A Review of Current Concepts of the Etiology and Treatment of Myopia

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Abstract: Myopia occurs in more than 50% of the population in many industrialized countries and is expected to increase; complications associated with axial elongation from myopia are the sixth leading cause of blindness. Thus, understanding its etiology, epidemiology, and the results of various treatment regiments may modify current care and result in a reduction in morbidity from progressive myopia. This rapid increase cannot be explained by genetics alone. Current animal and human research demonstrates that myopia development is a result of the interplay between genetic and the environmental factors. The prevalence of myopia is higher in individuals whose both parents are myopic, suggesting that genetic factors are clearly involved in myopia development. At the same time, population studies suggest that development of myopia is associated with education and the amount time spent doing near work; hence, activities increase the exposure to optical blur. Recently, there has been an increase in efforts to slow the progression of myopia because of its relationship to the development of serious pathological conditions such as macular degeneration, retinal detachments, glaucoma, and cataracts. We reviewed meta-analysis and other of current treatments that include: atropine, progressive addition spectacle lenses, orthokeratology, and multifocal contact lenses.

Key Words: Myopia—Myopia control—Atropine—Orthokeratology—Multifocal contact lenses—Progressive addition lenses—Axial elongation.

Myopia is a common and yet perplexing ocular disorder. Once viewed as a benign refractive condition, today myopia, even at low levels, is associated with increased risk for numerous ocular diseases.[1] Researchers have reported on the myopia epidemic, which is occurring worldwide.[2] Although the exact etiology of myopia remains elusive, it appears to have both genetic and environmental components,[3] making prevention and treatment both challenging and individualized. Stopping the progression of myopia has the potential to positively affect quality of life and ocular health. Popular control options today include progressive addition lenses (PAL), topical atropine, orthokeratology (OK) lenses, and multifocal contact lenses. The intent of this review is to provide the most current information about myopia etiology and treatment strategies with the goal that ocular health may be preserved.

PREVELANCE AND ETIOLOGY OF MYOPIA

Myopia is the most common ocular disorder worldwide.[4] The prevalence of myopia in the United States has increased from 25% to 44% between 1972 and 2004.[5–7] In urban communities in Asia, the prevalence is greater than 80%.[8,9] The prevalence is much lower in underdeveloped areas in the world such as Sherpa in Nepal.[10]

The economic burden of eye diseases is approximately $139 billion in the United States, with nearly $16 billion spent on myopia correction alone.[5,6,11] Myopia represents a major risk factor for a number of other ocular pathologies such as cataract, glaucoma, retinal detachment, and myopic maculopathy, which is comparable to the risks associated with hypertension for stroke and myocardial infarction.[1,12] Taking into account pathological complications of myopia and other serious pathologies associated with the disease, myopia not only negatively affects self-perception, job/activity choices, and ocular health,[13–15] but also represents one of the leading causes of blindness in the world.[16] The yearly incidence of retinal detachments is 0.015% in patients with less than 4.74 diopters (D) myopia and it increases to 0.07% in myopia greater than 5 D and 3.2% myopia greater than 6 D.[17,18] Myopic patients also have great risk of developing macular choroidal neovascularization, that is, 2X for patients with 1 D to 2 D of myopia; 4X with 3 D to 4 D of myopia; and 9X for 5 to 6 D of myopia.[19] It is estimated that 4.8 billion people (one half of the world's population) will be affected by myopia by 2050.[20] A recent study reported that 10% of Asian high school students have high myopia, which increases the risk for future retinal disease.[21]

Historically, some eye care professionals have believed that myopia is a hereditary anomaly, whereas others have believed that myopia is environmentally induced. However, human and animal studies conducted over the last four decades suggest that development of myopia is controlled by both environmental and genetic factors.[22–25]

Human population studies have revealed that environmental factors, such as near work and reading, play an important role in

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the development of myopia.[26–32] However, this is not without some controversy.[33] Zylbermann et al.[34] analyzed the incidence of myopia in two groups: Orthodox Jewish students (male and female, where males, unlike females, spent the majority of the day reading) and secular Jewish students (male and female, where both men and women spent less time reading than the male students in the orthodox Jewish schools). They found that the Orthodox Jewish male students had a much higher incidence and degree of myopia as compared to the other three groups of students. This finding suggests that reading was the factor that caused myopia.

In addition, there are a number of epidemiological studies that show that myopia is more common in urban areas, among professionals, educated patients, computer users, university students, and associated with increased intelligence.[35–43] There is evidence that the intensity of reading may be more important than the actual time spent reading.[44] Myopia is also increased in individuals who perform tasks requiring increased use of eyes such as microscopists.[45] These and other findings of the association between near work and myopia were complemented by the observations that near work and reading are associated with the lag of accommodation, that is, insufficiently strong accommodative response to near objects, which places the plane of best focus behind the retina (hyperopic defocus) when the subject performs near work tasks.[46,47] This observation led to the theory that the optical blur such as produced by the lag of accommodation may be the signal that drives excessive eye growth and causes myopia.[27,46,48–51] This theory is supported by the numerous animal studies, which have found that degradation of visual input using either diffusers or negative lenses causes excessive eye growth and myopia in species as diverse as fish, chickens, tree shrews, monkeys, guinea pigs, and mice.[52–67]

Wiesel and Raviola were the first to induce experimental myopia in an animal model. They placed a translucent screen over a monkey's eye causing it to become severely myopic; however, when total occlusion was used instead, there was no change in the length of the eye.[61,68] Thus, stimulation of the retina with a blurred image results in alteration of the growth signals within the eye. Numerous studies performed in animals using both positive and negative lenses have demonstrated that the eye will change its axial length (AL) to accommodate for the lens placed in front of the eye.[69–72] This change is reversible because some animals are able to recover when the visual stimuli is removed.[73] This change in AL occurred even if the optic nerve was severed.[74] It occurred in half the eye, if only half the eye was exposed to blur using a diffuser or plus or minus lenses.[75] The fact that the eye responds to local blur with local changes even when the optic nerve is severed demonstrates that the signaling cascade regulating refractive eye development is within the eye itself and does not require a feedback from the brain (Fig. 1). Rada et al.[76] reported that the retina provides remodeling signals to the sclera by which the eye alters its shape to place an image on the retina, that is, emmetropization.

Smith et al. experimentally asked the most important question. Does the eye respond to foveal blur, peripheral blur, or equally to both?[77,78] Smith created a series of lenses in which the center was minus and the periphery was plus and lenses in which the center was plus and the periphery was minus. In both cases, the length of the eye changed in response to the peripheral lens power. For instance if the central lens was plus and the peripheral part of the lens was minus, the eye elongated. Lastly, Smith et al.[79] ablated

the macula of a number of monkeys. In this instance, the eyes still changed their AL in response to the lens power. These studies suggest that defocus information is summed up across the entire surface of the retina and the integrated signal regulates the growth of the eye (Fig. 2).[74,78,80] Many clinicians and researchers believe that these animal studies have a direct relationship to the development of axial elongation or myopia and they have suggested that treatment should be based on these models.[2,78,81]

Myopia seems to progress the most between ages 8 and 15 (Caucasians X=0.6 D/year. and Asians X=0.7 D/year.) and then begins to slow down.[82–84] Mutti et al.[85] reported that in a large cohort of subjects, which developed myopia, a year or two before the onset of myopia, hyperopic defocus developed in the periphery of the eye along the horizontal meridian. This relative hyperopia is believed to be growth signal. If this hyperopic, defocus is altered optically to create myopic defocus by using plus power in the periphery; according to this theory, a stop signal is created. This is the basis for most optical treatments.[77]

Myopia increases the most during the winter and the least during the summer months.[86,87] It is unknown if this is because of increased school work, decreased sunlight, or decreased time outside. In previous generations, myopic progression was assumed to end at age 18.[88] However, that has changed since more students have entered graduate school followed by jobs requiring 8 hr of sustained computer work.[43] This conjecture was recently studied in a cohort of post-university graduates with a mean age of 35.[89] Myopia was found to progress in approximately 10% of the cohort who spent a lot of time in front of computers. Those subjects who did not spend time in front of computers did not progress as much. In addition, Bullimore et al.[90] reported that 21% of contact wearers between the ages of 20 and 40 years of age progressed at least 1 D over 5-year period of follow-up.

All these human and animal studies strongly suggest that environmental factors play a an important role in the development and progression of myopia; however, human population studies suggest the contribution of genetic factors accounts for at least 70% of variance in refraction.[91–95] It is clear that the incidence of myopia increases when both parents have myopia.[38,96] Numerous studies have shown that the refractive error of the parents is the most important predictor of the development of myopia.[97,98] Strong support also comes from studies comparing monozygotic[99] and dizygotic twins.[91,100,101] The refractive error is thought to be influenced by multiple interacting genes.[91–93] Multiple chromosomal loci, which are linked to human myopia, have been identified.[23,102–128] However, myopia appears to be a rather heterogeneous disease because the genetic loci and genetic variants associated with myopia in different families and ethnic groups are often distinct.[23,25,102–127] Considering that complex quantitative traits such as myopia are often controlled by dozens or even hundreds of chromosomal loci,[129] and that the identified chromosomal loci could account for less than 25% of myopia cases,[107] only a small fraction of chromosomal regions that control refractive eye development has been identified.

Thus, both environmental and genetics factors have been shown to contribute to myopia development[22–25]; however, it was not clear whether these factors act independently or if there was some form of interaction. Recent work by Tkatchenko et al.[3] has helped consolidate the dichotomy of views related to the etiology of myopia, that is, genes versus environment. These authors studied
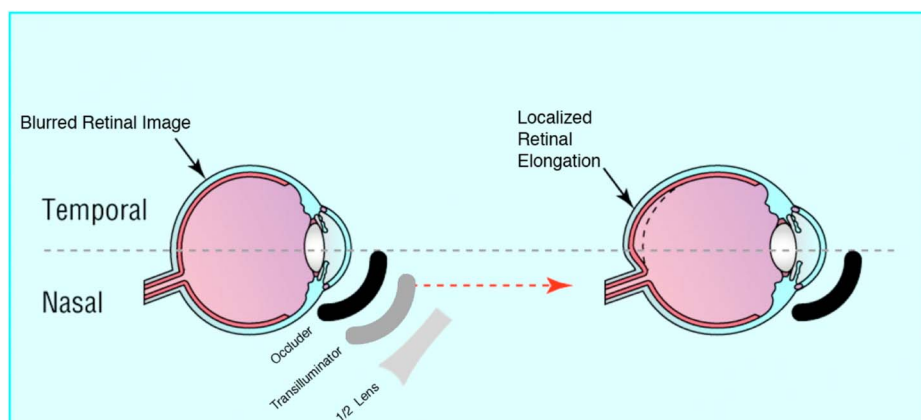
FIG. 1. Regional blur causes axial elongation. Regional retinal blur created in half the retina causes regional elongation of the eye. This occurs even when the optic nerve is cut, but will not occur if atropine is injected into the eye. The eye recognizes the direction of the blur, that is, plus or minus lenses and the region of retinal blur. Reprinted with permission from Cooper J, Schulman E, Jamal N. Current status on the development and treatment of myopia. *Optometry* 2012;83:179–99.

a three-way interaction between age, time spent reading, and genetic variation at *APLP2* gene locus. It was found that children who spent a "high" amount of time reading and who had the myopic version of *APLP2* gene were 5 times more likely to develop myopia compared to those children who spent "low" amount of time reading. On the contrary, children who carried a normal version of *APLP2* did not develop myopia even if they were exposed to high levels of reading. To confirm the human findings, they studied refractive eye development in *APLP2* knock-out mice and found similar interaction between *APLP2* and visual experience in mice. This study demonstrated for the first time gene–environment interaction in myopia development and suggested that genetic background of an individual determines the impact of environmental factors on refractive eye development.

TREATMENT OF MYOPIA

The incidence of retinal detachment and macular degeneration increases logarithmically above 2 diopters of myopia (Fig. 3).[1] To put this in perspective, keeping myopia at −1.00 versus −3.00 D reduces the risk of macular degeneration by 4 times and retinal detachment by 3 times. Brennan[130] reported that reducing progression by 33% would result in a 73% reduction in myopia progression above 5 D; if the reduction rate improved to 50%, then there would be 90% reduction of myopia above 5 D. Thus, myopia control becomes an increasingly important issue because recent environmental changes have not only resulted in a sharp increase in the incidence of myopia worldwide, but caused an increase in the age of progression and the ultimate increase in the magnitude of the refractive error. In our opinion, patients should be presented with the current risks and benefits of the various treatment options available for myopia control.

Animal and human studies have important practical consequences for the treatment of myopia. They specifically suggest that reducing lag of accommodation, reducing both central and peripheral defocus, and blocking myopiagenic signaling in the eye should slow the progression of myopia. Considering that the information about signaling pathways underlying myopia development is limited, the currently considered treatment modalities for control of myopic progression include optical correction such as bifocal spectacle lenses, progressive addition spectacle lenses, under-correction, OK, multifocal contact lenses, and increased exposure to outdoor activities, with the notable exception of atropine which has been shown to block myopiagenic signaling albeit with some uncomfortable side effects.[81]

Spectacles

Bifocal spectacle lenses were the first to be used extensively to control myopia progression. The lenses were prescribed based on the assumption that myopia was a response to prolonged accommodation producing optical blur.[51,81,131,132] There have been a number of retrospective studies, which showed that bifocals and PALs slow the progression of myopia.[133–135] On average, these studies suggested that myopia was slowed by 40%. However, these studies had some issues with experimental design, for example, they were retrospective, unmasked, etc. The COMET (The Correction of Myopia Evaluation Trial) study was designed to determine if a +2.00 D PAL slowed the progression of myopia as compared to a single-vision (SV) full correcting spectacle lens.[136] This NIH/NEI prospective, multicenter clinical trial demonstrated that in the first year, PALs slowed the progression of myopia by 20%. However, the effect was significantly reduced in years 2 to 4. The net reduction was 0.2 D, which was clinically insignificant but reached statistical significance. The progressive lenses were the most effective when both parents were myopic, there was a large lag of accommodation and/or the children had esophoria at near.[51,137]

Recently, Cheng et al.[138] studied the use of high fitting executive bifocal spectacle lenses with base-in prism as compared to SV lenses in a group of Canadian Asians. The experimental lens slowed the progression of myopia by 40%. However, this study was not masked and was not double-blinded. In 2011, Shi-Ming Li et al. performed a meta-analysis of 9 clinical trials in which powers of PALs ranged from +1.5 to +2.0 D and found that PALs slowed myopic progression by 0.25 D/year as compared to SV lenses. The effect was greater in Asian children as compared to Caucasians and also greater in children who had a higher level of myopia at baseline and who progressed at a more rapid rate (Fig. 4).[139]

In a novel experiment, spectacle lenses, which were designed to reduce peripheral hyperopic defocus, were evaluated to determine their effect on the progression of myopia in Chinese children aged 6 to 16 years.[140] The authors reported that none of the spectacle lenses had any significant effect in slowing the progression of myopia. Failure to achieve a significant result is believed to be

Uncorrected Myope   **Traditional Correction**   **Optimal Correction?**

FIG. 2. Image shells on the retina. Once the eye elongates in myopia, optical images from spherical lenses no longer fall on the retinal plane. The peripheral images are out of focus falling on a plane behind the retina. It is thought that the relative hyperopic error created is the stimulus for axial elongation. Current optical treatments move the peripheral focus in front of the retina.
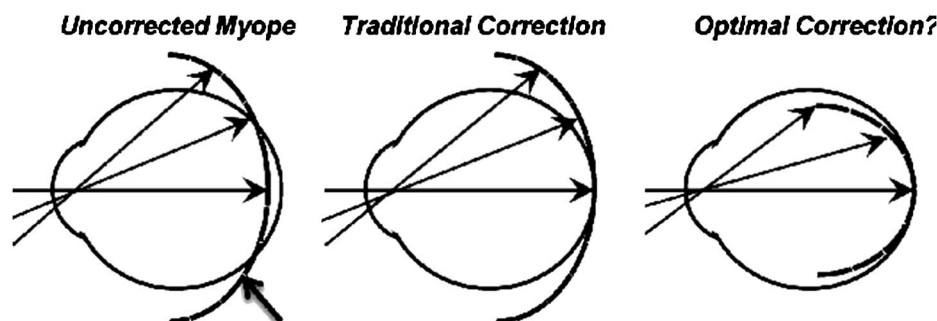
related to the constant changing of eye position when viewing through the lenses.

Historically, many eye care professionals have under-corrected myopia in the belief that the myopic progression will slow down as a result of reduced accommodation. However, with today's knowledge that blur affects the ability of the eye to become emmetropic, this is intuitively incorrect. Two recent studies have demonstrated that under-correction actually results in mild acceleration of myopia progression.[141,142] Thus, under-correction should not be used to slow myopic progression.

Contact Lenses

For years, it was believed that gas permeable contact lenses slowed the progression of myopia. However, it should be remembered that gas permeable contacts typically are prescribed

Fitted Power Regression for Myopic Maculopathy and Retinal Detachment

Regression Formula: OR = 1 + A.(-Ref)^B

□ Maculopathy data (Vongphanit)
— Power Model (A=0.032 ,B=3.98)
△ Detachment data (Ogawa)
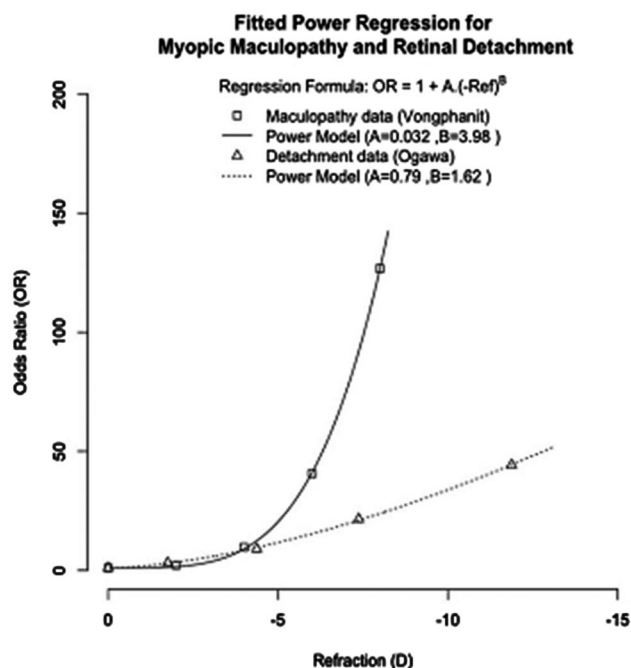····· Power Model (A=0.79 ,B=1.62)

FIG. 3. Risk of ocular disease with increased myopia. It is readily apparent that the risk of retinal detachment and macular degeneration increases logarithmically with the increase of acquired myopia.139 The risk begins with as little as 1.00 D of myopia. Reprinted with permission from Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res* 2012;31:622–60.

when myopia begins to slow down (12 and older) and that these contact lenses flatten the cornea. In a number of well-controlled clinical trials, it has been shown that neither conventional soft nor gas permeable contact lenses alter the progression of myopia.[143,144]

In 2003, Reim et al.[145] performed a retrospective study of 253 children (ages 6–18) on the ability of OK to slow the progression of myopia. He reported that the rate of progression was slowed from 0.5 to 0.13 D/year. Subsequently, there have been a number of prospective clinical trials, which have demonstrated that OK tends to slow the progression of myopia by 40% using AL measurements and wash-out cycloplegic measurements.[146–154] Two separate meta-analyses of these studies, which included 435 patients across 7 studies, demonstrated support for OK's ability to slow myopic progression.[155,156] All 7 studies reported AL changes after 2 years, whereas 2 studies reported vitreous chamber depth changes. The pooled estimates indicated change in AL in the OK group. Myopic progression was reduced by approximately 45% (Fig. 5).

Swarbrick et al.[152] studied 26 myopic children (11–17 years of age) of East Asian ethnicity using a crossover design study. All of the children were fitted with an overnight OK lens in one eye and a conventional rigid gas-permeable (RGP) lens for daytime wear in the contralateral eye. After 6 months, the lens–eye combinations were reversed and lens wear was continued for another 6 months. After 6 months of lens wear, the average AL of the RGP eye had increased by an average of 0.04 mm, whereas the OK eye showed no change. After the second 6-month phase of lens wear, the OK eye showed no change from baseline in AL, whereas the conventional RGP eye demonstrated a significant increase in mean AL, that is, 0.09 mm. In summary, the conventional RGP lens-wearing eye showed progressive AL growth (myopic progression) throughout the study while the OK eye did not.

There have been two other OK studies that have some reasonable long-term data (5 years and 7 years) demonstrating the myopia control effect of OK.[153,154] Orthokeratology provides patients with a "wow" factor and the elimination of daily wearing of contact lenses or glasses. This is particularly beneficial for more athletic children. Visual acuity is quite good with the majority achieving 20/20 and over 90% achieving 20/30.[157]

Many eye care professionals believe that the change in the curvature of the cornea is achieved by mechanical flattening of the cornea. However, there is a strong evidence that the change in refraction is achieved by horizontal movement of epithelial cells that occurs from the reverse pressure made from the seal created in the mid-periphery bearing area of the lens.[158,159] Proper fitting
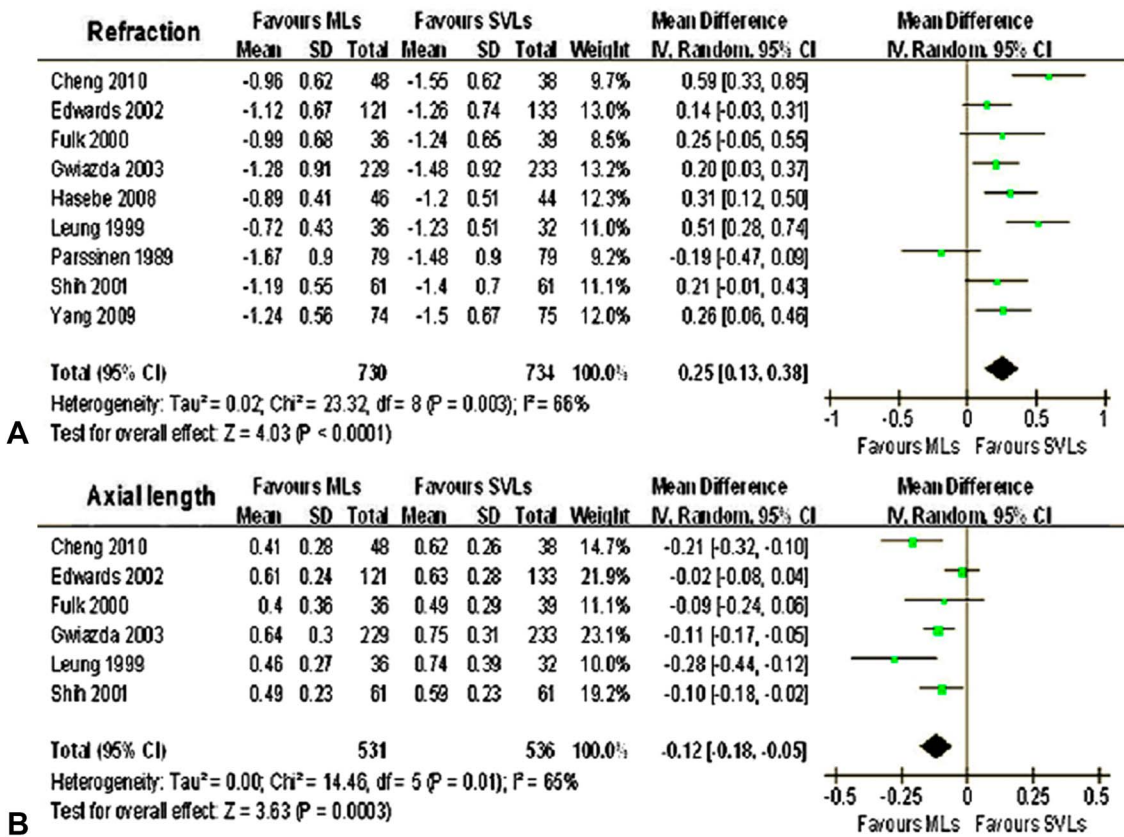
FIG. 4. Meta-analysis of progressives and bifocal spectacle lenses. Meta-analysis[139] of 9 clinical trials in which progressive additional and bifocal spectacle lenses (MFL) are compared with single-vision lenses (SVL) using spherical equivalent (A) and axial length (B). Mean difference between SVL and MFL was 0.25 D per year and in those that reported axial length changes, the difference was 0.012 mm.[137,244–251] The benefit of MFL was greater in Asian versus white children (0.32 D vs. 0.10 D) and/or those that initially had a higher baseline refraction. (Less than 3 D at baseline = 0.16 D vs. greater than 3 D at baseline 0.39 D). It should be noted that these findings were not replicated in an analysis of 16 treatment protocols for myopia.[243] Reprinted with permission from Li SM, Ji YZ, Wu SS, et al. Multifocal versus school-age children: a meta-analysis. *Surv Ophthalmol* 2011;56:451–60.

requires a 20-μm postlens/precorneal tear film. The most significant complaints found with OK are halos secondary to the spherical aberration, which also reduces visual acuity and contrast sensitivity, or discomfort from the lenses.[160]

The true risk of infection with OK is unknown.[161] Any risk from infection in a voluntary treatment program that involves children must be weighed against the potential benefit of future reduction of ocular complications such as retinal detachment and macular degeneration. The best estimate of the risk of microbial keratitis (MK) from OK is slightly less than from extended wear of contact lenses. The overall rate is 7.7 per 10,000 years of wear.[162] This compares to 1.4 per 10,000 patient years of wear in nonwearers, 11.9 per 10,000 patient years of wear in silicone hydrogel daily wearers, and 20 per 10,000 patient years of wear in soft contact lens extended wear.[163] This is not a surprise because the lenses are on for a maximum of 8 to 10 hr per day compared to 24 hr for extended wear lenses, the lenses are more oxygen permeable than soft lenses, and the surface of the lens is smoother or slipperier than soft lenses, so that a biofilm does not stick to the lens as easily. The incidence of MK is higher in children than adults.[164] The low incidence should not be dismissed; however, the majority of in-fections can be handled with aggressive antimicrobial therapy. The rare cases that result from Acanthamoeba or Fusarium infection often result in an avoidable damage to the cornea.[165] Thus, proper hygiene and cleaning is imperative. These lenses, like all other contact lenses, should never be soaked in tap water. Because of the nature of the wearing of the lenses at night, there is greater opportunity for the parents to supervise the wearing of these lenses versus regular soft lenses.

The largest effect from OK is achieved in children who have moderate myopia (between 1.25 and 4.0 diopters) and have larger pupils. It is more difficult to get good results with lower (presumed to be because of the lower mid-periphery plus induced) or higher myopia (inability to achieve targeted prescription).[154,166–168] Infrequent corneal infiltrates can be minimized by the use of hydrogen-peroxide solutions and mild flattening of the landing zone of the lenses. Published dropout rates are around 20%; however, the children who stay in the program are happier than children fit with traditional contact lenses.[148]

Cho and Cheung[169] evaluated the rebound effect when OK lenses were discontinued by comparing the AL in two groups. Group 1 wore OK lenses for 24 months, discontinued lens wear
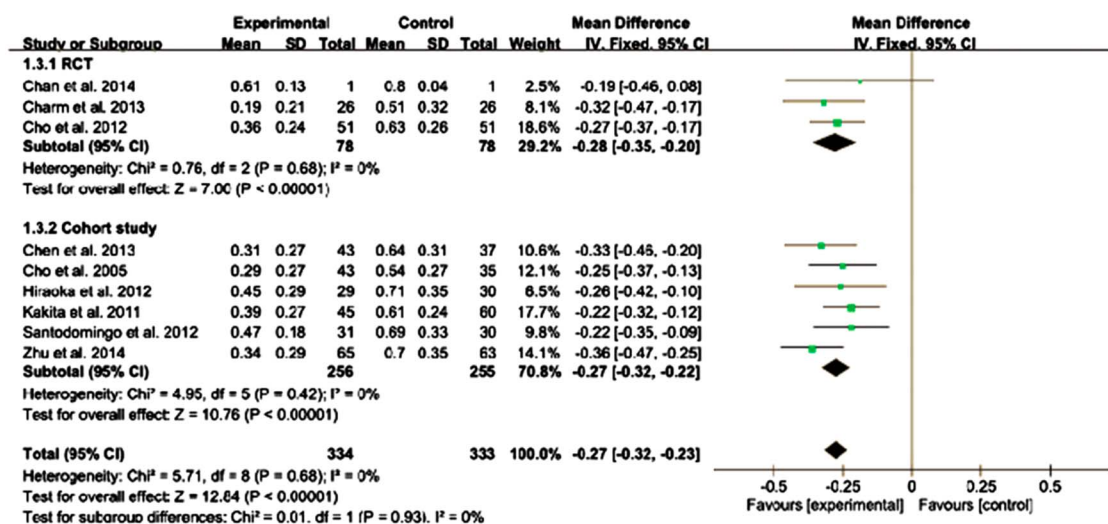
FIG. 5. Meta-analysis of orthokeratology. Meta-analysis of 7 OK studies[155,156] was performed, which included 435 subjects who were aged between 6 and 16 years.[148,150,151,241,252–254] Meta analysis found a mean difference between controls and OK patients of 0.26 mm over 2 years. This is a 40% reduction in the progression of myopia. Reprinted with permission from Si JK, Tang K, Bi HS, Guo DD, Guo JG, Wang XR. Orthokeratology for myopia control: A meta-analysis. *Optom Vis Sci* 2015.

for 7 months, wore SV spectacles (phase I), and then resumed OK lens wear for another 7 months. Group 2 was a control group, which wore spectacles. Stopping OK lens wear resulted in a more rapid increase in AL as compared to those wearing spectacles during the initial 2-year myopia control study (rebound effect). Axial elongation slowed again when OK was resumed. This study suggests that there is a rebound effect with OK lenses.

Recently, there has been renewed increased interest in the use of soft lenses to create similar optics as OK.[170–176] To design an optically similar lens, one would need to manufacture a multifocal lens with a distance center. Smaller optic zones are preferable because the larger the retinal area stimulated with strong plus lenses, the greater the effect in slowing the progression of myopia. Walline et al.[175] fit 40 children with soft multifocal contact lenses (Proclear Multifocal "D"; CooperVision, Fairport, NY) with a +2.00 D add power and compared them to a historical age-matched control group of SV distance lens wearers. The adjusted mean progression of myopia at 2 years was -1.03 ± 0.06 D for the SV contact lens wearers and -0.51 ± 0.06 D for the soft multifocal contact lens wearers ($P<0.0001$). The adjusted mean axial elongation was 0.41 ± 0.03 and 0.29 ± 0.03 mm for the SV and soft multifocal contact lens wearers, respectively ($P<0.0016$). Soft multifocal contact lens wear resulted in a 50% reduction in the progression of myopia and a 29% reduction in axial elongation during the 2-year treatment period. One may question Walline's findings, however, because they were compared to a historical control. In addition, it is well known from the COMET studies that the greatest myopia-controlling effect of any intervention happens in the first year. Lastly, there are no data on discontinuing the lenses with possible rebound effects.

In a recent study, children, who were found to have myopic progression after 1 year of traditional contact lens or spectacle use, were placed in 1 of 3 groups: (1) radial refractive gradient (SRRG) contact lenses, (2) OK, and (3) a SV glasses.[176] The SRRG is an experimental soft contact lens with a distance center and high plus in

the mid-periphery. After 2 years, the mean myopia progression values for the SRRG, OK, and SV groups were -0.56, -0.32, and -0.98 D, respectively. This represents a reduction in myopic progression of 43% and 67% for the SRRG and OK groups as compared to the SV group. In addition, the AL increase was less by 27% and 38% in the SRRG and OK groups as compared to the SV group. Although these results are encouraging, the SRRG lens is not currently commercially available. In a different study, Aller et al.[177] used an Acuvue Bifocal (Johnson & Johnson, Jacksonville, FL) center distance bifocal soft contact lens in selected myopic esophoric patients and achieved almost a 70% reduction of myopia after 1 year, but the applicability of this finding outside of esophoric patients is not known. A meta-analysis (Fig. 6), which included 587 subjects, from 8 studies found that concentric ring and distance centered multifocal designs slowed myopia progression by 30% to 38% and 31% to 51% for axial elongation over 24 months.[178] Turnbull et al.[179] performed a retrospective case series analysis of 110 myopic children and reported that multifocal soft lens and OK slowed myopic progression equally, that is, OK before treatment progression X=-1.17 to after treatment -0.09 D/year; dual focus soft contact lens before progression X=-1.15 to after treatment -0.10 D/year. Using a similar retrospective case series analysis as was used by Turnbull et al.,[179] Cooper et al.[180] performed a retrospective case series of 32 myopic children and reported that a center distance extended depth of focus soft multifocal contact lens design slowed myopic progression with before progression X=-0.85 D to after treatment -0.04 D/year right eye and before progression X=-0.90 D to after treatment -0.04 D/year left eye.

Figure 6 presents a meta-analysis of the use of soft multifocal contact lenses to slow the progression of myopia.[178]

Pharmaceutical Agents

In addition to manipulating visual input with lenses to control myopia, atropine has been shown to slow the progression of the disease. Atropine was first used by Wells in 1900 to stop the
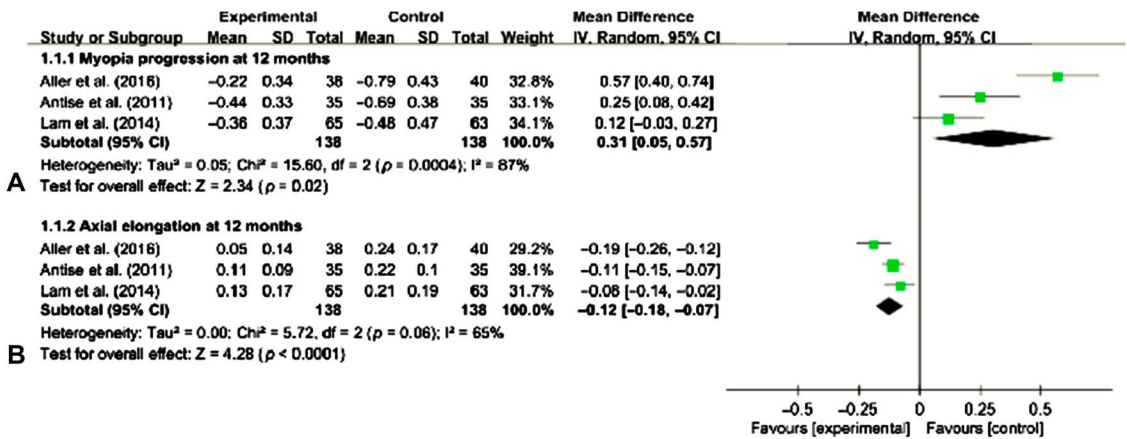
FIG. 6. FIG. 6. Meta-analysis of multifocal contact lenses. Meta-analysis,[178] which included eight studies published between 1999 and 2016, that compared single-vision soft lenses with both concentric ring bifocal soft contact lenses (CCML)[170,177,255–257] and peripheral add soft contact lenses (MCL).[171,175,176] There was less myopia progression with both lenses (the CCML had a weighted mean difference [WMD] of 0.31 D and reduced axial elongation WMD of –0.12 mm, whereas MCL had a WMD of 0.22 D and less axial elongation of 0.10 at the end of 1 year). This represented a 31% reduction of progression with the CCML and 51% reduction with MCL. Axial length reduction was also noted: 38% with the CCML and 51% with MCL after 2 years. Reprinted with permission from Li SM, Kang MT, Wu SS, et al. Studies using concentric ring bifocal and peripheral add multifocal contact lenses to slow myopia progression in school-aged children: a meta-analysis. *Ophthalmic Physiol Opt* 2016.

progression of myopia by "paralyzing" accommodation. Analysis of a number of retrospective studies using atropine has shown that 1% atropine tends to slow the progression of myopia by almost 80% (Table 1).[181–193] The effect is by a nonaccommodative mechanism,[70,80,194] because a number of studies have shown that atropine inhibits AL: in animals that have no accommodative mechanism[195]; when the optic nerve has been cut thus eliminating feedback necessary for accommodation[74]; or when regionally induced AL changes occur from blur.[71] Though the exact mechanism by which atropine inhibits myopia progression is unknown, multiple studies have indicated that atropine has an effect altering the sclera.[196–198] It has, also, been suggested that ultraviolet (UV) light (secondary to pupil dilation) may increase collagen cross-linking within the sclera, thereby slowing scleral growth.[199]

The most common complaints when using atropine, however, are pupil dilation and temporary paralysis of accommodation. These issues can be mitigated by photochromic, PAL glasses. There have been, also, some concerns of increased UV exposure and long-term retinal damage.[200] However, UV exposure (other than oblique rays) can be reduced by the use of UV coatings on the lenses, and the lost accommodation can be mitigated by the use of PALs. Besides enjoying a good safety profile with long-term clinical use,[201] Electroretinogram results (which are a sensitive indicator for early retinal damage) are normal in patients using atropine for a long term.[81,201–203] In the 2-year ATOM study (N=400), there were no serious adverse effects. Reasons for withdrawal included: allergic or hypersensitivity reactions, discomfort (4.5%), glare (1.5%), blurred near vision (1%), logistical difficulties (3.5%) and others (0.5%). Similar minimal adverse rates have been reported by other atropine studies. The use of 1% atropine seems to have its strongest effect in year one. Many of these earlier studies demonstrated long-term effectiveness of atropine[186,189,192] (Table 1). Chiang et al.[204] studied the effect of 1% atropine used

once a week for 1 month to 10 years. They reported a mean progression rate of 0.08 D/year in the compliant group and 0.23 D/year in the partially compliant group.

Chua et al.[205] (ATOM1) studied the effect of 1% atropine in a group of 400 children (13.5% dropout rate) where one group received atropine, whereas the other group received a placebo. Only one eye of each child was chosen for treatment. The mean progression in the control eye after 2 years was 0.6 D/year and in the atropine-treated eye was 0.14 D/year. This represents a 77% reduction in the progression of myopia. Furthermore, the AL measurements in the eyes, which received atropine, remained essentially unchanged (0.02 mm over 2 years). There were no serious adverse events with the atropine being well tolerated. Figure 7 depicts the percentage of progression in patients on 1% atropine versus control.

There have been a number of studies that evaluated the relationship of dosage of atropine to the reduction of progression. Shih et al.[206] evaluated the effect of different doses of atropine on 200 children (6–13 years of age) who were randomly prescribed one drop of 0.5%, 0.25%, or 0.1% atropine, or 0.5% tropicamide (control group) in both eyes nightly. The mean progression of myopia was 0.04 ± 0.63 D/year in the 0.5% atropine group, 0.45 ± 0.55 D/year in the 0.25% atropine group, and 0.47 ± 0.91 D/year in the 0.1% atropine group, as compared to 1.06 ± 0.61 D/year in the control group. At the end of the 2-year treatment period, 61% of children in the 0.5% atropine group, 49% in the 0.25% atropine group, and 42% in the 0.1% atropine group had no myopic progression (Fig. 8). In another study, the concentration of atropine was varied from winter (0.5%) to summer (0.1%) based on the assumption that myopia progresses less during the summer. This allowed children to have less pupillary dilation during the summer months when the sunlight and photophobia is the greatest.[207] This regimen slowed myopic progression by 77%. Fang et al.[208] evaluated the efficacy of 0.025% atropine to prevent

TABLE 1. *Retrospective Studies of Atropine 1% to Slow Myopic Progression*

Author	No. of Children Completed Study	Length of Study	Treatment	Control Group (Mean Progression)	Atropine Group (Mean Progression)
Gimbel,[181] 1973	594	3 yrs	Atropine 1% qhs	0.41 D/yr	0.14 D/yr
Kelly et al.,[182] 1975	282	3 yrs	Atropine 1% qhs	0.51 D/yr	+0.58 D/yr
Kelly et al.,[182] 1975	168	2–8 yrs	Atropine 1% qhs	Change in myopia: no change or improved: 2%; −0.75 D: 14%; 1.00 to 1.75 D: 35%; 2.00 to 2.75 D: 22%; 3.00 D: 27%	Change in myopia: no change or improved: 47%; −0.75 D: 34%; 1.00 to 1.75 D: 8%; 2.00 to 2.75 D: 7%; 3.00 D: 1%
Sampson,[184] 1979	100	1 yr	Atropine 1% qhs and bifocal 2.25	No control	Change in myopia: −0.25 to +0.50 D: 79%; +0.75 D to +1.00 D: 15%; >+1.00 D: 6%
Bedrossian,[186] 1979	90 children on atropine (62 followed for 2 yrs, 28 followed for 4)	4 yrs	Atropine 1% in only eye	−0.82 D/yr	+0.21 D/yr
Gruber,[188] 1985	200	1–7.5 yrs	Atropine 1% qhs	−0.28 D/Y	−0.11 D/yr
Brodstein,[189] 1984	399	1–9 yrs	Atropine 1% qhs and bifocal 2.25	−0.34 D/Y	−0.12 D/yr
Brenner,[190] 1985	79	1–9 yrs		No control	−0.20
Yen et al.,[191] 1985	96	1 yr	Atropine 1% qhs and bifocal 2.25	−0.91 D/Y; change in myopia: no change: 6.25%; < or =−0.50 D: 31.25%; −0.51 to −1.0 D: 31.25%; >−1.0 D: 31.25%	−0.22 D/Y; change in myopia: no change: 56%; < or =−0.50 D: 22%; −0.51 to −1.0 D: 19%; >−1.0 D: 3%

Earlier studies that used atropine 1% demonstrated a 90% reduction in the progression of myopia. The studies varied from 1 to 15 years of follow-up. In the first year, many of the studies found a small but clinically significant reduction in the amount of myopia.[181–191] Reprinted with permission from Cooper J, Schulman E, Jamal N. Current status on the development and treatment of myopia. *Optometry* 2012;83:179–199.

the development of myopia in a group of children presenting with the signs of myopic progression. There was a 50% reduction in the number of children who converted from emmetropia to myopia. The highest concentration of atropine, which does not cause any symptoms related to pupil dilation or decreased accommodation when atropine is used is 0.02%.[209]
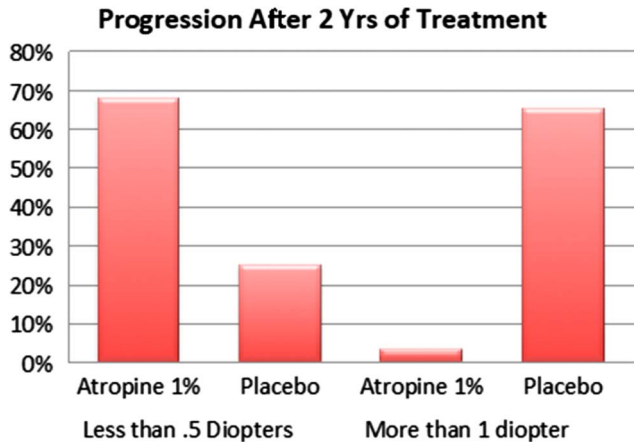

FIG. 7. Atropine 1% versus control in slowing myopic progression. Data from the ATOM 1 study are pictorially presented and clearly show the effectivity of atropine over control.[205] Seventy percent of the atropine subjects had less than 0.5 D of progression compared with less than 20% of the controls. It is apparent that atropine 1% results in strong control of myopia progression. Reprinted with permission from Cooper J, Schulman E, Jamal N. Current status on the development and treatment of myopia. *Optometry* 2012;83:179–99.

The ATOM 2 study[200] evaluated various concentrations of atropine, including the one below that threshold, that is, 0.5%, 0.1%, and 0.01%. After 2 years, researchers found that all 3 concentrations slowed the progression of myopia. The mean progression with each concentration (spherical equivalent) was 0.15 D/year (0.5% atropine), 0.19 D/year (0.1% atropine), and 0.25 D/year (0.01% atropine)[210] (Fig. 9). On first glance, the ATOM 2 study suggests that myopic progression was slowed with all concentrations, with similar effects between moderate and low concentrations. However, this conclusion is not justified if one uses AL to measure myopic progression rather than refractive error. Figure 10 depicts the axial change measurements from ATOM 1 and 2 studies combined at the end of 2 years. The ATOM 1 study showed a minimal 0.02 mm change in AL over 2 years of time with the use atropine 1%, whereas the ATOM 2 showed no statistical difference between the placebo and atropine 0.01% group. This is important for two reasons. First, if the primary purpose of slowing myopia progression is to reduce axial elongation which in turn decreases future retinal complications, then the lower concentrations are not nearly as effective as atropine 1%. Second, minimal difference between placebo and atropine 0.01% AL changes versus significant refractive changes between placebo and atropine 0.01% should make the clinician question of the "true effect" of atropine 0.01%.

After 2 years, all participants in the ATOM 2 study discontinued the use of atropine for 1 year. At the end of that year, 24% of the 0.01% group, 59% of the 0.1% group, and 68% of the 0.5% groups in the original ATOM 2 trial progressed more than 0.5 D of myopia and were retreated with 0.01% atropine for an additional 2 years.[211] This rebound effect was much greater with cycloplegic refractions
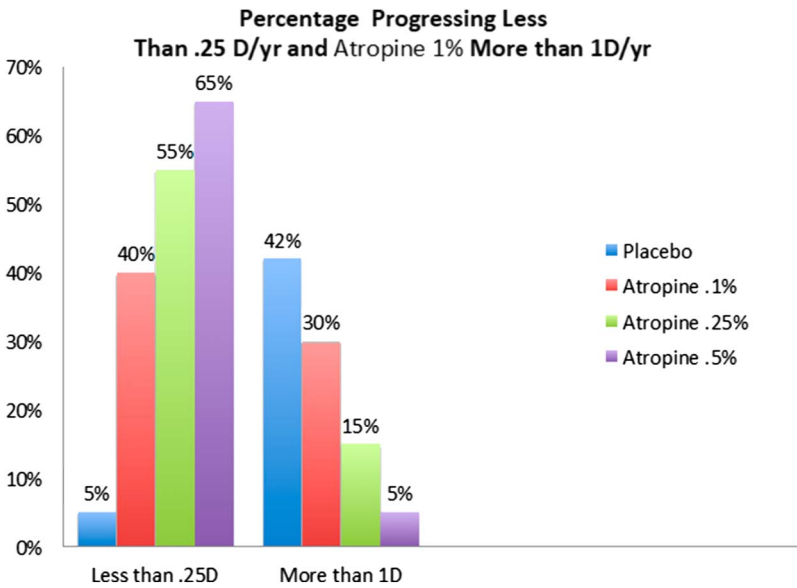
FIG. 8. Myopic progression with various doses of atropine. Shih et al. demonstrated that the ability of atropine to control progression is directly related to concentration.[206] The higher the dosage, the more effective atropine is in slowing the progression of myopia. It is clear that even at a relatively low dosage of atropine 0.01%, there is a clinically effective retardation of the progression of myopia. Reprinted with permission from Shih YF, Chen CH, Chou AC, Ho TC, Lin LL, Hung PT. Effects of different concentrations of atropine on controlling myopia in myopic children. *J Ocul Pharmacol Ther* 1999;15:85–90.

as compared to AL changes. The "rebound effect" observed in the ATOM studies can be partially explained by the fact that atropine has greater cycloplegic effect than 1% cyclopentolate used for the follow-up refractions, creating an impression that atropine slows the progression of myopia more than it really does in the first year. This creates an impression of the rebound effect, which is, in fact, much smaller than what is observed when doing cycloplegic refractions. Because atropine suppresses the signal for axial elongation, an abrupt stopping of higher dosages would result in faster elongation than discontinuation of lower concentrations. These findings suggest that atropine use should be tapered down rather than be abruptly discontinued.[212]

After stopping the use of atropine drops for 1 year, the patients were re-assessed.[213] It was found that the progression of myopia have resumed in some patients or appeared to have completely stopped in others. Those patients, in whom progression stopped, were presumed to be abated (future data are needed to substantiate this claim), whereas progression continued in others. Those with continued progression after phase 2 were restarted on 0.01% atropine and reassessed 2 years later (total of 5 years).[211] Those who did not progress after the discontinuation phase usually did not progress during the next 2 years of observation. The authors concluded that 0.01% atropine was more effective than the higher dosages in slowing the progression of myopia. A recent meta-analysis suggests that there is no clinical difference between the effectively of low and high concentrations of atropine to slow the progression of myopia.[214] As mentioned previously, this conclusion must be viewed cautiously in light of AL measurements.
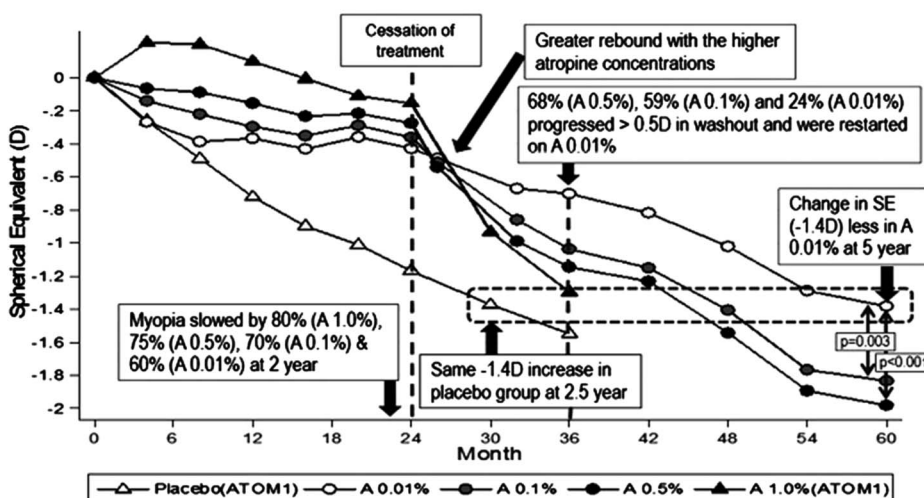

FIG. 9. Progression of myopia during 3 phases of ATOM studies. This graph depicts the cycloplegic refractions (spherical equivalent) in all 3 phases of the ATOM 1 and 2 studies.[212] The first phase was for 2 years during which subjects were randomized to receive various concentrations of atropine (1%, 0.5%). After 2 years, treatment was stopped in all groups for 1 year of time. Those patients still showing more than 0.50 diopters of myopia progression were placed on atropine 0.01% and followed for another 2 years. Reprinted with permission from Chia A, Lu QS, Tan D. Five-year clinical trial on atropine for the treatment of myopia 2: Myopia control with atropine 0.01% eyedrops. *Ophthalmology* 2016;123:391–99.

Changes in Axial Length and Spherical Equivalent (SE) Over 2 Years of Time
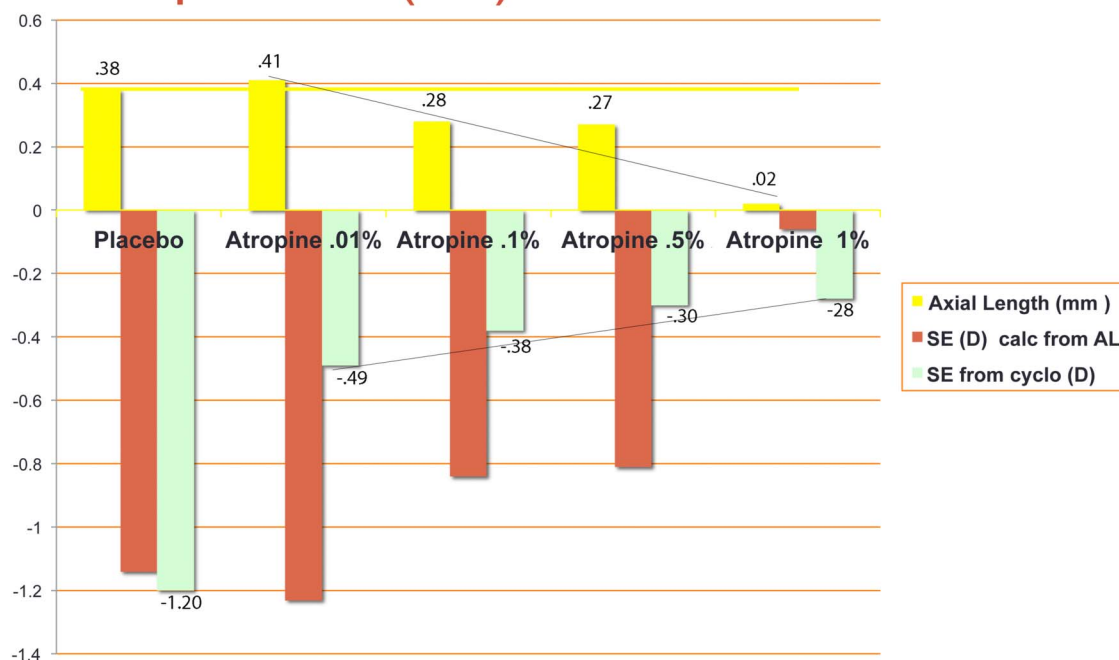

FIG. 10. Changes in AL and SPH EQ after 2 years of treatment. Figure 10 depicts the changes in axial length in millimeters (yellow bars going up); spherical equivalent in diopters calculated from the axial length data (red going down); and cycloplegic automated refractor measurements in diopters (green going down) at the end of the 24-month treatment period. The measurements were derived from the ATOM 1 study for atropine 1% and placebo and ATOM 2 for atropine 0.01%, 0.1%, and 0.5%, respectively. It is readily apparent that there is no real difference between axial length measurements after 24 months between placebo and atropine 0.01%; moderate changes with atropine 0.1% and 0.5%; and dramatic changes with atropine 1% (yellow bars). However, the spherical equivalent measurements (green bars), compared with placebo in diopters, show a much greater change over time again being greatest for atropine 1%. The difference between the effect of atropine 0.01% and atropine 1% is not nearly as great as the concentration differences.

The rebound results also need to be evaluated with caution: clinicians do not usually put patients on 1% atropine for 2 years and then stop the medication. Patients are usually treated with atropine for many years without interruptions. Studies, in which 1% atropine has been used for many years, found that atropine did not lose its effectiveness over the long run. The subjects who were least affected by the atropine treatment had the following characteristics: (1) 2 myopic parents, (2) developed myopia earlier, and (3) progressed more than the average of 0.66 D/year.

The 5 years of data suggest that 0.01% atropine was more effective (and with fewer side effects) in slowing progression of myopia compared with higher concentrations of the drug. One must keep in mind, however, that in normal clinical practice, atropine treatment is typically continued for more than 2 years without interruption. In summary, these findings suggest that myopia did not progress with 0.01% atropine in the first 2 years of the study. Myopia did not progress once treatment was stopped (discontinuation phase), and individuals no longer needed further treatment to slow myopia.

Those who progressed more than 0.5 D, when atropine was discontinued, were more likely to have been on a higher dosage and needed further treatment. These data suggest that over the long run, 0.01% atropine is more effective than higher concentrations and causes minimal symptoms secondary to pupillary dilation or loss of accommodation, and the 0.01% concentration can be used for 5 years and then stopped. If progression recurs, treatment with 0.01% atropine can be resumed. If higher concentrations of atropine are required atropine 0.02% may be tried, the treatment should be stopped gradually by tapering down the concentration of the drug.[209] The ATOM 2 study does provide compelling support to begin treatment of myopia with 0.01% atropine, but our clinical experience is that it might be less effective than suggested. In addition, if one uses AL measurements rather than refractive error to monitor effectively of 0.01% atropine versus control to slow myopic progression, it is apparent that there is no difference between the 2 treatment arms.

Time Spent Outdoors

Several recent studies suggest that time spent outdoors slows both onset and progression of myopia in children.[215–224] It was also found that the effect of outdoor activities on myopia is not necessarily related to physical activity and that the shear exposure to outdoor environment has therapeutic effect.[217] These findings triggered a number of investigations trying to pinpoint the exact factor

Meta Analysis of Tx for Myopia
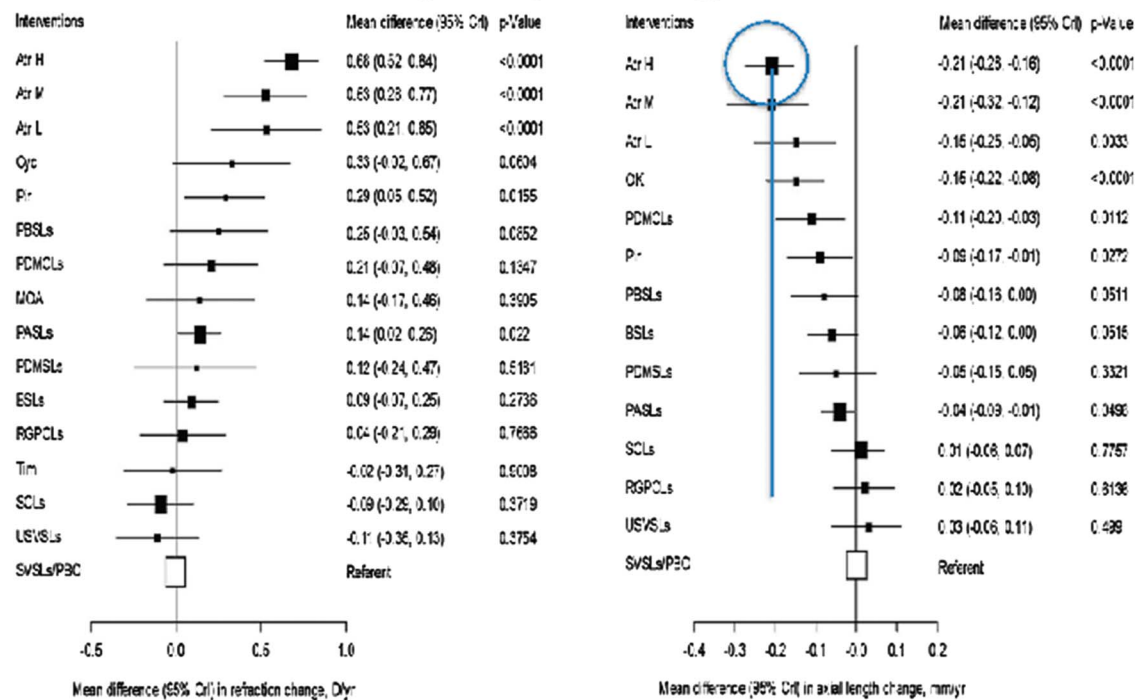## *Huang et al Ophthalmology 2016*

FIG. 11. Meta-analysis of 16 different treatments. A meta-analysis[243] of 16 different treatments for myopia was performed using a comparison with either placebo or single-vision spectacle lenses with the following: high-dose atropine (refraction change: 0.68; axial length change –0.21); moderate-dose atropine (refraction change: 0.53; axial length change: –0.21); low-dose atropine (refraction change: 0.53 axial length change: –0.15); pirenzepine (refraction change: 0.29; axial length change: –0.09); OK (axial length change: –0.15); multifocal contact lenses (axial length change: –0.11); and progressive-addition spectacle lenses (refraction change: 0.14 axial length change). Reprinted with permission from Huang J, Wen D, Wang Q, et al. Efficacy comparison of 16 interventions for myopia control in children: A network meta-analysis. *Ophthalmology* 2016;123:697–708.

(s) responsible for the effect of outdoor activities on myopia. Several studies suggested that exposure to brighter light, increased levels of vitamin D, increased levels of dopamine, or UV light by itself are responsible for the effect of outdoors on myopia onset and progression.[225–234] However, further studies essentially ruled out the role of vitamin D and UV light in the inhibition of myopia development by exposure to outdoors.[235,236]

Recently Torii et al.[234] demonstrated that violet light (VL) (360–400 nm wavelength) suppresses myopia progression in chicks and humans. They retrospectively measured the AL elongation among myopic children, who wore either VL blocked eyeglasses or one of two types of contact lenses (partially VL blocking and VL transmitting). They found that the VL transmitting contact lenses suppressed myopia progression more than VL blocking lenses. They suggested that because VL exposure is limited by UV protection from being indoors; filtered out UV by panel window glass; and filtered out UV by glasses, some contact lenses and sunglasses that increased VL exposure may be a preventive strategy against myopia progression.

There is, also, evidence that increasing the illumination in classrooms decreases the incidence of myopia.[237] Bright light was also shown to inhibit form-deprivation myopia and reduce lens-induced (defocus-induced) myopia in animal studies.[227–231] However, there is no information whether bright light might have caused animals to close their eyes because of photophobia caused by high light intensity, thus, reducing visual input. Moreover, studies that assessed the effect of outdoors on myopia did not take into

Treatment	Meta	Cooper
Atropine high dosage	65%	85%
Atropine moderate dosage	65%	76%
Atropine low dosage	45%	60%
Ortho K	45%	45%
Multifocal soft contact lens	33%	40%
Progressive Lens/Bifocals	12%	16%
Single Vision	0%	0%
Undercorrection	–9%	–8%

FIG. 12. Percentage of reduction of myopia progression with various treatments. Calculated percentage of reduction of progression of myopia for each treatment. Meta-analysis numbers[243] were used to calculate the reduction in progression. Meta-analysis only included prospective clinical trials. Cooper et al.[81] previously calculated the reduction in progression from all published studies without regard to methodology.

account the use of sunglasses in bright light, which would reduce the importance of bright light exposure and emphasize other factors. Such factors would be the overall substantial differences in the visual environment between indoors and outdoors.[238] The indoor activities create far more hyperopic defocus (causing myopia) across the entire surface of the retina than any outdoors activities. Outdoor activities essentially eliminate any defocus across the entire visual field that serves as a stop signal for the eye growth (thus, inhibiting development of myopia). Brighter light intensity also leads to pupil constriction and increased depth of focus, which reduces optical blur and increases contrast. Change in contrast, in turn, would affect the function of amacrine cells, which might explain the role of dopamine in myopia development in animal models. Although the exact mechanism responsible for the effect of outdoor activities on myopia is unknown, spending more time outdoors clearly has a substantial therapeutic effect on myopia onset and possibly progression. Therefore, it should be recommended that children, especially those who have two myopic parents or show signs of myopia development or progression, spend more time outdoors as preventive measure of developing myopia.

CONCLUSIONS

In summary, there is strong evidence that myopia is a result of an interaction between genes and environment and can be slowed by a variety of treatments. Parents should be aware of what is and is not effective including the risks and benefits associated with each treatment option (Figs 11 and 12). Despite none of these interventions having FDA approval/clearance at this time to treat myopia progression, we believe that with informed consent, an appropriate treatment plan should be instituted. Today, treatment preferences seem to vary by country and profession. More eye care professionals in China advocate the use of OK; whereas in Taiwan and Singapore, more advocate atropine; and in the United States, some eye care professionals prescribe soft multifocal contact lenses, and/or advocate OK and some ophthalmologists advocate atropine. In Taiwan, over 60% of the children with myopia are on atropine.[239] Recently, there are data supporting the additive effects of optically correcting myopic children with OK and low dosages of atropine, that is, after a year in the study "OK only patients" increased AL by 0.19 mm, whereas "OK and atropine" increased AL by 0.09 mm.[240] Because they use different stop mechanisms, it is not surprising that their effects are additive. There is obviously the need for more studies into the mechanisms of myopia and refractive eye development, but the future is encouraging.

Ongoing research already provided some insights into molecular pathways underlying myopia and could be expected that it will soon produce new drug targets and drugs for treatment of myopia. In the meantime, children who have high-risk factors (myopia first noted around 4 or 5 years. with aggressive progression and parental myopia) should probably be started with 1% atropine. One might consider the prophylactic use of atropine 0.01% in children with a strong risk of development of myopia, that is, 2 parents being myopic and decreasing hyperopia of 0.5 D/year. On the other hand, children who become myopic after the age of 8 can be treated with 0.01% atropine, soft multifocal contact lenses or OK. In addition, patients with more than 6 diopters of myopia can wear soft multifocal contact lenses or a combination of OK contact lenses and glasses to obtain an effective treatment result.[241] Because soft

multifocal contact lenses, OK and low dosage of atropine seem to be equally effective,[242] patient concerns and compliance may help guide treatment selection.

Some children tend to prefer their glasses and thus require atropine. Children who are more athletic usually prefer OK or soft multifocal contact lenses. Parents who are fearful of overnight contact lens wear often choose low concentrations of atropine or soft multifocal contact lenses, whereas parents/patients concerned about the long-term effects of atropine usually choose OK. Some patients are concerned with the risks of OK associated with sleeping in lenses, whereas others are concerned about the long-term effects of atropine even at low dosages. In addition, distance center soft contact lenses may have a better indication in myopes with less than −2.00 D because effectiveness is related initial refractive error. We often prescribe distance center soft multifocal contact lenses even though the published clinical evidence is not yet as strong; however, the perceived risk is less. Finally, children should be encouraged to spend more time outside and the public and policymakers should be informed of the potential benefits of outdoor activities, so that school schedules, perhaps, could be adjusted to allow more time for outdoor activities during school hours and after school.

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