

Use of Atropine to Slow the Progression of Myopia: A Literature Review and Guidelines for Clinical Use

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ABSTRACT

Atropine 1% and various lower concentrations of atropine (0.5-0.01%) have been used to slow the progression of myopia. Cumulative data and meta-analysis from a number of studies have demonstrated that the most effective method for slowing the progression of myopia is atropine 1% instilled daily (progression is slowed by almost 80%). Atropine's side effects of mydriasis and cycloplegia have kept it from being prescribed more frequently.

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Recent studies have demonstrated that lower concentrations of atropine 0.025% to 0.01% are effective with significantly lower side effects. Discontinuing atropine treatment has displayed a rebound of myopia progression with higher amounts of rebound associated with higher atropine concentrations. Ocular side effects of atropine can be effectively managed with photochromic progressive lenses. In summary, atropine is not only safe, but it is also an effective drug to slow the progression of myopia.

INTRODUCTION

Myopia is a common eye condition capable of impacting ocular health and quality of life. Recent studies indicate that even low levels of myopia possess significant ocular disease associations.¹ Increased risk of myopic maculopathy, retinal detachment, glaucoma, and cataracts have been associated with myopia as low as one diopter (-1D) and their associations increase with increasing amounts of myopia.¹ Myopia is one of the major causes of blindness in East Asia.² The prevalence of myopia has increased significantly over the past several decades in the United States (US). A large study revealed an increase of more than 60% in myopia prevalence from the early 1970's to 2004 in the US among individuals 12-54 years old. The prevalence of myopia in 2004 was reported to be 41.6% while 30 years earlier it was reported at 25%.³ In another large study in Asia, the reported prevalence of myopia was 84% of the students 16-18 years old.⁴ Myopia is increasing in numerous countries worldwide. It is estimated that by 2050, over half of the world's population will be myopic.⁵ This alarming increase in both the magnitude and prevalence of myopia has prompted researchers and clinicians to understand the etiology, mechanisms for emmetropization, and ultimately the treatment of myopia.^{6,7} Currently, there are two broad scientifically supported methods of treatment. The first

type of treatment changes the visual input to the eye (amount of light, wave-length of light, or the optics of light coming into the eye, i.e. refraction). The second type of treatment alters the biochemical signals that are responsible for eye growth. Several research studies have displayed the important role that orthokeratology and multifocal contact lenses can play in the slowing of myopic progression.^{8,9} One avenue of treatment currently not used often in the US for myopia control is ophthalmic atropine. Currently, the use of atropine for myopia treatment is not an indication for use approved by the U.S. Food & Drug Administration (FDA) and is considered an "off-label" use in the US.^{10,11} The purpose of this paper is to demonstrate how atropine may be a valuable tool in the pursuit against myopia progression.

BACKGROUND

Atropine is a natural alkaloid occurring in plants of the Solanaceae family. In the first century BC, Cleopatra is thought to have used atropine to dilate her pupils for enhanced cosmesis.¹² Atropine is a non-selective muscarinic antagonist. Mydriasis and cycloplegia result from atropine's blockage of acetylcholine action on the iris sphincter and the ciliary body. Topical installation of atropine 1% causes maximum mydriasis within 30-40 minutes with recovery of mydriasis in 10-14 days. The onset of cycloplegia starts within 30 minutes and recovery takes 7-10 days.¹³ Additional clinical uses for atropine include cycloplegic refractions and penalization treatment in amblyopia.^{13,14} In 1864 Donders described the usefulness of atropine for cycloplegic refractive error determination. He also depicted atropine as a possible treatment of asthenopia and myopic increase associated with spasm of accommodation.¹⁵ The first reported use of atropine to slow myopia progression was by Wells in the 19th century.¹⁶ Early use of atropine to slow progressive myopia was unpopular because

of the patients' symptoms of blur and photophobia. In the 1970's atropine therapy was revitalized as a more common treatment to slow the progression of myopia because of the development of progressive lenses to eliminate blur and photochromic lenses to eliminate photophobia. Initially, atropine was used to slow the progression of myopia because of its cycloplegic effect since myopia was assumed to be secondary to excessive accommodation. The concept that myopia evolved from the extensive use of the eyes during near vision was credited to Cohn in 1886, but has been mentioned as early as 1611 by Kepler.^{17,18} Recent studies have demonstrated that myopia is associated with several traits and environments, including intelligence,¹⁹⁻²¹ academic advancement,^{20,22-25} avocations requiring near vision use,²⁶⁻³⁰ professional school,^{31,32} caged versus free-ranging animals³³ and people confined to restricted spaces such as submarines.^{34,35} The implication of most of these studies is that the greater the time spent performing near work results in an increased incidence of myopia.³⁶⁻³⁹ This concept, however, is not universally accepted.¹⁸ More recent research has described the influence of specific genes and environmental conditions on the development of human myopia.⁴⁰

Hubel and Wiesel during their historical studies of occlusions of cats' eyes in the 1960s, noted not only did they alter the way the cortex responded to visual information, but also the animals eyes elongated when the eyes were provided with blurred stimuli via refractive lenses.⁴¹⁻⁴³ This has led to numerous articles exploring the effect of lenses on visual development. Researchers interposed plus and minus lenses in front of visually immature animals across several species whereby there was a linear change of axial length with the power of the lens.^{44,45} Studies have shown that the influence of lenses on axial length is a localized phenomenon. If half of the retina is exposed to the lens, only that portion of the retina would have an associated change

in axial length.^{46,47} However, these changes did not occur if atropine was injected into the animal's eyes.⁴⁸ (See Figure 1)

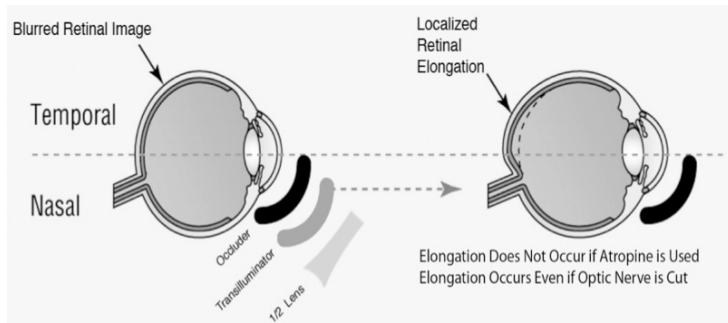


Figure 1: Regional retinal blur induced by ophthalmic lenses, or translucent lenses in half the retina results in regional elongation of the eye. This even occurs when the optic nerve is cut, but will not occur if atropine is injected into the eye. (Reprinted with permission from Cooper J, Schulman E, Jamal N. Current status on the development and treatment of myopia. *Optometry*. 2012;83(5):179-199)

Initially, the use of atropine to slow the progression of myopia or slow axial length elongation was based on the assumption that myopic development was a result of excessive accommodation at near. This hypothesis was supported by the fact that atropine slowed axial elongation in animal studies. However, the accommodative hypothesis has been challenged by a number of experiments.⁴⁹ First, axial elongation occurred when minus lenses were placed in front of a chicken eye in which the optic nerve was severed.^{50,51} Accommodation requires cerebral feedback, thus, the results of this experiment showed that the axial elongation was not due to accommodation. However, if atropine was injected into the eye even with the optic nerve severed, elongation did not occur. Second, Stone⁵² demonstrated that axial elongation from form deprivation was slowed significantly by atropine in chicks who did not have muscarinic receptors in the ciliary body, and McBrien⁴⁸ demonstrated that axial elongation could occur in mammals that had no accommodation. Lastly, when studies using hemi-retinal translucent and refractive lenses caused asymmetric elongation in half the eye, atropine stopped the process from occurring;

again suggesting that accommodation could not have caused the elongation.⁴⁹ These studies demonstrate that the ability of atropine to slow axial elongation is not likely based on an accommodative mechanism.⁵³ Today atropine is thought to biochemically block the signal for axial elongation. More specifically it is thought to involve both M4 and M1 muscarinic receptor signaling pathways.⁵⁴ There is some evidence that it effects the structural integrity of the sclera.⁵⁵

In humans recent evidence has become very strong that myopic development is driven by the interplay of both genetic and environmental factors.⁵³ Recently, Tkatchenko et. al.⁴⁰ performed an analysis of the interaction between time-spent reading at age 8–9 years and the presence of the APLP2 genetic variant. It was found that children who spent a “high” amount of time reading (more than 2 hrs. per day) and who had the APLP2 gene were associated with a progressive increase in myopia. In the absence of the APLP2 gene, high levels of reading did not show a progressive increase in myopia.

These studies point toward evidence that the environment together with genetic influences can create myopia, and that antimuscarinic drugs such as atropine or pirenzepine may slow this process.⁵⁶ The mechanism of atropine to slow myopia is likely not one of accommodation influence, but rather related to blocking the signal for axial elongation of the eye.⁵⁷

Clinical Studies Supporting the Use of Atropine to Slow the Progression of Myopia

A number of retrospective studies demonstrated that atropine 1%, used with progressive/transitional lenses, slowed the progression of myopia by almost 80%.⁵⁸⁻⁷⁰ (See Table 1) However, there was a concern that atropine dilation might increase ultra violet light (UV) exposure with long term increased risk of cataract and/or macular degeneration. Atropine 1% has its strongest effect in the first year of

Table 1. Retrospective studies of atropine 1% demonstrated a 90% reduction in the progression of myopia. The studies varied from 1 to 15 years of follow-up. Multiple studies often showed a small reduction in the amount of myopia during the first year of the study. (Reprinted with permission from Cooper J, Schulman E, Jamal N. Current status on the development and treatment of myopia. Optometry. 2012;83(5):179-199).

Author	# of children completed study	Length of study	Treatment	Control Group (mean progression)	Atropine Group (mean progression)
Gimbel(59) 1973	594	3 yrs	Atropine 1% qhs	0.41 D/yr	0.14D/yr
Kelly et al(60) 1975	282	3 yrs	Atropine 1% qhs	0.51 D/yr	+0.58D/yr
Kelly et al 1975	168	2-8yrs	Atropine 1% qhs	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(62) 1979	100	1yr	Atropine 1% qhs & bifocal 2.25	No control	Change in myopia: -0.25 to +0.50D: 79% +0.75D to +1.00D: 15% >+1.00D: 6%
Bedrossian(64) 1979	90 children on atropine (62 followed for 2 yrs, 28 followed for 4)	4 yrs	Atropine 1% in only eye	-0.82 D/yr	+0.21 D/yr
Gruber(65) 1985	200	1-7.5 yrs	Atropine 1% qhs	-0.28D/Y	-0.11 D/yr
Brodstein(66) 1984	399	1-9 yrs	Atropine 1% qhs & bifocal 2.25	-0.34D/Y	-0.12 D/yr
Brenner(67) 1985	79	1-9 yrs		No control	-.20
Yen et al(68) 1989	96	1yr	Atropine 1% qhs & bifocal 2.25	-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%

use, resulting in a small reversal of myopia when measured during a cycloplegic refraction.⁷¹ Part of the effect of atropine in the first year is an artifact since atropine has a greater cycloplegic effect than cyclopentolate 1%, thus, creating the appearance that atropine is more effective than it really is. Measurement of myopic progression using axial length eliminates any artifacts induced by the lens. Many of the earlier atropine studies demonstrate long-term effectively without any re-bounce effect.^{63,66,69} Chiang et al.⁷² Studied the effect of atropine 1% used once weekly for 1 month to 10 years. He reported a mean progression rate of .08

D/year in the compliant group and .23 D/yr. in the partially compliant group.

Most of the earlier atropine studies were not prospective, randomized clinical trials. In 2006 Chua et al. conducted a large study to determine if topical atropine 1% could be used safely and effectively to prevent myopia progression in Asian children 6-12 years of age (the study known as ATOM 1).⁷¹ This was a randomized, double-masked, placebo-controlled trial where 346 of the initial 400 children completed the two-year study. Each child either received atropine 1% or the placebo eye drop each night for two years. Only one eye in each child was treated.⁷¹

After two years, the myopic progression in the placebo treated eyes was $-1.20 \pm 0.69D$ while the progression in the atropine 1% treated eyes was $-0.28 \pm 0.92D$. In addition, the axial length increase in the placebo treated eyes was 0.38 ± 0.38 mm while the axial increase in the atropine 1% treated eyes was -0.02 ± 0.35 mm. After two years, the use of atropine 1% resulted in approximately 77% reduction in myopic progression when compared to the placebo treatment. Furthermore, the atropine 1% treated eyes displayed basically no change in axial length increase (.02mm) as compared to a 0.38 mm increase in the non-atropine treated eyes.⁷¹ In this study, there were no serious adverse events observed with the atropine treatment and it was generally well tolerated. The researchers concluded that atropine 1% was well tolerated and effective in slowing myopic progression and axial elongation in children. Figure 2 summarizes the results of ATOM 1.

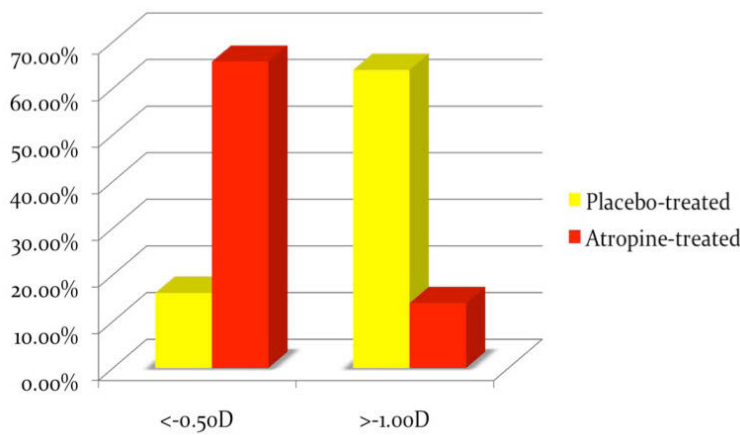


Figure 2: Data from the ATOM 1 study is demonstrates the effectivity of atropine over control.⁷¹ Seventy percent of the atropine subjects had less than 0.5D of progression compared to less than 20% of the controls. It is apparent that Atropine 1% provides a strong control of myopia progression. (Reprinted with permission from Cooper J, Schulman E, Jamal N. Current status on the development and treatment of myopia. *Optometry*. 2012;83(5):179-199)

Dosage

There have been a number of studies that have evaluated the relationship of concentration of atropine to the reduction of myopic progression. Shih et al.⁷³ reported on

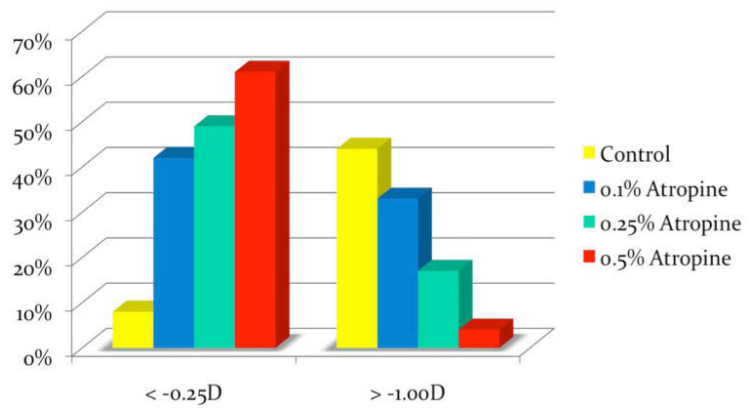


Figure 3: Shih and his co-workers demonstrated that the ability of atropine to slow myopic progression is related to concentration.⁽⁷³⁾ The higher the dosage the more effective atropine is in slowing the progression of myopia. Relatively low dosage of Atropine 0.01%, is a effective in the retardation of myopia progression. (Reprinted with permission from Shih YF, Chen CH, Chou AC, Ho TC, Lin LL, Hung PT. Effects of different concentrations of atropine on controlling myopia in myopic children. *J Ocul Pharmacol Ther*. 1999;15(1):85-90.)

200 children, 6 to 13 years of age, who were randomly prescribed one drop of 0.5%, 0.25%, or 0.1% atropine, or 0.5% tropicamide (control treatment) in both eyes nightly. The mean progression of myopia was 0.04 ± 0.63 D/year for the 0.5% atropine group, 0.45 ± 0.55 D/year for the 0.25% atropine group, and 0.47 ± 0.91 D/year for the 0.1% atropine group, as compared to 1.06 ± 0.61 D/year in the control group. At the end of the 2-year treatment, 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. (See Figure 3) In a novel study, the concentration of atropine was varied from winter (0.5%) to summer (0.1%) based upon the assumption that myopia progresses less during the summer. This allowed the children to have less pupillary dilation during the summer months when the sunlight and photophobia was the greatest.⁷⁴ This regimen slowed myopic progression by 77%. Fang et al⁷⁵ evaluated the effectivity of atropine .025% to prevent the development of myopia in a group of children presenting with early myopic progression signs. There was a 50% reduction in the number of children who converted

from emmetropia to myopia. Cooper et al found that Atropine 0.02% is the minimal dosage in which patients will not have any symptoms related to dilation or decreased accommodation.⁷⁶

In 2012 Chia et al. published a study to compare the effectiveness and visual side effects of three lower doses of atropine in the prevention of myopic progression in Asian children 6-12 years of age (the study known as ATOM 2).⁷⁷ This study was a double-masked, randomized study with 355 of the initial 400 children completing the two-year study. The children were randomized to receive 0.5%, 0.1%, or 0.01% atropine nightly in both eyes. After two years, researchers found that all three concentrations were effective at slowing the progression of myopia. The researchers found

a dose related response on myopia but the differences among the three treatments was clinically small. The final myopia progression for the 0.01% atropine group was -0.49 ± 0.63 D while the 0.5% atropine group was -0.30 ± 0.60 D. The axial length change after two years for the 0.01% atropine group was 0.41 ± 0.32 mm while the 0.5% atropine group was 0.27 ± 0.25 mm. More importantly the ATOM 1 study showed a minimal .02 mm change in axial length over 2 years of time with the use atropine 1%. (See Figure 4) However, the ATOM2 showed no statistical difference between the placebo and atropine 0.01% group. This is very important on two counts :

- 1) If the primary purpose of slowing myopia progression is slowing axial elongation to decrease the potential of future retinal

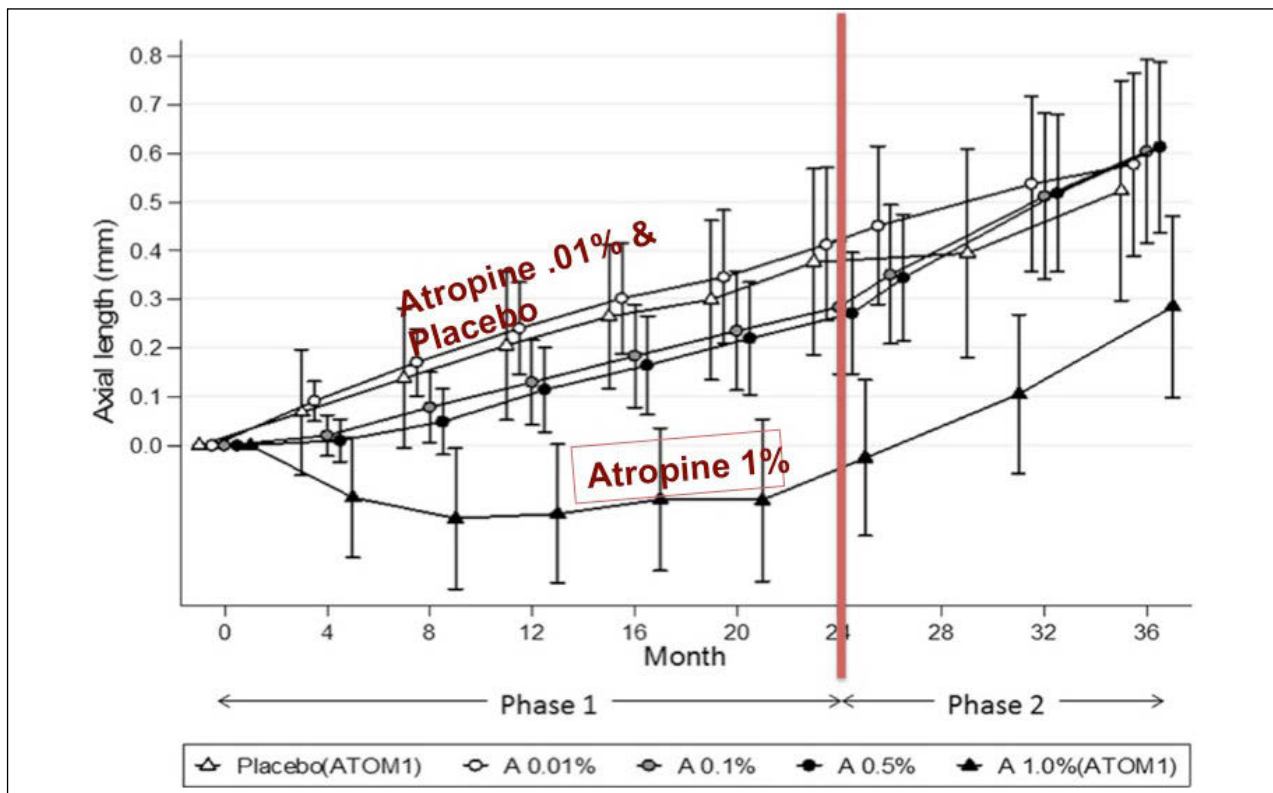


Figure 4: The axial length measurements from ATOM 1 and ATOM 2 are presented in both phase 1 (treatment) and 2 (withdrawal). Phase 1 is the treatment phase, which ended after 24 months and is denoted by a vertical line. It is readily apparent that rebound axial length changes are less dramatic than refractive changes depicted in figure 5; atropine 1% is clearly the most effective inhibitor of myopia progression; and axial length changes appear later than refractive changes. After Phase 2, during which all treatment is stopped for 12 months, there is an apparent rebound of myopia that was larger with higher concentrations of atropine. However, even with the effects of rebound taken into account higher dosages of atropine, i.e. atropine 1%, were associated with smaller axial length changes at the end of the study. (Reprinted with permission from Chia A, Chua WH, Wen L, Fong A, Goon YY, Tan D. Atropine for the treatment of childhood myopia: changes after stopping atropine 0.01%, 0.1% and 0.5%. *Am J Ophthalmol.* 2014;157(2):451-457 e451).

complications, then the lower dosages may not be very effective while atropine 1% is very effective.

2) The minimal difference between placebo and atropine 0.01% of axial length changes should make the clinician suspect of the “true effect” of atropine 0.01%. Table 2 depicts the axial change measurements of both ATOM 1 and 2 studies at the end of 2 years. The axial length measurements were either measured or derived from spherical equivalent data.

Table 2. This table compares the various dosages of atropine and placebo drops from both ATOM studies over 2 yrs. The first column depicts the mean A-scan axial length (AL) measurements for each dosage. The second column used the AL measurements from the first column to calculate the equivalent spherical equivalent (SE) changes. The third column is the reported cycloplegic (SE) changes over 2 yrs. for each dosage. It is readily apparent that there is a dichotomy between the AL measurements and the SE. It is also apparent that placebo arm had the largest increase in myopia over time. At first glance, Atropine .01% seems effective in slowing myopia progression when using SE measurements, but on closer inspection both placebo and atropine .01% also had similar AL changes during the treatment phase. Atropine 1% was the most effective in slowing SE changes and AL over time.

	Axial Length (mm)	SE (D) calc from AL	SE from cyclo (D)	
Placebo	0.38	-1.14	-1.20	Atom 1
Atropine .01%	0.41	-1.23	-0.49	Atom2
Atropine .1%	0.28	-0.84	-0.38	Atom 2
Atropine .5%	0.27	-0.81	-0.30	Atom 2
Atropine 1%	0.02	-0.06	-0.28	Atom 1

The visual side effects and adverse events were less with the 0.01% atropine than with the 0.1% and the 0.5% atropine groups. For example after two years, accommodation measured 11.8D for the 0.01% atropine group versus 6.8D and 4.0D for the 0.1% and 0.5% groups respectively. Further, the near visual acuity (logMAR) was 0.01 for the 0.01% versus 0.10 and 0.29 for the 0.1% and 0.5% groups respectively. Finally, the more common adverse events included allergic events (allergic

conjunctivitis and allergic dermatitis) and were only observed with the 0.1% and 0.5% atropine groups. The authors concluded that the lowest concentration atropine, 0.01%, was efficacious in controlling myopia progression, while exhibiting minimal side effects compared to the 0.1% and 0.5% atropine concentrations.⁷⁷

Studies have been conducted to determine the rebound effect after discontinuation of atropine. Chia et al examined the same group of children from the ATOM 2 study 12 months after discontinuation of their atropine treatment (either 0.5%, 0.1%, or 0.01% atropine).⁷⁸ Over this 12-month “washout” period, myopic progression had the largest increase in the 0.5% group (-0.87 ± 0.52 D) followed by the 0.1% group (-0.68 ± 0.45 D), and the lowest for the 0.01% group (-0.28 ± 0.33 D). Recovery of pupil size and accommodation was quicker in the 0.01% group compared to the 0.1% and 0.5% groups. Interestingly, at the end of the 12-month discontinuation, the axial length increase was greatest for the 0.5% group and least for the 0.01% group. However, by the end of the 36-month study period, the overall change from baseline axial length was similar for all three treatment groups. The authors suggested that perhaps myopic increase was also associated with other changes occurring such as a change in corneal curvature or lens thickness, and that further investigation was warranted. Furthermore, the authors stated that while the exact mechanism is uncertain, it is thought that atropine regulates the muscarinic receptors in the sclera and retina and therefore may affect ocular elongation.⁷⁸ In this study, it was suggested that the lower doses of atropine might act on a different site or affect various muscarinic receptors differently. The authors summarized that atropine 0.01% showed less myopic rebound and a more sustained effect on myopia control. In addition, this lowest study concentration provided the quickest recovery of pupil dilation and accommodative recovery.

In 2016, Chia et al published the results of the five year long study involving the

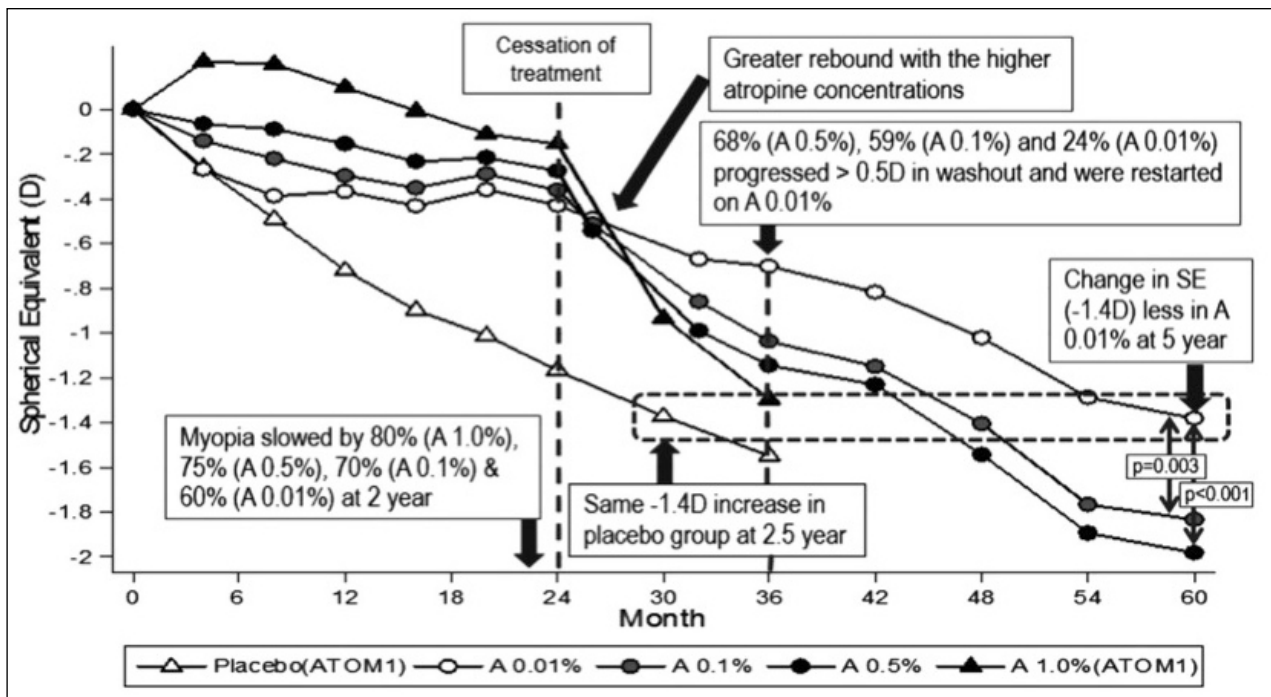


Figure 5: This graph depicts the Cycloplegic refractions (spherical equivalent) in all three phases of the ATOM 1 and 2 studies.⁽⁷⁹⁾ The first phase was for 2 years during which subjects were randomized to receive various concentrations of atropine (1%, 0.5%). After 2 years, treatment was stopped in all groups for 1 year of time. Those patients still showing more than 0.50 diopters of myopia progression were placed on atropine 0.01% and followed for another 2 years. (Reprinted with permission from Chia A, Lu QS, Tan D. Five-Year Clinical Trial on Atropine for the Treatment of Myopia 2: Myopia Control with Atropine 0.01% Eyedrops. *Ophthalmology*. 2016;123(2):391-399.)

safety and efficacy of different concentrations of atropine for myopia control in children.⁷⁹ Figure 5 presents a summary of all three phases including the results of ATOM 2 using spherical equivalents as an end point. After the one year washout period described above in ATOM 2, children who had a myopic increase of $> -0.50\text{D}$ in at least one eye were retreated with atropine 0.01% for two more years. Interestingly, fewer children (24%) in the 0.01% initial treatment group qualified for retreatment compared to the 59% and 68% who qualified from the 0.1% and 0.5% groups respectively. At the end of the five year study the overall increase in myopia was less for the 0.01% atropine group ($-1.38 \pm 0.98\text{D}$) than the 0.1% group ($-1.83 \pm 1.16\text{D}$) and the 0.5% group ($-1.98 \pm 1.10\text{D}$). The authors proposed that atropine 0.01% daily is an effective first-line treatment in children 6-12 years with myopic progression $> 0.50\text{D}$ in the previous year. Furthermore, fewer visual side effects were noted when compared to higher doses of atropine.⁷⁹ The effects of rebound

were even greater with atropine 1% in the ATOM 1 study.⁸⁰

Rebound effects appear to be different when measured by changes in cycloplegic refraction (spherical equivalent) as compared to axial length measurements. Part of the explanation is that the cycloplegic effect of atropine is greater than that found with cyclopentolate 1%. This created the impression that atropine 1% slows the progression of myopia more in the first year of use and that the measured rebound from the atropine baseline is greater than it really is. These rebound findings are not surprising when one realizes that atropine suppresses the normal signals for elongation in attempt to create emmetropization or adaptation. Atropine discontinuation should be performed using a tapered schedule and the patient must be warned to the possible consequences by abruptly stopping use of atropine.

After stopping the drops for 1 year the patients were re-assessed.⁸¹ They found patients either resumed the progression of

myopia or appeared to stop. Those that stopped were presumed to be cured (future data is needed to substantiate this claim) while the others progressed again. Those that progressed (previously in one of three groups atropine 0.5%, 0.1%, or 0.01%) were put on atropine 0.01% and reassessed 3 years later (total of 5 yrs.). The authors concluded that atropine 0.01% was more effective than the higher dosages in slowing the progression of myopia. However, there is a major problem with the design of the study when applying their conclusions to clinical care. Clinicians do not typically prescribe atropine 1% for two years and then stop the treatment abruptly. When atropine 1% is prescribed it is used for years, and it is usually switched to another myopic controlling method, e.g. orthokeratology or multifocal lenses. In those studies in which atropine 1% was used for a long term, atropine was found to be effective over the long run with no evidence of losing its effectiveness.^{62,70} Subjects who had the least effective response from the treatment with atropine had the following characteristics: two myopic parents, development of myopia at an earlier age, and myopia progression of more than the average of .66 D/yr.⁸²

At the end of 5 years, the authors conclude that atropine 0.01% was more effective in slowing myopia progression when refractive error was used as an endpoint with fewer side effects compared with higher concentrations.⁷⁷ However, these conclusions may not be justified. No other published studies have provided any evidence that discontinuing atropine 1% over time results in a rebound effect. Also, as previously stated if one looks at axial length over the 5 years of the study, there is no significant difference in axial length between the patients in the control group and the patients in the atropine 0.01% group. Currently, there is no explanation for this discrepancy. However, part of it might be explained by measurement variability that occurs with A-scan measurements (used in the

ATOM studies) vs improved partial coherent Interferometry measurements (IOLMaster)⁸³ Patients in the atropine 1% group clearly had the least amount of axial elongation as compared to the lower concentration.^{71,77} Thus, from these studies it might be inappropriate to conclude that lower concentrations are more effective than higher concentrations. On the other hand, they do provide evidence that lower concentrations might have a more effective stop signal for myopia progression. These studies do provide evidence that one should begin treatment with the lowest concentration to control myopia progression i.e. atropine 0.01% in each eye at bedtime. However, in our experience, atropine 0.01% is often not effective enough, and therefore we have switched back to using atropine 0.02% at night.

In summary, these findings suggest that myopia is slowed the most with atropine 1% but lower concentrations had a larger effect than expected by the end of the first 2 years of the study. The effect is large enough to suggest in moderately to slowly progressive myopia (less than 1D per yr), that atropine 0.01% should be used initially to treat. However, one must monitor progression and be prepared to increase the concentration. In the second phase of the study (cessation period), myopia did not progress when treatment was stopped in 50% of the patients (discontinuation phase). Those that stopped progressing during the cessation stage were presumed to no longer needed further treatment to slow myopia. Those who progressed more than 0.5D when atropine was discontinued were more likely to have been on the higher dosage and needed further treatment. The authors suggest that over the long run atropine 0.01% is more effective than higher concentrations, causes minimal symptoms secondary to pupillary dilation or loss of accommodation, and the 0.01% concentration can be used for 5 years and then stopped. If progression reoccurs, atropine 0.01% can be resumed. If higher

concentrations are required, the concentration of atropine should be tapered.⁷⁹

Safety of Atropine

As previously mentioned, myopia control is not an FDA indication for atropine sulfate ophthalmic solution 1%¹¹ and concentrations less than 1% must be compounded. Elevation of blood pressure from systemic absorption has been reported after ocular instillation of recommended doses of atropine 1%. Other systemic adverse reactions reported include skin, mouth, and throat dryness, restlessness, irritability or delirium, tachycardia, and flushed skin of the face and neck. Atropine 1% is generally not recommended for use with monamine oxidase inhibitors (MAOI) because of the potential for hypertensive crisis. Ocular adverse reactions include decreased lacrimation, allergic conjunctivitis, contact dermatitis, and lid edema. Due to potential systemic absorption, atropine 1% is not recommended for children less than 3 months old. For children under 3 years old, use is recommended to no more than one drop per eye per day. Toxic overdose is possible with atropine 1%.¹¹ Decreased salivation and drying of the mouth are the first signs of toxicity. In ATOM 1 study (N= 400 children) there were no reported serious adverse events.⁷¹ The reasons for withdrawal included: rare allergic reactions or hypersensitivity reactions, 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.

Shih et al.⁷³ reported that the incidence of adverse effects was 22% of the children using 0.5% atropine mostly related to complaints of light sensitivity after 3 months of use. Fifteen percent of the atropine 0.5% group 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 a study of children using 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.⁸⁴ No child reported irritation or an allergic reaction. In another study using 0.025% atropine,⁷⁵ 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.

Several recent, large studies involving atropine use with concentrations varying from 1%, 0.5%, 0.1% and 0.01% for one to two years nightly reported no serious adverse events among the study children.^{71,77,85} Furthermore, multifocal electro-retinograms (mfERG) were conducted in children two to three months after stopping the atropine 1% or the placebo treatment of two years duration (ATOM 1 study).⁸⁶ The electrophysiological findings showed no significant effect of the atropine treatment on retinal function. Future retinal abnormalities from atropine were considered unlikely as atropine concentration in the retina would decrease over time. Lastly, atropine 1% has been used in numerous PEDIG clinical trials without any significant side effects reported.⁸⁷⁻⁸⁹

In 2013 Cooper et al published a study⁷⁶ to determine the maximum dosage of atropine, which would not cause clinical symptoms such as pupillary dilation or diminished accommodation. They found that 0.02% was the highest dosage of atropine in which their participants did not report associated symptoms. This study was the first to include Caucasian patients, and systematically vary the

dosage to determine side effects. Loughman and Flitcroft reported that there were no side effects or symptoms when atropine 0.01% was used in Caucasians.⁹⁰

The ATOM study⁷¹ noted that any side effect was temporary and disappeared 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.⁷¹

Clinical Considerations and Guidelines for the Use of Atropine

Clinically, atropine 1% is effective for slowing the progression of myopia. It has been shown to be very effective over a wide range of myopia, and has been shown to be effective when used either daily or once weekly. It should be noted that a recent meta-analysis has challenged this conclusion. Gong et. al.⁹¹ found that there was no difference between atropine concentrations in slowing myopia progression, but higher dosages were associated with more symptoms. The largest disadvantages with atropine 1% are the induced complaints secondary to dilation and cycloplegia. These are well managed with photochromic progressive lenses. Previous studies have shown a 20% dropout rate secondary to blur and/or photophobia. Clinical experience has shown that patient symptoms and treatment dropout rates are not always this high. If used one must be careful to taper the dosage if a decision is made to stop using atropine 1%. Atropine 1% in our practice is typically reserved for young patients (age 4-5 years) who have rapid myopic progression as well as significantly myopic parents or in patients who continue to progress on lower dosages (see Figure 6).

Currently, our clinical treatment typically starts with either atropine 0.02% or 0.01%,

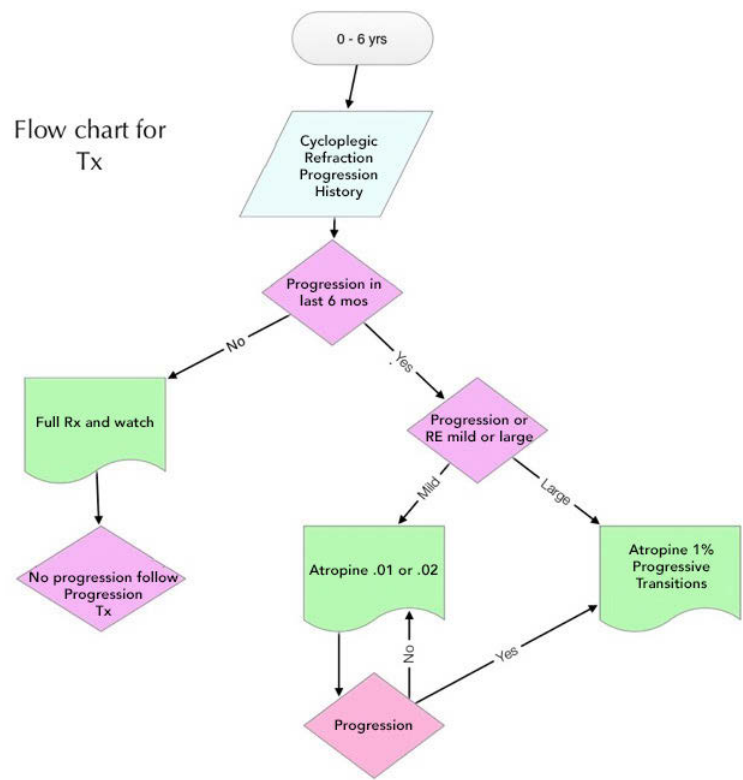


Figure 6: This is a flow chart for young children, who are either myopic, or trending towards myopia. Children with very progressive myopia (greater than 1D per yr.) and two parents that are myopic should be started on Atropine 1%. However, if there is concern about using higher dosages of Atropine, one may begin with a lower concentration and monitor progression with a IOL Master to determine if there are axial length changes. Children with low amounts of myopia should be placed on Atropine .02%, while children who appear to have incipient myopia should be started on Atropine .01%

since neither dosage is expected to clinically induce symptoms of blur or sensitivity of light. Dosage is decided based upon clinical perception of future progression. Lighter eyes are more prone to slightly more asymptomatic dilation than with 0.02%, thus, 0.01% atropine with frequent progression monitoring is a good starting point. The best way to monitor progression is with either the IOLMaster or Lenstar, since they are sensitive to ± 0.01 mm (.06 diopter) changes.^{92,93} We also advise of taking at least 15 measurements and using the calculated mean measurement of the instrument. Any increase greater than .04 mm or approximately .1 D is clinically meaningful. If an IOLMaster or equivalent is not available, a cycloplegic auto-refraction with cyclopentolate 1% is an alternative for checking progression.

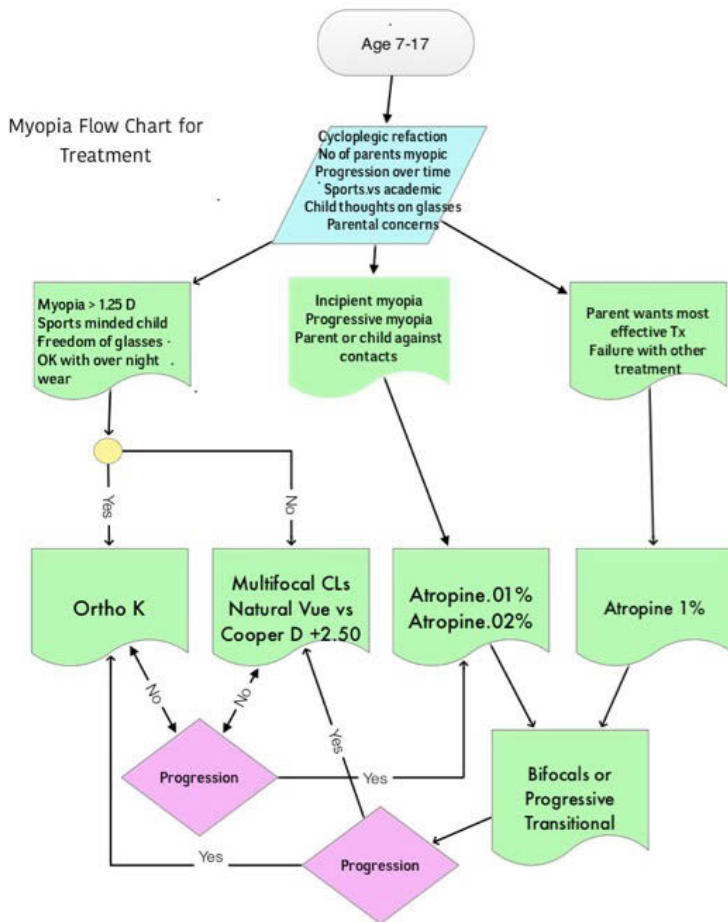


Figure 7: This is a flow chart for young children, who are either myopic, or trending towards myopia. Children with very progressive myopia (greater than 1D per yr.) and two parents that are myopic should be started on Atropine 1%. However, if there is concern about using higher dosages of Atropine, one may begin with a lower concentration and monitor progression with a IOL Master to determine if there are axial length changes. Children with low amounts of myopia should be placed on Atropine .02%, while children who appear to have incipient myopia should be started on Atropine .01%

Follow up appointments are based on past and expected future progression rates. For patients with a history of rapid progression (1.00 D or more per yr.), a three-month follow up is appropriate. For moderate and slow progression (.75 D or less per yr) the follow up is typically six and 12 months respectively. (See Figure 7)

In summary, atropine has been used in myopia control studies and amblyopia studies with a minimal number of ocular side effects and no serious systemic side effects.^{71,77,87,89,94} Anecdotally, the senior author has used atropine 1% for the last ten years on over 100

patients without any serious side effects noted. Most children surprisingly tolerate atropine with minimal complaints. However, before atropine is prescribed, risks and benefits must be presented to the parents and patient. Usage of atropine 1% must be combined with photochromic/transitional lenses. Children who cannot tolerate the effects of atropine 1% can be managed by changing the concentration from atropine 1% to another concentration, such as atropine 0.02%.

A common clinical question often arises for the recommendation of either orthokeratology, multifocal soft contact lenses (Visioneering Technologies, Inc, Natural Vue 1 Day Multifocal Contact Lenses, Alpharetta, GA),⁹⁵ or a low dosage of atropine. From a research literature standpoint they are equivalent. Drawing from personal clinical experience, however, atropine 0.01% is less effective than either atropine 1% or orthokeratology. As a matter of practicality, it is important to obtain the child's treatment permission and opinions. If a child does not want contact lenses both orthokeratology and multi-focal soft lenses will prove unsuccessful. If a child likes his or her glasses then a low dosage of atropine 0.02% is added to the treatment plan. Although evidence is limited, progressive lenses seem to slow the progression of myopia when prescribed with a low dosage of atropine. Typically, low myopes (-0.25 D to -1.25D) are less motivated to wear contact lenses, are poor candidates for myopia control with ortho-keratology, and are prime candidates for the prescription of low dosages of atropine 0.02%. Clinically, we believe that more aggressive atropine treatment of 0.01% should be recommended for children who are converting from hyperopia to myopia, becoming more myopic, and having parents with high myopia. These children are at high risk for continued myopic progression. Treatment is based upon clinical findings, the parents' as well as the child's opinions and concerns. Communication with the parents and patients helps to answer questions and

Table 3. This table presents the combined data on various treatment strategies to slow myopia determined by Meta analysis⁹⁶ and Cooper et. al.⁶

Myopia Progression Treatment	Meta-Analysis Effectiveness	Effectiveness as determined by J. Cooper, OD
Atropine (high dosage)	65%	85%
Atropine (moderate dosage)	65%	76%
Atropine (low dosage)	45%	60%
Orthokeratology	45%	45%
Multifocal Soft CL	33%	40%
Progressive/Bifocal Glasses	12%	16%
Single Vision	0%	0%
Under Correction	-9%	-8%

concerns, and seems to be greatly appreciated by the participants.

If myopia is not adequately controlled in those children who have elected treatment with orthokeratology or multifocal contact lenses we add atropine 0.01% to the treatment plan. Clinically, there exist patients who exhibit myopia progression after the age of 20 years and we offer atropine 0.01% treatment. We are careful to advise them that there is no research to support the use in older patients. When the patient elects to be treated with low dosage of atropine, a follow up of 3 or 6 months based upon previous progression. (i.e. 3 mos. if greater than .75D per yr.) is recommended. At the first exam, one week after using low dosages of atropine a careful refraction and near testing including near cover test and negative and positive relative accommodation are done to determine an add power if necessary. (See Table 3 for relative effectiveness of each treatment modality.)

Illustrative Case Examples

Case 1

A four year old is brought to clinic by his concerned parents. His glasses are from a previous doctor from one year ago and measure -2.50 DS OU. His cycloplegic refraction this day is -3.50 DS OU. Both parents have high myopia, greater than six diopters. This is a

child who is at high risk for continued rapid progression of myopia, and would therefore benefit from a more aggressive therapy of atropine 1%. After discussion with his parents the following treatment plan was decided: Glasses prescription of -3.50 OU/+2.50 photochromic progressive polycarbonate glasses lenses with atropine 1% one drop instillation OU at bedtime. The patient's myopia remained stable and at age nine he was fit in orthokeratology lenses. By age 14, his myopia has only increased by -0.50 D.

Case 2

A five year old patient presents for his yearly exam and has a cycloplegic refraction of plano in each eye. At age three his refractive error measured +1.50 DS OU and age four it measured +0.75 DS OU. Parents are both myopic and are concerned about their child's progression toward myopia. After the treatment options are discussed, the parents elect for atropine 0.01% OU nightly. A follow up was scheduled for 6 months in which there was no evidence of any refractive change. At the one year mark there was no evidence of myopia. Further follow-up has been extended to yearly follow-up. This patient remains glasses free.

Case 3

An eight year old child has a cycloplegic refraction today of -3.25 DS OU. His one-year-old glasses measure -2.50 DS OU. He is very happy with his glasses and expresses no interest in wearing contact lenses. After discussion with him and his parents, the treatment plan consists of -3.25 DS single vision lenses with 0.01% atropine nightly OU. With increasing age, the patient will likely have more interest in orthokeratology lenses or soft multifocal lenses, such as Natural Vue 1 day Multifocal lenses.⁹⁵ Depending on his myopic progression, atropine may or may not be recommended with contact lens wear.

Case 4

A 9 year old female is currently wearing -2.50 OU; and using atropine 0.01% nightly OU. She is returning for her one year follow-up and is now -3.00 OU and measures ortho at distance and 10 E'. The calculated ACA is $(15 + 10)/2.5$ or 10/1 ACA (variable IPD measurement have little effect on the ACA measurements and were excluded from calculations; distance-near calculations give the most accurate measurement for determination of the add at near). +1.00 would eliminate the esophoria, but we want to leave the patient exophoric so I gave the patient -3.00 OU/+1.50 Add and prescribe atropine .02%; the highest dosage without symptoms. One year later she returned with any evidence of progression. She was advised to continue treatment.

Case 5

A 43 year old female presented with a history of refractive surgery 15 years ago. She has a chief complaint of blur secondary to increasing myope subsequent to her refractive surgery. Prior to PRK she was originally -9.00, and she has slowly increased her myopic. Her subjective refraction was -4.00 D in each eye and a small Fuch's spot was not noted in the right eye. She was sent for a retinal consult and treated with anti-VEGF injections. The retina flattened with no signs of choroidal neo-vascularization. After a discussion of benefit and risks we both decided that a nightly prescription of atropine 0.01% was appropriate. Since she still had residual accommodation, the final add prescription was determined after she was using atropine for two weeks,. She is currently wearing -4.00/+1.50. She has not progressed in 2 years and has had no further retinal degeneration or need for further anti-VEGF injections. Though there is no way of knowing if the use of atropine is the real reason why her myopia stopped progressing, and she has not had further myopic progression, the treatment is logical, and appears to be successful.

CONCLUSION

Atropine is a safe, effective medication to slow the progression of myopia. It may be prescribed in the higher traditional dosage of 1%, or lower dosages such as atropine or 0.02% or 0.01%. Currently, atropine 0.01% which must be compounded, is the most commonly prescribed dosage. Most of the atropine studies involve Asian eyes and younger populations when myopia is the most progressive. Atropine therapy may be used alone or in combination with other treatment options. Its side effects are minimal and easily managed with progressive, photochromic lenses. Atropine therapy may act as a valuable treatment for myopia control either as an alternative or adjunct to orthokeratology and multifocal contact lenses.

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