# ADVANCES IN MYOPIA CONTROL STRATEGIES FOR CHILDREN

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**Abstract**

Myopia has long been a global threat to public health. Timely interventions are likely to reduce the risk of vision-threatening complications. There are both established and rapidly evolving therapeutic approaches to slow myopia progression and/or delay its onset. The effective methods for slowing myopia progression include atropine eye drops, defocus incorporated multiple segments (DIMS) spectacle lenses, spectacle lenses with highly aspherical lenslets target (HALT), diffusion optics technology (DOT) spectacle lenses, red light therapy (RLT), multifocal soft contact lenses, and orthokeratology. Among these, 0.05% atropine, HALT lenses, RLT, and +3.00 peripheral addition soft contact lenses yield over 60% reduction in myopia progression, whereas DIMS, DOT, and MiSight contact lenses demonstrate at least 50% myopia control efficacy. 0.05% atropine demonstrates a more optimal balance of efficacy and safety than 0.01%. The efficacy of 0.01% atropine has not been consistent and requires further validation across diverse ethnicities. Combining atropine 0.01% with orthokeratology or DIMS spectacles yields better outcomes than monotherapy. Increased outdoor time is an effective public health strategy for myopia prevention while recent studies suggest that 0.05% low-concentration atropine and RLT therapy have promising potential as clinical myopia prevention interventions for high-risk groups. Spectacle lenses, being the least invasive, are safe for long-term use. However, when considering other approaches, it is essential to ensure proper instruction and regular follow-ups to maintain safety and monitor any potential complications. Ultimately, significant advances have been made in myopia control strategies, many of which have shown meaningful clinical outcomes. However, regular use and adequate safety monitoring over extended durations are imperative to foster confidence that can only come from extensive clinical experience.

## Introduction

Myopia has long been a global threat to public health with increasing prevalence across many regions in past decades, especially in East Asia.[1-3] It has been predicted that around half of the world's population will become myopic and one-tenth highly myopic by the year 2050.[4] While myopia can be optically corrected, such corrections cannot address the core issue, the abnormal elongation of the eyeball. The excessive globe elongation places myopic individuals at a higher risk of sight-threatening complications that lead to poor vision and even blindness.[5] It has currently been indicated that no identified level of myopia can be considered safe concerning the ocular complications associated with it.[5] Thus, the concern of slowing myopia progression and ultimately preventing its onset has grown significantly. This has generated significant research interest in developing effective methods to slow the progression of myopia and/or delay its onset. Several clinical trials have demonstrated the beneficial effects of various myopia control strategies, some of which have been adopted in mainstream clinical practice. This review provides an overview of established therapeutic approaches and evolving methods for controlling myopia onset and progression.

## Search strategy and study selection

A comprehensive literature search was conducted across multiple databases, including MEDLINE, PubMed, EMBASE, and Web of Science. The search terms included "Peripheral Defocus," "Myopia," "Myopia Progression," "Myopia Incidence," "Myopia Management," "Myopia Control," "Atropine," "Low Concentration Atropine," "Low Dose Atropine," "Repeated Low-Level Red Light," "Low-Intensity Red Light," "Red Light," "Bifocal," "Progressive Addition Lenses," "Orthokeratology," "Contact Lenses," "Spectacle Lenses," "Levodopa," "Outdoor time," "Outdoor," "Combination," and "Combined," in varying combinations. The search was defined using the Boolean operators "AND" and "OR", as well as truncations. Published studies were considered eligible if they met the following criteria: (1) clinical trials (3) included children, aged 17 years or younger (5) reported axial length elongation and/or change in spherical equivalent refraction (6) reported treatment with red light, atropine optical interventions, or outdoor time (7) published in 1989 or more recent.

## Increased Time Outdoors

Earlier research found that increased participation in weekly sports and outdoor activities was associated with a lower risk of developing myopia.[6] However, the protective role of outdoor time against myopia first came to prominence in the Sydney Myopia Study.[7] Global studies have subsequently supported that increased outdoor time can prevent myopia onset.[8] Randomized clinical trials have also demonstrated the efficacy of outdoor time interventions in reducing myopia incidence. The Guangzhou school-based clinical trial showed a 23% relative reduction in incident myopia over 3 years with the addition of 40 minutes of outdoor time daily.[9] In the ROC studies in Taiwan, the relative reduction in the incidence of myopia was approximately 52% when children spent 80 minutes of outdoor time per day.[10] A later phase of the ROC studies found a lesser relative reduction in the incidence of myopia, but this was against a background of now co-existing mandated time to be spent outdoors in Taiwanese schools.[11] Limited evidence suggests outdoor time may slow myopia progression. Wu et al. found a 30% reduction in children already myopic,[11] aligning with reports showing slower myopia progression during summer compared to winter.[12-16] Recent reports indicated accelerated myopia progression during the COVID-19 lockdowns in China and Hong Kong, correlating with reduced outdoor time compared to pre-COVID era.[17-24]

In clinical settings, incorporating clinical recommendations to increase outdoor time could be beneficial in managing myopia progression. Discussing the benefits of spending more time outdoors and providing specific recommendations to children can help reduce the risk of myopia development and progression. Outdoor time is a simple and cost-effective intervention although the optimal duration and frequency for myopia prevention is unclear. Current recommendations suggest at least 2 hours per day. Longer or more frequent outdoor sessions may be more effective, but UV protection measures are important considerations. It is important to consider using outdoor time as a complement to myopia control, alongside other interventions. A recent study demonstrated that decreased time outdoors during COVID-19 confinements reduced the treatment efficacy of Defocus Incorporated Multiple Segment (DIMS) spectacle lens.[25] Clinicians have a crucial role in advocating for the relevant public health interventions for myopia and promoting best clinical practices. Practitioners should provide advice on lifestyle and the visual environment, especially to patients whose parents or siblings are myopic, as well as those with high-risk

ancestry,[26 27] such as encouraging a minimum of 2 hours of daily outdoor time[7 28] and less than 2 hours per day of leisure near work. Increasing viewing distance and having frequent breaks during near work (with any material) should also be recommended.[29-31]

Beyond the clinic, promoting outdoor time can serve as a policy-level intervention, especially in educational settings. This approach may include creating environments and implementing policies that encourage outdoor activities, such as incorporating outdoor tasks into school curricula and providing dedicated time for outdoor activities during recess periods. Locations such as Taiwan, Singapore, and China have pioneered outdoor programs. The Ministry of Education in Taiwan implemented the Tian-Tian 120 program, advocating 120 minutes of daily outdoor activities, which reduced the national prevalence of poor visual acuity in primary school children from 49.4% in 2012 to 46.1% in 2015, reversing the increasing trend of 34.8% to 50% observed from 2001 to 2011.[32] The implementation of Taiwan's Sports and Health 150 program, that promotes 150 minutes of exercise at school per week, is an additional valuable measure.[33] It is worth emphasizing that it's the exposure to natural daylight during these activities that is key to preventing myopia, rather than exercise alone.[7] The Singapore program 'Kids for Nature' aimed to provide an educational program in National Parks as an incentive for primary school children and their parents to spend more time outdoors, however, compliance with the program declined over six months. In China, the guidelines for myopia prevention prioritize the importance of spending time outdoors and emphasize the role of schools in facilitating this. The government's "Double Reductions" policy, aimed at reducing homework and after-school tutoring while increasing after-school care, indirectly facilitates more outdoor activities, providing opportunities for increased time outdoors.[34]

The implementation of increased outdoor time in schools raises concerns about lowering educational standards. However, a cross-sectional analysis of data from the STORM study in Shanghai suggests that increased outdoor time may play a positive role in increasing academic performance.[35] This observation finds support in the 2018 rankings of the Organization for Economic Co-operation and Development (OECD) Programme for International Student Assessment (PISA), which indicate that many European countries achieved reading performance levels similar to those of Hong Kong without a myopia epidemic.[36] The real challenge is that in a modern environment of digitized educational, children may be heavily used to a more indoor

lifestyle and feel reluctant to disconnect from excessive use of their electronic devices. Besides, myopia epidemic had already reached a critical stage before the widespread adoption of computers and smartphones. Therefore, simply reverting to using books as a solution is not effective. Instead, addressing the problem requires efforts to reduce overall near work activities and promote increased time outdoors. The proposed mechanism, which suggests that increased retinal dopamine release due to brighter light outdoors slows the rate of axial elongation, has been supported by studies conducted on experimental myopia in animals.[37-40] Preliminary findings suggest that this mechanism may also extend to humans.[41]

## Pharmacological Interventions

### *Low-concentration atropine*

Atropine, an antagonist to acetylcholine muscarinic receptors, was initially used for myopia control based on the hypothesis that excessive accommodation of the eye contributes to myopia. However, subsequent animal studies revealed that accommodation was not involved and that non-accommodative mechanisms contribute to the development of myopia.[42 43] Thus, the focus of research has shifted towards non-accommodative mechanisms. This has involved a search for the specific site of action of atropine through studies directed at the posterior segment of the eye as the location of action of the anti-myopic effect of atropine. Evidence has been presented against the sclera as a site of action for muscarinic antagonist control of myopia,[44 45] leaving the retina as the most likely site per the available evidence. Atropine rapidly reversed the downregulation of retinal ZENK mRNA during form-deprivation in chicks, resulting in elevated expression levels compared to control eyes, indicating a strong likelihood of a retinal site of action.[46] However, whether atropine acts on muscarinic receptors in controlling axial elongation is not clear, since other studies have suggested possible interactions with a non-muscarinic receptor in the retina, ɣ-aminobutyric acid receptors (GABA-R), suggesting a potential off-target effect.[47 48]

Clinical trials have consistently shown that atropine is potentially effective in slowing myopia progression and axial elongation (**Table 1)**. High concentration of 1% atropine conferred significant axial elongation and myopia control effects, but was associated with greater rebound and adverse events, limiting clinical uptake.[49-52] This resulted in a transition towards using lower concentrations. The break-through came with the use of 0.01% by the Atropine for the Treatment of Childhood Myopia (ATOM) 2 study, which showed that 0.01% atropine was the

most effective over 2 years and 5 years compared to 0.1% and 0.5%, with minimal side effects and rebound.[53 54] However, the findings is debatable due to the absence of a placebo control. Subsequent placebo-controlled trials in Asian children testing the efficacy of 0.01% atropine yielded inconsistent results.[55-63] In Europe and the United States, four of seven studies found no significant impact of 0.01% atropine on axial length or spherical equivalent refraction compared to control.[64-71] (Table 1)

The low-concentration atropine for myopia progression (LAMP) study introduced a placebo group and investigated 0.05%, 0.025%, and 0.01% atropine eye drops for myopia control and found a concentration-dependent effect. The findings indicated a satisfactory safety profile that persisted for three years.[58 72 73] Notably, younger children showed a less treatment effectiveness, requiring the higher concentration of 0.05% atropine to achieve similar reduction in myopia progression as older children using lower concentrations.[74] Additionally, it was evident that low-concentration atropine induced choroidal thickening along a concentration-dependent response.[75] The LAMP study suggests that 0.05% atropine optimally balances efficacy and safety. It is currently being used for myopia control in Hong Kong but has not gained a widespread clinical uptake in other regions of the world. In light of the limited efficacy of 0.01% atropine in American and European children in recent large RCTs,[66 67 71] there have been suggestions to use higher concentrations of atropine, particularly when addressing axial length elongation in white children.[67 76 77] Shifting to higher concentrations of 0.025% to 0.05% atropine will ensure timely implementation of an effective dose for myopic children, especially when they are younger and/or at greater risk of rapid progression, serious eye complications, and vision loss.

Atropine eye drops have also been explored in the prevention of myopia onset. An earlier prospective study by Fang et al. found that 0.025% decreased onset of myopia in 6-12 year-old pre-myopic children.[78] Subsequent findings by the LAMP2 clinical trial showed that nightly use of 0.05% atropine resulted in a 46.4% reduction in a 2-year cumulative myopia incidence in 4-9-year-old non-myopic children.[79] Results from a crossover trial also revealed that 0.01% atropine reduced myopia incidence among children aged 6 to 12 years.[80] However, the long-term effect needs further validation. Additionally, it is unclear how early atropine treatment should be initiated. One significant challenge is identifying pre-myopes who could benefit from the delaying effect of atropine, particularly since they may not seek eye examinations until after

myopia has already developed, highlighting the need for public health approaches, enhanced screening methods and prediction models. China has made significant progress in the process of screening for refractive errors in schools, and this is now being expanded nationwide.[34 81] This is expected to help address the issue of clinical referral of premyopes, who may also tend to be pseudomyopes. While atropine is promising for myopia prevention, the extent to which its need for intervention can be prevented with increased time outdoors has not been specifically studied. Thus, it is recommended to consider atropine alongside outdoor time when managing premyopic children. There have been expressions of concern regarding the sustained efficacy of atropine eye drops and the possibility of rebound effects occurring following cessation of treatment. The rebound effect refers to the resurgence of a condition after the discontinuation of treatment, resulting in a more rapid progression in the treatment than in the control group and the loss of accumulated effect. The ATOM1 and ATOM2 studies[50 53] and subsequently the LAMP study,[73] demonstrated a concentration-dependent rapid axial elongation and myopia progression following the cessation of treatment. While tapering off 1% atropine has been shown to reduce rebound,[82] it is currently unclear whether this is also the case for lower concentrations. The mechanisms underlying the rebound phenomenon are currently unknown.

***Levodopa***

Continuing efforts to enhance treatment outcomes for myopia have led researchers to investigate and develop new interventions. In recent investigations, levodopa has shown promise as a potential treatment option. In a clinical setting, it is common practice to combine levodopa with carbidopa to prevent its early conversion to dopamine before it reaches the desired tissue. This coadministration approach plays a vital role in enhancing treatment outcomes.[83] Preclinical research involving animal models has demonstrated that the application of levodopa/carbidopa in a topical form can effectively inhibit experimental form-deprivation myopia (FDM) and that induced by optical manipulation.[84-86] This inhibitory effect shows a dose-dependent relationship, with higher concentrations of levodopa/carbidopa offering complete protection.[84 86] Additionally, these findings highlight a significant increase in treatment efficacy when using topical levodopa/carbidopa compared to levodopa alone.[85] Consistent with the safety findings in preclinical studies, the first randomized controlled trial demonstrated that the daily application of an ophthalmic solution containing levodopa/carbidopa over a period of one month was well-

tolerated. This treatment did not cause any alterations in anterior surface integrity, visual function, ocular health, or refraction/ocular biometry in healthy adult males.[83] These findings provide a foundation for future investigations into the effectiveness of levodopa/carbidopa eye drops as a potential treatment for myopia in humans. The probable mechanism through which levodopa exerts its anti-myopic effects is by stimulating the synthesis and release of dopamine within the retina.[85]

## Optical Devices

### *Novel spectacle lenses*

It has long been known from animal studies that the wearing of a minus lens during development, thereby creating hyperopic defocus (that is, shifting the point of focus behind the retina), could induce compensatory axial elongation, resulting in a myopic eye.[87] This later generated the hypothesis of the peripheral hyperopic defocus theory, which was that early relative peripheral hyperopic defocus was the underlying cause of myopia. In support of this, Smith et al. demonstrated in rhesus monkeys that laser ablation of the fovea did not hinder the development of myopia in response to optically induced relative hyperopic defocus or form deprivation.[88] The findings were corroborated by cross-sectional studies in humans, which reported greater relative peripheral hyperopia in myopic children compared to relative peripheral myopia in emmetropes and hyperopes.[89-91] A major hindrance to this argument was that it was unclear whether relative peripheral hyperopic defocus was the cause or the consequence of myopia.[90] However, subsequent evidence from longitudinal studies has shown that the emergence of relative peripheral hyperopic defocus is more a consequence of the development of myopia rather than a cause since it manifests simultaneously with the onset of myopia and does not precede it.[92-94] While these findings indicated that foveal visual signals are not essential for regulating axial length growth, they did not conclusively prove that central defocus has no impact on refractive error development, and this is what later informed the simultaneous competing defocus theory as a potential mechanism for defocus myopia control spectacle and contact lenses.[95-97] It involves achieving clear central vision while simultaneously inducing relative myopic defocus across a significant portion of the peripheral retina. The theory is based on the principle that in situations where competing defocus signals occur simultaneously, the least hyperopic or more myopic focal plane takes precedence and exerts a stronger influence on refractive development. Although there have

been studies on simultaneous competing defocus, the basis of myopia control spectacle and contact lens designs stems more from research emphasizing the importance of myopic defocus on its own rather than from competing defocus.

*MyoVision lenses: reducing relative peripheral hyperopic defocus*

The first trial on defocus spectacle lenses tested three highly aspherized designs intended to reduce relative peripheral hyperopic defocus. The lenses differed in the size of the central optic zone and the magnitude of the relative positive power in the periphery.[98] The only successful lens type, later named MyoVision lenses, significantly slowed myopia progression by 30% only in only in a subgroup of 6-12-year-old children with parental history of myopia, but had no significant effect on axial length elongation. Later, a multicentre clinic trial in Japanese children with a family history of myopia found no significant difference in myopia progression between MyoVision lenses and mono-focal glasses,[99] indicating that the lenses had less useful clinical impact. This implies that reduction of relative peripheral hyperopia may be insufficient to control myopia progression.

*Multiple segments spectacle lenses: inducing myopic defocus in the mid-periphery of the retina*

The defocus-incorporated multiple segments (DIMS) spectacle lens was designed following the success of the Defocus Incorporated Soft Contact (DISC) lens that imposed myopia defocus across the retina.[100] The spectacle lenses, unlike DISC, were designed to have a central zone (diameter 9mm) of myopic refractive correction giving clear vision and a surrounding zone of lenslets that create myopic defocus across the mid-periphery of the retina.[101] In a 2-year randomized controlled trial, 8-13-year-old Chinese children who wore DIMS spectacle lenses had myopia progression retarded by 52% and axial length elongation by 62%.[101] Approximately 21% of the children who wore the DIMS spectacle lenses had no myopia progression over the 2-year period. Subsequent findings of the study demonstrated that DIMS lenses offered sustained efficacy over the course of six years without any negative side effects.[102] Clearly, the DIMS spectacle lenses are an effective and safe approach to managing progressive myopia in children.

Another version of a spectacle lens that uses multiple segments of myopic defocus has been developed by Essilor[103] and uses multiple concentric rings of lenslets of varying myopic defocus, described as aspherical lenslets.[104] These spectacle lenses also feature a central optical zone intended for correcting distance refractive error. The aspherical lenslets have been designed to deviate light in a manner that creates a volume of myopic defocus.[103] Thus, the size of the functional zone responsible for generating mid- peripheral myopic defocus is greater, but does not result in a better efficacy than the DIMS lens. In a 2-year trial, it was found that lenses with a highly aspherical lenslets target (HALT) were more effective than single vision lenses in slowing myopia progression in Chinese children aged 8-13 years (reduced myopia progression by 55% and axial elongation by 51%), over a period of 2 years.[103] Additionally, the concentric aspherical design demonstrated a dose-dependent efficacy concerning both the degree of asphericity of the lenslets and the duration of lens wear.[103 105] In the third-year report, children who continued to wear the HAL demonstrated less axial elongation and myopia progression compared to those who wore single-vision lenses and are currently being followed for two more years.[106] Efforts can be directed towards refining the HALT design by increasing asphericity of the lenslets while maintaining wearer comfort. Finding this delicate balance could be instrumental in further improving the efficacy of HALT lenses. These lenses are marketed as the Stellest$^{TM}$ myopia control glasses.

***Diffusion optics spectacle lenses***

Contrast modulation is a novel mechanism of action employed in the Diffusion Optics Technology (DOT) spectacle lenses.[107] The lens is designed to control myopia by slightly reducing contrast at the retina by softly scattering incoming light to the eye.[107] The design is based on the principle that low contrast visual experience, like that from a natural outdoor environment, weakly stimulates the visual system and elicits low-level, more natural bipolar cell activity that does not appear to disrupt normal eye growth,[108] whereas elevated contrast signaling in the retina, whether from genetic predisposition[107 109] or the modern urban visual environment, may overstimulate bipolar cells leading to overstimulation of axial elongation and myopia progression.[108] The DOT lens consists of a central clear aperture surrounded by a pattern of numerous micro-dot scattering centres spanning the treatment zone of the lens from edge to edge, each dot gently dispersing light to slightly lower artificial contrast to mimic more natural contrast.

In a two-year clinical trial, DOT lenses were more effective compared to control lenses, delaying myopia progression by 59% and axial elongation by 38% over 2 years.[110] After 4 years, the lenses remained safe and more effective compared to standard single-vision control lenses.[111]

### *Bifocal and progressive addition spectacle lenses*

Bifocals and progressive addition lenses were initially considered for myopia management because they reduce accommodative lag and near-point esophoria, which have been associated with myopia progression. However, available studies using bifocals indicate either a slight effect or effectiveness limited to a specific subset of children with accommodative lag or near esophoria.[112 113] Multiple studies also suggested that progressive addition lenses have limited efficacy in controlling myopia, again often restricted to children with accommodative lags or near esophoria.[114-118] Thus, bifocals and progressive addition lenses cannot be considered universally effective interventions and do not achieve meaningful clinical benefits for the majority of myopic children.

To conclude, the reported outcomes suggest that DIMS, HALT, and DOT lenses are effective and demonstrate significant clinical benefits. Myopia control spectacle lenses provide the added benefits of being safe and less invasive. The lenses are easy to integrate into daily wear, requiring minimal adjustments to visual habits. However, some of these spectacle-based interventions may reduce high contrast visual acuity and contrast sensitivity at higher spatial frequencies when viewed off-axis through the myopia control elements.[104 119 120] There is no evidence to suggest that any of these side effects influence compliance with the lenses.

## Contact Lenses

### *Orthokeratology lenses*

Orthokeratology (Ortho-K) uses overnight gas-permeable lenses to reshape the cornea for myopia correction. Upon morning removal, the flattened central cornea improves distance vision eliminating the necessity for glasses or contact lenses. This is especially convenient for individuals who prefer not to wear optical corrections during waking hours or engage in sports or activities where glasses or contact lenses may hinder their performance. In 2005, a pilot study suggested that Ortho-K might also reduce myopia progression.[121] In searching for an explanation of this effect, reports have suggested that Ortho-K not only reshapes the central cornea but also induces relative

peripheral myopic defocus[122] through changes in spherical aberration.[123] Studies in Asia have reported significant axial length control efficacies of 36% to 46% over 2 years.[121 124-126] This provides an interesting parallel to the findings of similar 2-year studies conducted in Spain (32%), Denmark (59%), and the United States (55%).[127-129] Earlier reports suggest that the efficacy of Ortho-K is particularly notable during the first and second years of treatment, especially when it is initiated at an early age of 6 to 8 years.[130 131] However, successful Ortho-K fitting requires advanced imaging and practitioner expertise, leading to longer clinic visits and added costs. Besides, even successful treatments can increase corneal irregular astigmatism and higher-order aberrations, sometimes reducing contrast sensitivity.[132 133] Moreover, sleeping in contact lenses creates an environment for the development of cases such as *Acanthamoeba and Pseudomonas* keratitis which can result in permanent scarring of the cornea and, in severe cases, vision loss.[134]

***Multifocal soft contact lenses***

Similar to findings from novel spectacle lenses, there is a consensus that soft contact lenses with a central distance zone and peripheral positive power can slow myopia progression. In this section, we explore two types of soft contact lenses for myopia control: progressive peripheral add (multifocal) contact lenses and concentric ring (bifocal) soft contact lenses. Both designs have a central zone for myopic correction. Peripheral addition lenses gradually adjust defocus from the center to the periphery [135] while concentric ring bifocal lenses alternate between distance correction and plus power addition.[100]

*Progressive peripheral add soft contact lenses: multifocal*

Based on the theory of reducing relative peripheral hyperopia to control myopia and using similar principles as the MyoVision spectacle lenses, contact lenses were developed that increased the level of reduction in relative peripheral hyperopia and increased the size of the treatment zone, moving it closer to the visual axis than had been designed for the spectacles. The contact lenses had a maximum add power of +2.00D, and over 12 months, reduced myopia progression and axial length elongation by 34% and 33%, respectively,[135]but further longitudinal outcomes were not reported. Other studies employing progressive peripheral add power reaching +2.00D have reported 2-year axial length and myopia control efficacies of 27% - 29% and 43% - 50%, respectively. [136 137] The BLINK study reported comparable results for lenses with a maximum

add power of +2.50D, showing a 36% decrease in axial elongation and a 43% decrease in myopia progression over a 3-year period.[138] Increasing the add power to a maximum of +3.00D, Raffa et al. observed a 66.6% control of myopia progression and 63.2% reduction in axial elongation over a period of 18 months.[139] An effort was made to use contact lenses with positive spherical aberration to control myopia by correcting retinal hyperopic blur caused by negative spherical aberrations associated with accommodation. Although the lens achieved a 38.6% reduction in axial length elongation over the course of a year, it was deemed clinically unviable as this reduction did not lead to a significant effect on the progression of myopia.[140] Given that spherical aberrations are not the sole higher-order aberrations linked to myopia,[141] the outcomes were not unexpected.

*Concentric ring bifocal soft contact lenses*

In a 2-year clinical trial, the DISC which later led to the development of DIMS, exhibited 32.4% less axial elongation and a 25% reduction in myopia progression.[100] The DISC was never released for commercial availability. MiSight contact lenses are dual-focus soft contact lenses with a central correction zone surrounded by a series of treatment and correction zones producing 2.00 D of simultaneous myopic retinal defocus. These have demonstrated up to 52% decrease in axial elongation and a 59% reduction in myopia progression over three years.[142-144] Aller et al. reported a 72% decrease in refraction and 80% reduction in axial elongation with multi-ring bifocal soft contact lenses (Acuvue Bifocal by Vistakon, Inc.), but this was in children with eso fixation disparity. The Acuvue Bifocal has been discontinued. [145]

Unlike the typical dual-focus or multifocal soft contact lens designs, the non-coaxial ring focus contact lens generates a ring focus that falls in front of the retina but off the line of sight, enabling a larger treatment zone and the incorporation of a higher add power while maintaining comparable visual performance.[146] To examine the balance between reducing myopia and improving visual quality, two experimental lenses were used: one designed to enhance efficacy (EE) and the other to enhance vision (EV). Both lens types consist of two concentric, annular treatment zones of +7.00D non-coaxial plus power with the EE design featuring an additional +10 D coaxial treatment zone for greater efficacy without compromising visual acuity, due to the dispersal of the light rays. The EE lens (commercialized as ACUVUE® Abiliti™) produced the most significant effect with a mean difference in axial length elongation being 0.11mm compared to the control.

Efficacy of the peripheral addition multifocal contact lenses seems to be dependent on the magnitude of the add power and zones of correction, with high-addition lenses yielding relatively better outcomes. A consensus on the optimal amount of defocus and the ideal zones to correct is required. The MiSight® and ACUVUE® Abiliti™ lenses demonstrate efficacy levels comparable to those reported for the simultaneous competing defocus spectacle lenses, probably because of the similar design principles. Myopia control with soft contact lenses can serve as viable alternatives for patients who are not indicated for or are unsuccessful in undergoing orthokeratology treatment or who may not wish to wear spectacles. Soft contact lenses, placed directly on the eye, may provide a broader peripheral view and less distortion than spectacles, benefiting activities like sports and driving. Nonetheless, soft contact lens wear is associated with the risk of corneal infiltrative events and requires strict adherence to treatment regimen and lens care.[147]

**Red Light Therapy**

Another emerging method for myopia control is light exposure therapy. Animal experiments had suggested that long-wavelength (red) light irradiation could produce a hyperopic shift in infant and juvenile rhesus monkeys as well as in infant tree shrews.[148 149] This is the reverse of what would be expected in longitudinal chromatic aberration (LCA), which involves matching the focal plane of the dominant wavelength by increasing the speed of growth when the dominant wavelength is long and decreasing the speed of growth when the dominant wavelength is short.[148 150] More recent human clinical trials have shown that red light therapy (RLT) is effective in controlling myopia progression over one and two years.[151 152] At two years, a 75% reduction in both axial length elongation and myopia progression was found, following a treatment plan of 3 minutes per session, twice daily, and with a minimum interval of 4 hours. Comparable results have been reported in trials from other centres at 6 months and at one year.[153-156] RLT has also yielded up to 54.1% uninterrupted treatment efficacy in preventing incident myopia after a year.[157] Of note, the prophylactic effect in children whose spherical equivalent refraction was close to -0.50D was lower, as the intervention was introduced late, implying that early intervention with RLT could confer a higher efficacy.

While the mechanisms are not fully understood, it is recognized that increased choroidal thickness through increased retinal blood flow and metabolism contributes to a minor portion of these

observed changes.[158 159] It is unclear whether red light interacts directly with the cones or if the critical mechanism is photobiomodulation, which involves the reduction of nitrite to nitrous oxide through cytochrome c oxidase in response to red light.

Available evidence of safety suggests red light is a low-risk therapy that causes no significant adverse events and that it has been used in amblyopia treatment in China for over a decade with no long-term negative effects reported regarding its usage.[152 154-156] In a recent clinical case report, a 12-year-old girl experienced a decrease in best-corrected visual acuity for a period of two weeks following five months of regular exposure to RLT for myopia control.[160] Fundus photographs showed darkening of the foveae, hypoautofluorescence of the maculae, as well as OCT examination revealing disruptions in the bilateral foveal ellipsoid zone and interdigitation zone. After 3 months without RLRL therapy, the bilateral outer retinal damage recovered, and the visual acuity improved. Despite acknowledging potential retinal phototoxicity sensitivity and the fact that this could be an atypical case or a suspected Stargardt disease, it is crucial to maintain ongoing attention and vigilance by thorough clinical assessments and closely monitoring both the visual acuity, colour sensitivity, and retinal health of patients throughout the treatment with RLT.

The available device can be administered at home and requires the child to sit by the device and use for the recommended duration. This will allow parents to actively monitor adherence and ensure that the child follows the treatment regimen. However, due to the size and power requirements of the device, it is less portable compared to the other interventions. Adopting lightweight designs like spectacles will enhance convenience and ease of use, especially during long periods of travel away from home. Additional long-term studies are encouraged to clarify the mechanism and safety of red light therapy for myopia control.

**Combined therapy**

Combined treatments, targeting multiple pathways, are emerging as a more effective approach to myopia control than monotherapy. Recent studies indicate that combining 0.01% atropine with Ortho-K consistently outperforms either treatment alone in slowing axial length elongation, especially in younger children with shorter baseline axial length.[26–34,35] While the precise mechanisms are not fully understood, it is plausible that since the mechanisms appear to be different, their effects could be cumulative.

The efficacy of atropine combined with myopia control spectacles has been investigated in a few studies. Shih et al demonstrated a significant additive effect of atropine 0.5% when multifocal spectacle lenses were also worn but not with multifocal spectacle lenses alone.[36] Similarly, enhanced efficacy has been found in combining 0.01% atropine with DIMS spectacle lenses compared to DIMS spectacle lens or atropine monotherapy, in both Chinese children[167] and European subjects.[168] The mechanism underlying the additive effect of atropine and spectacle lenses is unclear; however, the improved efficacy may be attributed again to the differing mechanisms or to the use of atropine resulting in larger pupil diameter, leading to increased retinal illumination and positive spherical aberration, and thereby enhancing the myopic defocus effects of optical interventions. On the contrast, the Bifocal and Atropine in Myopia (BAM) study found that combining 0.01% atropine and soft multifocal contact lenses (SMCLs; add: +2.50-D) did not significantly improve myopia control over the SMCLs alone.[169]

Future studies may focus on higher concentrations of atropine, such as 0.05% atropine, combining with orthokeratology to effectively control myopia in individuals with high myopia, fast myopia progression, or poor response to orthokeratology. It is worth indicating that the enhanced efficacy of the combined therapy has only been investigated in children with low to moderate myopia, and it is necessary to exercise caution when applying results to other situations.

## Conclusions and future directions

There has been significant advancement in the development of myopia control methods over the past few years, with some methods demonstrating an acceptable balance between efficacy and safety. Specifically, 0.05% atropine, DIMS spectacle lenses, DOT lenses, lenses with HAL, RLT, concentric ring soft contact lenses, and orthokeratology lenses demonstrate favorable outcomes. Among these, the myopia control spectacle lenses are the least invasive and safest although all have demonstrated tolerable safety profiles. The efficacy of peripheral addition soft contact lenses is inconsistent, and it is obvious that a consensus is needed on the optimal amount of defocus to incorporate and the ideal zones to correct. Increased outdoor time, 0.05% low-concentration atropine, and RLT demonstrated efficacy in reducing myopia incidence. While outdoor time is well-established, atropine and RLT need further studies for clinical validation. Considering the rapid increase of myopia, promoting outdoor time for prevention and reserving clinical interventions for refractory cases is essential for broader impact. It is important to recognize that

there is an inherent growing of the eyeball and associated shift in refractive state that occurs in childhood, even in non-myopic children. Thus, the goal of myopia control interventions is not to completely halt these natural changes but reduce the risk of developing high myopia and subsequent sight threatening complications. Therefore, the level of myopia control that can be deemed effective and protective is when an intervention reduces the progression of myopia at a rate that can be projected to prevent the development of high myopia or myopia-associated ocular complications by the time myopia stabilizes. This emphasizes the need for individualized approaches to myopia management, considering rate of myopia progression, ethnicity, age, severity of myopia, and potential adverse effects.

Variations in ethnicity and age groups of participants have been major hindrances to extrapolating results and directly comparing the effectiveness of different treatment methods. This may make it challenging for eye care practitioners to confidently recommend the most effective intervention to their patients. There has not been widespread clinical uptake of some potentially efficacious interventions like red light and atropine 0.05% and this could be due to the predominantly Asian population of the participants who were enrolled in the trials. Future trials involving other races are warranted.

Finally, it should be noted that these therapies are directed at slowing excessive axial elongation of the eye, rather than affecting other optical components. While axial elongation is the predominant reason for the generation of myopia, it is worth noting that there are at least two other circumstances that can lead to myopic refractive errors, namely keratoconus and myopia of prematurity that is lenticular in origin. The use of the treatments to slow axial elongation are likely not to be appropriate in these cases and therefore preliminary ocular biometric measures and birth history must be considered carefully before commencement of these therapies. It is yet unclear how efficacious these treatments might be in cases of syndromic myopia and possibly familial high myopia, which are likely to be genetic in origin. Trials in children affected with these conditions have yet to be conducted and should be approached with clear understanding that outcomes are unknown.

EZ and XZ contributed equally.

## Contributors

XJZ conducted the literature search, article selection, data extraction, preparation of tables, and wrote the main manuscript. EZ conducted the literature search, article selection, data extraction, preparation of tables, and wrote the main manuscript. FYT carried out the data extraction, prepared the tables, and edited the main manuscript. KWK and AF critically revised the main manuscript. CCT carried out data interpretation and critically revised the main manuscript. LJC carried out data interpretation and critically revised the main manuscript. CPP carried out data interpretation and critically revised the main manuscript. JCY designed the study, carried out data extraction and interpretation, prepared the tables, and critically revised the manuscript.

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