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INVITED REVIEW

Myopia Control 2020: Where are we and where are we heading?

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Abstract

Purpose: This review arms practitioners with the evidence-based information they need to fully manage myopia.
Recent findings: The recent peer-reviewed literature is critically evaluated to provide a comprehensive analysis of the safety and efficacy of behavioural, optical and pharmaceutical myopia management. Importantly, the paper addresses not only who to treat, but how to treat them, and when to stop or modify treatments. Finally, the paper discusses expectations for treatment and why slowing myopia by even 1 dioptre improves long term health outcomes.
Summary: The management of an individual child should be underpinned by the evidence-based literature and clinicians must stay alert to ongoing myopia research that will undoubtedly result in an evolution of the standard of care for the myopic and pre-myopic child.

Introduction

The global prevalence of myopia is increasing and it is projected that half the world will be myopic by 2050 with 10% having myopia worse than −5 dioptres (D).[1] Asian countries are at the front of this wave, for example, over 20 years ago, 84% of 16 to 18 year olds in Taiwan were found to be myopic.[2] Recent estimates of urban populations in South Korea and China are also over 80%.[3] Western countries are following behind; the proportion of myopic children in the United Kingdom has doubled in the last 50 years[4] and, among a sample of the 1958 British birth cohort, 49% individuals in their early 40s were found to be myopic.[5] Myopia can develop in adolescents and adults too.[5,6] Thus, the prevalence of myopia in the UK among working adults may exceed 50% already. Estimates of prevalence of course vary with the criterion, although the most common definition is a spherical equivalent of −0.50 D or worse.[7]

Myopia has functional consequences in terms of reliance on optical or surgical correction and an accompanying economic burden.[8] Furthermore, as discussed later, increasing levels of myopia are associated with higher risk of ocular disease, some of which is untreatable.

The International Myopia Institute's special issue of *Investigative Ophthalmology and Visual Science* features a series of white papers on defining and classifying myopia, potential interventions, clinical trials and instrumentation, industry guidelines and ethical considerations, clinical management guidelines, experimental models of emmetropisation and myopia, and the genetics of myopia.[7,9–15] These comprehensive articles summarise the current knowledge in the field and show trends for future developments.

This review does not seek to repeat nor update the above comprehensive body of knowledge, but rather to present a snapshot of the rapidly-evolving field of myopia control and to address concerns that a clinician might reasonably have. This paper will:

1. Review the peer-reviewed literature on commonly-employed myopia control modalities and expected outcomes;
2. Address challenges to the implementation by clinicians including who to manage and when to stop;
3. Review the safety of myopia control modalities;
4. Consider the potential benefits of lowering a patient's ultimate level of myopia by 1 or more dioptres; and
5. Discuss potential future avenues of myopia control of which the clinician should be aware.

How effective are various methods of myopia control?

The first consideration in reviewing studies is the quality of the data. In studies of myopia control, the following are considered highly desirable:

- Refractive error and myopia progression are measured by cycloplegic autorefraction as this avoids accommodative artefacts and minimises examiner bias[15];
- Axial length is measured, preferably by partial coherence interferometry or optical coherence tomography (OCT), as axial elongation underlies myopia progression.[15] Ideally, this should be done under cycloplegia, but valid measures can be obtained without.[16] In studies of overnight orthokeratology, refractive error is confounded by the intended corneal flattening, so axial length is often the primary outcome measure. Although the ratio varies with age and refractive error,[17] 0.1 mm can be considered to be equivalent to 0.20 to 0.25 D based on progression data from 3-year clinical trials.[18,19]
- Randomisation and masking of both examiners and patients, when possible;[15] some case series of myopia control present data before and after management is initiated, but these are subject to recruitment and examiner bias and should not be considered as evidence-based.
- Concurrent controls, matched by, or analysed accounting for age, ethnicity, and other factors, and
- Multiple years of data, as results in the first 6 or 12 months may not be borne out by longer term results.[20]

The efficacy of various methods of myopia control has been fully evaluated elsewhere. Here, we review some of the key studies, nearly all of which have been published in the past 20 years, with many in the last decade. The rapid pace with which this field is moving is demonstrated by the 2011 systematic review[21] sponsored by Cochrane that concludes:

> The most likely effective treatment to slow myopia progression thus far is anti-muscarinic topical medication. . . . .Further information is required for other methods of myopia control, such as the use of corneal reshaping contact lenses or bifocal soft contact lenses with a distance center are promising, but currently no published randomized clinical trials exist.

This statement was based on evidence available in the literature as of October 2011, and as we discuss below, much has happened since then. Although an update was published in 2020,[22] it only includes publications through February 2018 and thus does not include several important recent clinical trials.[18,23–27]

Spectacles

There was much excitement 20 years ago following a report that progressive addition spectacle lenses (PALs) slowed myopia by 0.50 D or more over 2 years.[28] Unfortunately, this was not borne out by three randomised clinical trials that, collectively, report on over 800 children.[20,29,30] The largest found a 3-year reduction in progression of 0.20 D among PAL wearers compared to single vision wearers in US children[20]—statistically significant, but clinically irrelevant. Also, virtually all of the effect was observed in the first year. The slowing of axial elongation was 0.11 mm, consistent with the myopia control effect. A corresponding 2-year trial in Hong Kong found no difference in in myopia progression between the two groups (0.14 D) and virtually no difference in axial elongation (0.02 mm).[29] The smallest of these trials randomised children for 18 months and then switched treatments for an additional 18 months.[30] Curiously, there was a 0.31 D benefit of PALs in the first 18 months, but no effect in the second period. So collectively, these three clinical trials show that PALs are a largely ineffectual modality for myopia progression.

Greater success has been reported recently for executive bifocals. Cheng *et al.* randomised 135 Chinese-Canadian children aged 8 to 13 years to single-vision lenses, +1.50 D executive bifocals, and +1.50 D executive bifocals with 3-Δ base-in prism in the near segment of each lens.[31] Mean 3-year myopia progression was −2.06, −1.25, and −1.01 D for single vision lenses, bifocals, and prisms bifocals, respectively. The corresponding axial elongation was 0.82, 0.57, and 0.54 mm, respectively. Both types of bifocals were effective, although for children with low lags of accommodation, the effect of prismatic bifocals (0.99 D) was greater than of bifocals (0.50 D). The main findings contradict a previous clinical trial of 207 children, aged 6 to 15 years, randomised to single vision lenses, +1.00 D add, or +2.00 D add executive bifocals for a period of 3 years.[32] Although only 124 subjects completed the study, the mean progression was −0.34, −0.36 and −0.34 D/year^{-1} for subjects wearing single vision lenses, +1.00 D add bifocals, and +2.00 D add bifocals, respectively.[32] It is unclear why two these trials would find such contrasting results.

The aforementioned COMET Study[20] reported a larger treatment effect of PALs in children with higher accommodative lag and with esophoria. This prompted a clinical trial of myopic children with high accommodative lag and near esophoria.[33] Children were again randomised to receive either +2.00 D PALs or single vision lenses. The mean 3-year progression was −0.87 and −1.15 D in the PAL and single vision groups, respectively—a difference of

0.28 D that, like the original COMET study, was statistically significant but not clinically important. Some practitioners still point to the original COMET study[20] as justification for continuing to prescribe PALs to esophoric myopes, without recognising that the second clinical trial does not support this approach.[33] Interestingly, the aforementioned Cheng *et al*. study reported that their treatment effect of executive bifocals, both with and without prism was independent of the child's near phoria status, but found a marginal interaction between accommodative lag and slowing of progression. The prismatic bifocal was more effective for lower lags, but equally effective as the regular bifocal for higher lags.[31]

Newer spectacle lens technology has since emerged with mixed success. First, lenses designed to reduce peripheral hyperopic defocus—essentially concentric PALs—were evaluated.[34,35] Sankaridurg *et al*. randomised 210 Chinese children aged 6 to 16 years to three study lens designs or single vision lenses.[34] No differences were observed in the rates of progression with the novel designs compared to single vision lenses, although potential benefit was observed in younger children with at least one myopic parent. This subgroup was subsequently evaluated using a design that was commercialised (MyoVision, Carl Zeiss).[35] The authors randomised 207 myopic children aged 6 to 12 years with at least 1 myopic parent to single vision or MyoVision lenses. The mean 2-year progression in the MyoVision group (−1.43 D) was no different from that in the control group (−1.39 D).

Greater success was recently reported with *Defocus Incorporated Multiple Segments* (DIMS) spectacle lenses developed at the Hong Kong Polytechnic University.[25] This design comprises a 9-mm central optical zone and a 33-mm annular zone with multiple 1-mm segments having a relative positive power of +3.50 D, thus making the lens appear to have multiple 'dimples' in the periphery, although close inspection is required to see them. The developers randomised 183 myopic Chinese children aged 8 to 13 years to either DIMS or single vision lenses. Among the 160 children completing the 2-year study, the mean myopic progression was –0.41 D in the DIMS group and −0.85 D in the control group. Mean axial elongation was 0.21 and 0.55 mm in the DIMS and SV groups, respectively. While the 2-year axial elongation in the control group was similar to previous studies on Hong Kong children,[29,36] the myopic progression is much lower than the −1.26 D previously reported in the control subjects in a PAL trial.[29] These lenses are now being manufactured by Hoya in parts of the world and Essilor is evaluating similar designs (ClinicalTrials.gov Identifier: NCT04048148). Finally, other novel, annular designs are in clinical trials (SightGlass Vision, Inc., ClinicalTrials.gov Identifier: NCT03623074).

Atropine and other drugs

Atropine has a long history in myopia control,[37–39] but only recently has it been subjected to randomised clinical trials. Around the turn of this century, researchers in Taiwan began to report success with concentrations between 0.1 and 1%.[40,41] Shih *et al*. randomised 227 myopic children aged 6 to 13 years to 0.5% atropine with PALs, PALs alone, or single vision spectacles. Among the 188 children completing the 18-month trial, mean progression was −0.41, −1.19, and −1.40 D in the atropine +PAL, PAL, and single vision groups, respectively. The corresponding axial elongations were 0.22, 0.49, and 0.59 mm. This trial was important because it demonstrated that the slowing of progression was largely axial in nature and that it was the atropine and not the PAL that had the greatest therapeutic benefit.

There then followed a larger trial conducted in Singapore —the Atropine in the Treatment Of Myopia (ATOM) study.[42] Four hundred myopic children aged 6 to 12 years received either 1% atropine or vehicle eye drops nightly for 2 years. An often-overlooked detail is that only one eye of each subject was treated. Of the 346 children completing the study, mean myopia progression and axial elongation in the treated eyes was −0.28 D and −0.02 mm, respectively, compared with −1.20 D and 0.38 mm in the control eyes. After the original 2-year clinical trial, treatment was ceased and the subjects followed for an additional year.[43] The atropine-treated group showed a marked acceleration with a one-year progression of −1.14 D—similar in magnitude to the *two-year change* in the control eyes. The previously placebo-treated eyes progressed by −0.38 D over this third year. The axial elongation in this third, treatment-free year was 0.31 and 0.14 mm in the previously-treated and control eyes, respectively. Thus, overall, the treatment effect was diminished due to this rebound.

The dramatic rebound prompted the Singapore group to conduct a trial evaluating lower doses of atropine: 0.5%, 0.1%, and 0.01%.[44] Unfortunately, there was no control group in this ATOM2 study—apparently the expectation was that no slowing would be observed in the 0.01% group, so this would be the *de facto* control. Four hundred myopic children aged 6 to 12 years were randomly assigned in a 2:2:1 ratio to bilateral, nightly 0.5, 0.1, and 0.01% atropine. Among the 355 children completing the 2-year study, the mean myopia progression was −0.30, −0.38, and −0.49 D in the 0.5%, 0.1%, and 0.01% groups, respectively. The authors contrast this to progression in the ATOM study of −1.20 and −0.28 D in the placebo and 1% atropine groups, respectively. In other words, the treatment benefit for even the lowest concentration (0.71 D slower = 1.20–0.49) approached that of 1% (0.92 D = 1.20–0.28) while the children retained an average of 12 D of

accommodation, experienced little more than 1 mm of pupil dilation, and retained normal near visual acuity.

The above results have led to widespread use of 0.01% atropine, particularly in East Asia. A recent survey reports that 345 out of 493 paediatric ophthalmologists managing myopia use pharmacological therapy with 277 prescribing 0.01% atropine (80%).[45] The next most frequently used therapy is 1% atropine, but only 44 do so (13%). For optical therapies, 92 of 393 respondents prescribe PALs (23%) and 83 fit orthokeratology (21%).

Lost in this enthusiasm was the fact that 0.01% atropine had no influence on axial elongation.[46] In ATOM2, the mean elongation was 0.27, 0.28, and 0.41 mm in the 0.5%, 0.1%, and 0.01% groups, respectively.[44] Note that the corresponding elongation in the control eyes in ATOM was 0.38 mm.[42] Fortunately, additional clinical trials of low concentration atropine have been undertaken, with many others planned or underway. The recently-published Low-concentration Atropine for Myopia Progression (LAMP) Study randomised 438 myopic children aged 4 to 12 years to 0.05%, 0.025%, and 0.01% atropine or placebo for 1 year.[27] Mean myopia progression was −0.27, −0.46, −0.59, and −0.81 D in the 0.05%, 0.025%, and 0.01% atropine, and placebo groups, respectively, with corresponding mean axial elongation of 0.20, 0.29, 0.36, and 0.41 mm. The authors conclude that 0.05% atropine was most effective, slowing 1-year progression by 0.54 D and axial elongation 0.21 mm. In contrast, 0.01% was clinically ineffective with slowing of progression by only 0.22 D and axial elongation by 0.05 mm. The 2-year results lack a concurrent control group as the placebo group was converted to 0.05%. The range of axial elongation in year two is smaller, ranging from 0.19 mm for 0.05% to 0.24 mm for 0.01%.[47]

Japanese investigators recently presented results from a 2-year randomised clinical trial of 0.01% atropine with a 0.14 mm slowing of axial elongation (mean treated: 0.63 mm; mean control: 0.77 mm).[48] Other recent studies of 0.01% atropine for myopia can be found using Medline, but are not discussed here because they rely on pre-treatment progression rather than a prospective control or do not provide sufficient data to support their conclusions.

Atropine is a non-selective antimuscarinic that is believed to act via receptors in the retina,[49] although the exact mechanism is unclear.[50] This has led to the exploration of selective antimuscarinics, notably pirenzepine, for myopia control.[51] While pirenzepine does not appear to be subject to ongoing investigation, other antimuscarinics will likely begin to appear in the next few years.

Overnight orthokeratology

Overnight orthokeratology is the application of a rigid gas permeable contact lens with a base curve significantly flatter than the corneal curvature to temporarily reduce myopia. Reverse-geometry designs and highly gas permeable materials made this a viable and effective modality some 20 years ago, with night-time wear leading to good visual acuity throughout the day.[52] Soon thereafter, reports of overnight orthokeratology for myopia control began to emerge.[53,54] A number of subsequent non-randomised studies published broadly similar results.[36,55–62]

The first randomised clinical trial assigned 102 children, 6–10 years old, to either orthokeratology or spectacles.[63] For the 78 patients completing the 2-year study, the mean axial elongation was 0.36 and 0.63 mm in the orthokeratology and control groups, respectively. Meta-analysis of the efficacy of orthokeratology on myopia progression suggests that the 2-year slowing of axial elongation is 0.28 mm (95% CI: 0.20 to 0.35 mm).[64]

Hiraoka *et al.* reported 5 year data on 43 of 59 originally enrolled subjects, (22 orthokeratology and 21 control).[56] The increase in axial length was 0.99 and 1.41 mm for the orthokeratology and control groups, respectively. Santodomingo-Rubido *et al.* examined 14 of their original 29 orthokeratology patients at 7 years along with 16 of the 24 control subjects.[65] The 7-year change in axial length was 0.91 and 1.36 mm for the orthokeratology and control groups, respectively. By this time, the subjects were all between 17 and 19 years old and myopia would have begun to stabilise in the majority of subjects, regardless of treatment.[66] Importantly, the difference of 0.45 mm is the largest average cumulative treatment effect across the entire myopia control literature.

The vast majority of marketed orthokeratology lenses are not approved for myopia control, their use for this purpose is considered off label. The exception is Menicon Bloom that recently received CE marking for myopia control in Europe (*Conformitè Europëenne*, or European Conformity, indicates conformity with health, safety, and environmental protection standards within the European Union).

Soft contact lenses

A number of studies have shown that soft contact lenses with a central distance zone and increased positive power in the periphery can significantly slow myopia progression. The lens designs vary, with manipulation of power in the lens periphery by either spherical areas of positive power,[67,68] or multiple concentric treatment zones.[23,69–71] or other induction of spherical aberration.[72] Some designs were never commercially available[67,70,72] while others have been discontinued.[71] A comprehensive table appears in a recent publication,[18] but discussion here will be limited to commercially-available designs with at least 2 years of data. As with orthokeratology lenses, few of the lenses are approved for myopia control in the US and Europe.

Sankaridurg *et al.* reported on a 2-year, five-arm randomised clinical trial,[26] wherein children were randomised to single vision soft contact lenses, two soft lens designs that imposed myopic defocus across peripheral and central retina, or two extended depth of focus (EDOF) soft lens incorporating higher order aberrations to modulate retinal image quality. The single vision group progressed by −1.12 D while all other groups had progression ranging from −0.78 to −0.87 D. The corresponding axial elongation was 0.58 mm in the single vision group compared with 0.41 to 0.46 mm in other groups. One of the EDOF designs is now available in some markets from Mark'ennovy as the MYLO lens and is CE marked for myopia management.

Chamberlain *et al.* recently published results of a 3-year randomised clinical trial of the MiSight 1-day dual-focus soft contact lens.[18] Myopic children aged 8 to 12 years were randomised to either the MiSight lens or Proclear 1-day spherical lens (both omafilcon A), with both worn on a daily disposable basis. Both contact lenses are identical in all regards apart from optical design. For the 109 of the 144 enrolled subjects who completed the clinical trial, mean myopia progression was 0.73 D less in the MiSight group than in the control group (−0.51 vs −1.24 D). Likewise, axial elongation was 0.32 mm lower in the MiSight group (0.30 vs 0.62 mm). These results formed the basis of the approval of MiSight by the US Food and Drug Administration for myopia control in children—the first such indication—and follows its previous CE marking. A similar 2-year clinical trial of the MiSight lens reported on children aged 8 to 12 years of whom 41 wore the MiSight lens and 33 single vision spectacles.[23] The effect was similar, albeit slightly smaller to Chamberlain *et al.*, with less axial elongation in the MiSight group compared to the single-vision group (0.28 vs 0.44 mm). It should be acknowledged that the MiSight lens is a derivative of a previously evaluated experimental dual-focus soft contact lens.[69]

When should myopia control be implemented and on which children?

In the aforementioned survey of paediatric ophthalmologists around the world,[73] indications for initiation of myopia management were described by 70% of those that treat myopia (319 respondents) and the most common indication was the rate of myopia progression (239, 75% of respondents). On average, a progression rate of 1.10 D/year^{-1} was reported as the criterion for initiation of management. Unfortunately, a single, progression-based criterion of treatment is not feasible as the age and ethnicity of the child, parental myopia history, and methods of measurement can influence the rate measured and may not adequately predict the final amount of myopia.

The age of the child is the most important factor affecting myopia progression. For example, in the COMET study —a 3-year clinical trial of PALs for myopia progression— children in the single vision lens group who were 6 or 7 years old at baseline progressed twice as fast as the 11 year olds: mean = −2.19 vs −1.04 D over 3 years.[19] Donovan *et al.* published a review of the rates of myopia progression based on 20 papers meeting their inclusion criteria.[74] The estimated progression rates were dependent on baseline age, with decreasing progression with age. Brennan *et al.* reported corresponding data for axial elongation.[75] In myopic Asian children the mean annual elongation is around 0.4 and 0.3 mm/year^{-1} for children age 9 and 11 years, respectively. In myopic white children the rates at 8 and 11 years are around 0.3 and 0.2 mm/year^{-1}.[75]

Ethnicity is another significant factor influencing rate of progression. It is evident from the literature that myopic children in Asian countries progress faster than children in western countries. Donovan *et al.* estimated annual myopia progression at a mean age of 9.3 years to be −0.55 D (95% CI: −0.39 to −0.72 D) for populations of predominantly European extraction and –0.82 D (95% CI: −0.71 to −0.93 D) for Asians.[74] In other words, the Asian children progress 50% faster. This same ratio holds for axial elongation.[75]

It is less clear whether children of Asian descent in North America progress faster than children of western descent. The 36 Asian-American children in the COMET study progressed faster than the African-American children, but no faster than whites or Hispanics.[19] Other data on the influence of ethnicity among US children are scarce, with nearly all published studies lacking meaningful diversity. It is interesting to note that, in Cheng *et al.*'s executive bifocal trial,[31] the progression rates among their Chinese-Canadian children wearing single vision spectacles was −2.06 D over 3 years.[31] This is 39% higher than the single vision spectacle group in the COMET study (−1.48 D), but closer to the −1.71 D in the 14 Asian-American children, even though the Chinese-Canadian children were, on average, a year older. Likewise, the single vision-wearing subjects in the clinical trial reported by Cheng *et al.* showed almost 0.4 mm axial elongation over a year.[31,72] Thus, these almost entirely Asian American children with a mean baseline age of 9.7 years, showed axial elongation at a rate more consistent with Asian natives, than American white children. Regardless of the variations in progression rate, there is no evidence to date that treatment effect varies with ethnicity.[18,76] For example, orthokeratology has been shown to be similarly effective in studies in three continents with diverse ethnicities.[36,55–62]

There are many studies demonstrating the effect of parental history of myopia on the incidence and prevalence of myopia.[77,78] There are fewer studies of the effect of parental history of myopia on the *progression* of myopia and only one clinical trial of myopia control appears to have included parental refractive error as a covariate.[79] Saw *et al.* reported on 153 Singapore children aged 6–12 years.[80] The mean progression rate for the 124 children with a parental history of myopia was −0.63 D/year^{-1} compared to −0.42 D/year^{-1} for the 23 children whose parents were not myopic. Interestingly, the rates were nearly identical for children with one myopic parent and those with two. The COMET Study reported myopia progression in a subset of the original cohort ($N = 232$; 49% of initial group) between the baseline and 5-year visit.[79] Progression was higher with increasing numbers of myopic parents in the children wearing single vision lenses. Children with two myopic parents progressed faster than those with zero or one myopic parents (−0.78 and −0.55 D, respectively), although the difference between those with zero and one myopic parents was not significant.

Recommendation: manage the school age myopic child

Progression is faster in younger children, and possibly those of East Asian descent or geographic location and those with a parental history of myopia. It is rare to see a myopic child of recent onset who does not progress. In the recent MiSight clinical trial, the mean progression among 8–12 year old children wearing single vision lenses was −1.24 D over 3 years, but only 9% progressed by −0.50 D or less.[18] Thus, the vast majority of young myopes progress. The previously described survey of paediatric ophthalmologists[73] indicates that fast progression is the primary reason to intervene, but it is becoming evident that past progression does not predict future progression. Hernandez *et al.* analysed a large dataset of 916 myopic children between 7 and 14.5 years of age and found that knowledge of prior individual myopia progression and axial elongation adds little to prediction of future individual progression.[81] They conclude that historical data improve the prediction of future fast progression by only 2%. In other words, fast progression may just be a variation in average progression and thus should not be a criterion for intervention. Nearly all young myopes progress, which argues in favour of managing all of them, irrespective of their estimated progression rate. Only managing the supposedly faster progressors will lead to ignoring large numbers of children who could benefit from myopia control.

Finally, it is difficult to predict the refractive trajectory of an *individual* patient. The rate will vary as will the age of stabilisation (see below), although the *mean* progression rate of large samples of myopes is relatively consistent. Consider the control groups from three 3-year clinical trials —COMET,[20] ACHIEVE,[82] and MiSight.[18] All comprised children largely of European descent, and their 3-year progression rates were –1.48, –1.10 and –1.24 D. The COMET children were, on average, a year younger, so progress faster. If we include only the 10 year olds—corresponding to the mean age in the other two studies—the mean progression is −1.23 D,[19] virtually identical to the MiSight cohort, even though the studies were conducted 15 years apart.

An ultra-conservative viewpoint is that we should not manage any children until we know who will benefit most. It is impossible to quantify the benefit an individual patient has derived, because we can never know how they would have progressed in the absence of intervention. We may be able to individualise therapies at some future date, but given that a broad range of therapies slow myopia by a clinically meaningful amount, and the risks associated with intervention are small relative to the risk of not treating (see later section on safety), it seems more appropriate to educate and offer management for all children.

Unfortunately, there is little to no research on the 'pathological' or high early onset myope. Myopia of onset prior to 5 years should be further evaluated, including genetic testing, as it may be part of a syndrome with other signs not yet manifest, e.g. Marfan syndrome or Stickler syndrome.[83] A useful rule of thumb is, if the dioptres exceed the age, then refer (Caroline Klaver, personal communication). An alternative is: −5 (dioptres) by 5 (years), then refer (Ian Flitcroft, personal communication).

When should myopia control be discontinued?

The benefits of myopia control should, in theory, continue to accrue as long as myopia is progressing, although nearly all studies demonstrate that the treatment effect is greatest in the first year[18,42,84] but axial elongation continues to be slowed through 5 years.[56,65] So when does myopia stabilise, such that myopia management can be concluded? Data are scarce and for decades, the only comprehensive estimates were courtesy of Goss and Winkler who analysed the records of 299 myopes from three optometry practices with at least four examinations between the ages of 6 and 24 years.[85] Age of stabilisation was estimated using four different graphical and statistical methods. Their results suggest that myopia stabilises earlier in females than in males with cessation ages for the four methods ranging from 14.4 to 15.3 years in females and 15.0 to 16.7 years in males. The authors note, however, considerable variability in cessation age. The study was based on non-cycloplegic refraction, so there may have been a tendency to prescribe additional minus. Likewise, progressing myopes are more likely to return to a practice more frequently, introducing a potential source of bias in all studies of this kind.

The COMET Group estimated the age and the amount of myopia at stabilisation in their original cohort—a large ethnically diverse group of 469 myopic children.[66] In all, 426 of the original cohort had at least seven measurements over 11 years. The data were fitted with curves to describe the average progression and stabilisation. The mean age at myopia stabilisation was 15.6 ± 4.2 years, and the mean amount of myopia at stabilisation was −4.87 ± 2.01 D. The age and the amount of myopia at stabilisation were correlated ($r = -0.60$). African Americans stabilised earlier than other ethnicities (mean = 13.8 years) and had the least myopia (mean = −4.36 D). Participants with two myopic parents were around 1.00 D more myopic at stabilisation than those with no myopic parents, but did not differ in age at stabilisation. The mean age at stabilisation is similar to the previous estimate, but contrary to Goss and Winkler,[85] there was no significant difference between the sexes.

In a subsequent paper, the COMET group reported on the stabilisation of axial elongation in the same cohort.[86] Age at stabilisation was defined as the age at which the annual axial elongation rate was less than 0.06 mm/year^{-1}. Among 431 subjects, 19 (4%) had stabilised at baseline and 48 (11%) had not stabilised at their last visit. For the remaining 364 participants, the mean age was 16.3 ± 2.4 years with an average axial length of 25.2 ± 0.9 mm at stabilisation. Thus, axial stabilisation occurred at a later age than myopia, but the two ages were well correlated. Age at stabilisation was not associated with ethnicity, sex, or number of myopic parents, but axial length at stabilisation was associated with sex and number of myopic parents, but not ethnicity.

The COMET authors[66] noted a large variation in age of stabilisation of refractive error:

> 48% of the cohort had stable myopia by age 15 years;
> 77% of the cohort had stable myopia by age 18 years;
> 90% of the cohort had stable myopia by age 21 years; and
> 96% of the cohort had stable myopia by age 24 years.These values are very useful when considering how long to continue with myopia control and for discussions with parents, but there are two important caveats. First, the age at stabilisation was defined as the 'age at which the estimated spherical equivalent refraction was within 0.50 D of the asymptote.'[87] In other words, subjects progressed by up to −0.50 D beyond their 'age at stabilisation.' Second, this cohort was recruited at a relatively young age. They needed to be younger than 12 years with at least −1.25 D of myopia and their mean age at baseline was 9.3 years. Given the −1.25 D entry requirement, the mean age of onset was likely around 7 or 8 years. Thus, it is unclear whether the age of stabilisation in this cohort of early-onset myopes can be generalised to myopia of later onset. Intuitively, myopia emerging during the teenage years would progress, on average, beyond the age of 15 years, but we are unaware of any data to support this.

It is important to note that a large number of adult myopes report age of onset of myopia after the age of 15 years—the mean age of stabilisation in the above cohort of early-onset myopes. Bullimore *et al*. reported the age at which subjects began wearing spectacles—a surrogate for age of myopia onset—in 395 university-employees aged 25 to 35 years.[6] Using a cut point of 15 years, 248 were classified as early-onset myopes and 147 as late-onset. In other words, over a third of adult myopes report onset after the age of 15 years. The proportion may be even higher in some professional groups.[87–89]

Similarly, myopia progression occurs well into adulthood. Parssinen *et al*. reported a mean progression of −0.45 ± 0.71 D over eight years in 147 subjects from 23 to 31 years.[90] Progression was at least –0.50 D in 45% of cases. Likewise, Bullimore *et al*. reported that 16% of 219 myopes (mean age = 31 years) progressed by at least −0.50 D over 5 years.[91]

In summary, individualised and comprehensive myopia management is important. Assuming the myopia control is effective, it should be continued as long as the benefits outweigh potential risks or additional costs associated with treatment. Monitoring annual refractive progression and, if possible, axial elongation should inform such decisions.

What will happen if treatment is discontinued?

There is some evidence regarding accelerated myopia progression, or rebound, following cessation of some treatments. As described in a previous section, following 2 years of treatment with 1% atropine, myopia progression accelerated to almost twice the normal rate,[43,92] but less acceleration occurred following discontinuation after the use of lower concentrations.[92] Likewise, carefully conducted randomised clinical trials have shown that no acceleration occurs following 1 year of treatment and 1 year of discontinuation of progressive addition spectacle lenses or multifocal soft contact lenses.[72,76] In both cases, progression in the year following cessation of treatment was identical in the treated and control groups. The verdict is still out when it comes to rebound following cessation of overnight orthokeratology, with very limited data available. Cho and Chueng enrolled orthokeratology patients aged 8 to 14 years who had just completed a two-year myopia control study, of whom 16 continued orthokeratology and 15 discontinued lens wear for seven months and wore single-vision spectacles, then resumed orthokeratology for another seven months.[93] The patients who discontinued wear showed more rapid axial elongation

(mean = 0.15 mm) than those who continued (mean = 0.09 mm). This marginal difference is confounded by the fact that subjects discontinuing wear had elongated by 0.12 mm more than the continuing-wear group during the 2-year trial. In other words, given the failure to randomise patients, the authors may have simply observed regression to the mean, wherein those who progressed more than average during the first 2 years, progressed less than average during the next period. The reversal of corneal flattening and associated corneal thickening may also have contributed to the difference in axial elongation, although only by 0.01 or 0.02 mm.[94]

In summary, clinicians should be aware of the potential for accelerated progression once myopia control is discontinued and should monitor the patient closely. Mid to high dose atropine treatment should, hypothetically be tapered, although there are no data to inform by how much and for how long. Intuitively, the older the child, the slower the underlying progression, and the less the likelihood of any acceleration. Nonetheless, given the underlying variability in progression rate, it may be difficult to detect an acceleration in the rate of progression, particularly without instrumentation to take precise axial length measurements.

What risks are associated with myopia control?

The rate of serious and significant complications associated with myopia control options, particularly contact lenses, is well established.[95,96] It is logical to assume that most risks associated with myopia control spectacle lenses are small and the same as single vision spectacle lenses, although there may be some unknown risks associated with reductions in peripheral vision due to some optical lens designs. Likewise, the increasing number of clinical trials using atropine for myopia control[27,42,44] or monocularly for penalisation therapy for amblyopia[97–100] indicate that there is very little risk of systemic adverse events. The ocular side effects are anticipated, e.g., photophobia, reduced near vision, or ocular irritation due to preservatives.[27,101] Some clinicians have stated concern regarding a fixed or blown pupil with continued use of atropine, based on a feline study of myopia,[102] but this has not been reported in humans. The ATOM study found that amplitude of accommodation and near visual acuity returned to pre-treatment levels after 2 years of 1% atropine was discontinued. Finally, the American Academy of Ophthalmology's report on Atropine for the Prevention of Myopia Progression in Children does not list any safety concerns.[103] The FDA's 2016 review of atropine ophthalmic solution[104] states that 1% atropine is safe in 'children greater than 3 months of age' and is 'supported by adequate and well controlled studies.' Some clinicians have raised concerns about long-term use of atropine, citing the association between anticholinergic use and cognitive impairment in adults over 60 years old.[105–107] These studies report on patients taking 5 or 10 *milligrams* of strong anticholinergics, such as oxybutynin chloride or doxepinhydrochloride, for 3 years. Each drop of low concentration atropine contains fractions of a *microgram* of anticholinergic, so consistent with the FDA's assessment its long-term use should be considered safe.

Safety in contact lenses is a concern with any population, but concerns may be heightened in children as they represent a vulnerable population and have longer to live with any visual consequences. Contact lens wear can induce both chronic and acute inflammatory events due to hypoxic, toxic, bacterial or mechanical factors. Chronic inflammation can lead to corneal neovascularisation, or damage to the meibomian gland function, which may cause contact lens discomfort or dropout. Contact lens-related adverse events that are more likely to cause scarring and potential loss of vision include infectious episodes, usually referred to as microbial keratitis, and presumed non-infectious findings. The latter includes episodes of a painful red eye such as contact lens peripheral ulcer (CLPU), contact lens-induced acute red eye (CLARE) with and without infiltrates, and infiltrative keratitis. Corneal infiltrative events (CIEs) are defined as a non-infectious infiltration of white blood cells into the stroma, with accompanying hyperemia.[108] Microbial keratitis or infectious keratitis is a severe manifestation of CIE, but usually accounts for around 5% of all corneal infiltrative events in soft lens wearers,[109,110] although the ratio may be higher among orthokeratology lens wearers.[96] Because microbial keratitis is rare, the incidence is usually presented in terms of cases per 10 000 patient years of wear, e.g., 3.3 per 10 000 patient years of wear, rather than 0.000033 per year.

Overnight orthokeratology

Beginning in 2001, a number of case series and case reports of microbial keratitis associated with overnight orthokeratology, particularly in children, appeared in the literature. Watt and Swarbrick summarised the first 50 published cases from the 16 peer-reviewed papers.[111] Subsequently, the American Academy of Ophthalmology published a report on the Safety of Overnight Orthokeratology for Myopia.[112] The main source for the publication was 38 case reports or noncomparative case series, representing more than 100 cases of infectious keratitis. The report concluded that sufficiently large studies are needed to quantify the risks of treatment and risk factors for complications, and the efficacy of the modality for slowing the progression of myopia in children. The report was unable to identify the incidence of complications associated with overnight orthokeratology, nor the risk factors for various complications.

The only estimate of the incidence of microbial keratitis associated with overnight orthokeratology comes from a large retrospective study.[96] Randomly selected practitioners provided information on patients from up to 50 randomly-selected lens orders, including comprehensive details on any episode of painful red eye in these patients that required a visit to a doctor's office. Data were submitted by 86 practitioners on 1494 unique patients, resulting in sample of 1317 patients (49% adults 51% children) representing 2599 patient years of wear. Of the 50 episodes of painful red eye reported, eight presented with a corneal infiltrate of which two were judged to be microbial keratitis by a five-person masked, expert review panel. Neither resulted in any long-term loss of visual acuity. The overall estimated incidence of microbial keratitis was 7.7 per 10 000 patient years (95% CI: 0.9 to 27.8). Both cases occurred in children giving an incidence of 13.9 per 10 000 patient years (95% CI: 1.7 to 50.4). Based on the upper confidence interval, we can state that the expected incidence of microbial keratitis is no greater than 50 in 10 000, or 1 in 200 years of wear.

It is important to acknowledge that overnight orthokeratology wearers were overrepresented in case series of Acanthamoeba keratitis conducted by the US Centers for Disease Control. In a case-control study of 37 rigid gas permeable (RGP) contact lens-wearers with a diagnosis of Acanthamoeba keratitis, 8 (22%) wore RGP lenses for orthokeratology.[113] In contrast, none of the controls wore RGP lenses for orthokeratology. Risk factors across all cases included storing lenses in tap water (odds ratio, 16.0). Li *et al.*[114] reviewed 61 cases of Acanthamoeba keratitis related to contact lens over 18 years at a tertiary hospital in China. A total of 33% of the patients wore soft contact lenses and 67% of patients used overnight orthokeratology. Among the orthokeratology patients, 88% rinsed their lenses, cases or both with tap water. Thus, it is critical that all practitioners educate all patients to avoid tap water and other non-sterile water coming into contact with their contact lenses and lens case.

Soft contact lenses

Rates of microbial keratitis associated with soft contact lens wear have been well researched over the past few decades. The incidence is 20 to 25 per 10 000 patient years (1 in 400–500 years of wear) in patients wearing soft hydrogel or silicone hydrogel lenses on an overnight basis. The rate is greatly reduced (around 2 per 10 000 patient years) for daily-wear patients.[115–121] For adults in daily wear soft contact lenses, the incidence of corneal infiltrative events has been estimated as 300 to 400 per 10 000 patient years.[109,110,122] These large epidemiological studies tell us little about children wearing contact lenses, as most of the largest studies only report cases in patients 15 years and older.[121,123,124]

The Contact Lens Assessment in Youth (CLAY) Study sought to address this gap.[125] The investigators reviewed charts from 3549 patients, representing 14 276 office visits.[110] Across all patients there were 187 corneal infiltrative events over 4663 soft contact lens patient years. Importantly, the incidence varied dramatically with age with the 8 to 12 year olds having the lowest rates of adverse events and young adults had markedly higher rates. The incidence of corneal infiltrative events for 8 to 12 year olds was 97 per 10 000 patient years (95% CI: 31 to 235) compared to 335 (95% CI: 248 to 443) in 13 to 17 year olds, and 571 (95% CI: 248 to 443) in 18 to 25 year olds.

These findings were confirmed by a comprehensive review of prospective studies of soft contact lens wear in young children.[95] Six published studies were identified with at least 150 patient years of lens wear reporting safety outcomes.[18,72,82,108,126,127] These and a handful of smaller studies comprise over 2,000 patient years of soft contact lens wear, mostly in children between 8 and 12 years. There were no reports of microbial keratitis and only two studies observed corneal infiltrative events. Combining all prospective studies, the estimated incidence of corneal infiltrative events in children is 54 per 10 000 patient years (about 1 in 200 years) and the upper 95% limit is 86 per 10 000 patient years (about 1 in 100 years). Even in the absence of any cases, the upper 95% limit for visually-threatening microbial keratitis is at most 18 per 10 000 patient years (less than 1 in 500 years).

In summary, the risk associated with soft contact lens wear in children aged 8 to 12 years—whom are the target age for myopia control—is no higher than in adults and may be substantially lower.[95] It is important to note that no more than 15% of cases of microbial keratitis result in loss of two or more lines of visual acuity,[121] with some studies reporting rates of 4% or lower.[120,123]

What are the benefits of myopia control?

Bullimore and Brennan[128] recently articulated three broad, long-term benefits of lowering a young patient's ultimate level of myopia:

- Better vision when uncorrected and corrected: lower myopes have better visual performance, even when corrected.[129]
- Better options for, and outcomes from, surgical myopia correction: the lower the myopia, the less average residual refractive error, the fewer surgical enhancements, and the lower probability that corneal thickness prohibits ablative procedures.
- Reduced risk of visual impairment.

The third of these has the broadest public health impact. The authors analysed data on over 21 000 adults across three continents and demonstrated that each dioptre of myopia is associated with a 67% increase in the prevalence of myopic maculopathy.[128] Subsequent analysis using data from 15 000 patients[130] has shown that each additional dioptre of myopia is associated with a 25% increase in visual impairment.[131] Given this compelling relationship between increasing myopia and increased frequency of both ocular disease and visual impairment, it seems reasonable to assert that reducing myopia should lower the risk. For example, slowing myopia such that patients' refractive error is lower by 1 dioptre should reduce the likelihood of them developing myopic maculopathy by 40% (1–1/1.67) and reduce the risk of visual impairment by 20% (1–1/1.25). Of course, the long-term benefits are extraordinarily difficult to demonstrate. For example, one would have to intervene in a group of myopic children and then some 50–60 years later determine whether they have a lower rate of diseases known to increase at higher levels of myopia—retinal detachment, glaucoma, cataract, choroidal neovascularisation, optic neuropathy, and myopic macular degeneration.[132] But requiring data from such unlikely long-term studies could be construed as extraordinarily conservative.

A recent thoughtful editorial in the journal of the American Academy of Ophthalmology[132] includes the following proactive, forward-looking statements:

> It is essential for ophthalmologists to work with optometrists, who are frontline providers, to determine a collaborative framework and referral patterns to prevent myopic progression, educate patients on the risks of myopia, and proactively address associated pathology to serve the best interest of our patients.
>
> An epidemic of this proportion will require macroscopic thinking. As such, ophthalmologists will need to reach out and work with optometrists, pediatricians, and even school administrators to develop the best research, reach the broadest population, and achieve the greatest impact.

Hopefully, optometry organisations will be similarly proactive regarding their recommendations for myopia control.[133]

Evidence-based myopia control vs the challenges of managing the individual patient

While mean rates of progression and treatment effects are known, we have little very ability to predict actual future progression rates for an individual child.[81] Initiating myopia control further confounds our interpretation, as we are no longer able to separate underlying progression from the benefits, or otherwise, of treatment. In a managed child where the progression is slow, patient and parent management is straightforward and continued treatment is easy. In a child progressing faster than hoped, the discussion is more challenging. It is possible that the child would have progressed more rapidly without intervention, but the clinician needs to discuss with the parent and make a recommendation whether to stay the course, switch to another management option, or add a second therapy. Setting expectations for safety and efficacy are key. Parents should also be aware that contact lens and spectacle options not only have the potential to slow progression, but also correct the child's vision. This benefit must be balanced with the expectation for proper wear and care of lenses.

With overnight orthokeratology, the myopia will have been temporarily reduced and the child has clear, correction-free vision throughout the day. That alone has value, but we can no longer assess progression by measuring refractive error. A crude estimate of progression can be obtained by performing an over-refraction (preferably auto-refraction) while the patient is wearing the lenses, but these estimates are potentially confounded by variations in treatment across the pupil. Thus, treatment effectiveness can only truly be assessed by measurement of axial length. While tempting, treatment success should never be evaluated on the basis of ongoing clear vision without the lenses, because the patient may have been initially over-corrected and thus have a hyperopic buffer. With multifocal soft contact lenses[18] and spectacles,[25] myopia progression and axial elongation are generally well correlated, but axial length measures can still provide valuable information, especially when there is only progression in one eye, or the subjective and objective refractive assessments do not agree.

With atropine treatment for myopia, the clinician has a unique opportunity to evaluate the potential effectiveness/ocular penetration of the drug based on changes to accommodation and pupil size.[134] This can be achieved by beginning nightly treatment on one eye only and assessing pupil size and accommodation after 2–4 weeks of use. Atropine is equipotent across all muscarinic receptors, so pupil dilation and reduced accommodation can be taken as evidence of the bioavailability of the drug.[135] Why one eye? Because anisocoria is easier to assess than changes in pupil size over time. Little or no dilation in the treated eye at the follow-up visit is an indication that the prescribed concentration is too low, that the patient is not compliant, or there are issues with drug stability in the bottle. Atropine is most stable at a pH between 3 and 6[136,137] and, in our experience, compounding pharmacies pay little attention to this when diluting an existing solution. Treating one eye initially also allows the clinician to consider higher concentrations like 0.05%, without fear of disrupting near vision. If accommodation is reduced by too much, then the prescribed

concentration can be reduced prior to beginning bilateral treatment.

Astigmatic myopes have fewer soft contact lens, and in some cases spectacle, options and may be more challenging to manage using orthokeratology. Atropine, or off label use of toric soft or orthokeratology contact lenses, or contact lenses with spectacle over-correction should still be considered.

How will we manage myopia 10 years from now?

Technological advances and the regulatory process will undoubtedly provide practitioners with an increasing array of options for the management of the myopic child. In the US, multiple three-year clinical trials are underway on low-concentration atropine and novel spectacle lenses and other diverse interventions will no doubt follow. Likewise, the studies of atropine in the UK will hopefully pave the way for its use by optometrists.

The rising prevalence of myopia can only be reversed by prevention. The recent International Myopia Institute's report on Defining and Classifying Myopia introduced the concept of pre-myopia, which they define as 'A refractive state of an eye of between +0.75 D and −0.50 D in children where a combination of baseline refraction, age, and other quantifiable risk factors provide a sufficient likelihood of the future development of myopia to merit preventative interventions.' They note that the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study[138] found that the onset of myopia is well predicted by a refractive error <+0.75 D at 6 years, <+0.50 D at 7 to 8 years, <+0.25 D at 9 to 10 years, and less than plano at 11 years. The report goes on to state that 'the predictive accuracy of baseline refraction alone is likely to be insufficient to justify therapeutic interventions.'

The pre-myopic patient and parent are likely to be resistant to optical preventive measures without a visual benefit. Plus, contact lenses may not be worth the perceived risk and effort, but a nightly eye drop might be considered a feasible option. Indeed, clinical trials of low-dose atropine for delaying myopia onset are underway. It is possible that atropine or other drugs will find a role in myopia prevention if results are favourable, but proactive clinicians might choose to pursue this option, in spite of results of clinical trials not yet being available. It is well-established from epidemiological studies that greater time spent outdoors is associated with lower prevalence of myopia.[139,140] Early clinical trials show that myopia incidence can be lowered by interventions that involve increased outdoor time.[24,141–143] Furthermore, one recent study found that, in existing myopes, increased outdoor time slowed myopia progression and axial elongation by 0.23 D (95% CI: 0.06 to 0.39 D) and 0.15 mm (95% CI 0.02 to 0.28 mm), respectively, over 1 year.[24] Optometry, as a primary care profession, should embrace this message as it may also have tangible benefits on childhood obesity and cardiovascular health and encourage increased outdoor activity.

Myopia of onset during the early school years (6 to 9 years) is particularly deserving of early and aggressive myopia control as earlier onset is associated with increased risk of high myopia in adolescence and beyond.[144] Again, atropine can play an important role here and parents should be counselled on the evidence to suggest that a higher dosage should be used, assuming it is well tolerated. The experienced Dutch team at Erasmus use 0.5% atropine in children at high risk of high myopia and report that when combined with photochromic PALs, the atropine is well tolerated.[145] As stated previously, initial monocular atropine should be considered when higher concentrations are being prescribed so that the impact on near vision can be assessed proactively. The child's refractive error still needs to be corrected, so with or without atropine, a proven optical therapy should also be prescribed. If near vision is compromised by the atropine, then PALs or bifocals should be prescribed. If residual accommodation is sufficient, then optical myopia control can be considered in combination with the atropine, although there are limited data on combining optical and pharmaceutical treatments. Some practitioners advocate using overnight orthokeratology in young children since the parents can insert and remove the lenses and the children only wear the lenses while at home. Combination therapies have only recent begun to be evaluated, and it is unclear whether the reported increased effectiveness of combining atropine with orthokeratology is due to pharmacology or a larger pupil enhancing the optical effects.[146–149]

Soft contact lens wear is an equally effective option for myopia management. It is important that both the child and parent understand the risks and benefits. If children are able to remove a soft contact lens on their own and demonstrate proper wear and hygiene practices, then myopia control contact lenses should be considered. Children should never be sent to school in lenses that they cannot remove independently. Research has shown that children as young as 8 years old are able to do so, and there are many clinical reports of even younger children independently managing soft and orthokeratology contact lenses.[150] Continued parental oversight might further enhance safety among older children.[110] A daily disposable modality should be preferred as solutions and storage cases are two major risk factors for infectious and inflammatory events.[121] Given that 50% of myopes continue to progress beyond the age of 15 years, and 25% beyond 18 years, it would be desirable to keep teenagers from switching to regular soft lenses from myopia control soft lenses until their refractive error and axial length stabilise.

Summary

In conclusion, there may soon exist a continuum of care for myopia starting with delay of onset and followed by optical and pharmaceutical interventions to slow progression. It may be that all spectacle prescriptions for myopic children incorporate a design that has been shown to slow progression and traditional single vision lenses will no longer be recommended. Likewise, standard single vision soft contact lenses may not be recommended to myopic children and adolescents. Instead, multifocal and orthokeratology contact lenses, or other modalities proven to slow progression, may become the standard of care. Safety of all refractive correction and management options must also remain at the forefront of practitioners' recommendations. Of course, this will be somewhat dependent on regulatory approval of devices and drugs along with coverage by insurance or governmental organisations in some countries.

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