Review of the Development and Treatment of Myopia
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 much 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 approximately 30\% in children 6 to 7 years of age, and increases 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.\(^15\, 16\) This rapid trend of earlier myopia inflicting a large segment of the population is now occurring in the United States.

Patients 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.\(^19\) Specifically, myopia significantly increases the risk of retinal detachments in patients having between 4-8D of myopia. This risk is greatest after having an uneventful cataract extraction following by a YAG capsulotomy (A necessary procedure after a cataract to clear the cloudy capsule that holds the lens). The incidence of retinal detachments is increasing dramatically as a direct result of the increase in myopia. Retarding the progression of myopia in children could ultimately impact the lives of approximately 42 million adults in the United States.\(^20\)
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 early retinal changes.\textsuperscript{2,1,22} 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.\textsuperscript{22} 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.\textsuperscript{24, 9, 25-28} In one study of Singaporean children, the prevalence and magnitude of myopia correlated with the time spent in education.\textsuperscript{29} School-age myopia is found more commonly in urban areas (versus rural areas), and industrialized countries.\textsuperscript{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).\textsuperscript{1} It has different characteristics as compared to the school age onset myopia, specifically it is associated with focusing anomalies and near vision dominated occupations such as computer viewing.\textsuperscript{31} Myopia progression in all three groups is due to the elongation of the eye ball, resulting in the eyeball becoming eggshape.\textsuperscript{32}

To control myopia, the rate of eye elongation must be slowed. The rate of myopia progression is highest for young children who usually stabilize around 16 years of age.\textsuperscript{33} Once myopia begins to develop, the mean rate of progression in children 8 to 13 years of age is 0.5 D/year for Caucasian children;\textsuperscript{33} 0.6 D/year for Hong Kong Chinese children;\textsuperscript{34} and 0.8 D/year determined for Asian children by meta analysis.\textsuperscript{35} Thus, the earlier the onset, the longer the period of time of progression and the faster the progression. Remember, these are grouped data, and individual variations are significant.

The cause, 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.\textsuperscript{2, 19, 22} The strongest evidence for genetic factors comes from comparing the prevalence of myopia in fraternal versus identical twins. Fraternal twins have a higher prevalence of myopia as compared to identical twins, thus supporting the genetic influence on the development of myopia.\textsuperscript{11} Studies have shown that having one or two nearsighted parents is a risk factor for
the development of myopia.\textsuperscript{37-40} It should be remembered that parents share both genetic and environmental factors with their offspring, thus, the parental relationship does not necessarily support a genetic cause.

The concept that myopia evolved from the use and abuse of the eyes during near vision activities was first described Cohn in 1886 and has been traced back to Kepler.\textsuperscript{41} More recent studies demonstrate a positive correlation between the presence of myopia and the following: intelligence,\textsuperscript{24, 42, 43} academic advancement,\textsuperscript{44, 46} avocations requiring near vision use,\textsuperscript{45, 46} after professional school,\textsuperscript{31, 47} caged versus free-ranging animals,\textsuperscript{48} and people confined to restricted spaces such as submarines.\textsuperscript{49} The best evidence for the effect of education and reading comes from Zylberman\textsuperscript{50} He studied children in religious schools, and 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. On the other hand the incidence of myopia in Jewish females was similar to secular (non-religious) Jewish male cohorts who attended non-religious schools who spend much less time reading and studying. Zylberman\textsuperscript{50} 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 near vision focusing, i.e. reading and computer use are somehow indirectly responsible for axial length elongation. The common thought is the constant looking at objects at 16-26 inches causes the focusing system to get stuck at the near reading or computer distance. Abnormal focusing findings have lead to a host of treatment methods to reduce excessive focusing of the eyes including bifocals, progressive addition lenses (PALs), atropine therapy, and vision therapy or exercises. Some recent studies have 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.\textsuperscript{62, 63, 64} The time spent outdoors is an independent variable, not the inverse of time spent indoors reading. Many of the studies involving amount of sunlight exposure were performed on school-aged myopes and may not be relevant to adult onset myopia.

The most compelling studies implicating the impact of the environment on myopia come from numerous animal studies. Wiesal and Raviola\textsuperscript{65, 66} sutured the lids of monkeys, allowing only a minimal amount
of light to penetrate. The deprivation of formed images resulted in the animals developing myopia. Similar effects were observed when translucent diffusers were placed over an eye rather than suturing the lid closed.

One group of researchers used translucent lenses to create a clear image on one half of the back of the eye and a clear image on the other half. Myopia due to elongation of the eyeball, occurred only in one side of the eye in which the blurred image, i.e., asymmetrical elongation of the globe (see figure 1). Lastly, these changes occurred in animals in which the optic nerve was cut demonstrating the effect was local to the eye and not dependent on a brain "seeing." Schaeffel and his associates used plus and minus contact lenses to create artificial farsightness or nearsightness. When lenses were placed in front of the animals eyes, the animals eyes changed size 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 an eye alternate its shape to obtain a clear, image.

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. This occurs even when the optic nerve is severed, demonstrating that cortical feedback is not necessary for localized elongation.

Previously, the macula (including the fovea where we see 20/20), which was thought to be sensitive to blur and respond by changing its length to accommodate for the blur. However, recent animal studies have demonstrated that the peripheral retina has a greater influence than the macula to blur and ocular growth.
For example, wearing peripheral blurring lenses causes primate eyes to become myopic. This even occurs in when the fovea is destroyed by a laser. Myopia progression results in the peripheral posterior pole of myopic eyes to become relatively farsighted relative to the central retina due to the round shape of the globe. (See Fig. 2)

**FIGURE 2 – PERIPHERAL BLUR DRIVES THE EYE TO ELONGATE**

If either the macula is ablated, or if 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).

When the eye becomes more myopic or nearsighted, it becomes longer or more egg shaped. Thus, when glasses or contact lenses are prescribed only back of the retina (macula) is corrected or in correct focus while the rest of the eye is out of focus. Recent evidence suggests that the peripheral retinal defocus may actually act as a signal for axial elongation. Hoogerheide et al. noted that pilot trainees were most at risk for becoming myopic when the eyeball was oval instead of round. Monkeys reared with centrally unrestricted vision (plano lens) and -3.00 D (myopic lenses) in the periphery produced myopia. (See Fig. 2) Liu and Wildsoet 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 Fig. 3)
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 at 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.

The preceding findings have resulted in a renewed interest in orthokeratology (lenses that mold the shape of the cornea) and novel spectacle and contact lens designs to correct the peripheral defocus in order to eliminate the signal elongation (to be discussed later). In addition, we know that there are neuro-retinal signals for ocular elongation which have a biochemical basis. Thus, if one can block the signal, then one might slow or stop myopia progression. Atropine and pirenzepine 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.\textsuperscript{139} The rationale was that if accommodation or focusing caused an increase in myopia, then bifocals or multifocals would reduce the accommodative response and thus slow myopia progression.

Goss\textsuperscript{140} performed a retrospective analysis of children to assess the effect of bifocal lenses on the rate of myopia progression. When Goss looked only at the children who tended to over converge (esophoria), 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.

Bifocal lenses, as compared to progressive addition lenses, are not as cosmetically appealing, and do not vary in power for different working distances. Leung and Brown\textsuperscript{145} conducted a clinical trial to evaluate the efficacy of progressive lenses on slowing myopia progression. The mean myopic progression over the 2-year study was 0.7 D for the +1.50 D add group, 0.6 D for the +2.00 D add group, and 1.2 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. This small study of children demonstrated a positive effect in using bifocals to slow myopia progression. Similar findings were reported by Fulk.

The Correction of Myopia Evaluation Trial (COMET), a 3 year prospective, randomized, double-masked clinical trial, evaluated the effect of progressive lenses in 469 myopic children 6 to 11 years of age\textsuperscript{146} After three years, there was a statistically significant, but clinically insignificant, 0.20 D reduction in myopia. Lenses as compared to single vision lenses: 1.08 D versus 1.72 D, respectively. However the three year treatment effect decreased after five years to 0.49 D or .1D/year.\textsuperscript{147} (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.)

Cheng D, Schmid KL, et al.\textsuperscript{149} measured myopic progression in a group of Chinese Canadian children,
who were progressing more than .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 .77 D/year in the single-vision lenses group, .48 D/year in the +1.50 executive bifocal group, and .35 D/year for prismatic bifocal group (+1.50 add with 3 prism (Δ) base in (BI) in each eye): axial length increased proportionally to the refractive changes. Cheng et. al.\textsuperscript{150} 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%.

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.\textsuperscript{145, 149, 150}

The major benefit of any progressive lenses, or bifocals, is the low risk of complications or adverse effects, and their effectiveness in esophoric myopic children, which constitute about 30% of myopic children.\textsuperscript{143}

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.\textsuperscript{151, 152} 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. 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. 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., 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 special 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. The lenses flattens the central cornea while creating mid peripheral steeping which corrects the error in the peripheral retina which ordinary glasses and contact lenses do not correct. In 2003, Reim and his associates performed a retrospective chart review of myopia progression in children between the ages of 6 and 18 with myopia who wore ortho K lenses. 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.

Cho and associates, in the Longitudinal Orthokeratology Research in Children (LORIC) study, compared the axial length of the eye in patients wearing ortho-k lenses and patients wearing glasses. 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. 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\textsuperscript{160} performed a study to determine whether corneal reshaping contact lenses slow eye growth in the Corneal Reshaping and Yearly Observation of Nearsightedness (CRAYON) Study. Seventy percent of the children completed the 2 year study; none of the dropouts were due to complications as most were due to lack of interest in wearing 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.\textsuperscript{162} recently conducted a study to assess the influence of overnight orthokeratology on axial elongation in children using spectacle lens wearers as a control group. After two years the axial length increased 0.39 mm for the orthokeratology group and 0.61 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.

Swarbrick et al.\textsuperscript{163} 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. Swarbrick et al.\textsuperscript{163} found that overnight orthokeratology lens wear inhibited axial length increase and myopia progression over a 12-month period. After 12 months, the orthokeratology 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\textsuperscript{164} measured refractive and central corneal curvature for 34 children wearing ortho-k lenses and for 36 children who wore spectacles 6-year or a longer. Average myopic progression of the overnight Ortho-K contact lens was 0.37 D (.05 D/year) while average myopic progression
of the single-vision spectacle group was 2.06D (.29 D/year) after 7 years. Lastly, there was no reported infections 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.

In summary, ortho-k results in an approximately 40% reduction in the progression of myopia. Its advantages are that it eliminates both the need for daytime of contact lenses 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.\(^{168, 169, 170}\)

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. Antsttice and Phillips\(^ {168}\) 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 lenses and worn for another 10 months (period 2). The mean change in spherical equivalent refraction with Dual-Focus lenses (-0.44 D) was less than with the control lenses (-0.69D); mean increase in axial length was also less with Dual-Focus lenses (0.11mm) than with the control lenses (0.22 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.\(^{170}\) Progression of myopia with the experimental lens was significantly less than with the control, -0.26 D versus 0.60 D. Similarly, axial length increase was less with the experimental lens as compared to the control lens, 0.08 mm versus 0.25 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.”

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.\(^{172}\) 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%.\(^{146}\) 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. 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 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 causes maximum pupillary dilation within 40 minutes of the initial drop and loss of focusing within 5-48 hours after the first drop. The residual effects on focusing last 10-14 days.

The first report describing the use of atropine to slow myopia progression was by Wells in the 19th century, during which time atropine was used extensively to slow myopia progression. The use of atropine declined after the turn of the 20th century due to loss of focusing and sensitivity to sunlight from the dilation.

In 1964, Bedrossian and Gostin presented a report on seventy-five patients prescribed one drop of 1% atropine in one eye for the first year and then one drop of atropine in the other eye for following year. After one 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. 105, 108

Subsequently, Gimbel,106 Kelly et al.175, Dyer,110 Sampson,107 Bedrossian,105, 108, 112 Gruber,111 Brodstein,109 Brennar,113 and Yen115 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. Chiang et al.176 performed a retrospective, study on 706 Caucasian children from 6 to 16 years of age who were treated with one drop of 1% atropine once weekly in both eyes. Seventy percent of the children were compliant with the regimen. 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.120 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 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.124 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.
After 2 years, the mean progression of myopia in the placebo-treated eyes was 1.20D and only 0.28 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 mm, whereas in the atropine-treated eyes the axial length was essentially unchanged. 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.

Shih et al. evaluated the effectiveness of 0.5% atropine to slow the progression of myopia. At the end of 18 months, the mean myopic progression was 0.42 D in children using 0.5% atropine with multifocal glasses, as compared to 1.19 D and 1.40 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. Progression of myopia in all the groups was highly correlated with an increase in axial length.

Shih et al. evaluated the efficacy of various concentrations of atropine in slowing myopia progression (0.5%, 0.25%, or 0.1% atropine, or 0.5% tropicamide in both eyes nightly). Children prescribed 0.5% atropine were given a bifocal (+2.00 add), children prescribed 0.25% atropine were undercorrected by 0.75D, and children using 0.1% atropine were given their full distance prescription. The mean progression of myopia was 0.04 D/year in the 0.5% atropine group, 0.45 D/year in the 0.25% atropine group, and 0.47 D/year in the 0.1%
atropine group, as compared to 1.06 D/year in the mydriacyl 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, See Fig. 5.

**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.119 A recent study suggests that the effectivity is not significantly dependent on the concentration.179

Lu et al.178 investigated the effect of seasonal modifications in the concentration of atropine used on slowing the progression of myopia. 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). After one year, mean myopia progression was 0.28 D for children using
atropine, and 1.23 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.\textsuperscript{125} conducted a retrospective chart review to evaluate the efficacy of 0.05% atropine in slowing myopia progression. Mean progression of myopia was 0.28 D/year in the 0.05% atropine group, as compared to 0.75 D/year in the control group. 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.\textsuperscript{128} evaluated the efficacy of 0.025% atropine for prevention of myopia onset in pre-myopic children. Mean myopic shift was 0.14 D/year in the 0.025% group, as compared to 0.58 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.

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. \textsuperscript{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

\textbf{TABLE 2}
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

The previous studies clearly demonstrate the effectivity of atropine retarding the progression of myopia. However, before embarking on treatment using atropine, one must be cognizant of the risk.

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 1950.173, 182, 183 There are many more deaths associated with common drugs like aspirin or excessive water ingestion. 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.182, 173 Thus, there have been no fatal occurrences in children over 3 years of age with appropriate atropine dosing.

<table>
<thead>
<tr>
<th>Treatment method</th>
<th>Percentage Reduction</th>
<th>Projected increase in myopia after 1 year</th>
<th>Projected increase in myopia after 8 years</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undercorrection</td>
<td>-8%</td>
<td>0.65</td>
<td>5.18</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Spectacle control</td>
<td>0%</td>
<td>0.60</td>
<td>4.80</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Peripherally correcting glasses</td>
<td>1%</td>
<td>0.59</td>
<td>4.75</td>
<td></td>
<td>1, 10</td>
</tr>
<tr>
<td>Progressive glasses</td>
<td>4%</td>
<td>0.58</td>
<td>4.61</td>
<td>26</td>
<td>1, 2</td>
</tr>
<tr>
<td>Bifocals</td>
<td>16%</td>
<td>0.50</td>
<td>4.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eccophoria + bifocals</td>
<td>20%</td>
<td>0.48</td>
<td>3.84</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Pirenzpine QD</td>
<td>34%</td>
<td>0.40</td>
<td>3.17</td>
<td>22</td>
<td>4, 5, 8</td>
</tr>
<tr>
<td>Peripherally correcting CLs</td>
<td>40%</td>
<td>0.36</td>
<td>2.88</td>
<td>22</td>
<td>8, 9, 10</td>
</tr>
<tr>
<td>Pirenzpine BID</td>
<td>44%</td>
<td>0.34</td>
<td>2.69</td>
<td>22</td>
<td>3, 4, 5, 10</td>
</tr>
<tr>
<td>Orthokeratotomy</td>
<td>45%</td>
<td>0.33</td>
<td>2.64</td>
<td>22</td>
<td>3, 9</td>
</tr>
<tr>
<td>Atropine 0.25%</td>
<td>58%</td>
<td>0.25</td>
<td>2.02</td>
<td>22</td>
<td>9, 10</td>
</tr>
<tr>
<td>Atropine 0.01%</td>
<td>60%</td>
<td>0.24</td>
<td>1.92</td>
<td>22</td>
<td>9, 10</td>
</tr>
<tr>
<td>Atropine 0.1%</td>
<td>62%</td>
<td>0.23</td>
<td>1.82</td>
<td>22</td>
<td>7, 8, 9, 10</td>
</tr>
<tr>
<td>Atropine 0.001%</td>
<td>65%</td>
<td>0.21</td>
<td>1.68</td>
<td>22</td>
<td>7, 8, 9, 10</td>
</tr>
<tr>
<td>Seasonal atropine</td>
<td>67%</td>
<td>0.20</td>
<td>1.58</td>
<td>22</td>
<td>7, 8, 9, 10</td>
</tr>
<tr>
<td>Atropine 0.025%</td>
<td>76%</td>
<td>0.14</td>
<td>1.15</td>
<td>22</td>
<td>7, 8, 9, 10</td>
</tr>
<tr>
<td>Atropine 0.5%</td>
<td>80%</td>
<td>0.12</td>
<td>0.96</td>
<td>23</td>
<td>3, 7, 8, 9, 10</td>
</tr>
<tr>
<td>Atropine 1%</td>
<td>90%</td>
<td>0.06</td>
<td>0.48</td>
<td>23</td>
<td>5, 7, 8</td>
</tr>
</tbody>
</table>
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. 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.

During the 2-year ATOM study 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. Similar findings were reported by Shim et al. study of 200 children.

In the Amblyopia Treatment Studies (ATS), which included 204 patients 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%). Atropine was not discontinued due to its side effects in any other patients. No other systemic side effects of atropine were reported.

Similar findings were found in the ATS3, of 201 patients. The ATOM study 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 ability to focus the eyes was better 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.
DISCUSSION

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.

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 though atropine has been used for over 100 years, for long durations in patients with uveitis, and in multiple studies for 1 to 4 years, that 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.

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 its ability to eliminate the need for glasses during the day and decreased progression of myopia. It should be acknowledged that orthokeratology comes with its own risks of discomfort, keratitis, and potential corneal ulceration.

**FIGURE 6 – EFFECT OF TREATMENT OVER TIME OF A 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.

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 fig. 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 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

![Figure 7 – Progression of Myopia Over Time by Treatment](attachment:image.png)

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 .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 .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.

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 risk factors (i.e., parents having myopia, 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 and sleeping with contact lenses, and using medications, a non-proven treatment using a CooperVision Biofinity Multifocal “D” +2.50 addd lens, 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 wanting to slow the process but who require or desire traditional contact lenses are prescribed UV filtering daily wear contact lenses. Ultimately, the decision of which treatment or combination of treatment should be used should be based upon the wants and needs of the patient.
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