IMI 2023 Digest

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Latest research from topic areas covered in previous IMI white paper series was reviewed by experts and findings summarized in the IMI 2023 digest.

Myopia definitions
Although the first IMI white paper defining myopia set refractive thresholds as ≤−0.5 D for myopia and ≤−6.0 D for high myopia, the paper also recognised the challenges and limitations of fixed thresholds and recommended adapting definitions to suit the nature of research. Rather than stipulate the use of cycloplegia, the definition applied when "ocular accommodation is relaxed" as it is difficult for primary eye care clinicians to access cycloplegic agents in many parts of the world. Based on recent literature, it is recognised that refraction results differ with and without cycloplegia and a higher threshold for myopia in non-cycloplegic surveys may be more appropriate for myopia but not a less myopic threshold for high myopia. Employing corrective formulas may also be a viable method to use when accounting for differences. However, with most recent studies, there was good consensus on the threshold values of −0.5 D for myopia and −6.0 D for high myopia, but varied on use of ≤ or < within the definition.

In the original IMI white paper on myopia definitions, "pre-myopia" was also defined. Recently, there have been an increasing number of publications reporting on pre-myopia. Identifying predictive factors for myopia onset during the pre-myopic phase offers the potential for early intervention. Although more research, including longitudinal studies, is needed to understand this phase fully, in Taiwan and China, it is reported to be the most common refractive state in preschool and primary school children. Ongoing trials are exploring interventions like atropine for pre-myopia, with promising results in small trials but there is a need for more research with data from larger trials.

Experimental models of emmetropization and myopia
Animal model research has been instrumental in shaping our understanding of myopia development and treatment strategies. The updates include;

- *Signalling pathways;* although the signalling cascade from the retina to the sclera is not fully understood, research is continuing to characterise the pathways with recent research in chicks indicating that interleukin 6 and lumican may play a role in visually guided eye growth.
- *Temporal Integration of Myopiagenic Stimuli;* brief periods of unrestricted vision or darkness in marmosets can mitigate myopic eye growth in response to hyperopic defocus, highlighting the nonlinear nature of defocus integration.
- *Peripheral Retina as a Myopia Control Target:* myopic defocus in the far periphery, beyond 20° from the fovea, does not consistently guiding refractive development in monkeys.
- *Pharmacologic Treatments;* topical caffeine was effective in controlling myopia in rhesus monkeys but a study using 2% topical caffeine in Vietnamese children showed no effect.
- *Circadian Rhythm, Dopamine, and Illumination Intensity;* studies in various animal models, including chicks and mice, support dopamine's role in controlling myopia, with potential implications for treatment using levodopa and carbidopa combinations. Additionally, findings in mice lacking melanopsin indicate its importance in refractive development and slowing myopia progression, while studies in rhesus monkeys suggest that reduced ambient lighting impairs emmetropization.
- *Longitudinal Chromatic Aberration (LCA):* Experiments with tree shrews using LCA i.e., where short wavelengths focus in front of longer wavelengths, have shown that a chromatic simulation of myopic blur can counteract a myopiagenic environment, highlighting the significant role of chromatic cues in emmetropization.
- *Narrowband Ambient Illumination;*

    - Long-wavelength red and amber light have been found to induce hyperopia in tree shrews and rhesus monkeys, but their effects vary across different animal models, posing a puzzle in understanding their mechanisms.
    - Short-wavelength; blue light has shown potential in slowing myopia progression in chicks and guinea pigs, while recent attention has shifted towards violet light, with studies suggesting its potential antimyopiagenic effects mediated by the opsin neuropsin (OPN5).
- *ON Versus OFF Pathways:* Photoreceptors (rods and cones) respond to light by hyperpolarizing. ON and OFF pathways are important for detecting luminance increments and decrements. Recent studies in mice indicate that disruption of the ON pathway leads to greater deficits in visual function and dopamine signalling than disruption of the OFF pathway. Additionally, the presence of dedicated ON bipolar cells for short-wavelength cones suggests that emmetropization might rely more on short-wavelength contrast processed through the ON pathway.
- *Scleral Cross-linking*: As individuals age, emmetropization stops due to the sclera becoming more rigid from natural collagen cross-links. In animal models such as tree shrews and guinea pigs, methods of accelerating collagen cross-linking were effective in myopia control but were associated with retinal pathology. The use of blue light-riboflavin has been shown to effectively induce cross-linking without pathology in monkeys and rabbits but the effectiveness for myopia control has not been tested.

Clinical trials

Participants: The number of prospective clinical trials on myopia control is rising. Departure from recommended criteria (page 7 of the IMI 2023 Digest) will generally lead to the apparent efficacy of a treatment being under- or overestimated, with differences in approaches making it more difficult to compare across studies.

Study design: Published studies are becoming longer and more complex in design, however studies show reduced efficacy after 1 year highlighting the need for longer term trials (at least 2 years). Due to ethical dilemmas of including a control group, historical control groups may be considered if there is matching for important covariates such as age, sex, season (for shorter studies), refractive error, axial length, environmental exposure, parental myopia, and race/ethnicity. Larger, multisite studies are rare but help increase generalizability.

Outcome measures: These are categorized into primary (refractive error and axial length), secondary (patient-reported outcomes and treatment compliance), and exploratory measures (including peripheral refraction and choroidal thickness). Recent updates advocate for reporting both percentage and absolute reductions in myopia progression, emphasizing the importance of confidence intervals and pre-planned subgroup analyses for accurate interpretation of results and forming new hypotheses.

Myopia control interventions

There has been an increasing number of specialty optical products for myopia control and there is also more data on efficacy of existing products and combinations. Evidence from randomized controlled clinical trials reveal:

- Data from multi-year studies with myopia control spectacles and dual focus contact lenses show continued efficacy over longer trial periods (>1 year) and with older children (up to 15 years of age).
- Visual acuity (VA) and visual function remain largely unaffected by treatments. Central VA with centre distance contact lenses, DIMS and HAL spectacles and different doses of Atropine is comparable to control groups. When viewing through the peripheral “treatment” area of myopia control spectacles, VA reduction is less than one line.
- For orthokeratology (OK), smaller treatment zones (i.e., smaller back Optic Zone Diameter) are showing better myopia control efficacy. OK may be a more beneficial option for those with Anisometropia as more myopia control is occurring in the more myopic eye.
- OK combined with 0.01% Atropine has greater efficacy compared to OK alone, but Atropine combined with multifocal contact lenses shows no additional efficacy.
- Red light therapy is gaining popularity in China and studies show high efficacy, but safety needs to be established. Violet light appears to have little effect on myopia control as observed in one study.
- Other treatments generally appear safe but longer-term trials are needed.

Industry & Ethical considerations

Safety: From the current evidence, it appears that children do not have a higher risk than adults of contact lens-related complications. Whilst spectacles may be safer from an infection standpoint, visual function e.g. peripheral contrast sensitivity, self-perception and life satisfaction needs to be considered. Atropine is known to cause cycloplegia and photophobia at higher concentrations. In relation to light therapies at present, there is a lack of comprehensive data and review of safety.

Efficacy: Axial elongation is the preferred primary outcome measure due to a stronger correlation with visual impairment, precision, immunity to accommodation artifacts and corneal changes caused by overnight ortho-k.

Regulatory status: The regulatory approval process for myopia control indication varies around the world. The FDA typically requires 3-year data from a controlled randomised clinical trial, with 1-year follow up after cessation of treatment to assess rebound. Other jurisdictions vary in their assessment or acceptance of forms of evidence. The range of products that have been approved for slowing myopia progression and marketed in different countries has grown since the 2019 IMI reports.

Clinical Management guidelines

Comparative treatment efficacy: There is a growing debate regarding the most appropriate method for reporting and comparing treatment outcomes across various interventions. Variation in control group characteristics, study duration, and wear time renders control group data incomparable between studies. Consequently, the reporting of percentage efficacy, which is relative to the control, may yield misleading conclusions when comparing trials. Only a limited number of studies have directly compared different treatment modalities within the same trial, utilizing identical control groups. These comparative studies have revealed similar efficacy levels across treatments.

Unlike percentage efficacy, which is limited by study factors such as duration and participant characteristics, Cumulative Absolute Reduction in Axial length (CARE) measures the absolute reduction in axial growth, allowing for comparisons across diverse studies. Utilising this metric, a review compared absolute efficacy outcomes of spectacle, multi-focal soft contact lenses (MFSCLs), and OK interventions, revealing no superior treatment. Recent trials supported this, showing comparable myopia control efficacy between MFSCLs and OK, as well as between MFSCLs and extended depth of focus contact lenses. In addition to efficacy, eye care practitioners should factor in their own skill set, availability of treatments, patient and parent preferences and capacity as well as regulatory considerations when choosing a treatment plan for an individual patient.

Maximising outcomes: Wearing time and /or compliance was found to be a potential avenue to maximise treatment outcomes with greater benefits with longer wearing times. Combination strategies offer another method to improve the efficacy of existing myopia control treatments, but the outcomes have been mixed with some indicating a benefit whereas others found no benefit to combining treatments. Proactive treatment of all young myopes, particularly those under the age of 12 years is recommended.

Summary

Myopia research is rapidly expanding. IMI definitions are being widely adopted and continue to be refined and adapted. Animal studies are shedding light on visual feedback mechanisms and signalling pathways influencing eye growth, while human clinical trials are exploring promising new treatments. Although further research is needed to establish long-term efficacy and safety, current evidence supports proactive myopia control prescribing in clinical practice.

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