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CLINICAL SUMMARY

IMI Interventions for Myopia Onset and Progression Report

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INTRODUCTION

The published IMI intervention white paper represents a review of the research into myopia-related interventions, organized under four categories: **optical, pharmacological, behavioral and surgical**. The evidence for treatment efficacy contained in relevant published studies were evaluated and recommendations made, based on the quality of the studies and the strength of the evidence. An overview of the key findings of this report are provided here.

KEY FINDINGS

Optical interventions

The use of **spectacles lenses** for slowing myopia progression has many advantages over other optical options for children, in that they are easy to fit, are mostly well accepted and tolerated, are affordable by most, and are minimally invasive. Spectacle lens-based interventions include both standard and customized **single vision (SV) lens designs, as well as bifocal and progressive spectacle lenses**. Findings from animal studies predict that undercorrection of myopia with **SV spectacles**, leaving residual myopic errors for distance viewing, will slow progression. However, since 2000, three randomized clinical trials examining the effect of under-correction (by +0.50 to +0.75 D, over 1.5 to 2.0 years), found either increased myopia progression or no benefit, compared to progression in fully corrected SV spectacle wearers. However, a recent study in rural China examining progression rates in children unintentionally uncorrected or undercorrected, yielded contradictory results, pointing to likely confounding factors. That intentional undercorrection leads to behavioral changes, including reduced outdoor activities, is among possible explanations for these different study outcomes.

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Other findings from animal studies offer strong evidence for contributions by the peripheral retina to eye growth regulation and refractive error development. Of note, imposition of hyperopic defocus on the retinal periphery accelerates eye growth, while the converse is true for imposed myopia. Based on reports of relative peripheral hyperopia in myopic eyes corrected with SV spectacles, it has been speculated that such hyperopic errors may drive myopia progression. However, randomized clinical trials of three **novel spectacle lens designs** aimed at reducing relative peripheral hyperopia yielded generally disappointing results, with no clinically significant decreases in myopia progression achieved. Likewise, two more recent trials, one involving a positively aspherized

lens design (MyoVision lens), in Japanese children and the other, a combination of relative peripheral myopic defocus and a progressive addition zone for near, found no benefit from either.

The use of **bifocal spectacles** for myopia control has a long history, the traditional rationale for their use being to reduce or eliminate lags of accommodation during extended near work. Accommodative lags are a source of hyperopic defocus, which is known to accelerate eye growth in animal studies. The possibility that sustained ciliary muscle contraction may adversely influence eye growth, perhaps through interactions with the overlying sclera, has also been the subject of speculation. **Progressive addition lenses** are used with a similar rationale to bifocal spectacles. Either way, reducing accommodation through the prescription of multifocal spectacles could be beneficial. Furthermore, all multifocal lens designs, including bifocal lens designs, induce relative myopic shifts in peripheral refractive errors experienced by the superior retina. However, with just a few exceptions, results of clinical trials of the same have yielded equivocal results, one of the former involving high-set executive bifocal spectacles with base-in prism prescribed to a subgroup of subjects who also showed the best myopia control. Such differences in study outcomes once again point to the importance of behavior as a confounding variable. In the case of multifocal spectacles, results from one study of Japanese children suggested that children do not always make use of the addition zone for near vision. Thus high set additions are expected to improve compliance, as may appropriate prism prescriptions for those with near exophoria.

In terms of **contact lenses**, the literature covering the effects on myopia progression of conventional SV soft contact lens wear is limited, although significant design-dependent differences in their effects on peripheral (off-axis) refractive errors have been reported, to include increases in relative hyperopia with some. Two recent trials involving SV gas-permeable lenses confirmed that their use does not adversely impact axial elongation, at the same time overturning an old belief that such lenses slow myopia progression; instead, apparent myopia control was attributed to induced corneal flattening. Trials of multifocal soft contact lenses, in most case representing off-label use of presbyopic corrections, have yielded far more promising results. For 8 trials published over the 2011-2016 period, there was a 38.0% slowing of myopia progression and a 37.9% slowing of axial elongation, based on sample size-weighted averages. Interstudy differences in measurement protocols and the ocular profiles of subjects are reflected in interstudy differences in outcomes, indexed by refractive error versus axial length changes. Thus some studies report greater slowing of myopia progression than of axial elongation, while the converse was true for some others, and for still others, changes in myopia progression approximately matched changes in axial elongation. For example, concentric ring designs appear to offer better control over axial elongation than progressive designs (44.4 vs. 31.6%), yet their effects on myopia progression were similar (36.3 vs. 36.4%). In terms of treatment efficacy, effects on axial elongation must always be given more weight.

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Orthokeratology (OK) involves reshaping (flattening) of the cornea to reduce myopic refractive errors. The initial goal of OK was to eliminate the need for daytime optical corrections and development of reverse geometry rigid gas permeable lens designs has revolutionized OK, by allowing sufficient reshaping of the cornea to be achieved with overnight wear. OK has also proven to be very effective in slowing axial elongation in myopes. Because corneal flattening with OK is largely limited to the central cornea, it also results in relative myopic shifts in peripheral refractive errors, consistent with one explanation for its myopia control effect, although a role for altered high order aberrations cannot be excluded. That relative treatment efficacy may decrease with time has been suggested, although interpretation of longitudinal data is confounded by a number of factors, including the well-documented age-related slowing of myopia progression. That early termination of OK treatment might lead to rebound acceleration in axial elongation is also suggested by results of a few studies in children, although similar trends are not evident in results for university students with adult-onset, progressive myopia. Once again, a cautionary note is offered in interpreting of such differences, as the optical appliances used to correct myopia are likely to significantly impact behavior, especially in children.

Pharmacological control

Of the drugs trialed for control of myopia progression, to-date topical **atropine** has dominated both clinical trials and clinical practice, where it is now widely used, mostly off-label. Atropine is a nonselective irreversible antimuscarinic antagonist, as reflected in the prolonged mydriasis and cycloplegia induced by one drop of topical

1% atropine. In relation to eye care, it has a long history of use, as a cycloplegic agent for evaluating refractive errors in very young children and penalizing the preferred eye in amblyopia therapy; it is also occasionally used as a component of therapy for uveal inflammatory conditions.

In terms of evaluating the efficacy of topical atropine as a myopia control therapy, arguably changes in axial length more accurately reflect treatment effects than refractive error data, being free from the confounding effect of cycloplegia. Even with low concentrations of atropine, its chronic use may lead to significant intraocular accumulation and thus cycloplegia over time and so it is not surprising that refractive error data typically suggest better control than equivalent axial length data. Thus the efficacy of the lowest, 0.01% concentration included in the ATOM series of clinical trials from Singapore, has recently been challenged by results from a short (12 month), dosing study from Hong Kong. Nonetheless, high concentrations, e.g., 1% as used in very early studies, have been linked to larger side-effects and rebound effects after termination of extended treatment. The clinical trial data also point to individual differences in responsiveness and changes in treatment efficacy over time. Thus while there is little doubt about the efficacy of topical atropine as a myopia control therapy, many questions related to optimal dosing regimens remain to be resolved.

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Other pharmacological agents subjected to clinical trial for myopia control include oral **7-methylxanthine** (7-MX), an adenosine antagonist. Its use is limited to Denmark, the site of the only clinical trial of 7-MX and where it is now approved for use as pharmacy-compounded tablets, with reimbursement from the Danish National Health Insurance for patients up to 18 years of age. While it appears relative ineffective compared to other treatment options for myopia control, 7-MX as well as caffeine, of which 7-MX is a metabolic byproduct, are targets of on-going, related studies in monkeys.

Recommendations for the use of ocular hypotensive drugs for myopia control appear in a number of early publications, the underlying premise being that lowering IOP would reduce the tension on the wall of the eye and so slow ocular elongation. In this context, there are reports of positive treatment outcomes for epinephrine, labetolol, a combination of pilocarpine and timolol, and timolol alone, although results from a large randomized clinical trial of twice-daily topical 0.25% timolol, a nonselective beta-adrenergic antagonistic, were disappointing. However, recent positive findings in two independent animal studies, involving latanoprost, a prostaglandin analog, and brimonidine, an alpha2 adrenergic agonist, have renewed interest in this approach to myopia control, with potential prophylactic merit, as myopia is linked to an increased risk of glaucoma.

Environmental Influences & the Role of Time Outdoors

Results from a series of influential studies point to the importance of **time outdoors,** which appears to afford protection against the development of myopia, with somewhat weaker evidence linking increased time outdoors with slowed myopia progression. The underlying mechanism for this outdoor effect remains unresolved. That the increased intensity of visible light outdoors may be a contributing factor is supported by data from animal studies involving form deprivation-induced myopia, which is inhibited by bright light exposure, yet results from studies involving lens-induced myopia are less convincing. While one study from China reported a reduction in incident myopia one year after **elevating light levels** in school classrooms, from approximately 100 to 500 lux, it should be noted that the higher light level is well below that typically used in related animal studies. However, the initial light level (100 lux) is also comparatively low by modern standards, consistent with the notion that dim light is myopigenic.. While another study reported an association between the use of fluorescent desk lights and myopia, it did not control for socioeconomic status. To-date there have been no related studies into the influences, if any, of newer light sources, such as light-emitting diodes (LEDs). Quite apart from the potential impact of differences in the types of activities undertaken in indoor and outdoor environments, also of potential relevance to the protective effect of outdoor exposure are differences in retinal image profiles (spatial, temporal & defocus).

Studies pointing to a protective role of outdoor exposure have also raised interest in the possible link between **vitamin D** deficiency and myopia, as synthesis of Vitamin D in the skin, which contributes significantly to serum levels, is catalyzed by ultraviolet radiation and thus dependent on exposure to sunlight However, current data tend to argue against a causal relationship between Vitamin D deficient and myopia; instead, serum vitamin D levels more likely represent a surrogate for outdoor exposure.

Surgical interventions

Procedures for stabilizing the sclera, by way of preventing or slowing further axial elongation in highly myopic eyes aim to reduce or eliminate associated pathological retinal and choroidal complications. Interventions fall into three main categories: scleral buckling surgeries, scleral injection-based treatments and scleral collagen cross-linking. Only the first of these options have seen substantial deployment in the clinic, with the other two remaining largely experimental at this time. In the case of the former, surgeries have been mostly limited to unstable, highly myopic eyes and posterior scleral buckling, in which donor scleral tissue is implanted over the posterior pole. To-date, twelve related studies, mostly involving retrospective case or case-control series, have been published, with generally positive outcomes, although many publications lack key surgical details.

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CONCLUSION

There are currently multiple avenues for intervention in all categories, with the options within each category continuing to grow. However, at this time, there is no "one size fits all" intervention for preventing or slowing progression of myopia and most options fall short of achieving 100% efficacy, at least over an extended period. Further research is critical to understanding underlying mechanisms, and so the factors contributing to such variability, and is also fundamental to developing evidence-based recommendations for treatments and combinations of the same. Developments in this space to-date largely can be viewed as incremental in nature and thus there is also both room and a need for research into more novel approaches to myopia control.

Reference: Wildsoet CF, Chia A, Cho P, Guggenheim JA, Polling JR, Read S, et al. IMI - Interventions Myopia Institute: Interventions for Controlling Myopia Onset and Progression Report. Invest Ophthalmol Vis Sci. 2019;60(3):M106-M31.

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