MYOPIA CONSENSUS STATEMENT - 2025

Contents

INTERVENTIONS TO SLOW THE PROGRESSION OF MYOPIA - 2025

Myopia (commonly termed nearsightedness or shortsightedness) has increased in prevalence around the world. In addition to genetic factors, there now exists evidence of numerous environmental factors that contribute to myopia development. Common forms of childhood myopia are due to axial elongation (i.e., a longer eyeball). As a result of renewed research activity on myopia, some forms of early intervention slow the axial elongation process and thus the potential severity of myopia. In some myopes, the elongation process is associated with an increased risk of cataract, glaucoma, retinal detachment, myopic maculopathy and strabismus. At present we are unable to identify which myopes these will be. Additionally, functional deficits of uncorrected myopia, along with an impact on career choice can occur. It is not clear at this time if interventions to slow myopic progression can prevent or reduce these complications but there are sound hypothetical reasons to believe they are likely to do so. In this Consensus Statement all the interventions we have described are based on studies that have shown statistical and clinical significance and have at least 2 years of follow-up with peer-reviewed publication. We are for the first time including a separate appendix for emerging therapies that do not meet criteria yet to be included in the actual consensus statement.

What Does Not Work or Has Minimal Effect

In the past, physicians and optometrists tried numerous methods to slow down myopia progression, all yielding zero to statistically and clinically non-significant effects. Among these are under correction, pin hole glasses, blue light blocking glasses, bifocal glasses, progressive addition spectacle lenses (PALs), and daytime single vision soft contact lenses / rigid gas permeable contact lenses. There was also no benefit found in positively aspherized PALs (PA-PALs) which combined a peripheral defocus correction with a progressive addition zone to reduce lag of accommodation during near work.

What Appears to Work

1. Behavioural And Environmental Interventions

a. Increased Time Spent Outdoors

The evidence for the protective effect of increased time spent outdoors in preventing or retarding myopia progression is robust. There are cross sectional studies, longitudinal studies, randomized control trials (RCTs) and systemic metanalyses which all support this. Cross sectional studies: The 2008 Sydney myopia study (SMS) [1], the 2009 Singapore Cohort of Risk factors for Myopia (SCORM) [2], and the 2014 Beijing Myopia Progression Study (BMPS) [3].

Longitudinal Studies: 2013 Sydney Adolescent Vascular and Eye Study (SAVES) [4], 2012 Avon Longitudinal Study of Parents and Children (ALSPAC) [5], the 2011 Collaborative Longitudinal Evaluation of Ethnicity and Race (CLEERE)) [6], and the 2007 Orinda Longitudinal Study of Myopia (OLSM) [7].

Interventional RCTs: Five have been published in Chinese and Taiwanese patients [8] [9] [10] [11] [12] and they demonstrated reduction in myopia by incorporating 40-80 mins of interrupted time outdoors. One study [12] showed a dose-response relationship between the outdoor exposure time and myopia onset and progression with the protective effect associated with both duration and intensity of light.

Systematic Reviews and Metanalyses: There are 5 systematic reviews and / or meta-analyses [13] [14] [15] [16] [17] and 2 overviews of all the metanalyses and systematic reviews [18] [19], all affirming a protective impact of time spent outdoors against myopia and highlight a 24–46% reduction in relative risk of incident myopia for every additional hour of outdoor time per week. Importantly, it had been suggested that while increased time spent outdoors was protective in preventing myopia onset, it may not be effective in slowing the progression in eyes that are already myopic [14]. However, 4 interventional studies [8] [9] [10] [11] and a meta-analysis [19] ranging in publication dates from 2015-2022 have shown mitigation of myopia progression by increasing time spent outdoors [8] [9] [10] [11] with a pooled reduction effect of 0.13 to 0.17 D in myopic refractive error per year [19]. Taking all the literature into account, 2 hours daylight exposure appears to mitigate both onset and progression of myopia.

It is indeed luminance (Lux) that seems important. Greater than 1000 Lux appears to be protective against myopia progression [20]. An important study [21] found a stark contrast between light levels measured indoors and outdoors. Outdoor illumination, measured in Lux, was significantly higher, ranging from 11,080 to 18,176 Lux. In comparison, indoor light levels were much lower, between 112 and 156 Lux. The research identified several outdoor conditions that provided light levels above 1000 Lux. Outdoor light levels remained significantly higher (1,792 to 6800 Lux) than indoors even when under a tree shade (5,556 to 7,876 Lux), while wearing a hat (4,112 and 8,156 Lux) and even wearing sunglasses [21].

b. Reduced time on Near Tasks: Smartphones / Near Digital Devices / Reading

A meta-analysis of studies across five continents found that children who engage in more near work activities have an 80% higher risk of developing myopia compared to those who do less near work (while studying, watching TV or using computers). The study also noted that each additional hour of near work per week increases the odds of myopia by 2% [22]. However, the evidence is not entirely clearcut.

While longitudinal studies [23] using the definition of near as ‘reading’ have suggested a positive association between near work and myopia, as have some cross-sectional studies [24], other studies have not [3]. In the Generation R study, a connection was found between myopia and increased computer usage among 9-year-old children. Near work activities, including reading and computer usage, had an odds ratio of 1.072 (95% CI 1.047–1.098) for myopia. Firstly, an inconsistent definition of near work among authors complicates the process of comparing results and drawing a conclusion on the association between near work and myopia [25]. Also, different studies don’t always consider the presence of parental myopia. The confounding effect of this genetic influence is not always considered. For instance, one cross sectional study from Beijing

[25] concluded that taking parental myopia into account and outdoor exposure, they could not find a correlation between near work and myopia. It may be that near work has a behavioral effect, reducing outdoor exposure rather than a direct effect itself. An older study (significant due to its methodology) examined how intensive near work was. Longer time periods (>30 min) spent on reading for pleasure and a close reading distance (<30 cm) were significantly associated with more myopia [26]. It is likely that it is the act of near viewing itself and not necessarily the use of digital screens per se that can induce myopic shift. An Israeli study showed that in Orthodox Jews exposed to intense reading at the age of three and not allowed to use smartphones or computers on religious grounds, an 80% rate of myopia was recorded compared to the 30% rate of myopia in the general population [27].

Huang et al. from Taiwan reported similar results, finding that taking breaks to interrupt near work activities lasting 30 min or more, led to significantly less myopia after 6 months than was the case with children who did not interrupt long sessions (> 30 min) of near work [23].

The COVID-19 pandemic effect has been studied intensely. Two notable studies [28], [29] showed a noticeable increase in myopia progression, well above that seen in the highest recorded levels between 2015 and 2019 in younger children aged 6-8 years [28] and suggested that increased time spent on digital screens is associated with a higher risk of myopia [29].

This increase in myopia during the COVID-19 pandemic has been reported globally across all cultures, races and ethnicities [30] [31]. One recent study emphasized that the greatest increase in myopia was related to the period with most reduced outdoor time [32].

The role of dim or mesopic light on myopic progression has been studied more intensely. There is clinical epidemiological evidence that reading or spending time in mesopic or dim light conditions may drive myopia progression [33].

In summary the intensity and prolonged accommodation of near work are likely to play a role in myopia progression rather than frequency of near work tasks [34] and the recommendation of taking breaks to interrupt near work activities lasting 30 min or more seems reasonable. It is important to acknowledge that while evidence of prolonged task activity causing myopia progression is available, the role of reduced outdoor activity is a confounding factor [35]. It is also important to consider that time spent in and / or reading in mesopic or dim light may be associated with myopia progression.

2. Optical Treatment

The latest optical interventions (spectacles and contact lenses) for myopia control are designed to manipulate retinal defocus or contrast, which are key visual signals that regulate eye growth and refractive development.

2.1 Peripheral retinal defocus

Animal studies had shown that the peripheral refraction of the retina can influence ocular growth. It was shown that relative hyperopic defocus can induce myopia, while myopic defocus can induce

hypermetropia [36] [37]. Ablation of the foveal area did not alter these findings [38]. Human studies showed that although relative hyperopic defocus cannot predict the development of myopia in children, those who became myopic, developed relative peripheral hyperopia while those who remained emmetropic retained peripheral myopia [39]. Conventional single-vision ophthalmic lenses used to correct myopia have been shown to increase peripheral hyperopic defocus in a dose dependant fashion [40].

2.2 Contrast management

Contrast management represents another approach to myopia management. The human visual system, beginning in the retina, is organized to detect contrast and is more sensitive to contrast than to absolute luminance. The primary visual signals that influence eye growth are derived from defocus and contrast [41] [42] and are processed locally within the eye [43]. Many of the retinal neurons are, in essence, contrast detectors.

The potential therapeutic use of contrast management was first proposed following the discovery that L or M cone photopigment gene mutations are associated with abnormally high retinal contrast signalling and highly progressive myopia [44]. Additional genetic insights have also demonstrated retinal contrast signals can influence refractive development. Increased stimulation of the retinal contrast pathway in Congenital Stationary Night Blindness is associated with high myopia [45], whereas reduced contrast signalling in achromatopsia is often associated with hyperopia [46].

These genetic observations fit together with the clinical observations that (a) high contrast visual activities and environments, for example reading dark text on a white background, or digital devices and modern urban environments, are associated with progressive myopia [47], and (b) spending more time outdoors, amongst natural low contrast, is protective of myopia onset and possibly progression. These findings led to the contrast hypothesis that high retinal contrast, whether from genetic predisposition or the visual environment, may overstimulate the retina, promoting excessive eye growth and progressive myopia [48].

These findings suggest a potential therapeutic use of contrast management in myopia control.

a. Spectacle Lenses - Peripheral Retinal Defocus

While early attempts to use spectacle lenses which exert myopic peripheral defocus on the retina had disappointing results [49], there are several relatively new lenses in the market today. The two with published data of two years use or more, and available commercially, are the Defocus-Incorporated Multiple Segment (D.I.M.S.) & Highly Aspherical Lenslet (H.A.L.) lenses.

Defocus-Incorporated Multiple Segment (D.I.M.S.) Spectacle lenses (Hoya Miyosmart, Tokyo, Japan): This dual-focus spectacle lens consists of a central distance optical zone with diameter of 9 mm, surrounded by a honeycomb structure in the mid-peripheral zone that includes multiple (396) small round segments about 1.03 mm in diameter with a +3.50 diopters defocus power, to simultaneously allow clear central vision and introduce myopic defocus in the peripheral retina. In a two-year double-masked randomized trial that included 183 myopic Chinese children (93 DIMS

group/90 Control group) 8 to 13 years of age, the myopia control effect was 55% during the 2-year period. The average myopic progression over two years was lower in the DIMS group (−0.41 ± 0.06 D) than in the control group wearing single-vision (SV) spectacle lenses (−0.85 ± 0.08 D) [50]. The mean axial elongation was also less in the DIMS group than in the single vision spectacle lens group (0.21 ± 0.02 mm vs. 0.55 ± 0.02 mm). While the study was not randomized, the subsequent 3-year study showed that the myopia control effect was sustained in the third year in children who had used the DIMS spectacles in the previous 2 years and was also shown in the children switching from SV to DIMS lenses. A later study showed that the effect of the glasses was sustained even after 6 years [51]. The myopia control effect of DIMS lenses was better in children with baseline hyperopic relative peripheral refraction (RPR) than those with myopic RPR. As for the effect on visual acuity, in temporal and nasal gaze conditions, visual acuity with DIMS lens decreased by 0.23±0.19 logMAR compared to SV lens. A decrease in contrast sensitivity in the DIMS lenses only in the nasal and temporal gaze conditions and of only −0.12±0.20 and −0.18±0.20 logCS, respectively, corresponds to a defocus of about 0.5 D. Mid-peripheral blurred vision was the main visual complaint, which was noticed only once or twice a day.

Although DIMS lenses were not tested in randomized trials in European children, evidence exists that the glasses had similar effect in these children [52]. Comparison studies have shown that DIMS spectacles had similar effect on myopia progression as orthokeratology lenses [53].

Moreover, it was shown that atropine drops had an additive synergistic affect when used in conjunction with DIMS spectacles in children who continued to progress, especially in older children [54] [55]. There was no evidence of rebound after stopping the treatment with DIMS lenses [51].

Highly Aspherical Lenslet (H.A.L.) Spectacle Lenses (Essilor® Stellest®, Essilor International, Paris, France): 157 children (54 Highly Aspherical Lenslet [HAL] group / 53 slightly aspherical lenslets [SAL] group / 50 Control group) aged 8-13 years with myopia of −0.75 D to −4.75 D were randomized to receive spectacle lenses with HAL, spectacle lenses with SAL, or SV lenses. After 2 years, the HAL and SAL lenses slowed myopia progression by 0.80 and 0.42 D, and axial elongation by 0.35 and 0.18 mm, respectively [56]. The ocular growth rate in 90% of children wearing the HAL lens configuration was like the physiological rate of normal non-myopic children [57]. The study was extended for a third year, in which children who used the HAL lenses continued to use them, while children who used the SAL configuration or SV lenses switched to HAL configuration. An additional group of children using SV lenses was added. Myopia progression was significantly reduced in all three groups who used the HAL lenses in comparison with the SV lens group. The effect was most pronounced in children who switched to HAL from SV lenses. Low contrast visual acuity and reading was slightly reduced while high contrast visual acuity was unaffected when fixating through the periphery of the novel lens designs [58].

Besides the effect on the axial elongation, these lenses have been shown to affect choroidal thickness [59]. Compared to those in the SV lens group, choroid thinning was significantly inhibited in all the HAL groups. Wearing HAL for two years thickened the choroid. The results of wearing the lenses for 3 years showed that the HALs no longer had a choroidal thickening effect but could still

inhibit choroidal thinning compared to wearing SV lenses [60]. Also, binocular HALs were shown to reduce axial elongation in both eyes of children with unilateral myopic anisometropia [61].

The rebound effect, (acceleration of myopia progression following cessation of treatment) was not observed in children wearing HAL lenses [62].

b. Diffusion Optics Technology™ (DOT™) spectacle lenses

Recent well-structured clinical trials have demonstrated that mild reductions in retinal contrast imposed by spectacle diffusion lenses can slow myopia progression in children [63]. DOT spectacle lenses by SightGlass VisionTM (Dallas, TX, USA) are designed to slow myopia progression by slightly lowering retinal contrast to mimic more natural contrast. DOT technology, consisting of microscopic diffusers, was applied to the surface of the lens. Wide-angle scatter, rather than narrow-angle scatter, was used to achieve even contrast reduction over a large range of spatial frequencies while minimising any potential effect on visual acuity. Microscopic diffusers were integrated across the entire lens, except for an approximately 5 mm aperture centred on the optical centre of the lens. For test 1 (called DOT 0.2 commercially), diffusers were applied with 0.365 mm spacing. Test 2 had a higher density (i.e., closer spacing) of diffusers of 0.240 mm.

The Control of Myopia Using Peripheral Diffusion Lenses Efficacy and Safety Study (CYPRESS, NCT03623074) clinical trial aimed to evaluate the safety and efficacy of DOT spectacle lenses (SightGlass Vision™) in reducing juvenile myopia progression. It was a multicentre, randomized, controlled clinical trial that enrolled 256 children aged 6-10 years across 14 North American clinical sites. The original 3-year study was extended for 1 year, and the control group was retained throughout. The CYPRESS clinical trial provides robust evidence that DOT lenses are safe and effective in children from age 6. After 3 years, myopia progression was slowed by 0.84 D in cycloplegic Spherical Equivalent Refractive error (SER) and 0.32 mm in axial length in the 23 children aged 6-7 years, who wore DOT lenses. Children completing part 1 (n=200) were invited to enrol in CYPRESS part 2 (NCT04947735), in which T1 (n=35) and Control groups (n=42) continued with their original lens assignment and the T2 group (n=21) were crossed over to T1 lenses. T1 spectacle lenses demonstrated superiority to control in terms of both co-primary endpoints after 4 years. With a difference between means ± SE of -0.20 ± 0.09 mm for Axial Length (AL) [p=0.033] and 0.52 ± 0.22 D for cycloplegic SER [p=0.017]. This benefit continued to year 4 for the 61% who enrolled in the one-year extension study [42]. The CYPRESS clinical trial expands the evidence base for myopia control spectacle lenses. It has several unique aspects, as it is the only spectacle lens study to demonstrate myopia control efficacy in North American children from age six. These results support the hypothesis that managing contrast can slow myopia progression.

c. Contact Lenses - Myopic Defocus

There are two types of contact lens interventions: The Soft Contact Lenses for Myopia Control & Orthokeratology.

Soft Multifocal Contact Lenses: These soft multifocal concentric zones contact lenses have a centre-distance design and include lenses with concentric rings as distinct zones of relative plus

dioptre power and lenses with a gradient design which has increasing relative plus dioptre power toward the lens periphery. Soft multifocal contact lenses have shown a reduction in myopia progression of an average 36.4% and a decrease in axial elongation by 37.9%. The MiSight® 1 Day contact lens (CooperVision, USA) is a daily disposable dual focus contact lens with a central distance correction zone surrounded by alternating treatment and correction zones producing 2 D of myopic defocus. It is not a multifocal contact lens in the traditional sense of those prescribed for presbyopia. Use of this contact lens showed a change in spherical equivalent refractive error over a 3-year period in 144 children aged 8-12 was −0.51 ± 0.64 vs. −1.24 ± 0.61 D (59% reduction) compared to single vision contact lenses. Similarly, mean change in axial length was 0.30 ± 0.27 mm versus 0.62 ± 0.30 mm (52% reduction). The lenses were well tolerated with no significant adverse events reported during the study [64].

A subsequent publication showed that these dual-focus soft contact lenses continue to slow the progression of myopia in children over a 6-year period revealing an accumulation of treatment effect. There was no clinically meaningful myopia progression in 23% of eyes [65].

The relative peripheral hyperopia at 30° and 40° nasal and 40° temporal to the fovea was significantly correlated with a reduction in the progression of myopic refractive error and the amount of axial elongation by inducing peripheral myopic defocus.

The randomized clinical BLINK (Bifocal Lenses in Near-sighted Kids) study examined the efficacy of contact lenses with a central correction for myopia plus a high add (+2.50 D) or medium add (+1.50 D) power to the peripheral zone as compared to single-vision (no add) contact lenses in 292 participants aged 10.3 ± 1.2 years with a mean spherical equivalent refractive error of −2.39 ± 1.00 D. The contact lenses used were Biofinity Multifocal "D" with a +1.50-D add power, or Biofinity Multifocal "D" with a +2.50-D add power contact lenses (CooperVision, USA). The difference in the adjusted three-year myopia progression between the high add power group versus the single-vision group was −0.46 D and −0.23 mm, between the high add power group versus the medium add power group was −0.30 D and −0.16 mm, and between the medium add power group versus the single-vision group was −0.16 D and −0.07 mm. Statistical significance was reached only for the high add group. Thus, the optimum distribution of the refractive power to maximize myopia control while not impacting functional vision remains to be determined [66].

A recent study in Caucasian children also showed reduction of axial length elongation and myopia progression in Multifocal Contact Lenses (MFCL) (MYLO) use after 24 months compared to Single Vision Glasses (SVG), suggesting that there might not be racial differences in treatment response [67]. Increase in total aberrations and higher-order aberrations were reported in the use of MFCL compared to Single Vision contact lenses (SVCL), however no differences in focusing ability and depth perception [68].

Orthokeratology: In overnight orthokeratology (OK) the patient wears reverse geometry contact lenses overnight to temporarily flatten the cornea and provide clear vision during the day without any glasses or contact lenses. Correction of myopia (typically up to −6 D sphere and -1.75 astigmatism) is achieved by central corneal epithelial thinning, midperipheral epithelial, and stromal thickening.

Numerous systematic reviews and meta-analyses have concluded that orthokeratology lens wear reduces the axial elongation of the eye in children by around 0.25 mm in comparison to control groups of single-vision spectacle or contact lens wearers over a 2-year period, with a high drop- out rate in some studies [69].

Pooled data from three prospective studies {Retardation of Myopia in Orthokeratology (ROMIO) Study; Myopia control with orthokeratology contact lenses in Spain (MCOS) study; Myopia control using toric orthokeratology (Menicon Z Night lenses) [TO-SEE] study} evaluated orthokeratology in comparison to a control group of distance, single-vision spectacle lens wearers over a 2-year period in Hong Kong and Spain, showed a change in axial length of 0.41 ± 0.25 mm versus 0.65 ± 0.30 mm, thus providing a treatment effect of 0.24 mm (95 % confidence intervals: 0.15 to 0.34 mm) or 36.9%. 60% of the effect was obtained during the first year of treatment. The use of these orthokeratology lenses appeared to be very effective in 40% of lens wearers (2-years axial elongation ≤0.30 mm), and not effective at all in 25% (2-years axial elongation >0.59 mm).

Research to understand the mechanism underlying myopia control effect of OK lens is ongoing although the hypothesis is a decrease in relative peripheral hyperopia caused by the steepening of the midperipheral corneal surface. A recent review of the efficacy of OK in myopia control in inhibitory effect in axial elongation for 2 years was reported to be 32-63% compared to SVG and SVCL [70]. Individuals with larger than average pupil size may have a greater effect with OK. There has been conflicting evidence correlating greater reduction in the axial elongation with younger children and those with higher baseline myopia. These studies have relatively small samples sizes.

Rebound can occur after discontinuation or change to alternative refractive treatment [71]. It is shown that corneal remodeling after OK lenses wear would lead to myopic defocus on the peripheral retina thus causing rebound [72]. Potential complications include microbial keratitis, pigmented ring formation and altered corneal nerve pattern (fibrillary lines). The estimated risk of microbial keratitis in children wearing OK lenses is 13.9/10,000 patient-years, as opposed to 7.7/10,000 in all OK wearers. This contrasts with the risk in daily-wear corneal gas-permeable lens wearers (1.2/10,000) and is fairly similar to the risk in extended-wear soft contact lens wear [73] [74] [75] [76] [77] [78] [79] [80] [81] [82] [83] [84] [70] [85] [71].

3. Pharmacological Treatment - Atropine Eyedrops

Atropine blocks muscarinic receptors in a non-selective way. Muscarinic receptors are found in human ciliary muscle, retina and sclera. Although the exact mechanism of atropine in myopia control is not known, a non-accommodative mechanism is most plausible, involving retinal pathways affecting the sclera.

In 2006, the Atropine for the treatment of Myopia One (ATOM 1) study in Singapore showed that 1% atropine eyedrops nightly in one eye over a 2-year period slowed myopic progression by 77% and reduced the axial length elongation (mean axial length increase of 0.39 mm in control versus no growth in atropine group) [86]. In 2012, the ATOM 2 study evaluated lower concentrations and concluded that 0.01% atropine had the optimal treatment to side effect balance. Atropine 0.01% caused minimal pupil dilation (on average 0.8 mm), minor loss of accommodation (2-3 D),

and no near vision problems without the need for progressive additional lenses [87] [88]. Since then, low-dose atropine for myopia control has been extensively studied, especially in Asian children.

In the Low-Concentration Atropine for Myopia Progression (LAMP) study, involving Hong Kong children aged 4-12 years on atropine eye drops at 0.05%, 0.025%, and 0.01% concentration compared with placebo, there was a reduction of spherical equivalent (SE) progression by 27%, 43%, and 67%, and a slowing of axial length growth of 12%, 29%, and 51%, respectively after a year [89]. The second-year efficacy of 0.05% atropine eye drops and 0.025% atropine eye drops remained similar and improved slightly in the 0.01% atropine group. In the LAMP-II Study, the efficacy of 0.05% atropine eye drops was double that of the 0.01% eye drops and therefore the 0.05% was the optimal concentration [90]. In the third year, children in each group were randomized at a 1:1 ratio to continued treatment and washout subgroups. During the third year, continued atropine treatment achieved a better effect across all concentrations compared with the washout regimen. 0.05% atropine remained the optimal concentration over 3 years. During years 4 and 5, all continued treatment subgroups were switched to 0.05% atropine for continued treatment, whereas all treatment cessation subgroups followed a pro re nata (PRN) re-treatment protocol to resume 0.05% atropine for children with myopic progressions of 0.5 D or more over 1 year [91] [92]. Over 5 years, the continued 0.05% atropine treatment demonstrated good efficacy for myopia control. The cumulative mean SE progressions were -1.34 D, -1.97 D, and -2.34 D for the continued treatment groups with initial 0.05%, 0.025%, and 0.01% atropine, respectively. Similar trends were observed in AL elongation. Most children needed to restart treatment after atropine cessation in year 3. Restarting treatment with 0.05% atropine achieved similar efficacy as continued treatment.

A 2022 network Meta-Analysis involving 30 pairwise comparisons from 16 randomised controlled trials (3272 participants) ranked the 1%, 0.5%, and 0.05% atropine concentrations as the 3 most beneficial for myopia control, as assessed for both primary outcomes - 1% atropine (mean differences compared with control): refraction 0.81; axial length elongation (AXL) -0.35; 0.5% atropine: refraction 0.70: AXL -0.23; 0.05% atropine: refraction 0.62; AXL -0.21 [93]. In terms of myopia control as assessed by relative risk (RR) for overall myopia progression, 0.05% was ranked as the most beneficial concentration (RR 0.39).

A contemporary review looking at the most recent 16 recent RCTs among the initial 41 RCTs included studies conducted in Europe, USA, Australia, India and Iran with almost half done in East Asia, in predominantly Chinese ethnic children [94] [95] [96] [97] [98] [99] [100] [101] [102] [103] [104] [105] [106] [107] [108] [109] [110].

There were obvious differences in these studies in terms of sample size, study length, study design, age of subjects, location, dosage, frequency and study aims. While most studies demonstrated efficacy of atropine, the Myopia Outcome Study of Atropine in Children (MOSAIC) study in Ireland showed significant reduction of myopia progression in atropine 0.01% at 18 months but not at 24 months [107]. Axial length elongation was lower in the atropine 0.01% group at both 18 and 24 months. Similarly, the Western Australia (WA) ATOM study found only a modest myopia control effect of 0.01% atropine which was not significant at 24 months [96]. A 2-year study in the United

States by Repka et al. concluded that atropine 0.01% did not slow myopia progression or axial elongation [108]. This contrasted with the larger 3-year CHAMP (Childhood Atropine for Myopia Progression) study involving 27 clinical sites in North America and 5 countries in Europe, which found a significant but modest reduction in myopia progression and axial length elongation and significant increase in responder proportion by atropine 0.01% [109]. Paradoxically, atropine 0.02% did not significantly increase responder proportion or slow myopia progression but did slow mean axial elongation.

There are various reasons behind the variability of results. There might be a racial variation in the sensitivity / pharmacokinetics of atropine likely related to the amount of iris pigmentation. Atropine binds to melanin, so darker irises may result in slower release and longer active time for the drug, which may yield higher effectivity in Asian children. Myopia progression slows with age, so low dose atropine may be less likely to report a significant effect in older children. Iribarren et al. highlighted the differences in atropine eye drop composition, e.g., power of hydrogen (pH) and preservatives, which could affect drug penetration [111]. The studies in Caucasian populations [107] [108] [109] showing low to no effect on myopia progression, used the same preservative free formulation with pH of around 5.

The APPLE (Atropine Ophthalmic Solution to reduce myopia progression in Paediatric Subjects) study is the first study to demonstrate the efficacy of atropine at concentration lower than 0.01% with 0.005% but not 0.0025% being statistically significant [110].

A meta-analysis included 4 studies (644 children with premyopia aged 4-12 years) with atropine concentrations ranging from 0.01% to 0.05% and supports atropine's efficacy and safety for delaying myopia incidence [112].

Atropine in solution is intrinsically unstable and breaks down into tropic acid and tropine. 24 samples of 0.01% atropine from 9 different compounding pharmacies showed great variation in labelling practices, concentration, degradant product, pH, osmolarity, viscosity and excipients [113]. One quarter of samples were under the 90% minimum target concentration of 0.01%.

The debate over atropine's safety and effectiveness continues in Europe and North America. In Asia, there are more ongoing studies to determine the appropriate dose, frequency and tapering to minimize rebound. Stopping treatment at an older age and lower concentration were associated with a smaller rebound. Trials are exploring atropine's potential to prevent myopia onset in premyopic children.

Atropine eyedrops have not been approved for myopia control in many countries resulting in differing availability. Costs of atropine vary widely, and it is often used off-label due to lack of regulatory approval. In countries where low dose atropine can be obtained directly from a compounding pharmacy, inconsistencies and discrepancy between manufacturing facilities may affect its safety and efficacy.

A potential issue that may be a confounding variable is the effect of government led public health policies delivered within schools. It is perhaps not a surprise that where such policies have existed since the early 2000s (Singapore and Taiwan) or where studies have been conducted and behavioural interventions instigated as part of the study (especially outdoor time) the lower

atropine concentrations appear to be as effective as the higher ones. It is of note that such policies were not in place until 2019 in Hong Kong and that there are no such policies in North America [114].

Adverse effects

Although none of the trials have reported serious adverse effects, atropine causing photophobia, blurred vision, and the risk of increased ultraviolet light with its theoretical risk of resultant cataract can be a cause of concern. ATOM 1 reported allergic reactions in 4.5%, glare in 1.5% and blurred vision in 1%, mainly because the atropine concentration used was high, hence limiting its use. ATOM 2 reported allergy in 3.2% with 0.1% and 0.5% drops. Pupils were larger than 3 mm in 0.1% and 0.5% drops causing reduced near acuity and the increased need for progressive lens power in their glasses (70% and 61% respectively vs 6% in with 0.01%). Atropine-related side effects were uncommon with the 0.01% dose but a total of 11% reported one line decrease in visual acuity. Atropine 0.01% caused minimal pupil dilation (0.8 mm), minimal loss of accommodation (2-3 D), and no near visual loss compared with higher doses [87]. The LAMP study reported no difference in the quality of life in various groups [89].

Similar to response, there are interethnic differences regarding adverse events. Chinese children easily accept a higher dose atropine, while more side effects are reported in non-Chinese children. The recent ATLAS (Atropine Treatment Long-Term Assessment Study) examined 18% and 40% of the participants in ATOM 1 and ATOM 2, 20 and 10 years after cessation of treatment respectively. They reported no long-term side effects. There was no increased rate of cataract or other ocular complications [115]. However, they also found negligible difference in refraction and axial length. This may have been caused by a rebound effect since most of the study participants discontinued atropine treatment abruptly without tapering.

Other publications on long-term effects of atropine indicate that its use does not induce intraocular pressure elevation [116]. No systemic adverse effects were reported among the numerous clinical trials.

Rebound effect

Rebound effect, defined as faster progression of myopia following prompt cessation of atropine treatment, is well documented. An analysis of 13 studies involving 2060 children showed that rebound effect on SE and to a lesser extent on AL were significantly higher at 6 months compared to 12 months. The meta-analysis highlighted the temporal and dose-dependent rebound effect after discontinuation of atropine. Shorter treatment durations, younger age, and higher baseline SE levels were associated with more pronounced rebound effects. Transitioning or stepwise cessation and combining optical therapy may mitigate the rebound effect [117].

Non responders

There is a small fraction of patients who might not respond to topical atropine. In ATOM1, 12.1% of

children (younger, with higher myopia, and greater tendency of myopic progression) had myopia progression of more than 0.5 D after 1 year of treatment with atropine 1%. In addition, 13.9% of patients had progressed more than -1.0 D, in ATOM 1 study [86]. About 18% progressed by ≥1 D in all low dose concentrations in ATOM 2 [87]. There were more non responders with lower doses of atropine, 15.2% with 0.05%; 12.6% with 0.025% and 27.8% with 0.01% drops in LAMP study after one year [89]. Nearly 9.1% progressed by more than 2 D after using 0.05% for two years.

The LAMP study also suggested a concentration dependent response, so it would be possible that increasing the frequency of atropine eye drops to twice per day, may increase its efficacy in retarding myopia progression (although it wasn't a part of the study) or stepping up the concentration along with combination therapy could be tried as suggested by the authors. Similarly, there are non-responders to optical therapies also [50] [64] [66] [79].

Delaying the onset of myopia

While low concentration atropine is effective in reducing myopia progression, the role of atropine to delay the onset of myopia has also been studied. The Low-Concentration Atropine for Myopia Prevention (LAMP2) trial was conducted to assess the efficacy of low-concentration atropine in delaying myopia onset among children aged 4-9 years with cycloplegic spherical equivalent between +1.00 and 0.00 D, astigmatism of less than −1.00 D with one parent having myopia more than -3 D [95]. The treatments included a 1:1:1 ratio of 0.05% atropine; 0.01% atropine, and placebo, once nightly to 160, 159 and 155 participants. The 2-year cumulative incidence of myopia in the 0.05% atropine, 0.01% atropine, and placebo groups were 28.4%, 45.9%, and 53% respectively. The study has concluded that nightly use of 0.05% atropine eyedrops compared with placebo resulted in a significantly lower incidence of myopia and lower percentage of participants with fast myopic shift at 2 years. There was no significant difference between 0.01% atropine and placebo. Hence, the study provided evidence that atropine can be explored for delaying the onset of myopia (not preventing it) in children at high risk for the development of myopia. Like the other studies, since the participants were all Chinese, the study being single centric with high dropout rate, without neutralizing the effect of near work, the generalizability of the results is a question. The study is intended for another 6 years. The ongoing randomized clinical trial, ATOM3 (NCT03140358) was launched in 2017 to evaluate the role of 0.01% atropine in preventing or delaying the onset of myopia in younger children. The trial recruited children aged 5-9 years with at least 1 moderately myopic parent and premyopes with cycloplegic refraction between +1 D to -0.49 D in two phases - treatment (2.5 years), washout phase (1 year).

In summary, there is a dose-related response in atropine for myopia control. Low-dose atropine (0.01%-0.1%) has 30-60% efficacy. 20-30% of children who started on 0.01% may benefit from higher concentration, especially younger children with a family history of high myopia. High-dose atropine (0.5%-1%) is more efficacious at 60-80%. Overall, 10% may still respond poorly. Children on a higher dose may require photochromatic glasses with or without a reading add. Lower doses and older age groups are also associated with less rebound effect when stopped, whereas those

on high-dose atropine require a slow taper and should not be stopped suddenly. Patients may also need different doses at different times of their lives. Atropine has demonstrated a significant dose-dependent effect on both refractive change and axial elongation, with higher dosages of atropine resulting in less myopia progression and less axial elongation. Low-dose atropine shows a cumulative effect causing less myopia progression and less axial elongation in the second year of treatment.

4. Light Therapy

Repeated low-level red-light therapy

Repeated low-level red-light therapy, commonly known as RLRL, has more recently been studied for myopia control as an alternative to increased bright light exposure. There have been numerous randomized trials and systematic reviews on the use of red light (RL) therapy for myopia, with the proposed mechanism of enhancing blood flow to the back of the eye [118] [119] [120] [121] [122] [123].

One of the first studies in China was of the Eyerising RLRL device, which emits visible red light at 650 nm wavelength. The device had previously been approved for amblyopia treatment and had been incidentally found to stabilize axial length elongation. This 12-month study recruited 264 children aged 8-13 with myopia -1 to -5 D and astigmatism >2.5 D, and anisometropia <1.5 D randomized to receive RLRL therapy plus glasses or single vision glasses alone. The therapy was given at home for 3 minutes per session, twice daily, 5 days per week, and with an interval of at least 4 hours between sessions. The 117 children enrolled in the therapy group showed slowed AL elongation by 69.4% and SER by 76.6% as compared to the control group. The study also documented an increase in choroidal thickness by 16 microns, a finding which has since been replicated in several RLRL studies and is postulated to be related to RLRL's underlying mechanism on increasing blood flow. Compliance with the treatment protocol was reported to be 75%. Notable limitations of this study include its non-masking and a reduction in 6-month follow-up data points due to the COVID-19 pandemic [118].

This same cohort was then followed up for a second year in a real-world study, with some children in the control group voluntarily switching to RLRL (SVS-RLRL) and vice versa (RLRL-SVS). Among 114 included children, significantly lesser myopic progression was seen in children on RLRL in the second year in terms of both AL and SER. RLRL also showed sustained myopia control efficacy over 2 years, with the least myopic progression over 2 years seen in the group that remained on RLRL for both years (AL: 0.16 ± 0.37 mm; SER: −0.31 ± 0.79D). For those who switched from RLRL to SVS in the second year, a modest rebound effect was observed (0.42mm, -0.91D) like the degree of myopic progression in the first year of SVS (0.38mm, -0.741D).

There have since been over 20 peer-reviewed papers and over 5 systematic reviews and meta-analyses published on the effect of RLRL for myopia control. It has consistently been shown to slow AL elongation, with several papers consistently reporting on a phenomenon of axial shortening up until 12 months. For example, a retrospective multicentre analysis of 434 myopic children in China identified significant AL shortening >0.05mm / year in 26.5% of children [124]. More recently, RLRL has been demonstrated to show a particularly strong effect in high myopia, unlike other myopia

control treatments [125]. Finally, although all published literature to-date originates from China, Eyerising International as an RLRL manufacturer reports numerous international studies underway in Japan, Australia and Spain, with interim data provided to the WSPOS committee showing consistently promising results.

With regards to safety, a systematic review titled "Safety of Repeated Low-Level Red-Light Therapy for Myopia" evaluated the safety profile of repeated low-level red-light therapy (RLT) in controlling myopia progression [126]. The analysis encompassed 20 studies, including randomized controlled trials and observational studies, with a total of 2,380 participants aged 3-18 years, of whom 1,436 underwent RL therapy. From this systematic review, there were no cases of permanent vision loss. There were 2 case reports that described a single patient experiencing reversible decline in visual acuity and optical coherence tomography abnormalities, that resolved completely after 4 months cessation of treatment [127]. The review also highlights that the most common side effect of RLT was temporary afterimages that typically resolved within 6 minutes post-treatment. The incidence of side effects from RLT was 0.088 per 100 patient-years (95% confidence interval [CI], 0.02-0.50), comparable to spectacles designed for myopia reduction (0.22; 95% CI, 0.09-0.51; P=0.385), and significantly lower than for low-dose atropine (7.32; 95% CI, 6.65-8.05; P<0.001), orthokeratology (20.6; 95% CI, 16.7-25.0; P<0.001), and other anti-myopia contact lenses (19.3; 95% CI, 17.6-21.1; P<0.001). The review suggests that RLT does not cause irreversible visual function loss or ocular structural damage. However, it recommends conducting fundus photography and OCT before and during therapy, along with home monitoring of visual acuity and duration of afterimages, to promptly identify any side effects. The authors also call for further adequately powered studies of longer duration to evaluate the long-term safety of RLT [126].

A notable issue for RLRL as a new treatment modality is the lack of standardisation in the safety evaluation of different manufacturers' red-light devices, as each device has a differing degree of research basis and regulatory approval. A recent United States study evaluating two different LLRL (low-level red-light) devices available in China showed that 3 minutes of continuous viewing, approached or surpassed the maximum permissible exposure (MPE) of the ANSI Z136.1-2014 standard, possibly putting the retina at risk of photochemical and thermal damage. In China, where the device originated, the "Expert Consensus on repeated low-level red-light therapy for treatment of myopia in Children and Adolescents (2022)" published in the Chinese Journal of Experimental Ophthalmology, acknowledged that the lack of such unified safety standards in China increases the risks of potential adverse events. Therefore, as of 1st July 2024, the further sale of RLRL devices in China has been halted until each RLRL manufacturer attains a Class III medical device registration certificate which is crucially mandated on the national level (National Medical Products Administration, General Planning Finance Division, Drug Administration General Medical Device Notice Letter [2023] No 354). These guidelines demand that the manufacturers will conduct animal studies on primates and long-term histopathological studies that will be reviewed by the

regulatory authorities, which may delay continued RLRL uptake in China. Since none of the manufacturers in China have met these demands, this will probably pause the use of these devices in China [128]. However, it is important to note existing RLRL users in China may continue treatment and devices manufactured before 1 July 2024 may continue to be sold. Eyerising

International, the only RLRL device to thus far have achieved regulatory approval outside of China, has stated that this reclassification does not impact their regulatory approvals outside of China, where the device is now available across several countries in Europe and Asia.

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