ≤ -0.50 D): 12-y-olds: OR = 2.84 (95% CI 1.56–5.17) $P < 0.0001$; 17-y-olds: OR = 2.15 (95% CI 1.35–3.42); $P = 0.001$; Lost to follow-up: 51.6%
Mutti et al. (2002)[152] USA (OLSM), cross-sectional; $N = 336$	13–14 y, cycloplegic auto-refraction	Time outdoors (h/d) and myopia (SER ≤ -0.75D): OR = 0.92 (95% CI, 0.86 to 0.97); $P = 0.005$
Rose et al. (2008)[155] Australia (SMS), cross-sectional; $N = 2339$	6 and 12 y, cycloplegic auto-refraction	Time outdoors (h/d) and SER: 6-y-olds: $\beta = 0.05$; $P = 0.009$; 12-y-olds: $\beta = 0.07$; $P < 0.0003$
Dirani et al. (2009)[167] Singapore (SCORM), cross-sectional; $N = 1249$	11–20 y, cycloplegic auto-refraction	Time outdoors (h/d) and myopia (SER ≤ -0.50 D): OR = 0.90 (95% CI 0.84–0.96); $P = 0.004$
Low et al. (2010)[168] Singapore (STARS), cross-sectional; $N = 3009$	6–72 mo, cycloplegic auto-refraction	Time outdoors (h/d) and myopia (SER ≤ -0.50 D): OR = 0.95 (95% CI 0.85–1.07); $P = 0.44$
Guo et al. (2013)[169] China, cross-sectional; $N = 681$	5–13 y, noncycloplegic auto-refraction	Time outdoors (h/d) and myopia (SER ≤ -1.00 D): OR = 0.32 (95% CI 0.21–0.48); $P < 0.001$
Progression		
Jones-Jordan et al. (2012)[157] USA, cohort study (CLEERE); $N = 835$	6–14 y, cycloplegic auto-refraction	Time outdoors (h/wk) and SER change: $\beta = 0.03$ (99% CI −0.03 to 0.08); $P > 0.01$ for additional 10 h of outdoor time/wk
Li et al. (2015)[174] China, cohort study; (ACES), $N = 2267$	10–15 y, cycloplegic auto-refraction	Time outdoors (h/d) and AL change: $\beta = -0.036$ (95% CI −0.063 to −0.009); $P = 0.009$; Lost to follow-up: 16.6%

ACES, Anyang Childhood Eye study; ALSPAC, Avon Longitudinal Study of Parents and Children; CLEERE, Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error study; HR, hazard ratio; OLSM, Orinda Longitudinal Study of Myopia; OR, odds ratio; SAVES, Sydney Adolescent Vascular and Eye Study; SCORM, Singapore Cohort study of Risk Factors for Myopia; SMS, Sydney Myopia Study; STARS, Strabismus, Amblyopia and Refractive error Study.

progression, with faster myopia progression during the darker winter than the brighter summer months.[182,183] For example, the US-based COMET study reported less myopia progression in a cohort of ethnically diverse children across the summer than winter (–0.14 ± 0.32 vs. –0.35 ± 0.34 D, respectively; $P < 0.0001$).[183] Similar differences in myopia progression were reported among Chinese children (–0.31 ± 0.25 vs. –0.53 ± 0.29 D; $P < 0.001$), with axial elongation data being consistent with these refractive error data, that is, eyes elongated less in summer than in winter (0.17 ± 0.10 vs. 0.24 ± 0.09 mm; $P < 0.001$).[182]

4.3 Vitamin D and Myopia

Inadequate vitamin D has been suggested as a mechanism linking myopia and insufficient time spent outdoors.[184,185] Apart from dietary intake of vitamin D from animal products and vitamin supplements, it is also synthesized in the skin when exposed to sunlight and thus ultraviolet (UV) radiation. Both sources contribute to serum levels of vitamin D. A number of studies have reported lower levels of serum vitamin D in myopes compared with non-myopes.[185–191] Although an association between serum vitamin D and refractive error might seem inevitable, given the association between sunlight exposure outdoors and myopia (i.e., serum levels of vitamin D might simply represent a surrogate for outdoor exposure), evidence of a causal relationship comes from the smaller number of investigations that have reported serum vitamin D to be significantly associated with myopia (or greater AL) after adjusting for time outdoors.[187,189,192,193] Nonetheless, two studies that addressed the issue of causation more directly found minimal support. First, in a longitudinal study of European children, serum vitamin D did not account for the association between time outdoors and myopia.[188] Second, in a Mendelian randomization study by the CREAM consortium, naturally occurring genetic variants known to lower vitamin D levels were not associated with refractive error, strongly suggesting a noncausal relationship.[194,195]

4.4 Indoor Lighting and Myopia

Time spent outdoors is often low due to urbanized lifestyles. For instance, exposure to air pollution may be a concern to parents, rain or snow may be off-putting, or activities that occur outdoors may sometimes be organized to take place in the evening or at night. Therefore, there is interest in understanding if high indoor ambient lighting can prevent myopia development. A study from China found that elevating light levels in school classrooms from approximately 100 to 500 lux reduced the incidence of myopia in the following year (4% versus 10%; $P = 0.029$).[196] Although another study reported an association between fluorescent versus incandescent desk light use and myopia, it did not control for socioeconomic status.[197] To-date there have been no related studies into the influences, if any, of newer light sources, such as LEDs. Nonetheless, the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) recommended avoiding the use of LED light sources emitting cold-white light (light with a strong blue component) in places frequented by children (e.g., maternity wards, nurseries, schools, leisure centers), to prevent possible ocular phototoxicity.[198] Human myopia studies in this field are few in number,

although a recent large-scale, cross-sectional China-based study reported higher levels of myopia in young teenagers (13–14 years old), using LED compared with incandescent and fluorescence lamps for homework.[199] However, the light levels in many indoor environments, even rooms with windows, are also considerably lower than outdoors.[199]

5. Surgical Interventions for Controlling Myopia Progression

5.1 Introduction

It is well accepted that most human myopia is axial in nature, with the greater than normal ALs being the by-product of reduced collagen synthesis and increased collagen degradation (see accompanying IMI – Report on Experimental Models of Emmetropization and Myopia),[30] thereby leading to progressive thinning of the sclera and increasing biomechanical instability. Except in the very young, when emmetropization is still active, myopia is largely irreversible. The excessive ocular elongation that underlies myopia is coupled to secondary thinning of the retina and choroid,[200–202] which is linked to an array of potentially sight-threatening complications, including retinal detachment, retinoschisis, myopic maculopathy, and choroid atrophy.[203–205] High myopes may also present with limited ocular motility and/or strabismus, as the extraocular muscles become increasingly stretched and the space within the orbital space becomes increasingly crowded.

Among those most at risk of complications in adult life are children presenting with myopia at a very young age, as they tend to show faster myopia progression and the window for myopia progression is also consequently longer.[206–210] For those with high myopia, continued ocular elongation during adulthood unrelated to visual activities, such as scleral creep,[211,212] is not uncommon, further elevating the risk of retinal and choroidal complications, especially in the case of posterior staphylomas resulting from localized mechanical failure of the sclera.

Surgical interventions for stabilizing the sclera and so controlling further myopia progression have a long history, with interest revitalized more recently due to climbing myopia prevalence figures overall and also for high myopia. Procedures for stabilizing the sclera, by way of preventing or slowing further ocular elongation aim to reduce or eliminate the above pathological retinal and choroidal complications. Those described in the literature fall into three main categories: scleral reinforcement surgeries, such as posterior scleral reinforcement (PSR), injection-based scleral strengthening (SSI), and collagen cross-linking scleral strengthening (CCL), although the clinical application of these approaches has been largely limited to PSR, which has been used in both adults and children with high myopia.

PSR involves surgical implantation under general anesthesia, with a variety of materials having been used, ranging from fascialata, as first proposed by Shevelev in 1930,[213] and also used by Curtin (human fascia lata),[214] as well as lyophilized dura,[215] strips of tendon,[216] aorta,[217] and donor sclera.[218,219] Based on published reports, donor sclera has been and remains the most popular, although there appears to have been no head-to-head comparison of available materials to establish the best material for this reinforcement surgery. A range of scleral implant shapes also have been used, including X- and Y-shapes and single strips, with the latter being used in the technique described by Snyder and Thompson.[219,220] Their technique, which uses a single, wide strip of sclera placed vertically over the posterior pole, under the inferior oblique but superior to the insertion of superior oblique muscle, also appears to have been widely adopted. Currently, PSR for high myopia is mainly performed in Russia, Eastern Europe, and China, although there are also advocates for scleral reinforcement for pathologic myopia in the United States[221,222] and Australia.[223–225]

In terms of studies documenting the efficacy of the various surgical interventions for high myopia, there are 12. All but one of those documented in Western journals involve either retrospective case series or case-control studies and all involve PSR (Table 8), although many lack key details. Not well represented are studies undertaken in Russia, where PSR and also SSI appear to be in use.

5.2 Posterior Scleral Reinforcement

Table 8 shows the summary of results from 12 studies using PSR, published over the period 1961 to 2016.[214,218–221,227–232] The length of intervention and/or monitoring period varies across these studies, from 1 to 14 years, with subjects ranging from young children with high myopia to adults with extremely high myopia.

Most studies report positive outcomes, with PSR halting or retarding myopia progression and/or AL elongation. An exception is the 1987 study by Curtin and Whitmore,[227] which reported increases in AL of 0.3 mm or more in 90% of patients undergoing PSR, leading to a decline in popularity of this surgery in the United States, despite earlier upward trends in its use over the period 1960 to 1987. Of note, Curtin and Whitmore[214,227] used X-type implants in their PSR, which has seldom been used in other studies and was not adopted by Snyder and Thompson[219] in their simplified PSR technique, which uses a single, wide strip of sclera implanted over the posterior pole. The rationale for the latter choice was to increase scleral resistance in eyes with progressive myopia and posterior staphyloma. Over 10 years later, the effectiveness of this approach appears to be borne out by the 4-year results of a retrospective study of adult myopes[221]; eyes undergoing PSR showed an average axial elongation of 0.1 mm compared with 0.8 mm for fellow, untreated eyes. The baseline refractive error and AL parameters for these patients ranged from −9 to −22 D and 28 to 35 mm, respectively. Several more recent studies in China similarly reported PSR to be effective in retarding progression in highly myopic children and adults, although the average treatment effects, as measured in differences in axial elongation between eyes undergoing PSR and controls, vary widely, from as little as 0.18 mm[230] to 1.05 mm,[232] where additional sclera grafts were applied.

Complications reported in association with PSR surgery are wide-ranging, and although generally classified as minor, their occurrence along with the challenging nature of the surgery likely underlies the still relatively limited use of PSR by a small number of ophthalmic surgeons. Common complications include lid edema, chemosis, high IOP, anterior uveitis, choroid edema, and muscle imbalance. Retinal hemorrhage and retinal detachment have also been reported, although causal links to PSR were not conclusively established, with high myopia offering an alternative explanation. There is also a report of cilioretinal artery occlusion 3 years after PSR in a 12-year-old girl[233]; however, here also, a causal relationship seems unlikely.

5.3 Injection-based Scleral Strengthening

There are just two articles reporting on the results of SSIs in controlling progressive high myopia.[234,235] This approach involves the injection under Tenon's capsule of chemical

Table 8. Summary of Key Design Features and Results of Studies Involving PSR Surgery

Study and Country Origin	Implant Shape and Material	Study Design	Baseline (SER and/or AL)	Outcome Measures; Treatment vs. Control (SER Change per y and/or AL change per y)
Curtin et al. (1961)[214] (USA)	X-shape; fascialata	Retrospective (1.8-y FU, $n = 7$; fellow eye control), children	Mean: −13.29 D (range: −11 to −19 D)	0.79 vs. −0.81 D/y
Miller et al. (1964)[218] (USA)	Single wide strip human sclera%	Retrospective ($n = 63$; 27 children, 36 adults); no controls	Range: −9 to −44 D	0.83 D/y overall; 0.55 D/y, children; 1.03 D/y, adults; No increase/ decrease up to 3 D in 26% adults, 22% children
Snyder et al. (1972)[219] (USA)	Single wide strip human sclera	Retrospective (0.5 mo, 3.5 y FU; 7 children, 3 adults); no controls	−17.1 D	0.61 D/y overall; 0.02 D/y, children; 2.00 D/y, adults
Thompson et al. (1978)[220] (USA)	Single wide strip human sclera	Retrospective (1 mo-7 y FU; $n = 52$; 14 children, 37 adults); no controls	Mean: −13.45 D (range: −5.75 to −25 D)	0.48 D/y overall; −0.20 D/y, children; 1.03 D/y, adults
Thompson et al. (1985)[226] (USA)	Single wide strip human sclera	Retrospective (1−14 y FU; $n = 191$); no controls	Not reported	77 eyes improved 2 Snellen lines or more; 85 eyes stabilized within 1 Snellen line; 13 eyes lost 2 Snellen lines or more
Curtin et al. (1987)[227] (USA)	X-shape; autologous fascialata	Retrospective (5 y FU; $n =$ 23; fellow eyes control)	Means: −15.48 D; 28.22 mm	−0.19 vs. −0.06 D/y; 0.14 vs. 0.12 mm/y
Ward et al. (2009)[221] (USA)	Single wide strip human sclera	Retrospective; adults (4 y FU; $n = 59$; fellow eye control)	Ranges: −9 to −22 D; 27.8 −34.6 mm	0.07 vs. 0.21 mm/y
Chen et al. (2013)[228] (China)	Single wide strip human sclera	Retrospective; children (n = 64, 5 y average FU; 17 extra eyes as controls, 4.5 y average FU)	Means: −10.31 D; 26.55 mm	−1.5 vs. −3.02 D; 1.27 vs. 2.05 mm
Zhu et al. (2014)[229] (China)	Single wide strip human sclera + PIOL implantation	Retrospective; adolescents (3 y FU; $n = 11$ and 11 controls)	Means: −17.57 D; 30.09 mm	4.96 vs. −1.22 D/y; 0.08 vs. 0.37 mm/y
Xue et al. (2014)[230] (China)	Single wide strip human sclera	Retrospective; children (2.5 y average FU; $n = 30$, fellow eye control);	Means: −9.72 D; 26.2 mm	−1.12 vs. −1.82 D; 0.75 vs. 0.94 mm (over average 2.5 y FU)
Shen et al. (2015)[231] (China)	Single wide strip human sclera	Prospective; children (3 y FU; $n = 16$ and 16 controls)	Means: −11.82 D; 26.78 mm	−0.44 vs. −0.23 D/y; 0.20 vs. 0.44 mm/y
Li et al. (2016)[232] (China)	Single wide strip human sclera + additional scleral graft	Retrospective; adults (5 y FU; $n = 52$ and 52 controls)	Means: −16.12 D; 29.49 mm	−0.14 vs. −0.64 D/y; 0.06 vs. 0.27 mm/y

FU, follow-up; PIOL, phakic intraocular lens.

reagents intended to biomechanically stabilize ("fortify") the extracellular (collagen) matrix of the sclera. One describes a case series, and the other, a case-control study. No randomized clinical trials appear to have been undertaken to-date.

Both studies showed the effectiveness of SSI in retarding of myopia progression. In the earlier of the two studies by Golychev and colleagues,[235] myopia was reported to have stabilized in 61% of eyes after approximately 2 years. The latter study was published in the Russian literature, with only limited procedural details available[234]; a polymer gel containing a mixture of polyvinylpyrrolidone, acrilamidehydrazide, and ethylacrylate was delivered monocularly by a sub-Tenon's capsule injection, with fellow eyes serving as controls. This study also included a control group. Refractions are reported to have remained stable in 79.6% of eyes, 1 year after the SSI intervention, and in 52.9% cases, after 4 to 9 years, contrasting with figures of 40.3% and 13.3% for fellow eyes and 26% and 11.1% for the control group.

5.4 Collagen Cross-linking for Scleral Strengthening

CCL is increasingly used worldwide for the management of biomechanically unstable corneas, be they of disease origin, such as keratoconus, or a complication of refractive surgery. However, although there is significant interest in the viability of this approach for stabilizing the sclera in pathological myopia, testing to-date has been limited to experimental animals.

6. Gaps in Knowledge and Future Directions

6.1 Optical Interventions for Myopia Management

Although the results of trials provide convincing evidence for the efficacy of a number of optical interventions for myopia control, there remain many unanswered questions related to underlying mechanisms. These include but are not limited to the relative contributions of the central and peripheral retinal

regions to eye growth regulation, the influences if any, of altered aberrations, including imposed positive spherical aberration, as inherent in some of the contact lens treatments, and of add power. Studies using dual-power lenses based on the Fresnel principle to investigate the effects on eye growth of imposed myopic defocus in experimental animals[236–238] suggest that the retinal location may be less important than the total retinal area involved. This observation raises the question of whether near center soft contact lenses may also be effective in controlling myopia. Whether the OK lens can be further optimized to improve treatment outcomes remains an open question. Of note among new OK lens designs being explored is one that purports to provide simultaneously, both a vision correction area and a myopic defocus area (positive power within the pupil region) (US 9753309 B2). The effect of occasionally interrupting MF treatments, for example, to obtain more acceptable vision for specific tasks, on treatment efficacy, is also not known. On the other hand, for OK wearers with rapidly recovering corneas, it might be possible to combine OK with daily wear MF contact lenses, by way of extending in time, an optical treatment effect. At least some of these questions may be suitably addressed in further animal studies, as a stepping stone in designing follow-up clinical trials.

6.2 Pharmacological Control of Myopia

Although there have been many studies assessing atropine as an intervention for myopia control, and many more are currently under way, there remain a number of important unanswered questions. For example, the exact ocular site of action of atropine's inhibitory effect on myopia progression remains unresolved, with the sclera, choroid, and retina among possibilities; underlying cellular and pharmacological mechanisms also remain unresolved.[239,240] Until consensus is reached on the ocular tissue to be targeted, advances in drug delivery cannot been fully exploited to optimize formulations. Additional studies are also needed to establish optimal atropine dosing and treatment regimens, including how long treatment should be continued, when/how it should be stopped, and the possibility of "prescribing" short drug holidays to prevent tolerance with higher concentrations.[131,241] The safety of extended chronic atropine treatment in very young (<6 years), and its efficacy in older children (>12 years), and in both those who are not yet myopic, as a preventative strategy, and in those with very high myopia (>6 D), also can benefit from further research. The benefits in later adult life, of early intervention (e.g., in terms of protection against myopia-related pathological complications), as well as the potential for very long-term side effects are as yet unknown and warrant investigation. The predicted increasing need for myopia control treatments would also seem sufficient argument for further investigations into the efficacy of topical pirenzepine, which has dropped off the radar, despite promising early results.[143,146,147]

There is room for further research into 7-MX and related compounds. It is possible that efficacy could be improved with improved formulations (e.g., sustained-release formulations instead of a standard tablet formulation), given that even twice per day dosing may not be sufficient to maintain an effective serum concentration level of 7-MX, which has a relatively short half-life.[123] The effect of 7-MX on myopia progression is believed to rely on inhibiting adenosine receptors in the posterior part of the eye. However, although experimental studies involving rabbits and guinea pigs point to beneficial effects on the sclera, including thickening and increases in collagen fiber size,[242] adenosine receptors have also been localized in the retina, the retinal pigment epithelium, and the choroid, with significant choroidal thickening along with increased hyperopia being reported in a recent study involving young monkeys.[124] Thus, further research to understand underlying mechanisms is warranted. Investigations into the viability of topical ophthalmic formulations of 7-MX or related drugs would also allay concerns over systemic side effects, with its longer-term use in developing children. That 7-MX might be combined with other intervention methods, optical or pharmaceutical, to increase treatment efficacy, is also yet to be explored.

Although disappointing results of the timolol RCT by Jensen[130] generally dampened enthusiasm for further testing of IOP-lowering drugs as an approach to myopia control, it is possible that the choice of timolol was also poor. For example, it is known clinically that timolol has little effect on night-time IOP,[243] yet some animal studies have shown "myopic growth" to occur mostly at night.[244] The very positive results from a related clinical study involving carteolol, a partial beta agonist, undertaken in Argentina[245] and on-going experimental studies involving other ocular hypotensive drugs, including latanoprost, a prostaglandin analogue,[246] and brimonidine, an alpha2 adrenergic agonist,[247] argue for further exploration of this treatment option, given the potential secondary prophylactic benefit of such therapies against primary angle glaucoma for which myopes are at increased risk (see accompanying IMI – Defining and Classifying Myopia Report).[134]

6.3 Environmental Influences and the Role of Time Outdoors

In relation to environmental influences on refractive errors and, importantly, the potential for outdoor exposure to protect against myopia onset and perhaps also slow myopia progression, there remain as many unresolved questions as there are answers. What is the mechanism of action underlying the protective effect of outdoors and what are the key temporal factors? For example, does the reduced risk of incident myopia reach a plateau beyond a certain length of time outdoors and is 2 hours per day outdoors presented in one block more or as effective as two 1-hour exposures per day. Does the time of day matter and perhaps related, is there an optimum light intensity and spectral composition? Does the age of the child matter and does it matter what the child is doing when outdoors? For example, does it matter if the child is using a smartphone outdoors versus gazing at distant objects outdoors? Are the parameters different regarding protection against incident myopia versus myopia progression?

The role of differences in behavior as a determinant of susceptibility to myopia is just beginning to be addressed, with the adoption of wearable light sensors and accelerometers, which allow more accurate characterization of light exposure, including time spent outdoors, as well as physical activity, compared with traditional questionnaire-based studies. Tools already deployed in research include the HOBO and Actiwatch,[248,249] with preliminary testing of a smartwatch (FitSight) linked with a smartphone app, aimed at increasing outdoor exposure also covered in a recent publication.[250] Interest in measuring working distances stems, at least in part, from early reports linking habitually short working distances and pronounced head tilts with a greater risk of myopia,[251] as well as prolonged exposure to activities with near working distances with myopia.[252] With increasing reliance of electronic devices/screens in education as well as in daily life, it is now plausible to integrate into electronic devices/screens, applications that promote better reading posture. Previews of a customized spectacle-frame mounted distance sensor, the Cloudclip, and an eye tracker with attached distance sensor were presented at the 16th International Myopia Conference (Birmingham, UK, 2017), and it seems only a matter of time before such devices will be able to send reminders to wearers

to keep an appropriate distance from their reading material. In addition, smart garments, such as designed for spinal and posture alignment therapy, may also be used for providing feedback to children exhibiting chronically poor reading posture.[253] As smart technologies become integrated into myopia control treatments, as opposed to their use as research monitoring devices, evaluation of their effectiveness in slowing myopia progression will be required. Clinical trial design and tools for quantifying outdoor activity are covered in the accompanying IMI – Clinical Myopia Control Trials and Instrumentation Report.[133]

6.4 Surgical Interventions for Controlling Myopia Progression

There is accumulating evidence that PSR is somewhat effective in stabilizing high myopia, despite the limitations of the studies reporting on the efficacy of this procedure. Clinical evaluation of the other two surgical options, SSI and CCL, is either limited (SSI) or nonexistent CCL). Nonetheless, there are significant clinical advances being made in CCL for corneal applications[254] and strong interest in its application for human myopia control, with related on-going investigations using animal models for myopia.[255–257] For the PSR, the difficulty of surgery makes it unpopular with ophthalmic surgeons. Apart from the commonly reported complications, the possibilities of optic nerve contusion or compression, and retrobulbar hemorrhage due to vortex vein or ciliary artery injury, are other concerns. There is also the need for general anesthesia. Thus a simple and safe surgical technique that can be performed under local anesthesia and that would also allow precise localization of the scleral implant over the posterior pole (macular region) would be more appropriate. Perhaps more urgent is the need for a synthetic scleral implant that is both biocompatible and biostable; such materials would reduce the risk of infection and rejection; they would also address the longer-term concern of a future shortage of healthy donor sclera, given the continuing rise in myopia prevalence figures.

In the case of SSI, more extensive studies of the material already in use in Russia would help to allay concerns over potential ocular toxic effects on nearby tissues, including the choroid and retina. Testing of related materials in the chick as an experimental myopia model did not show slowing of ocular elongation in either of two studies,[258,259] although significant thickening of the outer fibrous layer of the chick sclera with a thermoresponsive material (poly[N-isopropylacrylamide-co-acrylic acid]) represents a positive finding. Another more recent study involving a potentially more biocompatible, hyaluronic acid–based polymer and a guinea pig myopia model did show slowed elongation, but curiously, so did sham-injected eyes.[260] These promising results, along with the fact that the procedure used in this study may be modified to avoid the need for general anesthesia, argues for further investigations into this approach, starting with exploration of alternative materials and more extensive investigations into both potential benefits and potential adverse ocular effects.

CCL techniques currently under investigation can be classified into two categories based on whether or not UV radiation is required as an initiator of the reaction. For highly myopic eyes with thinned scleras, possible damage of retina during UV irradiation makes protocols that do not rely on UV radiation more attractive. There is also another technical issue to be addressed, of how to adequately expose the posterior sclera of highly myopic eyes with the light activator, as required in all current protocols. Among other issues to be addressed is the enduring nature of scleral cross-linking; specifically, how long lived are any treatment-induced increases in scleral stiffness, and are changes sufficient to slow ocular elongation.

6.5 Combination Therapies for Myopia Control

Considering that no one intervention strategy of those currently available (optical, pharmacological, or behavioral) has proven effective in totally inhibiting myopia progression, in either refractive error or AL terms (see recent meta-analysis),[143] it would seem timely to begin exploring combination therapies as an approach for improving treatment efficacy.

Although there remain many unanswered questions in relation to the mechanism of action of topical atropine, used as a myopia control treatment, the possibility that sites other than the retina may be involved argues for its testing in combination with optical approaches. To-date, there is only one relevant clinical trial listed (clinicaltrials.gov identifier: NCT02955927) (Kinoshita N, et al. *IOVS* 2017;58:ARVO E-Abstract 2386). Nonetheless, the 1-year results for a 2-year trial, in which the efficacy of 0.01% atropine combined with OK is being compared with OK alone in 8- to 12-year-old children, are very promising. Specifically, the combination yielded an improved outcome (reduced axial elongation), by more than 50% (axial elongation: 0.09 ± 0.12 vs. 0.19 ± 0.15 mm). Also of potential relevance are investigations into the atropine release profile of soft contact lens materials[261]; should atropine be considered for combination therapy with MF soft contact lenses, then it would be reasonable in the interest of compliance to use the lenses as a drug-delivery device. The effectiveness of such drug-delivering lenses on slowing myopia progression would need to be substantiated with longitudinal studies in children. Combining contact lens–based treatments with other drug treatments, such as oral 7-MX or pirenzepine, both of which would avoid any concerns over adverse drug–contact lens interactions, are among other potential avenues to explore.

7. Overall Conclusion

The current myopia epidemic shows no sign of abating. This article covers a variety of interventions, aimed at preventing the development of myopia and/or slowing its progression. No one strategy appears to reliably achieve either outcome in all individuals. On-going research may lead to a better understanding of underlying mechanisms that can be applied to identify those most likely to respond to specific interventions and to also inform combination therapies, which are currently used on an ad hoc basis. This field also could benefit from longer-term studies of the various interventions covered in this article, to better understand the persistence of treatment effects over time, as well as from exploration of more novel approaches to myopia control.

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