



## CONTROLLING MYOPIA PROGRESSION IN CHILDREN

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### Abstract

Main aim of this article was a systematic review on causes and management of Myopia progression in children. Myopia is a general disorder, affecting just about one-third of the US population and over 90% of the population in some East Asian countries. Elevated amounts of myopia are connected with a bigger risk of sight-threatening troubles, such as retinal detachment, choroidal degeneration, cataracts and glaucoma. Slowing the progression of myopia could potentially advantage millions of children in the India. Few approaches used for myopia organize have proven to be useful. Treatment options such as undercorrection of myopia, gas permeable contact lenses, and bifocal or multifocal spectacles have all been proven to be ineffective for myopia control, although one recent randomized clinical trial using executive top bifocal spectacles on children with progressive myopia has shown to decrease the progression to nearly half of the control subjects. The most effective methods are the use of orthokeratology contact lenses, soft bifocal contact lenses, and pharmaceutical agents such as atropine, timolol or pirenzepine.

**Keyword:** Myopia progression, pharmaceutical agents, lenses, treatment.

### Introduction

Myopia in children remains a major public health problem worldwide, especially in some Asian countries such as China, Singapore and Japan. Although many interventions have been attempted, few have been proven to be effective in controlling onset and progression of myopia in children. Environmental factors, genetic susceptibility or ethnic differences can affect the efficacy of these interventions. However, many questions remain unclear and even controversial for controlling myopia. China has the biggest population with myopia, especially for children myopia. Thus, it is of importance to present what achievements Chinese scientists have made in the field of myopia control in children. We summarize the current findings on myopia control in children from the Anyang Childhood Eye Study, including epidemiological data, clinical trials, systematic reviews and meta-analyses, and compare them with studies in other countries to find potential clues for controlling myopia in children [1].

### DEFINATION AND CLASSIFICATION OF MYOPIA [2]:

Myopia has been the topic of scientific study for more than 400 years, but it is only more recently that it has been recognized as a serious public health issue, owing to its being a significant cause of visual loss and a risk factor for a range of pathologic ocular conditions. Its prevalence is increasing on a global basis and has reached epidemic levels in much of Asia. Myopia has been defined in a wide variety of ways in the past, such as based on its assumed etiology, age of onset, progression rate, degree of myopia

(in diopters), and structural complications. This has led to a confusing accumulation of terms. Hence this subcommittee's aim was to provide a standardized set of terminology, definitions, and thresholds of myopia and its main ocular complications. A critical review of current terminology and choice of myopia thresholds was undertaken to ensure that the proposed standards are appropriate for clinical research purposes, relevant to the underlying biology of myopia, acceptable to researchers in the field, and useful for developing health policy.

It is recommended that the many descriptive terms of myopia be consolidated into the following descriptive categories:

#### Myopia:

A refractive error in which rays of light entering the eye parallel to the optic axis, which are brought to a focus in front of the retina, when ocular accommodation is relaxed. This usually results from the eyeball being too long from front to back, but can be caused by an overly curved cornea, a lens with increased optical power, or both. It is also called near sightedness.

#### With qualifying terms:

##### Axial Myopia:

A myopic refractive state can be attributed to excessive axial elongation.

##### Refractive Myopia:

A myopic refractive state can be attributed to changes in the structure or location of the image-forming structures of the eye (i.e., the cornea and lens).

#### Secondary Myopia:

A myopic refractive state for which single and specific causes (e.g., drug, corneal disease, or systemic clinical syndrome) can be identified, that is not a recognized population risk factor for myopia development.

It was also recommended that in quantitative contexts, myopia should always be treated as a negative value and that mathematical comparison symbols be used in their strict mathematical sense. To provide a framework for research into myopia prevention, the condition of "premyopia" is defined.

#### Premyopia:

A refractive state of an eye of  $-0.75$  D and  $>0.50$  D in children where a combination of baseline refraction, age, and other quantifiable risk factors provides a sufficient likelihood of the future development of myopia to merit preventative interventions.

As a quantitative trait it is recommended that myopia be divided into myopia (i.e., all myopia), low myopia, and high myopia as based on the current consensus of publications:

**Myopia:** A condition in which the spherical equivalent refractive error of an eye is  $>0.5$  D when ocular accommodation is relaxed.

**Low Myopia:** A condition in which the spherical equivalent refractive error of an eye is  $>0.5$  D and  $>6.00$  D when ocular accommodation is relaxed.

**High Myopia:** A condition in which the spherical equivalent refractive error of an eye is  $>6.00$  D when ocular accommodation is relaxed.

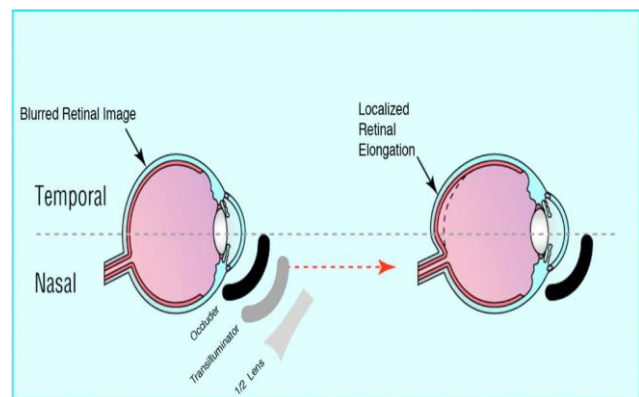
Although even low levels of myopia are associated with an increased risk of developing pathologic conditions such as myopia maculopathy and having a retinal detachment, "pathologic myopia" is proposed as the categorical term for the adverse, structural complications of myopia.

**Pathological Myopia:** Excessive axial elongation associated with myopia that leads to structural changes in the posterior segment of the eye (including posterior staphyloma, myopic maculopathy, and high myopia-associated optic neuropathy) and that can lead to loss of best-corrected visual acuity. A clinical classification is also proposed to encompass the scope of such structural complications.

#### PREVALANCE AND ETIOLOGY OF MYOPIA

Myopia is the most common eye disorder worldwide, but it is often misregarded as merely a refractive error that can simply be corrected by spectacles, contact lenses, or refractive surgery. As a matter of fact, high myopia is often associated with an increased risk of a range of serious ocular complications, which may result in irreversible vision loss. The World Health Organization (WHO) recently defined "high myopia" as  $-5$  Diopter (D) or greater, which is associated with increased risk of blindness [3]. Eyes with high myopia that develop degenerative changes in the macula, optic nerve and peripheral retina are considered as having pathologic myopia, and are at the highest risk of developing potentially blinding complications such as retinal detachments, myopic choroidal neovascularization (CNV), myopic macular degeneration, foveoschisis, glaucoma, and cataract [4,5]. Myopia has become a major public health issue because of its rapid increase of prevalence, especially in the East Asia, and its link to potential irreversible blindness.

Myopia is the most common ocular disorder worldwide. The prevalence of myopia in the United States has increased from 25% to 44% between 1972 and 2004. In urban communities in Asia, the prevalence is greater than 80%. The prevalence is much lower in underdeveloped areas in the world such as Sherpa in Nepal [6-12].



**Figure 1:** Regional blur causes axial elongation. Regional retinal blur created in half the retina causes regional elongation of the eye. This occurs even when the optic nerve is cut, but will not occur if atropine is injected into the eye. The eye recognizes the direction of the blur, that is, plus or minus lenses and the region of retinal blurs [13].

Although none of these modalities are US Food and Drug Administration-approved to slow myopia progression, they have been shown to slow the progression by approximately 50% with few risks. Both orthokeratology and soft bifocal contact lenses have shown to slow myopia progression by slightly less than 50% in most studies. Parents and eye care practitioners should work together to determine which modality may be best suited for a

particular child. Topical pharmaceutical agents such as anti-muscarinic eye drops typically lead to light sensitivity and poor near vision. The most effective myopia control is provided by atropine, but is rarely prescribed due to the side effects. Pirenzepine provides myopia control with little light sensitivity and few near-vision problems, but it is not yet commercially available as an eye drop or ointment. Several studies have shown that lower concentrations of atropine slow the progression of myopia control with fewer side effects than 1% atropine. While the progression of myopic refractive error is slowed with lower concentration of atropine, the growth of the eye is not, indicating a potentially reversible form of myopia control that may diminish after discontinuation of the eye drops. This review provides an overview of the myopia control information available in the literature and raises questions that remain unanswered, so that eye care practitioners and parents can potentially learn the methods that may ultimately improve a child's quality of life or lower the risk of sight-threatening complications [14].

#### CAUSES

The cause and underlying mechanism of myopia progression remain unclear; therefore, its increasing prevalence is not well understood. Several theories have been proposed to explain the recent increase and its earlier onset in children, including a decrease in outdoor activity, an increase in time spent doing near work, and an increase in urbanization. Despite these theories and studies showing that increasing outdoor activity and decreasing near work may help to retard myopic progression, other treatments have been sought. The prevention of myopia progression has been prioritized largely because the risks of increasing axial myopia include glaucoma, cataract, myopic macular degeneration, and retinal detachment [15-18].

#### PHYSIOPATHOLOGY AND BIOLOGICAL MECHANISMS OF MYOPIA

Since 1977 when Wiesel and Raviola accidentally discovered in animal models that visual form deprivation was implied in genesis of myopic axial elongation, the local control of retina on the eye growth was postulated. Several animal models have shown the response of axial eye growth in order to compensate an imposed defocus. In non-human primate models, it has been demonstrated that manipulating the peripheral retinal defocus with bifocal contact lenses can modify the eye growth and the refractive status. More in particular, axial myopia can be produced by imposing a peripheral hyperopic defocus. In another study on marmosets, Benavente-Perez et al. suggested that imposing a positive defocus on retina, could be considered an effective strategy in order to slow myopia progression. Additionally, it was found that this response could be elicited locally in the eye globe if the

visual deprivation was specifically directed to certain retinal areas. Thus, retina is involved in the modulation of the eye axial length when a sign of defocus is detected. More surprisingly, the underlying choroid can modify its thickness to move the retina closer to the focal plane [19-26].

However, applying on human models an imposed defocus would cause smaller modifications in eye axial length than animal experiments. In this regard, the COMET and STAMP clinical trials observed in children treated with progressive addition lenses a smaller modification in the refraction in proportion to the degree of refractive error imposed. Thus, they hypothesized that a more gradual accommodation, induced in children with progressive addition lenses, would reduce the retinal peripheral defocus and, therefore, the stimulus for the eye growth. Anyway, further clinical studies are needed to better establish the role of accommodation in relaying the retinal error signal and the consequent inhibition of eye growth in children. Higher amounts of myopia increase the risk of ocular complications such as glaucoma, cataracts, and retinal detachment and atrophy. Due to these sight-threatening complications and the high worldwide prevalence, research scientists have attempted many methods to reduce the progression of nearsightedness, including undercorrection of myopic refractive error, bifocal or multifocal spectacles, gas permeable contact lenses, topical pharmaceutical agents, orthokeratology contact lenses, and soft bifocal contact lenses [27-58].

#### Undercorrection of Myopia

Myopes read more and scholastically perform better than emmetropes or hyperopes, so accommodative effort and myopia may be associated. Myopic patients also have a higher accommodative lag than emmetropic patients, and the lag of accommodation focuses light behind the retina during near work, potentially acting as a putative cue for increased myopia progression. Undercorrection of myopia reduces accommodative effort and accommodative error (lag), and hence is thought to slow myopia progression. In actuality, undercorrecting a child's refractive error either increases or has no effect on myopia progression, and so undercorrection does not slow myopia progression [59-66].

#### Experimental Models of Emmetropization and Myopia Report [67]

Much of our current understanding of characteristics and mechanisms of postnatal eye growth and the development of myopia has come from detailed experimental studies using animal models. These models use a wide range of species, from primates to invertebrates, and include macaque and marmoset monkeys, tree shrews, guinea pigs, mice, chickens, fish, and squids. Considering that

these phylogenetically wide-ranging species all possess visually guided eye growth despite differences in ecology, ocular anatomy, visual function, and visual acuity, this supports the hypothesis that visually guided eye growth is an evolutionarily conserved process found in camera-type eyes. Each species provides unique experimental advantages to study the mechanisms of visually guided eye growth and the key signalling pathways that regulate refractive eye development across species; however, anatomic and physiological differences must be taken into account when interpreting and translating results to humans.

The report summarizes the anatomic similarities and differences between the eyes of the principal experimental species used for studies of emmetropization and myopia.

Surveying more than 800 published reports on the changes in eye growth and refractive state in response to experimental manipulations of visual conditions, the report offers a summary of the evidence supporting the role of vision in eye development and the mechanisms that underlie the visual regulation of eye growth and emmetropization development.

Also discussed are the key operating characteristics of experimental emmetropization to experimentally imposed retinal defocus including local retinal mechanisms controlling regional eye growth, the spatial and temporal integration of visual signals, the impact of simultaneous competing defocus signals, the relationships of various ocular circadian rhythms to induced changes in eye growth, and the critical periods for visual experience-invoked myopia. Studies of the characteristics of the visual signals affecting eye growth are also reviewed and discussed, including the intensity of ambient illumination, the spectral composition of light, longitudinal chromatic aberration, higher-order monochromatic aberrations, and astigmatism. The report reviews the biochemistry of refractive error development, including the roles of various retinal neurotransmitters, neuromodulators, and growth promoters such as dopamine, vasoactive intestinal peptide, melanopsin, glucagon, and insulin, and nitric oxide. Pharmacologic studies of the mechanisms of emmetropization and myopia are discussed including the effects of cholinergic, GABAergic, and adenosine antagonistic drugs and drugs affecting nitric oxide and neuropeptides. Finally, the article reviews the molecular biology of gene expression in the eye and retina and possible gene-environment interactions.

#### TREATMENT OF MYOPIA

The incidence of retinal detachment and macular degeneration increases logarithmically above 2 diopters of myopia. To put this in perspective, keeping myopia at 21.00 versus 23.00 D reduces the risk of macular

degeneration by 4 times and retinal detachment by 3 times. Brennan<sup>130</sup> reported that reducing progression by 33% would result in a 73% reduction in myopia progression above 5 D; if the reduction rate improved to 50%, and then there would be 90% reduction of myopia above 5 D. Thus, myopia control becomes an increasingly important issue because recent environmental changes have not only resulted in a sharp increase in the incidence of myopia worldwide, but caused an increase in the age of progression and the ultimate increase in the magnitude of the refractive error. In our opinion, patients should be presented with the current risks and benefits of the various treatment options available for myopia control. Animal and human studies have important practical consequences for the treatment of myopia. They specifically suggest that reducing lag of accommodation, reducing both central and peripheral defocus, and blocking myopiagenic signaling in the eye should slow the progression of myopia. Considering that the information about signaling pathways underlying myopia development is limited, the currently considered treatment modalities for control of myopic progression include optical correction such as bifocal spectacle lenses, progressive addition spectacle lenses, under-correction, OK, multifocal contact lenses, and increased exposure to outdoor activities, with the notable exception of atropine which has been shown to block myopiagenic signaling albeit with some uncomfortable side effects [56, 68]

#### Spectacles [68-77]

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

Recently, Cheng et al.<sup>138</sup> studied the use of high fitting executive bifocal spectacle lenses with base-in prism as

compared to SV lenses in a group of Canadian Asians. The experimental lens slowed the progression of myopia by 40%. However, this study was not masked and was not double-blinded. In 2011, Shi-Ming Li et al. performed a meta-analysis of 9 clinical trials in which powers of PALs ranged from +1.5 to +2.0 D and found that PALs slowed myopic progression by 0.25 D/year as compared to SV lenses. The effect was greater in Asian children as compared to Caucasians and also greater in children who had a higher level of myopia at baseline and who progressed at a more rapid rate.

### Lenses [78-87]

Spectacles are often used to correct myopia to give better distance vision. Traditionally, spectacle lenses use single-vision designs. However, some lenses with special designs, such as bifocal or multifocal, which are used for correcting presbyopia, have been used in attempts to control myopic progression in children. The evidence from meta-analysis showed that multifocal spectacles with powers ranging from +1.50 to +2.00 D produce statistically significant decreases in myopia progression in school-aged children compared with single-vision spectacles. Moreover, Asian children, predominantly East Asian children, appeared to have greater benefit from intervention with multifocal lenses than Caucasian children. Studies on soft contact lenses using design concentric ring bifocal and peripheral add multifocal designs confirm that it is the design of bifocal or multifocal, not the modality of spectacles or contact lenses, that is important for clinically effective control of myopia in children.

Bifocal or multifocal lenses, incorporating under correction around center of lenses for achieving better near vision, raise an issue on whether single-vision lenses designed with under correction can also slow myopia progression. To date, there were only two randomized controlled trials published on this issue. Chung *et al.* and Adler *et al.* found that under correction of myopia with respective amount of +0.75 D and +0.50 D enhanced rather than inhibited myopia progression in children. However, these two studies were conducted in Malaysia and in Israel, respectively. A randomized controlled trial (FUMET) conducted in Chinese children, who usually spend more time on near work and less time outdoors, is expected to show whether ethnic difference also exist in the effect of under correction of myopia.

Interestingly, data from the Anyang Childhood Eye Study showed that myopic children with under correction of myopia by wearing spectacles did not present with faster myopia progression than children with full correction over 1 year. Furthermore, the data showed that myopic children with no correction had significantly slower myopia progression (-0.76 D vs. -1.03 D,  $P < 0.01$ ) and less axial elongation (0.47 vs. 0.51 mm,  $P < 0.01$ ) than children with

full correction over 2 years. Moreover, myopia progression decreased significantly with an increasing amount of under correction in Anyang children. This is the first report in myopic children to support previous findings from animal model of lens-induced myopia (LIM) that myopic defocus slows myopia progression, and indicate that stronger or longer signal of myopic defocus may be needed in human beings for producing effective inhibition of eye growth than in animals. Further analysis from the Anyang data may reconfirm whether feedback control theory applies to myopia progression in children, namely continuous correction of myopia will open the feedback loop resulting in linear progression that increases myopia.

### PHARMACOLOGICAL CONTROL OF MYOPIA [88-106]

In relation to pharmacological control of myopia progression, to-date topical atropine has dominated both clinical trials and clinical practice, where it is now used widely as either an approved product or off-label. Atropine is a nonselective irreversible antimuscarinic antagonist, with a long history of use in ophthalmology as a potent and long-acting mydriatic and cycloplegic agent. Clinically, it is used as a diagnostic aid in the assessment of refractive errors in very young children, to penalize the preferred eye in therapy for amblyopia, and to immobilize the iris and ciliary muscles as a component of therapy for uveal inflammatory conditions such as iritis. Its use to treat myopia dates back to the 1960s.

The earliest cohort studies involving topical atropine were published in the 1970s. Since that time, numerous retrospective and cohort studies have been published.

The first randomized controlled trials (RCTs) to be published are those by Yen et al. (1989) and Shih et al. (1999). More recently, two large, back-to-back trials were undertaken in Singapore: the Atropine for Treatment of Myopia studies (ATOM1 and 2), followed by two smaller studies in

China by Yi et al. (2015) and Wang et al. (2017), carried out a very recent larger trial in Hong Kong. Two other antimuscarinic drugs appear in these studies: tropicamide, which is a short-acting drug and was used as a control treatment, and cyclopentolate, which has an intermediate duration of action and was tested for its efficacy as a myopia control agent.

Other pharmacological approaches trialed for myopia control include topical timolol, a nonselective beta-adrenergic antagonist, and oral 7-methylxanthine (7-MX), an adenosine antagonist. The latter was approved for use in Denmark, as pharmacy-compounded tablets, with reimbursement from the

Danish National Health Insurance for patients up to 18 years of age, after a small clinical trial of 7-MX in that

country; 7-MX is also generated by metabolism in the body from caffeine and theobromine, which are both ingredients of dark chocolate. To date there have been no follow-up trials in other countries, although it remains a drug of interest, with related on-going studies in the monkey myopia model.

Although recommendations for the use of ocular hypotensive drugs for myopia control appear in a number of early publications, including that by Curtin (1985), well-described clinical trials of these agents are limited, although there are reports of positive treatment outcomes for epinephrine, labetalol, a combination of pilocarpine and timolol, and timolol alone. Denmark was the site of the largest RCT of twice-daily topical 0.25% timolol for myopia control, by Jensen (1991). The driving principle for this approach is biomechanical (i.e., to lower IOP as a method of slowing ocular elongation). Topical timolol is widely available in many countries as a topical ophthalmic drug, approved for the treatment of open angle glaucoma. Reviews covering pharmacological interventions for myopia control include one focused on primary research, a Cochrane review, and a more recent one focused on atropine. In this article, results of relevant meta-analyses are also presented.

#### Atropine [93-107]

Based on changes in spherical equivalent refractive error as the outcome measure all studies have shown that atropine slows myopia progression. Bedrossian (1971) in an early study of 150 children aged 7 to 13 years reported no myopia progression in 75% of eyes treated daily with 1% atropine over a 1-year period compared with only 3% of controls. Similarly another early study by Gimbel (1973) in which 279 children received 1% atropine over 3 years reported a 66% reduction in myopia progression compared with that of 572 controls (0.41 vs. 1.22 D). The first two randomized controlled trials of atropine, both published in the 1990s, also reported very good control over myopia progression in children, with reductions exceeding 60% reported for the highest, 1% concentration. In the first randomized controlled trial by Yen and colleagues (1989), 247 children aged 6 to 14 years received topical 1% atropine, 1% cyclopentolate, or saline drops over a 1-year period. They reported 76% and 36% reductions in myopia progression in the groups treated with atropine and cyclopentolate, respectively, compared with the group treated with saline, although unfortunately, there was a large loss to followup (61%). In the second randomized controlled trial by Shih and colleagues (1999), 200 children aged 6 to 13 years were treated with 0.5%, 0.25%, or 0.1% atropine over a 2-year period; reported reductions in myopia progression were 61%, 49%, and 42%, respectively, compared with children treated with 0.5% tropicamide as the control treatment.

#### Timolol [108]

The RCT by Jensen<sup>130</sup> had three treatment arms: SV spectacles (n = 51), bifocal spectacles (n = 57), and SV spectacles þ timolol (n = 51). The timolol arm used 0.25% timolol maleate, twice a day. Children were followed for 2 years, with additional examinations 1 year after completion of the trial. The results were generally disappointing, with mean myopia progression over the 2-year study period in the control and timolol groups being almost identical (1.14 vs. 1.18 D, respectively), and not significantly different from each other. This was despite confirmation that timolol lowered IOP significantly, by approximately 3 mm Hg, with those with high IOP showing the largest treatment effect. Also, although there appeared to be a trend toward increasing noncompliance over time, progression rates did not appear to reflect compliance. Curiously, higher progression rates appeared associated with higher IOP in the control group, with this relationship reaching statistical significance for the girls, with a similar but not significant trend for boys.

#### SURVEY OF SOME REPORTED LITERATURES:

Myopia, or 'near sightedness', is the one of the most common refractive disease worldwide and is due to an excessive axial elongation of the eye as a major mechanism in children. According to the recent report published in Nature, myopia is becoming an epidemic in the developed countries of East and South-East Asia, where the prevalence reaches peaks of 80–90% in children attending secondary school, aged 17–18. Concomitantly, the European Eye Epidemiology Consortium (E3) demonstrated in a meta-analysis of a population based, cross-sectional study that also in the Western countries the prevalence of myopia is dramatically growing, with a significant variability between age groups, resulting higher (46%) in the 25 (years-old) subgroup than the 75 (years-old) one, with only 15% people affected [109-111].

This article analyzed all the possible behavioral, interventional and pharmacological strategies that can be adopted in the pediatric population, in order to slow the progression of myopia. The recent network meta-analysis published by Huang et al. compared the effectiveness of different interventions used to slow down the progression of myopia, including atropine and other anti-muscarinic agents, orthokeratology (OrthoK), soft bifocal contact lenses (SCLs), bifocal spectacles (PBSLs) and progressive lens spectacles (PASLs) and more outdoor activities [112].

In our review we will discuss not only the clinical efficacy of the investigated interventions, but we will also evaluate the side effects, the patient tolerability and the effective long-term advantages for the pediatric population.

The prevalence of myopia has increased worldwide in recent decades and now is endemic over the entire

industrial world. This increase is mainly caused by changes in lifestyle and behavior. In particular, the amount of outdoor activities and near work would display an important role in the pathogenesis of the disease. Several strategies have been reported as effective. Spectacles and contact lenses have shown only slight results in the prevention of myopia and similarly orthokeratology should not be considered as a first-line strategy, given the high risk of infectious keratitis and the relatively low compliance for the patients. Thus, to date, atropine ophthalmic drops seem to be the most effective treatment for slowing the progression of myopia, although the exact mechanism of the effect of treatment is still uncertain. In particular, low-dose atropine (0.01%) was proven to be an effective and safe treatment in the long term due to the lowest rebound effect with negligible side effects [113].

The prevalence of myopia is increasing globally. Complications of myopia are associated with huge economic and social costs. It is believed that high myopia in adulthood can be traced back to school age onset myopia. Therefore, it is crucial and urgent to implement effective measures of myopia control, which may include preventing myopia onset as well as retarding myopia progression in school age children. The mechanism of myopia is still poorly understood. There are some evidences to suggest excessive expansion of Bruch's membrane, possibly in response to peripheral hyperopic defocus, and it may be one of the mechanisms leading to the uncontrolled axial elongation of the globe. Atropine is currently the most effective therapy for myopia control. Recent clinical trials demonstrated low-dose atropine eye drops such as 0.01% resulted in retardation of myopia progression, with significantly less side effects compared to higher concentration preparation. However, there remain a proportion of patients who are poor responders, in whom the optimal management remains unclear. Proposed strategies include stepwise increase of atropine dosing, and a combination of low-dose atropine with increase outdoor time. This review will focus on the current understanding of epidemiology, pathophysiology in myopia and highlight recent clinical trials using atropine in the school-aged children, as well as the treatment strategy in clinical implementation in hyperopic, pre-myopic and myopic children [114].

Myopia occurs in more than 50% of the population in many industrialized countries and is expected to increase; complications associated with axial elongation from myopia are the sixth leading cause of blindness. Thus, understanding its etiology, epidemiology, and the results of various treatment regimens may modify current care and result in a reduction in morbidity from progressive myopia. This rapid increase cannot be explained by genetics alone. Current animal and human research

demonstrates that myopia development is a result of the interplay between genetic and the environmental factors. The prevalence of myopia is higher in individuals whose both parents are myopic, suggesting that genetic factors are clearly involved in myopia development. At the same time, population studies suggest that development of myopia is associated with education and the amount time spent doing near work; hence, activities increase the exposure to optical blur. Recently, there has been an increase in efforts to slow the progression of myopia because of its relationship to the development of serious pathological conditions such as macular degeneration, retinal detachments, glaucoma, and cataracts. We reviewed metaanalysis and other of current treatments that include: atropine, progressive addition spectacle lenses, orthokeratology, and multifocal contact lenses [115].

Literature searches were last conducted in December 2016 in the PubMed database with no date restrictions, but were limited to studies published in English, and in the Cochrane Library database without any restrictions. The combined searches yielded 98 citations, 23 of which were reviewed in full text, out of these, 17 articles were deemed appropriate for inclusion in this assessment and subsequently were assigned a level of evidence rating by the panel methodologist. Seventeen level I, II, and III studies were identified. Most of the studies reported less myopic progression in children treated with atropine compared with various control groups. All 8 of the level I and II studies that evaluated primarily myopic progression revealed less myopic progression with atropine (myopic progression ranging from 0.04-0.63 to 0.47-0.91 diopters (D)/year) compared with control participants (myopic progression ranging from 0.38\_0.39 to 1.19\_2.48 D/year). In studies that evaluated myopic progression after cessation of treatment, a rebound effect was noted. Several studies evaluated the optimal dosage of atropine with regard to myopic progression, rebound after treatment cessation, and minimization of side effects. Lower dosages of atropine (0.5%, 0.1%, and 0.01%) were found to be slightly less effective during treatment periods of 1 to 2 years, but they were associated with less rebound myopic progression (for atropine 0.01%, mean myopic progression after treatment cessation of 0.28-0.33 D/year, compared with atropine 0.5%, 0.87-0.52 D/year), fewer side effects, and similar long-term results for myopic progression after the study period and rebound effect were considered. The most robust and well-designed studies were carried out in Asian populations. Studies involving patients of other ethnic backgrounds failed to provide sufficient evidence of an effect of atropine on myopic progression. Level I evidence supports the use of atropine to prevent myopic progression. Although there are reports of myopic rebound after treatment is

discontinued, this seems to be minimized by using low doses (especially atropine 0.01%) [116].

To determine the effectiveness of different interventions to slow down the progression of myopia in Children, they searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov from inception to August 2014. We selected randomized controlled trials (RCTs) involving interventions for controlling the progression of myopia in children with a treatment duration of at least 1 year for analysis. The primary outcomes were mean annual change in refraction (diopters/year) and mean annual change in axial length (millimeters/year). Thirty RCTs (involving 5422 eyes) were identified. Network meta-analysis showed that in comparison with placebo or single vision spectacle lenses, high-dose atropine (refraction change: 0.68 [0.52e0.84]; axial length change: -0.21 [-0.28 to -0.16]), moderate-dose atropine (refraction change: 0.53 [0.28e0.77]; axial length change: -0.21 [-0.32 to -0.12]), and low-dose atropine (refraction change: 0.53 [0.21e0.85]; axial length change: -0.15 [-0.25 to -0.05]) markedly slowed myopia progression. Pirenzepine (refraction change: 0.29 [0.05e0.52]; axial length change: -0.09 [-0.17 to -0.01]), orthokeratology (axial length change: -0.15 [-0.22 to -0.08]), and peripheral defocus modifying contact lenses (axial length change: -0.11 [-0.20 to -0.03]) showed moderate effects. Progressive addition spectacle lenses (refraction change: 0.14 [0.02e0.26]; axial length change: -0.04 [-0.09 to -0.01]) showed slight effects. This network analysis indicates that a range of interventions can significantly reduce myopia progression when compared with single vision spectacle lenses or placebo. In terms of refraction, atropine, pirenzepine, and progressive addition spectacle lenses were effective. In terms of axial length, atropine, orthokeratology, peripheral defocus modifying contact lenses, pirenzepine, and progressive addition spectacle lenses were effective. The most effective interventions were pharmacologic, that is, muscarinic antagonists such as atropine and pirenzepine. Certain specially designed contact lenses, including orthokeratology and peripheral defocus modifying contact lenses, had moderate effects, whereas specially designed spectacle lenses showed minimal effect. This article provides a network meta-analysis of interventions proposed to reduce myopia progression. This network approach is an extension of a traditional metaanalysis that allows for both direct and indirect comparisons, even when 2 strategies have not been directly compared. A network meta-analysis integrates relevant data without losing the strength of randomization in individual randomized controlled trials (RCTs). We conducted this network meta-analysis with the aim of deriving evidence-based clinical guidelines for myopia control in children [117].

As a practice that emphasizes children, specialty contact lenses and research (including myopia control research), we often are referred patients seeking an alternative method of vision correction to reduce myopia progression. These patients are among the more than 41% of people in the United States suffering from myopia. Although there are currently no interventions that cease myopic progression, it has been suggested that a number of treatment options can decrease its progression. If we can slow this progression in children, not only could we potentially reduce the cost of U.S. vision care, but also possibly save them from the devastating vision loss due to myopic retinopathy, retinal detachment and glaucoma that is associated with myopia. Like many practitioners, we have found it challenging at times to address parent and patient questions regarding the methods and treatment options to stop or slow the progression. However, with several studies ongoing and many on the verge of publication, we might soon have more answers. In the last decade, we have seen an increasing interest in research to slow myopia progression—especially in children, given that we see the greatest amount of myopia progression before adulthood. Evidence has shown a reduction in progression using a number of treatments, including anti-muscarinic therapy and orthokeratology. While some of these treatment modalities have been approved in other countries, there are no FDA-approved treatment methods specifically targeting myopia control in the United States. As such, you will need to explain to patients that these interventions are off-label should you decide to use them in practice [118-120].

#### Spectacles [121-123]

While these various spectacle lens options offer mild help for some patients, we have not seen the significance to be large enough in our clinic to actively recommend any type of lens for patients on a regular basis. However, if a child is progressing in myopia and is unwilling or unable to use any of the other methods, we will consider progressive addition lenses (PALs). Additionally, we are keeping our eyes peeled on the studies looking at novel spectacle lens options for patients. Undercorrected Single Vision Lenses Parents often get concerned when their children's spectacle prescriptions increase, fearing that their child will end up highly myopic. So, many times, they ask us to prescribe lenses that are not as strong in order to "keep their child's prescription from getting worse." The bottom line is there's no evidence to back it up—in fact, it's just the opposite.

A 2006 study looked at myopic children between ages six and 15 years old over a period of 18 months. Twenty-three of the participants were fully corrected, while 25 were undercorrected by +0.50. Although statistically insignificant, there was a slight progression of myopia

(0.17D) in the children who were undercorrected. A 2002 study showed similar results of increased myopia progression (0.23D) over a two-year period. Although the increase was not significant, both studies suggest that undercorrecting myopes has a negative effect on the progression of myopia. Ergo, undercorrected single vision lenses should not be used for slowing the progression of myopia.

At our practice, we bring patients with a history of increasing myopia corrected by spectacle lenses back for refraction in six months to ensure their myopia is not progressing further. If we note that their myopia has progressed, we will make a change to their spectacles rather than waiting another six months (one year total), as we do not want them to be undercorrected for a significant period of time.

The data shows undercorrected children progress faster in their myopia—therefore, we make sure these children have a new update prescription as soon as their eyes change in an effort to stabilize their vision as best as possible.

#### Traditional Bifocal Glasses [124-128]

Since Dr. Robert Wick first reported on the use of bifocals to correct myopia in 1947, practitioners have been using them with varied success. One study noted that myopic children who were appropriately corrected showed an accommodative response to near objects that was weaker than emmetropic patients.

This inspired the hypothesis that patients with progressing myopia who have a decreased accommodative response may have a slight blur on the retina that stimulates increased myopia development. Thus, bifocal glasses may offer a benefit, as they compensate for the reduced accommodative response, especially in children who are esophoric as they show an even greater accommodative lag.

In 2000, researchers randomized 82 myopic children with esophoria to bifocals or single vision lenses. They found that bifocals reduced the progression of myopia by 0.25D over 30 months compared to single vision lenses. The mean change in vitreous chamber depth was 0.36 +/- 0.34mm in the bifocal group and 0.48 +/- 0.28mm in the single vision group. Overall, there was a 20% reduction in myopia progression with bifocal lenses vs. the single vision lens counterpart. Older studies have suggested that bifocals could provide reduction in myopia progression of 44% or more.

#### Progressive Addition Lenses [126-129]

Given the improvements that progressive addition lenses (PALs) offer to adult patients with presbyopia, it makes sense to consider using PALs for children with decreased

accommodative issues and as a consideration for decreasing myopia's progression.

PALs offer many advantages to patients, but for young children and adolescents, the appearance of the lenses cannot be overstated. Patients enjoy the smooth transition of vision from their distance to near vision without the distinct junction line. One of the inherent drawbacks to PALs is that there can be an adaptation period where the patient experiences peripheral distortion, and some patients are unable to adapt to PALs.

The Correction of Myopia Evaluation Trial (COMET) looked at the effect of PALs compared to single vision lenses on myopic progression. Investigators enrolled 469 subjects, age six to 11, with myopic prescriptions between -1.25 and -4.50 spherical equivalent. One arm of the study had single vision distance correction while the other had PAL lenses with a +2.00 add.

The researchers looked at the progression of myopia through cycloplegic refraction over the course of three years, and found a difference between PAL and single vision lenses of 0.20 D. Although their findings were statistically significant, the authors concluded that the use of PALs as a clinically significant treatment option is not warranted on a routine basis. Considering the significant cost of PALs compared to single vision lenses and how minimal the reduction is, PALs do not merit the frequent use that we currently see in the optometry field [128]

One theory related to myopia progression suggests a correlation to hyperopic defocus in the peripheral retina. One recent study looked at a control group of single vision-wearing children and compared them to patients wearing lenses that were intended to reduce peripheral hyperopic defocus. In this 12-month study, there was no statistically significant difference between the novel designs and the control group. However, when evaluating the differences between the control group and children who were younger (six to 12 years) with a parental history of myopia, there was a difference of 0.29D [129]

#### Contact Lenses [130]

Now that optometrists are fitting younger children with contact lenses, they are a much more viable option for treating myopia progression. While many children feel insecure about wearing glasses, contact lenses have been found to improve their self image and self worth, allowing them to both see and feel better. However, there are some drawbacks—namely, the possibility of infection and increased chair time. Luckily, the array of contact lenses in today's market gives us plenty of options to find the right fit for each patient.

#### Conclusions

In summary, under-correction of myopia is not recommended for myopia control as it is likely to speed up myopia progression instead. Among spectacles, PALs and multifocal lenses do not yield clinically meaningful effects on slowing myopia progression in children. Although the effectiveness of myopia control with atropine is relatively better than those of optical methods, the associated side effects, such as sensitivity to light and near blur, hinder its widespread clinical application. Optical interventions are less invasive, which will make it likely to become more popular compared to pharmaceutical treatments.

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