Current Status on the Development and Treatment of Myopia

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ABSTRACT
This is a review of the current literature describing the effect of atropine, bifocals, and/or contact lenses on slowing the progression of myopia. Cumulative data from a number of studies have demonstrated atropine instilled once a day in myopic eyes resulted in a 90% average reduction of myopia progression, as compared to untreated eyes, i.e., from 0.50 D/year to 0.05 D/year. Pirenzepine, a muscarinic pharmacological agent, has a minimal effect on pupil size and accommodation, and it has been shown to slow myopia by 44%. Bifocals and progressive lenses, which have been used for years to slow the progression of myopia, have recently been shown to produce, on average, only small, clinically insignificant treatment effects. However, their effectiveness is increased in children who are esophoric and have a large lag of accommodation, reducing myopia progression to between 0.25 and 0.40 D/year. Traditional correcting soft and gas permeable contact lenses, as well as novel spectacle lens designs, have not been shown to be effective in reducing myopic progression. Under-correction of the refractive error has been shown not only to be ineffective in slowing myopia, but has also been associated with an increased rate of myopia progression. Orthokeratology, using reverse geometry designed lenses, has been shown to be moderately effective in decreasing the progression of myopia by between 30 to 50% in a number of short-term, well-controlled studies, reducing myopia progression to between -0.25 and -0.35 D/year. Recently, there have been pilot studies using novel peripherally correcting soft contact lenses to slow the progression of myopia. Two of those lens designs have been shown to be moderately effective in slowing the progression of myopia, both of which had a 30% efficacy, reducing myopia progression to 0.35 D/year. In summary, myopia control is entering a new era with the use of contact lenses and pharmaceutical agents to effectively slow its progression with minimal side effects.

Myopia

Myopia is a common refractive condition affecting approximately 100 million people in the United States.[1] Its prevalence has increased over the past decades, leading to a growing concern among the public and scientific community.[2, 3] The prevalence of myopia varies in different parts of the world.[4-7] Generally speaking, myopia is more prevalent in industrialized countries and in cities as compared to rural areas.[8-12] In the United States, the prevalence rate has increased from 25% between 1971 - 1972 to 41.6% between 1999 – 2004.[1,2] The prevalence of myopia in Taiwan and Singapore is 20% to 30% in children 6 to 7 years of age, increasing to 60% to 80% in young adults.[13,14] The rapid increase in the prevalence of myopia provides strong evidence that current environmental factors must have a considerable influence on the development of myopia that can not be explained by a genetic model.[15,16] Understanding how the environment influences eye growth should be central to preventing the progression of myopia.

The widespread prevalence and rapidly increasing rates of myopia make it a significant public health concern. Persons with higher degrees of myopia have a greater risk of developing sight-threatening complications i.e., permanent visual impairment (or "blindness") from myopic macular degeneration, cataract, glaucoma, retinal holes and tears, and retinal detachments.[13,14,17,18] Myopia has been implicated as the sixth leading cause of vision loss.[19] Retarding the progression of myopia in children could ultimately impact the lives of approximately 42 million adults in the United States.[20] Thus, finding an effective method of slowing myopia progression is important in decreasing the morbidity associated with this condition.

Myopia has been broadly classified by age of onset as pathological, school age, or adult onset. Pathologic myopia, which usually presents before six years of age, is caused by abnormal and extreme elongation of the axial length of the eye, generally does not progress, and is usually associated with retinal changes.[21,22] School age myopia occurs between 6 and 18 years of age and is thought to progress and stabilize by the late teens or early twenties.[23] This type of myopia is associated with higher IQ scores, more time spent reading, and less hours of exposure to sunlight as compared to non-myopic patients.[24,9,25-28] In Singaporean children, the prevalence and magnitude of myopia correlates with the time spent in education.[29] In addition, school-age myopia is found more commonly in urban areas (versus rural areas), and industrialized countries.[9,30] Adult onset myopia occurs between 20 and 40 years of age (early adult onset) or after 40 years of age (late adult onset). It has different characteristics as compared to the school age onset myopia, particularly in that it is associated with accommodative anomalies and near vision dominated occupations.[31] Myopia progression in all three groups is due to the elongation of the axial length, which is primarily due to the elongation of the vitreous chamber depth of the eye.[32]

If myopia is to be controlled during development, the rate of eye growth must be slowed. The rate of myopia progression is highest for young children with an average age for stabilization of childhood myopia at 16 years of age.[33] Once myopia begins

to develop, the mean rate of progression in children 8 to 13 years of age is 0.55 D/year for Caucasian children;[33] between 0.63 D/year for Hong Kong Chinese children;[34] and 0.82 D/year determined for Asian children by meta analysis.[35] For an average baseline age of 9 years, estimated annual progression (combined ethnicities) was 0.80 D/year for females, and a significantly slower 0.71 D/year for males.[35]

The etiology, pathogenesis, and treatment of myopia have been debated for decades, and the exact mechanism of the development of myopia still remains unclear. Both environmental and genetic factors have been associated with the onset and progression of myopia.[2,19,22] The strongest evidence for genetic factors comes from comparing the prevalence of myopia in uniovular versus binovular twins. Uniovular twins have a higher prevalence of myopia as compared to binovular twins, thus supporting the genetic influence on the development of myopia. In addition, Angle and Wissman[36] found that near work explained only a small part of the variance in teenagers, and thus concluded that genetics is the most important factor in determining the development of myopia. Studies have also shown that having one or two nearsighted parents is a risk factor for the development of myopia.[37-40] However, this does not completely explain the role of genetics since parents share both genetic and environmental factors with their offspring.

The concept that myopia evolved from the use and abuse of the eyes during near vision activities has been credited to Cohn in 1886 and has been traced back to Kepler.[41] More recent studies demonstrate a positive correlation between the presence of myopia and the following: intelligence,[24, 42-43] academic advancement,[44,16,42] avocations requiring near vision use,[45,46] after professional school,[31,47] caged versus free-ranging animals[48] and people confined to restricted spaces such as submarines.[49] The implication of most of these studies is that the greater the time spent performing near work results in an increased incidence of myopia.[50-52] Zylberman,[53] while studying children in religious schools, noted that the incidence of myopia was much higher in Orthodox Jewish males who spent approximately 16 hours per day studying as compared to Jewish females who did not study as much. The incidence of myopia in Jewish females was similar to other Jewish male cohorts who attended non-religious schools. Zylberman[53] suggested that both groups of males had similar genetic make-ups, but the group that studied more became more myopic. In both groups, the females who studied a similar amount developed a similar amount of myopia.

The assumption in most use and abuse theories is that accommodation is somehow indirectly responsible for axial length elongation. There is some indirect evidence for this since myopes exhibit greater lags of accommodation,[54,55] higher ACA ratios,[56 57] more esophoria even when they are still emmetropic, [58] reduced accommodative amplitudes,[59] worse accommodative responses,[60,61,62] and deficient positive relative accommodation. [63] However, the difference in accommodative function between emmetropes and myopes is not great enough to explain the development of myopia. Secondly, it is difficult to determine which came first, the abnormal accommodative function or the myopia. Abnormal accommodative findings have lead to a host of treatment methods including bifocals, progressive addition lenses (PALs), base-in prism, atropine therapy, and vision therapy.

Mutti and Zadnik[64] recently challenged the near vision theories by noting that recent epidemiological studies suggested that the amount of time spent outside in sunlight is more closely related to the development of myopia than the amount of time spent reading, studying, or working on a computer.[65,66,67] In animals the level and/or amount of illumination during the day can affect refractive development.[68,69,70] A number of studies have documented a strong negative correlation between the amount of time children spend outdoors and their refractive error, i.e. myopia becomes more common in children who spend less time outdoors.[27,65,66] However, this finding has not been observed universally.[71,38,72] Guggenheim et.al[73] in a recent study determined that the amount of time spent outdoors was predictive of incident myopia independently of physical activity. They reported that the association of myopia observed for time outdoors and "sports/outdoor activity" is related to time outdoors rather than to the level physical activity.

The mechanism of sunlight has been ascribed to the pinhole effect causing a reduction of peripheral blur, UV exposure affecting cross-linking of the sclera, and/or alteration of the focusing shell when looking from distance to near. The prevalence of myopia varies minimally across geographical latitudes, that exhibit a wide range of both the length of day and the amount of ambient light.[74] Thus, Guggenheim et al.[73] concluded that it is likely that light levels regulate the eye's "gain" response to the visual cues that guide emmetropization rather than exerting a direct effect on eye growth. Mutti and Zadnik[64] makes a point of stating that the time spent outdoors is an independent variable, not the inverse of near work. When looking at epidemiological studies, one must be cognizant of the cohort being studied. For example, many of the studies involving amount of sunlight exposure were performed on school-aged myopes and may not be relevant to adult onset myopia. At the same time, most of the studies on accommodation used college aged students versus younger children (between the ages of 8 and 13 years).

The most compelling studies implicating the impact of the environment on myopia come from animal studies in which the environment has been manipulated to produce myopia, hyperopia, or astigmatism in visually immature animals. Wiesal and Raviola[68,75] sutured the lids of monkeys, allowing a minimal amount of light to penetrate. Form deprivation resulted in the animals developing myopia secondary to axial elongation of the vitreous chamber. They concluded that form deprivation disrupts the feedback mechanism for emmetropization and resulted in myopia across all species including humans. Similar myopiagenic effects were observed when translucent diffusers were placed over an eye rather than suturing the lid closed. However, myopia did not develop if the animal was patched with a totally opaque occluder or reared in total darkness, since total darkness eliminates any signal for visual feedback.[76,77]

Wallman et al.[78] used hemi-retinal sector occluders to create regional diffusion of light. Hemi-retinal diffusers result in a clear image on one half of the retina and diffused unfocused light on the other half. Myopia, with axial elongation, occurred only in the field in which the occluders diffused the light, i.e., asymmetrical elongation of the globe (see Figure 1). Myopia occurred in the occluded half of the retina, in the presence of equal illumination in both halves of the retina, and in the absence of accommodation. Smith and his associates reported similar results.[79] Lastly, these changes occurred in the absence of an intact optic nerve, demonstrating that changes were local to the eyeball.[80,81] Varying the amount of illumination by the degree of frosting resulted in varying the degrees of myopia. In a similarly designed experiment, Diether[82] used hemi-regional plus and

minus lenses to induce local retinal blur, which caused a localized change in axial length in young chicks. Diether suggested that these results provide further evidence that accommodation is not responsible for axial elongation. Schaeffel and his associates[83,84] used plus and minus contact lenses to create artificial hyperopia or myopia. When lenses between -10.00 and +15.00 were placed on primates' eyes, the growth of their eye(s) compensated for the focal length created by the lens in an attempt to eliminate blur. (It should be noted that the eye responded accurately to the direction of the error.) These studies demonstrate that emmetropization is driven towards the direction that results in a clear, higher contrast image. It has been postulated that near visual activity either disrupts the normal pathway of emmetropization or results in a change in ocular growth in order to adapt to the near enviorment.[85]

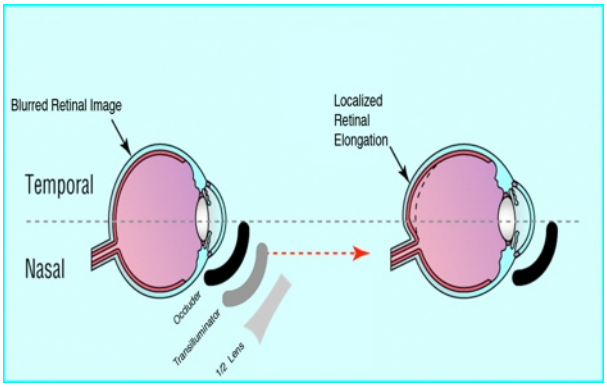

Figure 1 *Regional Deprivation Causes Localized Axial Elongation*

Panel 1 One of the following was placed in front of the nasal field of a visually immature animal's eye resulting in a blurred image on the temporal retina: occluder, translucent lens, or minus lens.
Panel 2 The blurred image on the temporal retina over time causes localized elongation of the eyeball.[205,79] This occurs even when the optic nerve is severed, demonstrating that cortical feedback is not necessary for localized elongation.[81]

Animal studies using positive and negative lenses have demonstrated that optical defocus can cause directionally controlled eye growth.[84,86-88] Thus, it would not be unreasonable to presume that hyperopic retinal blur from a larger lag of accommodation during near viewing could cause myopia progression in children[63, 89, 90] and the larger the amount of hyperopic defocus, the faster the rate of myopia progression.[91] In support of this hypothesis, Gwiazda et al.[57] reported an elevated lag of accommodation two years before the onset of myopia. Conversely, Mutti et al.[92] reported that accommodative lag in pre-myopic children was not elevated until a year after the onset of myopia. Rosenfield et al.[93] reported that young adults who became myopic had a smaller lag of accommodation before and after the onset of myopia. While there is no consensus regarding lag of accommodation prior to the onset of myopia, there is a consensus that the lag of accommodation is larger after the development of myopia.[94-96] Recently, Berntsen et al.[97] investigated the relationship between accommodative lag and the rate of myopia progression in a large sample of children; they reported that foveal hyperopic retinal blur during near viewing could not explain school-age myopic progression. Thus, the relationship of lag of accommodation in causing myopia is at best controversial.

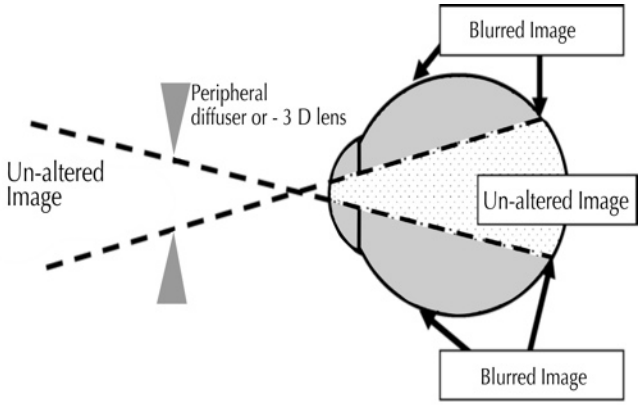

Figure 2 Peripheral Blur Drives The Eye to Elongate
If either the macula is ablated, a multifocal lens is placed over an eye (center plano, peripheral -3.00), or a diffuser placed over the peripheral portion of the eye while the center is un-obstructed, the eye will elongate in response to the peripheral blur. This occurs across species (including those with and without fovea.[98,176])

Previously, the macula (including the fovea), which dominates cortical vision in primates, was thought to be responsible for the process of emmetropization. However, recent animal studies have demonstrated that the peripheral retina has a greater influence than the macula over emmetropization and ocular growth.[98-102] For example, form deprivation causes primate eyes to become myopic, when only the peripheral retina is deprived. If peripheral form deprivation is eliminated during the critical period, the vitreous cavity decreases in size and the eye becomes more emmetropic.[102] This even occurs in the absence of an intact fovea after ablating the macula with a laser.[99] Myopia progression results in the peripheral posterior pole of myopic eyes to become relatively hyperopic relative to the central retina due to the round shape of the globe.[103] (See Figure 2.)

It has been suggested that this relative hyperopic defocus may actually act as a signal for axial elongation.[101] Hoogerheide et al.[104] noted that emmetropic or hyperopic airline pilot trainees were most at risk for becoming myopic when the relative peripheral refractive error was more hyperopic. In addition, Schmid[105] observed that there was a correlation between temporal retinal steepness and the development of myopia in humans. Monkeys reared with centrally unrestricted vision (plano lens) and -3.00 D in the periphery produced similar myopia as a full field lenses of -3.00 D of power, demonstrating that peripheral blur caused axial elongation irrespective of whether central vision was corrected.[98] (See Figure 2) Liu and Wildsoet[106] used peripherally designed lenses in young chicks to create myopia which resulted in a reduction of axial growth. These findings support the hypothesis that eye shape, associated with peripheral defocus, is one of the factors influencing axial eye growth. (See Figure 3.)

In the Orinda Longitudinal Study of Myopia, which included predominantly Caucasian subjects, Mutti et al[107] reported that myopic children had relative peripheral hyperopia, whereas emmetropic and hyperopic children had relative peripheral myopia. Relative peripheral hyperopia results in a more prolate

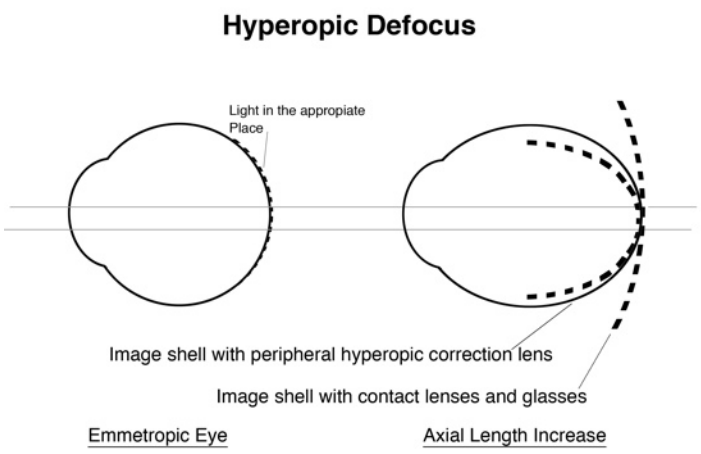

Figure 3 Image Shells Of Emmetropic Eyes And Myopic Eyes With Various Corrections

Panel 1. An emmetropic eye has the image shell congruent with the retina, i.e., both the macula and peripheral retina are in focus.

Panel 2. When the eye becomes more myopic, it becomes more elliptical (prolate), thus the anterior-posterior length increases without a change in the equator. This results in a more hyperopic periphery. Traditional lenses will correct the central retina leaving the periphery more hyperopic, i.e., image shell in the periphery is behind the retina. The amount of hyperopic defocus increases when looking near during accommodation. A lens that corrects the peripheral defocus, such as those used in orthokeratology, corrects the macula (image plane congruent to the macula), while the peripheral image shell is focused in front of the retina.

ocular shape in myopic eyes, in which the axial length exceeds the equatorial diameter. Similar findings have been reported in Chinese subjects with myopia.[107-111] Chen et al.[109] reported that relative peripheral refractive errors (RPRE) in Chinese children and adults with moderate myopia, low myopia, emmetropia, and low hyperopia were different. They reported that RPRE for the moderate myopia group had a relative hyperopic shift while subjects with low hyperopia demonstrated a relative myopic shift. The RPRE profile for the moderately myopic group was different for adults as compared to children. Adult eyes had a greater amount of hyperopic change. Thus, the periphery of a prolate shaped eye would experience hyperopic defocus, which might result in the onset and progression of myopia.[98,99]

The preceding findings have resulted in a renewed interest in orthokeratology and novel spectacle and contact lens designs to correct the hyperopic peripheral defocus in order to eliminate the local retinal signal for elongation (to be discussed later). In addition, the neuro-retinal signal for ocular elongation is thought to have a biochemical basis.[19] Thus, if one can block the signal, then one might slow or stop myopia progression. Atropine[112-138] and pirenzepine[139-147] have been shown to slow the progression of myopia via this presumed mechanism.

In summary, there is ample, solid evidence for both genetic and environmental factors producing myopia. It may be presumed that the genetic predisposition for myopia is triggered by environmental factors such as diet, amount of reading time, occupation, and amount of light. Currently, genetic make up cannot be altered, but the environmental factors can be. Thus, understanding the methodology of emmetropization is important in developing methods to control myopia.

TREATMENT: SPECTACLE CORRECTION

Bifocals and Multifocal Lenses

Optometrists first began using bifocal lenses to attempt to slow myopia progression in the 1940s.[148] The rationale was that if accommodation caused an increase in myopia, then bifocals or multi-focals would reduce the accommodative response and thus slow myopia progression. A more recent alternate theory suggested that myopic children do not accommodate as well as emmetropic children.[57] This inaccurate accommodation somehow creates a retinal blur that acts as a signal for myopia progression, similar to the blur-induced myopia that can be experimentally produced in animals.[54,55,60] Gwiazda et al. reported that myopic children with esophoria have a greater lag of accommodation than other myopic children and that myopic children have a greater lag of accommodation than emmetropic children.[54,55,60] A greater accommodative lag would cause retinal blur and possibly a stronger stimulus for myopia progression. Thus, the elimination of a lag of accommodation is thought to slow the progression of myopia.

Goss[149] performed a retrospective analysis of children between 6 and 15 years of age from three optometry practices to assess the effect of bifocal lenses on the rate of myopia progression. Sixty children wore bifocal lenses with an add power that varied between +0.75 D to +1.25 D, and 52 children wore single vision lenses. Children in the bifocal group displayed either esophoria at near, a low amplitude of accommodation, negative relative accommodation (NRA) and positive relative accommodation (PRA) which were more plus and/or less minus than normal values, a subjective refraction showing more minus than static retinoscopy, or a reported symptom of intermittent distance blur. As a group there was no statistically significant difference in progression between the bifocal group (0.37 D/year) and the single vision group (0.44 D/year). However, when Goss looked only at the esophoric children, there was a statistically significant decrease in myopia progression for children wearing bifocal lenses as compared to single vision lenses, 0.32 D/year versus 0.54 D/year, respectively. Myopia progression was also analyzed based on lens type and near cross cylinder findings. For children with a near cross cylinder finding greater than or equal to +0.50 D, there was also a statistically significant difference in myopia progression for children wearing bifocal glasses as compared to single vision glasses; 0.25 D/year versus 0.48 D/year, respectively.

Grosvenor et al.[150,151] randomly placed 207 children between the ages of 6 and 15 years into three treatment groups; single vision glasses, +1.00 D bifocals, and +2.00 D bifocals. At the end of the three year study, Grosvenor et al.[151] reported that for the 124 children who completed the study, there was no significant difference in myopia progression in children wearing single vision glasses or bifocal lenses. Goss[149] re-analyzed Grosvenor's data, looking only at the esophoric children, and reported that for this group, there was 0.20 D/year less myopia progression for the bifocal wearers compared to single vision lens wearers.

Fulk et al.[152,,153] conducted a prospective, randomized study of 82 esophoric children, (age 6 to 13), to evaluate whether bifocals (+1.50 D add) were effective in slowing myopic progression over 30 months. The authors noted that during at least one of five follow-up examinations, 33% of the bifocal wearers were observed to read over the top of their bifocals. Fulk reported that there was a 20% reduction in myopia progression for esophoric children wearing bifocal lenses as compared to single vision, a difference of 0.25D over 30 months. Fulk observed that if the outliers were excluded, which consisted of the five children who progressed more than 2.00 D over 30 months, then there was a 44% reduction in myopia progression for esophoric patients wearing bifocals. Myopia progression was 1.25 D or more in 25% of the bifocal group as compared to 44% of the single vision group, a 0.49 D difference over 30 months. The number of patients who demonstrated more than 2.00 D of myopia progression was similar in both groups. The authors concluded that improper bifocal use was associated with faster myopic progression; 67% of the children who progressed by more than -1.25 D were observed to look over the top of their bifocal on at least one of five follow-up visits.

Bifocal lenses, as compared to progressive addition lenses, are not as cosmetically appealing, and do not vary in power for different working distances. Both progressive lens and bifocals fit high should improve the proper use of the reading addition. Leung and Brown[154] conducted a clinical trial to evaluate the efficacy of progressive lenses on slowing myopia progression. Sixty-eight children between the ages of 9 and 12, who had myopia between 1.00 D and 5.00 D with less than 1.50 D of astigmatism, were fit with either progressive lenses or single vision lenses. The mean myopic progression over the 2-year study was 0.76 D for the +1.50 D add group, 0.66 D for the +2.00 D add group, and 1.23 D for single vision group. The progressive lens groups exhibited a statistically significant decrease in the amount of myopic progression associated with axial length changes as compared to the single vision lens group. There was no statistical difference between the two progressive lens groups. The axial lengths of the children in all groups increased with increasing degrees of myopia, and the majority of change occurred in the vitreous chamber. Leung and Brown noted that esophoric subjects wearing progressive lenses progressed 46% less than non-esophoric subjects wearing single vision lenses. The difference in myopic progression over 2 years between children with esophoria wearing single vision lenses as compared to progressive lenses was 0.71 D.

The Correction of Myopia Evaluation Trial (COMET), a 3 year prospective, randomized, double-masked clinical trial, evaluated the effect of progressive lenses (with a +2.00 D add) in 469 myopic children 6 to 11 years of age (spherical equivalent between -1.25 D and -4.50 D).[155] After 3 years, there was a statistically significant, but clinically insignificant, 0.20 D reduction in myopia progression over 3 years for children wearing progressive lenses as compared to single vision lenses. Children with larger accommodative lags (greater than 0.43 for a 33cm target) wearing single vision lenses had the most progression at the end of the 3 years. For children with both larger lags of accommodation and near esophoria, there was a statistically significant decrease in myopia progression in children wearing progressive lenses as compared to single vision lenses: 1.08 D verses 1.72 D, respectively. However the 3 year treatment effect decreased after 5 years to 0.49 D/year.[156] (Though, progressive lenses are more effective when one or both of the parents are myopic, there are no long-term data for this sub-group.)

A more novel use of multifocal glasses involves the use of specially designed glasses to correct for the central myopic error while, at the same time eliminating the peripheral hyperopic refractive error induced by traditional glasses.[109] This residual error results in a blur which is believed to be the stimulus for increased myopic progression. Sankaridurg et al.[157] reported on the effect of correcting peripheral hyperopic defocus on myopia progression in 210 Chinese children after 12 months of wear of one of three novel spectacle lens designs. The myopic children were randomized into one of four groups: wearing either one of three peripheral correcting spectacle lens designs or a conventional, single-vision spectacle lens. Both central and peripheral cycloplegic auto-refractions, and axial length were measured at 6 and 12 months. Myopic progression in eyes wearing special peripherally correcting lenses and traditional spectacle lenses at 6 and 12 months was 0.55 D ± 0.35 D and 0.78 ± 0.50 D, respectively. There was no statistically significant difference in the rates of progression with the peripherally correcting lenses as compared to traditional spectacle lenses. However, in one sub-group, the authors reported that the younger children (6 to 12 years) with parental history of myopia, had significantly less progression (0.68 D ± 0.47 D vs. -0.97 D ± 0.48 D) with one type of lens compared to traditional spectacles (mean difference of 0.29 D). One of the major problems with spectacle glasses is the inability to control where the patient looks through the lens, thus inducing variability in correcting the optics of the eye.

Cheng D, Schmid KL, et al.[158] measured myopic progression in a group of Chinese Canadian children, who were progressing more than 0.50 D/year as determined with cycloplegic refraction and ultrasonography. In this unmasked study subjects were placed in one of three lens treatment groups: myopic progression averaged 0.77 D/year in the single-vision lenses group, 0.48 D/year in the +1.50 executive bifocal group, and 0.35 D/year for prismatic bifocal group (+1.50 add with 3 prism base in prism in each eye): axial length increased proportionally to the refractive changes. Cheng et al.[159] concluded that bifocal lenses with and without BI prism can slow myopic progression in children with high rates of progression after 2 years of wear by approximately 45%. They reported that the effect of the bifocals was not related to any of the other concurrent variables measured: myopic duration before trial, lag of accommodation, hours of close work conducted per week, hours of outdoor activities per week, near phoria, and /or parental myopia.

Cheng, Woo, and Schmid[159] argue that the difference between their positive results and other studies, which did not show such a large effect, might be related to the lack of consideration for the proper add based on lag of accommodation, the lack of correction of the exophoria induced by relaxing accommodation with a near add, and/or the use of high fitting executive bifocals to ensure the use of the near reading add. A +1.50 add was chosen since it was close to the average lag of accommodation, and the BI prism prescribed was the average required to correct the exophoria measured at near. Cheng et al.[159] suggested that previous studies using multifocal progressive lenses suffered from the problem in not knowing what part of the lens the children viewed through. They felt that the prescription of a high fitting bifocal would eliminate this problem. (The practitioner needs to be aware of the cosmetic

problem that executive bifocals impose.) One must be careful in the interpretation of this data in light of the COMET study, which demonstrated a 5 year loss of the early effect of treatment with progressive lenses. Lastly, the most effective treatment with bifocals occurred in a very specific group of subjects who were children of Chinese origin, who progressed rapidly, and wore bifocals.[154,158,159]

The major benefit of any progressive lenses, bifocals, or novel peripheral correcting lenses, is the low risk of complications or adverse effects and their effectiveness in esophoric myopic children, which constitute about 30% of myopic children.[152] The major disadvantages of progressive lenses are cost, lack of strong scientific support of efficacy in the majority of non-esophoric myopic patients, and poor long-term data.

Under correction

Under-correction has been a popular method advocated by professionals to slow down the progression of myopia. In two separate studies, under-correction was associated with either an increase in the progression of myopia or no change as compared to fully corrected controls.[160,161] Thus, under-correction is associated with a faster progression of myopia, and should no longer be advocated.

CONTACT LENSES

Single vision contact lenses

Randomized clinical trials comparing soft contact lenses to spectacle lenses to slow the progression of myopia found no significant difference in myopia progression.[162] Walline et al., in the Contact Lens and Myopia Progression (CLAMP) Study, performed a randomized trial to determine if rigid contact lenses (RGPs) would affect myopia progression.[163] They found that children wearing RGP lenses had less myopia progression as measured by refraction than children wearing soft contact lenses. However, it was found that only the corneal curvature of RGP wearers was flatter than that of soft contact lens subjects; there was no significant difference in axial length in either cohort. Thus, refractive changes were most likely due to a temporary flattening of the cornea and did not represent a true slowing of myopia. In another randomized clinical trial by Katz et al.,[164] there was no significant difference in refractive error between RGP lens wearers and spectacle wearers. These studies suggest that RGPs do not reduce the progression of myopia as previously thought.

Orthokeratology

Orthokeratology (also called OK, ortho-k, corneal reshaping, corneal refractive therapy or CRT, and vision shaping treatment or VST), first described by Jessen in the 1960s, uses reverse geometry rigid gas-permeable contact lenses to reshape the cornea resulting in a temporary elimination of refractive error. There has been a resurgence in prescribing this treatment over the past decade due to better oxygen permeability of lens materials and improvement in the fit of the lenses.[165,166] The reverse geometry design flattens the central cornea while creating mid peripheral steeping which theoretically corrects hyperopic peripheral defocus, and in turn is thought to slow myopic progression. In 2003, Reim and his associates[167] performed a retrospective chart review of myopia progression in children between the ages of 6 and 18 with myopia between 0.50 D and 5.25 D. These subjects were fit with the DreimLens orthokeratolgy lens. In his cohort, 253 eyes were examined after one year of wearing the DreimLens, and 164 eyes were examined after 3 years of wearing the DreimLens. They reported a mean increase in myopia of 0.39 D over the 3 years, or 0.13 D/year. This was significantly less than the average reported progression of myopia, -0.50 D/year with single vision spectacle lenses.

Walline and associates,[166] in the Children's Overnight Orthokeratology Investigation (COOKI) pilot study, evaluated refractive error, visual changes, and biomicroscopy findings before and after 6 months of overnight orthokeratology in 29 subjects who were between 8 and 11 years of age, with 0.75 D to 5.00 D of myopia and less than 1.50 D of corneal astigmatism. Subjects were fit with Paragon corneal refractive therapy contact lenses. At the 6-month visit, the mean uncorrected visual acuity was 20/25, and the mean spherical equivalent refraction was -0.16 ± 0.66 D in each eye. During the morning visits, 58.8% of the children showed mild corneal staining, and only 35.3% of children showed mild corneal staining at the afternoon visit. No lasting adverse visual effects from corneal-reshaping contact lens wear were reported; thus Walline et al. concluded "overnight corneal reshaping contact lenses was efficacious for young myopic patients."

Cho and associates,[168] in the Longitudinal Orthokeratology Research in Children (LORIC) study, compared the axial length of the eye measured with A-scan ultrasound in subjects between the ages of 7 and 12 with myopia between 0.25 D and 4.50 D, with less than 2.00 D of astigmatism. The children were fit with either corneal reshaping contact lenses (N=35) or prescribed single vision spectacles. The single vision spectacle control group was selected from another study. Eighty one percent of the children completed the study. There was a significant slowing of eye growth in the ortho-k group, reflected in less of an increase in axial length (AL) and vitreous chamber depth (VCD) measurements; i.e., AL increased in the ortho-k group by mean 0.29 ± 0.27 mm, and by 0.54 ± 0.27 mm in the spectacle group. Similar results were found for VCD; i.e., 0.23 ± 0.25 mm increase for the ortho-k and 0.48 ± 0.26 mm increase for the control groups. The average myopic reduction was 46%, however, there was substantial variability in the amount of eye elongation for any subject, suggesting that there is no way to predict the effect of orthokeratology on myopia progression for any individual.

Walline and associates[169] performed a study to determine whether corneal reshaping contact lenses slow eye growth in the Corneal Reshaping and Yearly Observation of Nearsightedness (CRAYON) Study. Forty children, 8 to 11 years of age, who had between 0.75 D and 4.00 D of myopia with less than 1.00 D astigmatism, were fit with Corneal Refractive Therapy (Paragon Vision Sciences) contact lenses which they wore for 2 years. Seventy percent of the children completed the study; none of the dropouts were due to complications as most were due to lack of interest in wearing contact lenses. The control group subjects were selected from the Contact Lens and Myopia Progression (CLAMP) Study.[170] Axial length was measured using A-scan ultrasound for both children fit in corneal reshaping contact lenses and a matching control group of children wearing soft contact lenses. In children wearing corneal reshaping contact lenses, as compared to soft contact lens wearers, the rate of change in axial length was on average 0.16 mm per year less and vitreous chamber

depth was 0.10 mm per year less. This represents a 38% reduction in myopic progression.

Kakita et al.[171] recently conducted a study to assess the influence of overnight orthokeratology on axial elongation in children using spectacle lens wearers as a control group. Axial length was measured at the baseline exam, and repeated after 2 years using the IOL Master. After 2 years the axial length increased 0.39 ± 0.27 mm for the orthokeratology group and 0.61 ± 0.24 mm for the spectacle group; the difference was statistically significant. These findings demonstrated that orthokeratology slows axial elongation in myopic children by approximately 36%, and thereby slows the progression of myopia as compared to spectacle lens correction. In a similar study, Santodomingo-Rubido et al.[172] compared axial length growth in white children myopia wearing OK lenses and distance single vision spectacles (SV) for a 2-year period. They reported that the axial length increased significantly over time for both the OK group (0.47mm) and SV group (0.69mm). The difference represented a reduction of myopia.

Swarbrick et al.[173] compared changes in axial length and refractive error during overnight orthokeratology with daily wear rigid gas-permeable contact lens wear in myopic children. Twenty-six myopic children wore an overnight orthokeratology lens in one eye and a gas permeable lens for daily wear in the other eye for 6 months. After 6 months the lenses were reversed. Axial length was measured using the IOL Master and refraction was measured with an auto-refractor. Swarbrick et al.[173] found that overnight orthokeratology lens wear inhibited axial length increase and myopia progression over a 12-month period. After 12 months, the orthokertology eyes showed no change in axial length and a slight decrease in myopia, whereas the gas permeable eye showed increased axial length and myopic progression. Crossover of the orthokeratology lens with the gas permeable contact lens produced similar results and conclusions.

Kwok-Hei Mok and Sin-Ting Chung[174] measured refractive error and central corneal curvature for 34 children wearing Ortho-K lenses and for 36 children who wore spectacles 6 years or a longer. All the Ortho-K patients had a washout period that was determined to occur when the keratometry findings at the end of the study matched the findings prior to beginning the study. Myopic progression was calculated as a change of myopia from the baseline to the final visit. Average myopic progression of the overnight Ortho-K contact lens was 0.37 ± 0.49 D (0.05 D/year) while average myopic progression of the single-vision spectacle group was 2.06 ± 0.81 D (0.29 D/year) after 7 years. Lastly, there was no incidence of microbial keratitis in their patients. It is of interest to note the reduced rate of progression of both the Ortho-K group and the spectacle group, as compared to other studies. There were no A scans nor cycloplegic refractions. However, this preliminary study does provide good pilot data demonstrating the long-term effect of Ortho-K.

Recently Hiraoka et al. published a 5 year, long term study to compare axial length changes in myopic children receiving either overnight orthokeratology (OK) or spectacles as controls. There were 59 subjects who had axial length measured with an IOL Master. The increase in axial length during the 5-year study period was 0.99 mm ± 0.47 for the OK group and 1.41 ± 0.68mm for the control groups,. The difference was statistically significant for the first 3 years, but not for the fourth and fifth year. These findings are similar to the COMET bifocal study in which the treatment effect seems to diminish after 3 years. Thus, one needs to be careful to generalize short-term data to long-term conclusions. Like other OK studies the effectivity was approximately 30%.

It has been suggested that the peripheral retina plays a role in emmetropization, specifically that hyperopic peripheral defocus may stimulate axial myopia.[102,109,176] In animal studies, peripheral form deprivation produces axial myopia. In both humans and animals, myopic eyes are relatively hyperopic in the periphery since the radius of the peripheral retina is shorter than that of the central retina. When traditional glasses or contact lenses correct the error at the posterior pole, relative peripheral retinal hyperopic defocus is created which has been implicated as a signal for local axial elongation. Orthokeratology flattens the central cornea, which results in a steepening of the mid-peripheral cornea.[177] This mid-peripheral corneal steepening creates less peripheral defocus than single plane correction, which is the suggested mechanism for the effect on the progression of myopia. In support of this theory, Kang and Swarbrick,[178] noted in a recent study that myopic children have relative peripheral hyperopia as compared to their central refraction. After 3 months of wearing orthokeratology lenses in one eye, hyperopic shifts in refraction were measured between 30 degrees in the temporal visual field and 20 degrees in the nasal visual field. Peripheral refraction was similar to center at all positions in the temporal visual field while remaining significantly myopic at all locations in the nasal visual field. On the other hand, there was no change in either central or peripheral refraction in the control eye, which wore a traditional gas perm contact lens. Kang and Swarbrick[178] concluded that orthokeratology changes the relative peripheral hyperopia found at baseline to relative peripheral myopia after orthokeratology. They suggested that the induced myopic defocus in the periphery is thought to provide a mechanism for myopia control.

In summary, Ortho-K results in an approximately 40% reduction in the progression of myopia. Its advantages are that it both eliminates the need for daytime contact lens wear and reduces the progression of myopia. Its disadvantages include cost, risk of infection, discomfort, problems with insertion and removal, and reduced visual acuity as compared to glasses or daily wear contact lenses. In addition, it is difficult to determine which subjects will demonstrate slowing of their myopia and by how much. Lastly, there are no good controlled long-term studies demonstrating that the reduction continues after year one.

Multifocal Soft Contact Lenses

There have been two types of multifocal contact lens treatment strategies. The first involves the use of multifocal contact lenses, which are similar to progressive lenses to slow the progression of myopia. The second, more novel use, is that of multifocal lenses that are designed to eliminate the peripheral hyperopia induced with spherically correcting contact lenses.[179,180,181]

The success of orthokeratology has led both researchers and the major soft contact lens companies to design soft contact

lenses that might slow the advancement of myopia. Woods et al.[182] performed an experiment to determine whether lens induced myopia in chickens can be inhibited when the central minus power is combined with a hyperopic peripheral lens design. Chicks were fit unilaterally with peripheral correcting lenses, with the central power being a -10.00 D, or a conventional -10.00 D control lens of the same physical parameters as the test lens. Refractive error was measured by retinoscopy. This study showed that lens-induced myopia in chicks wearing conventional lenses can be reduced by using multifocal, peripherally correcting lenses. The difference in the induced myopia provides further evidence of the influence of peripheral retinal hyperopic defocus on eye growth.

Antstice and Phillips[179] tested the ability of an experimental Dual-Focus (DF) soft contact lens to reduce myopic progression. The experimental group wore a Dual-Focus lens that had a central zone that corrected refractive error and concentric treatment zones that created 2.00 D of simultaneous peripheral myopic retinal defocus during distance and near viewing. The control group wore single vision distance lenses with the same parameters but without treatment zones. Children wore the Dual-Focus lens in a randomly assigned eye (period 1) and the control lens in the other eye for 10 months. The lenses were then switched between eyes, and worn for another 10 months (period 2). Cycloplegic auto-refraction, axial length measured by partial coherence interferometry, and accommodation using an open-field auto-refractor, were measured at the end of each 10 month period. The mean change in spherical equivalent refraction with dual-focus lenses (-0.44 ± 0.33 D) was less than with the control lenses (-0.69 ± 0.38 D); mean increase in axial length was also less with Dual-Focus lenses (0.11 ± 0.09 mm) than with the control lenses (0.22 ± 0.10 mm). In 70% of the children, myopia progression was reduced by 30% or more in the eye wearing the Dual-Focus lens compared to that wearing the control lens. Visual acuity and contrast sensitivity with Dual-Focus lenses were similar to the control lenses. Dual-Focus lenses provided normal visual acuity and contrast sensitivity and allowed for normal accommodative responses to near targets.

Holden and The Vision CRC Myopia Control Study Group evaluated a soft contact lens designed to correct central vision but reduce relative peripheral hyperopia, which would slow the rate of myopia progression.[181] Cycloplegic auto-refraction and axial length were measured after 6 months of wear of the experimental lens group and spherical lens control group. Progression of myopia with the experimental lens was significantly less than with the control, -0.26 ± 0.25 D versus 0.60 ± 0.29 D. Similarly, axial length increase was less with the experimental lens as compared to the control lens, 0.08 ± 0.11 mm versus 0.25 ± 0.12 mm. Holden et al. concluded that after 6 months of wear, progression of myopia with the experimental contact lens designed to maintain clear central vision but reduce relative peripheral hyperopia, was 56% less than that with standard sphero-cylindrical spectacles. They also concluded that "longer experience with wear of such contact lenses is needed, however the data are promising with regard to a new generation of contact lenses aimed at myopia control."

In a subsequent study, Holden et al.[180] measured central high and low contrast visual acuity with a log MAR chart (VA) and contrast sensitivity (CS) in subjects wearing peripherally correcting lenses and conventional lenses. Peripheral VA & CS were measured at 30° nasal and temporal eccentricity. There were no differences for high and low contrast VA and central CS between groups. However, there was a significant improvement in measurements of peripheral VA at both 30° nasal and temporal eccentricity equivalent to a 3 line improvement in the experimental lens design group. Also, CS improved at 30° temporal eccentricity.

Holden et al.[169] reported that peripheral visual acuity was better with these lenses and that the improvement in peripheral vision was most likely due to a reduction in peripheral defocus. The authors concluded that these experimental lenses, designed to maintain clear central vision but reduce relative peripheral hyperopia, "have the capability of correcting central vision without blur, slowing the progression, and enhancing peripheral vision - a relatively unique and beneficial combination of effects."

More recently, Chinese children, aged 7 to 14 years, with baseline myopia between sphere -0.75 to -3.50 D, were fitted with the novel contact lens designed to reduce relative peripheral hyperopia (n=45) and were followed for 12 months.[183] Their findings were compared to a matched control group (n=40). The estimated progression at 12 months was 34% less, at -0.57 D, with the novel contact lenses as compared with -0.86 D for spectacle lenses. The baseline axial length was 24.6mm and after a year, the estimated increase in axial length (AL) was 33% less at 0.27 mm versus 0.40 mm for the contact lens and spectacle lens groups, respectively. The effectiveness was less in the second 6 months than the first six months. Most surprising was that almost 30% of the children dropped out of the study, due to discomfort of the lens. The 12 month data support the hypothesis that reducing peripheral hyperopia can alter central refractive development and reduce the rate of progression of myopia.

Yet, one needs to be careful in evaluating these results. In previous PAL studies, efficacy in the first year was 28%; however it decreased significantly in the second year to 17%.[155] By the end of the study there was only a small difference between the PAL lenses and the single vision lenses over the longer duration of the study.[156] The PAL study points to the importance of long term data before drawing broad general conclusions about a particular method of intervention. Lastly, none of these novel multi-focal contact lenses have been approved for wear. Currently approved contact lenses, that might conceptually correct both central myopia and relative peripheral hyperopia, include lenses designed to correct the distance centrally with a peripheral near add. The Biofinity multifocal D lens has a central optic zone that is fully corrected for distance. Beyond this central zone is an aspheric periphery that decreases myopic correction or increases hyperopic correction from the center moving outward in any direction. This design results in a clearer image focusing on the peripheral retina thus decreasing the amount of peripheral retinal blur. Although this specific lens has not been evaluated for its effect on slowing myopic progression, the hypothesis still applies. These lenses may ultimately be combined with atropine to compound their effect on myopia.

ATROPINE

Atropine is an alkaloid extracted from a variety of plants (Atropa belladonna, Datura stramonium, and Mandragora

Author	# of children completed study	Treatment	Length of study	Control Group (mean progression)	Atropine Group (mean progression)
Gimbel[106] 1973	594	1gtt 1% atropine OU	3 years	-1.22D (over 3 years)	-0.41D (over 3 years)
Kelly et al[175] 1975	282	1 gtt 1% atropine OU q.d. or b.i.d.	1 year	-0.52D (over 6 months)	+0.58D decrease in myopia (over 1 year)
Dyer[110] 1979	168	1 gtt 1% atropine OU qhs	2-8 years (avg. 4.2 years)	Change in myopia: No change or improved: 2% -0.75D: 14% 1.00-1.75D: 35% 2.00-2.75D: 22% 3.00D: 27%	Change in myopia: No change or improved: 47% -0.75D: 34% 1.00-1.75D: 8% 2.00-2.75D:7% 3.00D:1%
Sampson[107] 1979	100	1gtt 1% atropine OU qhs +2.25D bifocal	1 year	NO CONTROL	Change in myopia: -0.25 to +0.50D: 79% +0.75D to +1.00D: 15% >+1.00D: 6%
Bedrossian[108] 1979	90 children on atropine (62 followed for 2 yrs, 28 followed for 4)	1% atropine in 1 eye qhs x 1 year, next year atropine qhs in other eye	4 years	-0.82 D/Y (over first year, similar results during 4 years)	+0.21 D decrease in myopia (over first year, similar results during 4 years)
Gruber[111] 1985	200	1gtt 1% atropine OU qhs	1-7.5 years (mean treatment 1-2 years)	-0.28D/Y	-0.11D/Y
Brodstein[109] 1984	399	1 gtt 1% atropine OU qhs +2.25D bifocal	1-9 years (median treatment 3 years)	-0.34D/Y	-0.12D/Y
Brenner[113] 1985	79	1 gtt 1% atropine OU qhs	1-9 years (mean treatment 2.9 years)	NO CONTROL	Average refractive error at initial exam was -0.87D and increased over the nine years of maximum follow-up to an avg of -2.73D
Yen et al[115] 1985	96	1 gtt1% atropine OU qhs bifocals	1 year	-0.91D/Y Change in myopia: No change: 6.25% < or = -0.50D: 31.25% -0.51 to -1.0D: 31.25% >-1.0D: 31.25%	-0.22D/Y Change in myopia: No change: 56% < or = -0.50D: 22% -0.51 to -1.0D: 19% >-1.0D: 3%

TABLE 1 *Historical atropine studies are presented. It is apparent that in all of these studies, atropine is effective in slowing the progression of myopia. Though nearly all of these studies are retrospective, most do have some form of control. In these studies the researchers were not blind, and they were performed before sophisticated A-scan measurements. In spite of their limitations, the number of positive studies with minimal side effects is impressive. Also, there is some strong long-term data.*

officinarum). The name comes from the original use of dilating a woman's pupils during the 16th century to make them appear more attractive. Atropine is a non-selective muscarinic antagonist which causes maximum mydriasis within 40 minutes of the initial drop and cycloplegia within 5-48 hours after the first drop. The residual effects on accommodation last 10-14 days.[184]

The first report describing the use of atropine to slow myopia progression was by Wells in the 19th century, [185] during which time atropine was used extensively to slow myopia progression.

[22] The use of atropine declined after the turn of the 20th century due to paralysis of accommodation and photophobia.[129]

During the First International Myopia Conference in 1964, Bedrossian and Gostin reported on the beneficial effect of atropine on slowing myopia progression. This report provided a renewed interest in the treatment of myopia progression with atropine.,[33] Seventy-five patients in an A-B cross over design between the ages of 7 and 13 were prescribed one drop of 1% atropine in one eye for the first year and then the other eye for following year. After 1 year of treatment, the eyes treated with atropine had an average decrease of 0.21 D of myopia, as compared to the control eyes that had an average increase of 0.82 D of myopia. After the second year, the eye that received atropine had an average decrease of 0.17 D of myopia. The control eyes (which one year before were treated with atropine) had an increase in myopia on average of 1.05 D. Of the 150 treated eyes, 112 showed either a decrease in myopia or no change, whereas only 4 eyes that were used as the control had a decrease or no change in myopia.[114,117]

Recent studies using topical atropine have demonstrated both statistically and clinically significant reductions in myopia progression (See table 2). Chiang et al.[187] performed a retrospective, non-comparative case series to evaluate the treatment of childhood myopia with the use of atropine and bifocal spectacle correction. Seven hundred and six Caucasian children from 6 to 16 years of age were treated with one drop of 1% atropine once weekly in both eyes for 1 month to 10 years (median 3.62 years). Seventy percent of the children were completely compliant with the regimen and 30% were only partially compliant. The most common reasons stated for the partial compliance were photophobia, inconvenience, or headache. The mean rate of myopia progression in the completely compliant group was -0.08 D/year, as compared to -0.23 D/year in the partially compliant group.

Kennedy et al.[129] reported on 214 children aged 6 to 15 years old who were treated with one drop of 1% atropine once daily in both eyes for 18 weeks to 11.5 years (median 3.35 years). The mean myopia progression during atropine treatment was

Treatment method	Percentage Reduction	Projected increase in myopia after 1 year	Projected increase in myopia after 8 years	Pros	Cons
Undercorrection	-8%	0.65	5.18		1
Spectacle control	0%	0.60	4.80		1
Peripherally correcting glasses	1%	0.59	4.75		1, 10
Progressive glasses	4%	0.58	4.61	26	1 2
Bifocals	16%	0.50	4.03		1
Esophoria + bifocals	20%	0.48	3.84	22	8
Pirenzapine QD	34%	0.40	3.17	22	4 5 8
Peripherally correcting CLs	40%	0.36	2.88	22	8 9 10
Pirenzapine BID	44%	0.34	2.69	22	3 4 5 10
Orthokeratology	45%	0.33	2.64	22	3 9
Atropine 0.25%	58%	0.25	2.02	22	9 10
Atropine 0.01%	60%	0.24	1.92	22	9 10
Atropine0.1%	62%	0.23	1.82	22	7 8 9 10
Atropine0.05%	65%	0.21	1.68	22	7 8 9 10
Seasonal atropine	67%	0.20	1.58	22	7 8 9 10
Atropine 0.025%	76%	0.14	1.15	22	7 8 9 10
Atropine 0.5%	80%	0.12	0.96	23	3 7 8 9 10
Atropine 1%	90%	0.06	0.48	23	5 7 8

Table 2 *presents the best estimate of the effectively in reducing the progression of myopia for each treatment. First, we determined the mean myopic progression rate per year for spectacle lenses from each study, then, we determined the mean myopic progression for all the other treatment modalities (D/year). We then corrected each treatment, i.e., if the mean rate of progression of the control was different than our calculated. Column 3 depicts the findings after 1 year. We then assumed a linear progression and calculated the amount of increased myopia after 8 years (column 4). Columns 5 and 6 present pros and cons of each treatment. 1= Not effective, 2=Expensive, 3=Blur, 4=Redness, 5=Allergy, 6=Infection, 8=Mydriasis, 9=Minimal scientific data, 10=Not available, 21=Inexpensive, 22= Moderately effective, 23=Very effective, 24=Strong scientific data, 25= Long term studies, 26= Minimal side effects*

Subsequently, Gimbel,[115] Kelly et al.,[186] Dyer,[119] Sampson,[116] Bedrossian,[114,117,121] Gruber,[111] Brodstein,[118] Brennar,[122] and Yen,[124] from 1973 to 1989, reported in a number of studies that children using atropine had a reduction in the rate of myopia progression. These children demonstrated a range of progression, which varied from an increase of 0.22 D/year to a decrease of 0.58 D/year as compared to the control groups, which demonstrated an increase from 0.28 D/year to 0.91 D/year. Table 1 summarizes these studies. Most of the patients in these studies were between 6 and 13 years old, which is when the greatest progression of myopia occurs.

0.05 D/year, which was significantly less than the control subjects (0.36 D/year). Myopia progression after atropine was discontinued was calculated for 158 patients. Upon discontinuing atropine, children progressed 0.22 D/year, as compared to 0.13 D/year in the control group. However, this increase in myopia progression was not enough to offset the decrease in myopia progression during atropine treatment. The final refraction was still much lower in the atropine treated group.

Chua et al.[133] performed a prospective, randomized, double-masked, placebo-controlled study on 400 children, ages 6 to 13 years, evaluating the use of atropine as a method for myopia control. This study, known as the Atropine for the Treatment of Childhood Myopia study (ATOM), evaluated the efficacy and safety of topical atropine in slowing both the progression of myopia and axial elongation in Asian children. One eye of each subject was randomly chosen for treatment(one drop of 1% atropine), while the other eye received an eye drop placebo once nightly for 2 years. All children were prescribed progressive, photochromic lenses. Three hundred forty-six children completed the study. After 2 years, the mean progression of myopia in the placebo-treated eyes was 1.20 ± 0.69 D and only 0.28 ± 0.92 D in the atropine-treated eyes. Over a 2 year period, there was a 77% reduction in the amount of myopia progression for children using atropine as compared to the control. The mean change in axial elongation in the placebo treated eyes was 0.38 ± 0.38 mm, whereas in the atropine-treated eyes the axial length was essentially unchanged (decreased by 0.02 ± 0.35 mm). After 2 years, 65.7% of the atropine treated eyes progressed less than -0.50D, whereas only 16.1% of the placebo treated eyes progressed less than -0.50D. Only 13.9% of atropine treated eyes progressed more than -1.00D whereas 63.9% of placebo treated eyes progressed more than -1.00D.

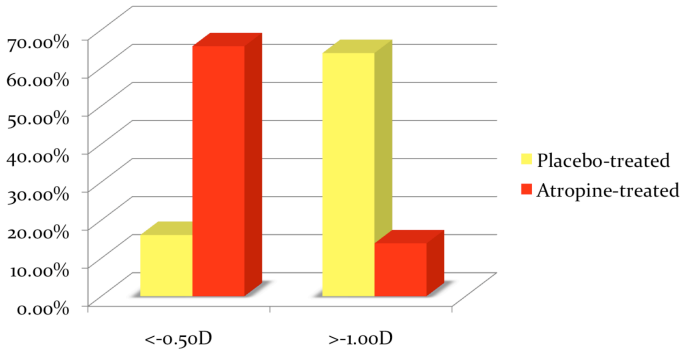

Figure 4 –Progression of Myopia in Eyes Treated or Not Treated with Atropine
This bar graph depicts the difference in percentage of children progressing less than -0.25 D in a year with either atropine 1% or a control, and those progressing more than -a diopter with atropine or a control. It is readily apparent that atropine is effective at slowing the progression of myopia over a 2 year period of time.[133]

Figure 4 compares the percentage of children who progressed less than -0.50 D and more than -2.00 D over the 2 years. The authors concluded topical 1% atropine was effective in slowing myopia progression.

Shih et al.[188] evaluated the effectiveness of 0.5% atropine to slow the progression of myopia. The randomized clinical trial included 227 children, 6 to 13 years of age, placed into one of three groups: group one received 0.5% atropine daily with multifocal glasses, group two received a placebo drop daily with multifocal glasses, and group three received a placebo drop daily while wearing single vision glasses. One hundred and eighty eight children completed the study. At the end of 18 months, the mean myopic progression was 0.42 ± 0.07 D in children using 0.5% atropine with multi-focal glasses, which was significantly less than the 1.19 ± 0.07 D and 1.40 ± 0.09 D for children using placebo drops with multifocal glasses and single vision glasses, respectively. There was no significant difference between the last two groups, thus the authors concluded that the reduction of myopia progression was due solely to the use of atropine and not the multifocal spectacle correction. Approximately 50% of the children using atropine with multi-focal glasses progressed less than 0.25 D/year and only 10% progressed greater than 0.75 D/year. Ten percent of the children using placebo drops with multi-focal glasses progressed less than 0.25 D/year, while approximately 60% progressed greater than 0.75 D/year. Approximately 5% of children using placebo drops with single-vision lenses progressed less than 0.25 D/year and 70% progressed greater than -0.75 D/year. The progression of myopia in all the groups was highly correlated with an increase in axial length.

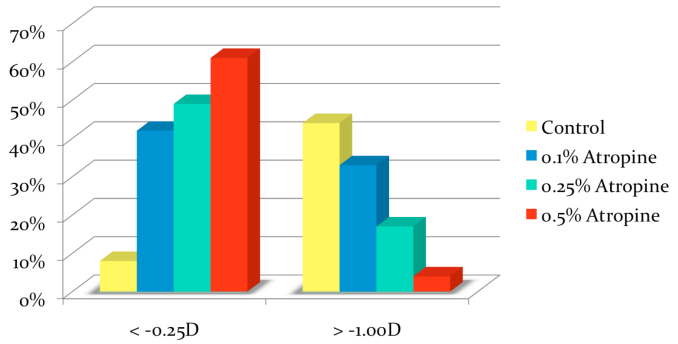

Figure 5 –Effect of Various Concentrations of Atropine in Slowing Myopia
This bar graph depicts the difference in percentage of children progressing less than -0.25 D in a year with various concentration atropine (0.1%, 0.25%, 0.5%) or the control, and those progressing more than -a diopter with atropine (0.1%, 0.25%, 0.5%) or the control. It is readily apparent that atropine is effective at slowing the progression of myopia over a 2 year period of time in Shih's study, and the effect on progression varies with the concentration, though the results may have been affected by the different lenses worn by each group.[128] A recent study suggests that the effectivity is not significantly dependent on the concentration.[190]

Shih et al.[128] evaluated the efficacy of various concentrations of atropine in slowing myopia progression. Two hundred children, 6 to 13 years of age, were randomly prescribed one drop of 0.5%, 0.25%, or 0.1% atropine, or 0.5% tropicamide (control treatment) in both eyes nightly. Children prescribed 0.5% atropine were given a bifocal (+2.00 add), children prescribed 0.25% atropine were under corrected by 0.75 D, and children using 0.1% atropine were given their full distance prescription. Ninety three percent of children completed the study. 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. The authors defined myopic progression to be greater than -0.25 D/year. At the end of the 2-year treatment, 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, whereas only 8% in

the control group had no myopic progression. The authors defined fast myopic progression to be greater than 1.00 D/year. Four percent of children in the 0.5% atropine group, 17% in the 0.25% atropine group, and 33% in the 0.1% atropine group demonstrated fast myopic progression, whereas 44% in the control group showed fast myopic progression. The authors concluded that all three concentrations of atropine were effective in slowing myopia progression, with 0.5% being the most effective, although their results may have been confounded by the differences in lenses that each group used. (See Figure 5.)

Lu et al.[189] investigated the effect of seasonal modifications in the concentration of atropine used on slowing the progression of myopia (n=120). The concentration was modified based upon season, sunlight intensity, and severity of myopia: 0.1% for summer, 0.25% for spring and fall, and 0.5% for winter for 63 children, while 57 children received no drops (control). For children less than 7 years of age with less than 0.50 D of myopia, 0.5% atropine was not used. The use of atropine was reduced to twice weekly for very low myopes (less than 0.75 D). Sunglasses with ultra-violet (UV) protection were prescribed for children to be used when outdoors, and progressive lenses were given for children who reported difficulty in the classroom. After one year, mean myopia progression was 0.28 ± 0.75 D for children using atropine and 1.23 ± 0.44 D for children in the control group. There was a 77% reduction in myopia progression for children using atropine as compared to the control group.

Lee et al.[134] conducted a retrospective chart review of 57 Taiwanese children 6 to 12 years of age to evaluate the efficacy of 0.05% atropine in slowing myopia progression. Twenty-one children received one drop of 0.05% atropine in both eyes every night while 36 children were not treated (control). Mean progression of myopia was 0.28 ± 0.26 D/year in the 0.05% atropine group, as compared to 0.75 ± 0.35 D/year in the control group. The authors considered myopia progression less than -0.50 D/year to be relatively stationary, whereas greater than 0.50 D of myopia progression/year to be poorly controlled. Eighty three percent of children in the treatment group had relatively stationary myopia progression, as compared to only 22.2% in the control group. In the 0.05% atropine group, 16.7% of children progressed greater than 0.50 D/year, whereas 77.8% of the control group progressed greater than -0.50 D/year. The authors concluded, "0.05% atropine regimen is a good starting point as medical treatment for the control of myopia progression."

Fang et al.[137] conducted a retrospective chart review of 50 Taiwanese children aged 6 to 12 years to evaluate the efficacy of 0.025% atropine for prevention of myopia onset in pre-myopic children (spherical equivalent refraction of less than +1.00 D, with cylindrical refraction of less than -1.00 D). Twenty four children received one drop of 0.025% atropine in both eyes every night and 26 children were untreated (control). Mean myopic shift was -0.14 ± 0.24 D/year in the 0.025% group, as compared to -0.58 ± 0.34 D/year in the control group. The authors considered a myopic shift greater than -0.50 D/year to be a fast myopic shift. Eight percent of children using atropine had a fast myopic shift, compared to 58% of the control group. The authors defined the onset of myopia as a change equal to or greater than 1.00 D in the myopic direction. Twenty one percent of children using atropine became myopic, as compared to 54% of children in the control group. The authors concluded, "topical administration of 0.025% atropine can prevent myopia onset and myopic shift in pre-myopic schoolchildren for a 1-year period."

Recently the ATOM2 studies were performed to evaluate lower concentrations of atropine. The mean myopia progression at 2 years was 0.15 D/year for atropine 0.5%; 0.19 D/year for atropine 0.1%; and 0.24 D/year for atropine 0.01% groups.[179] In comparison, myopia progression in ATOM1 at 2 years was -0.60 D/year in the placebo group and -0.14 D/year in the atropine 1% group. The authors found that differences in myopia progression (0.19 D) and axial length change (0.14 mm) between groups were small and clinically insignificant. Atropine 0.01% had a negligible effect on accommodation and pupil size, and no effect on near visual acuity. They concluded that atropine 0.01% had minimal side effects when compared with atropine at 0.1% and 0.5%, and retained comparable efficacy in controlling myopia progression. (See Table 2 for a comparison of each method of treatment over time.)

Prior to this paper, there had been two other reviews of various treatments for myopia. In each review the authors acknowledged the efficacy of atropine in slowing myopia progression. However, each author independently, without any supporting data from trial subjects, concluded that the benefit of atropine use for myopia control is outweighed by the possible systemic and ocular side effects.[191,192]

These conclusions warrant a review of the side effects associated with atropine. Systemic side effects associated with topical atropine use can be divided into three types: fatal, serious, and mild. There have been 8 deaths associated with atropine, and only one since 1950.[1184,193,194] All the deaths, except one, were in children 3 years of age or younger suffering from congenital health conditions and who were ill at the time of presentation. The one child without congenital defects received a fatal dose of 18.1 mg of atropine within a 24-hour period.[184,193] Thus, there have been no fatal occurrences in children over 3 years of age with appropriate atropine dosing.

Pupillary dilation and cycloplegia from atropine result in glare, photophobia, and near vision blur which are the most commonly reported side effects to atropine. These symptoms can be minimized with the use of photochromic progressive lenses, or the use of atropine in concentrations less than .025%. Serious systemic and central nervous system side effects occur at 20 times the minimum dose and include the following: hot and dry skin, facial flushing, dryness of the nose, loss of taste, constipation, difficulty swallowing, difficulty sleeping, drowsiness, excitement, changes in heartbeat, hallucinations, fever, headache, dizziness, nervousness, nausea, vomiting, and allergic reactions (rash, hives, itching, difficult breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue). Decreased salivation and drying of the mouth are usually the first signs of toxicity.[193] The side effects of atropine are serious, but are fortunately short-lived, and have never been fatal, in healthy children over 2 years of age.[193]

During the 2 year ATOM study[133] that included 400 children, no serious adverse events were reported. Reasons for withdrawal were: allergic or hypersensitivity reactions or discomfort (4.5%), glare (1.5%), blurred near vision (1%), logistical difficulties (3.5%) and others (0.5%). There was no decrease in best-corrected visual acuity. Glare and photophobia were minimized with the use of photochromic lenses.

Shih et al.[128] reported the incidence of adverse effects due to the use of topical atropine in their study of 200 children (186 children completed the study). Seventy eight percent of the children using 0.5% atropine had no complaints of light sensitivity after 3 months. Fifteen percent of the children who used 0.5% atropine dropped out of the study: two children complained of severe light sensitivity, two children were fearful of long-term side effects, one child had recurrent allergic blepharitis, and four children were unable to consistently put drops in every night. Children who used 0.25% or 0.1% atropine reported no systemic or ocular complications. One hundred percent of the children who used 0.1% atropine, and 93% of children who used 0.25% atropine, did not complain of photophobia or blurred near vision after 4 weeks of using atropine.

In Kennedy's study,[129] of the 214 patients who were using 1% atropine, 40% reported photophobia, 10.7% reported blurred vision, 3.7% reported ocular discomfort, 3.7% reported ocular allergic reaction, 2.3% reported headaches, 2.3% reported bad taste in their mouth, 1.9% reported dry mouth, 1.4% reported dry eyes, 0.5% reported psychological problems, and 0.5% reported dizziness. Though the percentage of patients with side effects appears high, they did not result in a significant dropout rate. (The high percentage of photophobia reported by Kennedy was prior to today's fast acting improved photochromic lenses which have eliminated most of the subjective complaints of photophobia.[133])

In a study of 21 children who used atropine 0.05%, seven complained of photophobia in the morning, but only one had photophobia that continued into the afternoon, and only two children reported blurred near vision.[134] No child reported irritation or an allergic reaction. In another study using 0.025% atropine,[137] only four children in the treatment group and two children in the control group reported photophobia (24 and 26 children completed the study, respectively). None of the children reported blurred near vision nor had any systemic side effects.

In the Amblyopia Treatment Studies (ATS),[195-197] 1% atropine was dosed unilaterally in a group of subjects being treated for amblyopia. In ATS1,[195] which included 204 patients less than 7 years of age, at least one ocular side effect was reported for 26% of children, most commonly light sensitivity (18%), lid or conjunctival irritation (4%), and eye pain or headache (2%). Two patients reported facial flushing, one of who remained on atropine with no further problems and one was switched to homatropine. Atropine was not discontinued due to its side effects in any other patients. No other systemic side effects of atropine were reported. In ATS3,[196] among 201 patients aged 7 to 13 years old, atropine was generally well tolerated. Four percent of patients discontinued treatment due to symptoms related to cycloplegia. Ocular side effects noted in ATS4,[197] (most commonly light sensitivity), were reported by 13 (16%) of the children receiving daily atropine and 25 (29%) of the children receiving weekend atropine. However, these symptoms did not result in a change in compliance with the treatment regimen.

The ATOM study[133] found that the paralysis of accommodation and the associated near vision blur secondary to atropine treatment was temporary and was reversible upon cessation of treatment. Six months after cessation of atropine, the measured amplitude of accommodation was larger than the pre-treatment level. In addition, at 6 months after terminating atropine, there was no significant difference in near visual acuity in the atropine-treated eyes as compared to placebo-treated eyes.[133]

In summary, atropine has been used in both myopia control and amblyopia treatment studies with a minimal number of local side effects and no serious side effects. In none of the studies were the local side effects serious enough to cause a large number of patients to discontinue atropine treatment. (Anecdotally, the first author of this paper has used atropine for the last ten years on over 100 patients without any incident of a serious side effect, and notes that most children surprisingly tolerate atropine with minimal complaints.)

There is always concern of long-term effects when using any medication. Luu et al.[198] assessed retinal function in children on atropine treatment, by performing multifocal electro-retinograms (mfERGs) on 48 children who received 1% atropine eye drops once daily for 2 years and 57 children who received placebo eye drops. Recordings were performed during the second and third month after the cessation of treatment. Both the response amplitude and implicit time of N1 and P1 and k21 were measured. The difference between the N1 and P1 amplitudes and implicit times between atropine-treated and placebo-treated eyes were not statistically significant. There was also no significant difference between k21 amplitude and implicit time between atropine-treated and placebo-treated eyes. The authors of this study concluded that since retinal function was not significantly affected soon after stopping atropine (when the concentration of atropine in the retina would be highest), that it is highly unlikely that there would be retinal impairment years later when the concentration of atropine would be less.

To assess whether the slower rate of myopia progression and axial length elongation would be maintained after stopping atropine, or if there would be a rebound effect that would eliminate the initial treatment effect, the patients from the ATOM study were evaluated up to 1 year after stopping treatment.[136] Only a small number of children dropped out after the two years of treatment, i.e., 3% of the placebo group and 5% of the atropine group. After atropine was discontinued for 2 years, the mean myopic progression in the atropine-treated group was 1.14 ± 0.80 D over 1 year, whereas the progression in placebo-treated eyes was 0.38 ± 0.39 D. In the first half of the third year, the mean rate of myopia progression in the atropine-treated eyes was 1.51 ± 1.40 D/year, as compared to 0.40 ± 0.65 D/year in the placebo-treated eyes. Over the second half of the third year, the mean rate of myopia progression in the atropine-treated eyes was -0.76 ± 0.70 D/year, as compared to -0.38 ± 0.58 D/year in the placebo-treated eyes. For the atropine treated eyes, the rate of myopia progression was significantly less in the second half of the third year as compared to the preceding 6 months. Over the entire 3 year period, the eyes treated with atropine still showed much less myopia than the placebo-treated eyes. Although the effect of atropine on the final refractive status was reduced after cessation of atropine for 1 year, the change in axial length of the atropine-treated eyes was significantly smaller than of the placebo-treated eyes, and did not change as much as the refractive error. Over the 3 years, the increase in axial length of the atropine-treated eyes was 0.29 ± 0.37 mm, as compared to 0.52 ± 0.45 mm in the placebo-treated eyes. The authors suggested that most of the increase in refractive status was not

due to a rebound effect but due to the more powerful cycloplegic effect obtained with atropine 1% as compared to cyclogel 1% which was used for measurements after termination of atropine.

In conclusion, since discontinuation of atropine had a small regression in refractive error but no effect on axial length, most of the change appears to be due to the difference in cycloplegic refraction achieved with cyclogel as compared to atropine. Atropine causes a greater cycloplegic effect than Cyclogel 1%, thus, the initial baseline for refractive error demonstrates more myopia with Cyclogel 1% than the amount measured immediately after beginning treatment with atropine 1%. This results in a greater perceived improvement of myopia control during the first year treatment and a falsely perceived rebound effect at the end of treatment. It is more important to note that axial length data did not change when atropine treatment was terminated. The study also showed that over the course of three years only 23% of atropine-treated eyes progressed more than 2.00 D as compared to 30% of placebo-treated eyes. Only 44% of atropine-treated eyes progressed more than 1.50 D as compared to 56% of placebo-treated eyes.

Atropine is a non-specific, muscarinic antagonist, which binds to muscarinic receptors on the ciliary muscle and thus blocks accommodation. Initially, atropine was suggested as a method for myopia control based on the thought that the act of accommodation influenced myopia progression; this presumed mechanism for control has since been disproven. McBrien et al. [125] were the first to demonstrate that atropine reduces experimental myopia and axial elongation via a non-accommodative mechanism. McBrien et al.[125] monocularly deprived (MD) chicks of pattern vision by placing a translucent occluder over the left eye, which has been found to cause an increase in axial elongation and myopia in human infants,[199] chicks,[125] tree shrews,[201] cats,[202] gray squirrels,[125] marmosets,[203] and monkeys.[204] Since the muscles of chicks contain only nicotinic receptors, atropine should not have had an effect on accommodation or pupil size. Chicks were treated with intra-vitreal injections of atropine or saline; after eight days of MD there was 20.9 D of experimentally induced myopia in saline-injected chicks, as opposed to only 2.8 D of myopia in atropine-injected chicks. This significant reduction in experimentally induced myopia in atropine-injected MD chicks was associated with a significant reduction in axial length elongation (0.21mm versus 1.04 mm). Corneal iontophoresis of 10% carbachol, which binds to nicotinic receptors, induced the same degree of accommodation in both atropine-injected and saline-injected eyes, demonstrating that accommodation was not affected by atropine. Thus, the authors concluded that, "chronic atropine administration prevents experimentally induced myopia in chick(s) via a non-accommodative mechanism."

Applying translucent lenses designed to deprive only part of the visual field in chicks results in local areas of axial elongation.[205] Atropine blocks the effects of local elongation. Since it is not possible to accommodate different amounts in the same eye, some other mechanism besides accommodation, must be responsible for localized elongation. Emmetropization can still occur even when the optic nerve is severed, disrupting the feedback mechanism necessary for accommodation,[83,81] which suggests that local retinal mechanisms may be sufficient for gross regulation of refractive error.[101] It has also been demonstrated that experimental myopia can be induced in a species that does not possess a functional accommodative system.[125] Lastly, experimental myopia can be produced in a species where the accommodative feed back loop has been blocked by bilateral destruction of the Edinger-Westphal nucleus.[83] Since accommodation does not play a major role in myopia development, the obvious question then is how does atropine prevent myopia progression? Muscarinic receptors located in the retinal pigment epithelium are believed to be involved in the development of refractive error.[206] However, the biochemical basis of how atropine inhibits axial elongation remains obscure, and there are doubts whether muscarinic receptors are involved at all. These findings have led to the search for other muscarinic drugs that do not affect accommodation or pupillary dilation.

Pirenzepine, an M1-selective muscarinic antagonist, has those attributes and has been used to retard the progression of myopia in animals without significantly affecting accommodation or pupillary size.[137] In experimental studies on humans, Bartlett et al.[134,207] demonstrated that pirenzepine caused minimal mydriasis or effect on accommodative amplitude. They concluded that the adverse events reported were mild or moderate (redness and irritation) in severity but resolved rapidly. Siatkowski et al.[146] evaluated the safety and efficacy of 2% pirenzepine ophthalmic gel in school-aged children with myopia. The children, aged 8 to 12 years, had spherical equivalents from -0.75 to -4.00 D, and astigmatism of 1.00 D or less. At 1 year, there was a mean increase in myopia of -0.26 D in the pirenzepine group versus -0.53 D in the placebo group. Eleven percent of the patients in the pirenzepine group discontinued participation in the study because of adverse effects while none of the placebo group did. Pirenzepine was effective (50%) and relatively safe in slowing the progression of myopia during a one-year treatment period. In the 2 year follow-up study, Siatkowski et al.[147] reported that the mean increase in myopia was -0.58 D in the pirenzepine group and -0.99 D in the placebo group. Only one more patient dropped out in the second year. They concluded that pirenzepine ophthalmic gel 2% was effective in slowing the progression of myopia over a 2 year period without significant side effects. It is of interest to note that axial length did not have a significant change in the treatment group. Pirenzepine unfortunately is not currently commercially available in the US.

Tan et al.[144] evaluated the safety and efficacy of pirenzepine 2% ophthalmic gel in slowing the progression of myopia in school-aged children using a parallel-group, placebo-controlled, randomized, double-masked study. Subjects received 2% gel twice daily (gel/gel), 2% gel once daily (placebo/gel), or placebo twice daily (placebo/placebo) for one year. At 12 months, there was a mean increase in myopia in the gel/gel group by -0.47 D, placebo/gel group by -0.70 D, and placebo/placebo group -0.84 D. Eleven percent of the pirenzepine group discontinued participation in the study due to adverse events. Tan et al. concluded that pirenzepine gel 2% twice daily resulted in approximately 45% efficacy in slowing the progression of myopia over a 1 year treatment period and was a relatively safe treatment.

DISCUSSION

The purpose of this literature review is to provide an updated review of the current research in regard to slowing myopia progression and to provide the reader with unbiased information to help make appropriate clinical decisions. Atropine used once a day in both eyes is clearly the most

successful treatment to slow the progression of childhood myopia. Cumulative data from a number of studies employing atropine 1% demonstrated up to a tenfold reduction in the rate of myopia progression as compared to untreated eyes, 0.05 D/year verses 0.50 D/year. Concentrations of less than 0.5% result in a decreased efficacy but still demonstrate a stronger effect on reducing myopia than other treatment regimens. Recent studies demonstrate that lower concentrations, i.e., .025% or .01% are more effective than Ortho-K or other soft lens designs.

The most common side effects of atropine include pupillary dilation, which leads to an increased sensitivity to light and UV radiation, and cycloplegia resulting in near vision blur. These problems have been minimized with the use of progressive lenses which incorporate photochromic properties, and UV filtration. The risk of other ocular and systemic side effects is minimal. In the studies included in this paper, more than 85% of children were able to tolerate the side effects, and continued with their assigned treatment protocol. The minimal local effects in most patients were not serious enough to cause discontinuation of atropine treatment. Previous reviews that state that atropine is not used or should not be because it is not tolerated by patients have no scientific basis. (Anecdotally, the first author, who has used atropine, progressive lenses, and contact lenses in the treatment of myopia, has had minimal problems with patient tolerance of atropine.) Only one of the long-term studies provided any evidence of rebound, while all of the others did not. However, this rebound effect was explained by the initial cycloplegic effect of atropine being greater than cyclogel. The exact mechanism of atropine in slowing myopia progression does not involve accommodation; it is presumed to block the signal stimulating the elongation of the globe via receptors at the retina.

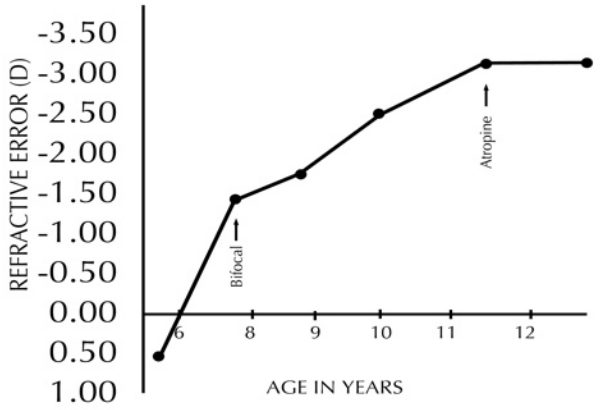

Figure 6 –Effect of Treatment Over Time Of Myopic Patient
This graph depicts the progression of myopia of a patient of one of the authors (JC). Progressive lenses initially slowed the progression of myopia in the first year but not in subsequent years. Once the patient was placed on atropine, the progression stopped. The patient, now 16 years old, was recently seen by (JC) without progression of his myopia. He has elected to stop using the atropine, and was recently fit with orthokeratology contact lenses without sequel. His unaided visual acuity in each eye is 20/20.

The studies reviewed using atropine in children vary in methodology, inclusion criteria, number of subjects, duration and completeness of follow-up, and data analysis. Despite this, they all show that the progression rate of myopia with atropine use is significantly lower than in the control group and the ability to control myopia is far superior to any other treatment. No study to date has determined how long a child needs to be on atropine to slow myopia progression, or how fast the myopia will progress after cessation of treatment for longer than 2 years. Parents may be concerned that although atropine has been used for over 100 years for long durations in patients with uveitis and in multiple studies for 1 to 4 years, the long term effects on a large population of children is unknown. Clinicians may be concerned by the possibility of long term-increased toxicity due to light exposure; however, current lenses that incorporate UV filters and photochromic lenses mitigate the risk.

Children with a strong family history of myopia who are rapidly progressing in myopia should be given the option of atropine use. Figure 6 depicts the long-term history of a patient treated with progressive addition lenses and atropine 1% at night. The atropine stopped the progression with a paucity of symptoms. If symptoms do develop while using 1% atropine, then 0.5% can be used. Currently, 0.5% atropine is not commercially available, but can be formulated at compounding pharmacies upon request. Seasonal variation can be used to titrate the appropriate concentration for symptoms, i.e., lower concentration during the summer when children are not reading as much and the sun is stronger. More recent studies have shown that even lower dosages such as atropine .01% may be used alone or to supplement orthokeratology or any other method of myopia control if initial reduction is not adequate. Clinically, the biggest problem with the higher concentrations of atropine is that the social desire to eliminate glasses cannot be met due to loss of accommodative ability and need for compensatory lenses.

For those children in whom myopia is progressing more slowly, or there is a need to eliminate glasses for either cosmetic or functional reasons, the second choice might be orthokeratology. Orthokeratology has a high acceptance rate with children and provides a "wow" phenomenon, often seen with LASIK. Patients are appreciative of it's ability to eliminate the need for glasses during the day and decreased the progression of myopia. It should be acknowledged that orthokeratology comes with its own risks of discomfort, keratitis, and potential corneal ulceration. Patients are often concerned about the risk of overnight wear of contact lenses. Even though the risk of complications with overnight wear of orthokeratology is appreciably less than with soft lenses, it still exists. The decreased risk is probably related to improved oxygen permeability of the lenses and reduced adhesion of either proteins or bacteria. Though not currently available, myopia-controlling soft multifocal contact lenses, which will attempt to correct for hyperopic peripheral retinal defocus, may have an exciting future. Since there are no currently FDA approved lens designs, the closest commercially manufactured lens today is either the Vistakon Oasis Presbyopic lens or the Cooper vision Biofinity Multifocal "D" lens. (See figure 7 for a comparison of each treatment.)

The last treatment recommended is progressive addition lenses for esophoric patients. Utilization of progressive lenses in other non-esophoric myopic patients provides minimal benefits, but

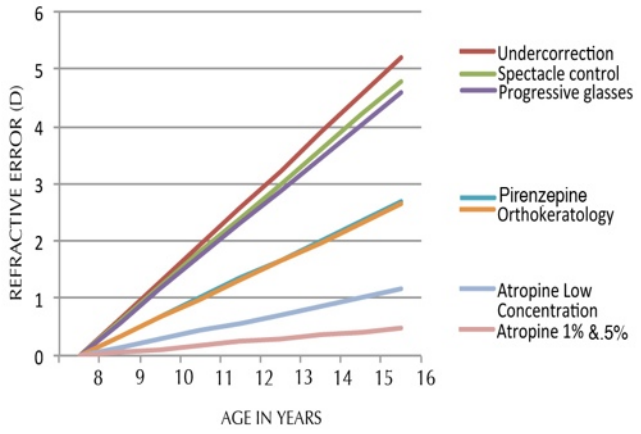

Figure 7 –Progression of Myopia Over Time By Treatment
This is a cumulative graph, based on the results of numerous studies, of the projected treatment effects of each treatment to control myopia over time. It is assumed that yearly progression with traditional glasses is 0.60 D/year (mean rate), and that the progression rate is linear (which may not be true). We recognize that the studies varied in findings and with ethnicity, thus, we used mean number. Each treatment result was corrected using a correction based upon the control group to maintain uniformity of treatment results in regard to the rate of progression of the control. For example, if the control progressed by 0.80 D/year then the treatment progression was decreased by .60/.80 or 75%. Atropine has been collapsed into two groups Atropine 1% and .5%, and low concentration of atropine, which include atropine .01% to .25%. It is readily apparent that atropine is the most effective treatment of myopic progression, followed by orthokeratology, and lastly, progressive lenses. According to the graph, under-correction is not an appropriate treatment of myopia. Lastly, when interpreting these results, one must be cognizant that the progression of an individual may be very differently than the mean.

also minimal risk. In the end, patients should be informed of the current status of myopia treatment with either an explanation or literature to explain the options. Caregivers and patients should be provided unbiased risks and benefits of each treatment strategy to help make informed decisions. It is the obligation of both optometrists and ophthalmologists to properly educate patients. There is a true risk of not slowing myopia progression; both patient and doctor have to make appropriate, scientifically and clinically valid assessments regarding appropriate treatment. (See Figure 7 for a comparison of effectivity of each treatment over time.)

As a general rule, the more sedentary the patient, the earlier the onset, the greater the risk factors (i.e., parents having myopia or family history of retinal holes or tears) the more likely that atropine will be suggested. Atropine dosage can be seasonally varied to reduce photophobia and blur complaints. On the other hand, patients who develop myopia later, associated with less progression, and/or are more athletic, the more likely that orthokeratology should be recommended. When parents have concerns about their children sleeping with contact lenses or using medications, a non-proven treatment using a Coopervision Biofinity Multifocal "D" +2.50 add, or Vistakon Oasys Multifocal lens is suggested. Lastly, there are those parents who are against the use of drops or contact lenses. If the child is esophoric , the use of progressive addition spectacle lenses can be recommended. Patients with myopia that want to slow the process but who require or desire traditional contact lenses should be prescribed UV filtering daily wear contact lenses. Ultimately, the decision of which treatment or combination of treatments to be used should be based upon the wants and needs of the patient.

CONCLUSION

In considering myopia treatment, remember what the 19th-century philosopher Arthur Schopenhauer[208] said: "All truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. And third, it is accepted as being self-evident."[208] Treatment of myopia with atropine is in the second stage, and orthokeratology is ending the second stage. Either atropine or orthokeratology will pass to the third stage or a better "atropine/orthokeratology" will come in to use. Atropine and orthokeratology are effective methods to slow the progression of myopia and should be in optometry's armamentarium to fight the effects of this growing pandemic.

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