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Interventions to Retard Myopia Progression in Children

An Evidence-based Update

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Topic: To evaluate the efficacy of interventions such as eyedrops, bifocal lenses, or contact lenses in retarding the progression of myopia in myopic children.

Clinical Relevance: Myopia is a common ocular disorder, and high myopia (myopia at least −6.0 diopters) is associated with potentially blinding conditions. At present, there are no general guidelines on interventions that may decrease myopia progression in children, but some interventions such as contact lenses are offered on an ad hoc basis.

Methods or Literature Reviewed: English and non-English language articles published from 1968 to 2000 were retrieved using a keyword search of MEDLINE, Embase, Cochrane Library, and Science Citation Index databases. Randomized controlled trials with comparisons of the effectiveness of interventions to decrease myopia progression in myopic children were reviewed.

Results: Ten clinical trials of different interventions to retard myopia progression were reviewed, including three trials that evaluated atropine and one trial that evaluated soft contact lenses. Atropine eye drops of 0.5% concentration were effective in clinical trials, but no significant effect was found for tropicamide or timolol eyedrops. Five of the six trials on bifocal spectacle lenses with various additions failed to show significant retardation, and results of the remaining trial were barely significant ($P = 0.047$). A trial of soft contact lenses failed to show significant effects.

Conclusions: The latest evidence from randomized clinical trials does not provide sufficient information to support interventions to prevent the progression of myopia. Long-term large-scale double-masked randomized clinical trials, including cycloplegic refraction, are needed before any recommendations about interventions in clinical practice to prevent high myopia in myopic children are considered. *Ophthalmology 2002;109:415–427*
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The prevalence rates of myopia are rising rapidly in several Asian countries.[1–3] In Taiwan, Hong Kong, and Singapore the prevalence rate of myopia in young adults is 60% to 80%; in the United States and Europe the prevalence rate in older adults is 20% to 50%.[1,2,4–6] The rate of progression of myopia is highest in young children, and the average age of stabilization of myopia is approximately 16 years. The onset of myopia may occur at a relatively young age, leading to higher risks of high myopia (myopia at least −6.0 diopters [D]) in adulthood.[1] High myopia is associated with potentially blinding complications, such as retinal detachment and glaucoma.[7,8] Often, the quality of life and daily visual activity of high myopes are compromised.[9] Complications of high myopia impact individuals at a time when they are economically active. As such, the socioeconomic effects of high myopia are huge. These factors imply that the prevention of myopia is of utmost importance.

There are many hypotheses that attempt to explain the development and progression of axial myopia. Suggested mechanisms for the development of myopia include excessive accommodation and uncoordinated eye growth medi-

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ated by retinal signals as a response to prolonged near-work.[10,11] In addition, the genetic basis of myopia has yet to be fully explained.

Various studies have suggested several interventions that may retard the progression of myopia in children, thereby decreasing the severity of myopia at maturity. Contact lenses may flatten the cornea or may retard axial elongation.[12] As a muscarinic antagonist, atropine may act through muscarinic receptors to paralyze accommodation; or it may have a direct effect on scleral growth.[13] Adrenergic or β-blocking drugs may reduce raised intraocular pressure in high myopes.[14,15] Bifocal lenses may reduce defective accommodative effort and improve retinal image quality in patients with high accommodative lag, thereby preventing potential aberrant eye growth.[16]

As conflicting results have been published in the literature, the clinician has been hard pressed to recommend any particular measure to prevent or retard the progression of myopia in children. The purpose of this study is to compile the latest evidence from all relevant randomized clinical trials evaluating interventions that could potentially decrease the progression rate of myopia in myopic children. Recommendations for each intervention have been made, and the strength of the evidence for each intervention is shown. Additional details will be presented in the Cochrane Review now in preparation.

Sources and Methods of Literature Search

Search Strategy for the Identification of Studies

A comprehensive search was conducted to identify all relevant randomized clinical trials with the primary objective of evaluating interventions to retard the progression of myopia in myopic children. Several databases (MEDLINE using PubMed, Embase, and Cochrane Collaborations) were searched (1968–2000) to identify English and non-English language articles on intervention studies in children to retard myopia progression. The search used the keywords *myopia, short-sightedness, near-sightedness,* or *myopia control,* combined with *progression of myopia* or *myopia prophylaxis* or *myopia prevention*. The publication type was limited to *clinical trials*. A total of 83 abstracts were found. Three different investigators (SMS, EC, AK) performed the search, and independent reviews of the abstracts were done. Two of the three reviewers were trained epidemiologists (SMS, EC), the third reviewer was an ophthalmologist (AK).

The bibliographies of existing reviews and retrieved articles were also reviewed to identify articles not captured by the different databases. Several drug companies involved in clinical trials for myopia control were contacted by mail or telephone to ask whether the company had conducted randomized clinical trials but had not reported their results. The proceedings of recent major international conferences on myopia research, such as the International Conference on Myopia and the Association for Research in Vision and Ophthalmology, were screened.

Criteria for Considering Studies for This Review

A total of 35 potentially relevant articles were retrieved. All three independent investigators (SMS, AK, EC) reviewed all articles to identify randomized clinical trials conducted in myopic children with a main objective of the prevention of the progression of myopia. The investigators met to resolve any differences in the interpretation of the articles. Articles excluded from the study included retrospective studies, nonrandomized clinical trials, non-controlled clinical trials, short-term ($<$1 year) ocular outcome evaluations, or those in which the primary purpose of the trial was not the retardation of myopia progression. As a result, study interventions using behavioral vision training, ocular exercises, orthokeratology, prismatic lenses, monofocal convex lenses, and hydrogel lenses were excluded.[17–20]

Data Extraction and Study Appraisal

Information on study design, conduct, outcomes, and analysis was documented on a data extraction form. Details include (1) study design: parallel or crossover randomized clinical trial; (2) masking: double, single or none; (3) method of randomization; (4) unit of randomization: eyes or patients; (5) description of intervention and control groups; (6) characteristics of study population; (7) similarity of the two groups at baseline; (8) equality of treatment for the two groups; (9) length of follow-up; (10) frequency of follow-up; (11) rate of loss to follow-up in each group; (12) whether intention-to-treat analysis was conducted; (13) eyes analyzed: right, left, worse, or average of two eyes; (14) outcome measures (e.g., change in refraction diopters per year [primary outcome]; and (15) adverse effects. Ten articles of randomized clinical trials were included, and, where necessary, we contacted the authors for further clarification and additional data. We grouped the articles according to the interventions: cycloplegic eyedrops, pressure-lowering eyedrops, bifocal spectacle lenses, or contact lenses. One article describing a randomized clinical trial of bifocal lenses and plus with prisms was not included, because the trial was conducted in adults (military academy students).[21] The studies were appraised for methodologic quality using the recently revised Scottish Intercollegiate Guidelines Network methodology checklist for randomized controlled trials (Table 1).[22]

Each article was rated according to the "strength of evidence" as recently defined by the American Academy of Ophthalmology's glaucoma panel.[23] Level I indicates that the data provided strong evidence in support of the recommendation, that the design of the study addressed the issue in question, and that the study was performed in the population of interest and executed in a manner that ensured production of accurate and reliable data, using appropriate statistical methods. Level II indicates that the data provided substantial evidence in support of the recommendation but that the evidence lacked some qualities. Level III indicates a consensus of expert opinion in the absence of evidence that met the requirements of levels I and II. Recommendations for clinical outcomes were assessed as level A, B, or C.[23] Level A indicates that the recommendation is very important to clinical outcome; level B indicates that the recommendation is moderately important; and level C indicates that the recommendation is relevant but not critical.

Outcomes and Analysis

The primary outcome reported for subjects completing the study in each group was the mean progression rate of myopia (D per year) and its standard deviation. The progression of myopia was measured as the change in spherical equivalent cycloplegic

Table 1. Patient and Study Characteristics of the 10 Randomized Clinical Trials

Study	Study Score	Country	Methods	Masking	Total Randomized	Intervention
Eyedrops						
Yen 1989[24]	+	Taiwan	Parallel RCT Baseline similar	No	247	1% atropine 1% cyclopentolate Normal saline*
Shih 1999[26]	+	Taiwan	Parallel RCT Baseline similar	Single	200	0.5% atropine 0.25% atropine 0.1% atropine 0.5% tropicamide*
Shih 2000[†]	+	Taiwan	Parallel RCT (central office) Baseline similar	Double	227	0.5% atropine Multifocals Single vision*
Schwartz 1981[27]	+	USA (registry)	Parallel RCT in twins Baseline similar	Single (assessor)	26 pairs	1% tropicamide Single vision*
Bifocal lenses						
Grosvenor 1987[34]	+	USA	Parallel RCT (random number table) Baseline similarity unknown	No	207	Bifocals + 2 D Bifocals + 1 D Single vision*
Parssinen 1989[25]	+	Finland	Parallel RCT (sealed envelopes) Baseline similar	No	240	Bifocals + 1.75 D Single vision (distance only) Single vision*
Jensen 1991[15]	+	Denmark	Parallel RCT Baseline similar	No	150	Bifocals + 2 D Single vision + 0.25% timolol Single vision*
Fulk 1996[29]	+	USA	Parallel RCT (sealed envelopes) Baseline similarity unknown	Single	32	Bifocals + 1.25 D Single vision*
Fulk 2000[30]	+	USA	Parallel RCT Baseline similar	Double	82	Bifocals + 1.50 D Single vision*
Contact lenses						
Horner 1999[31]	−	USA	Parallel RCT Baseline similar	Single	175	Soft contact lenses Single vision*

*Control group.

[†]By Shih et al (Proceedings of the VIII International Conference on Myopia, 352–6, 2000).

D = diopters; RCT = randomized clinical trial.

refractive error and secondarily measured as a dichotomous variable (fast progressor: yes/no) in several studies. Fast progressors were defined as at least 0.25 D per year or at least 0.5 D per year.

Summary of Evidence

Of the 10 trials, 5 were three-arm parallel studies, 1 was a four-arm parallel study, 1 was a matched-pair (twin) study, and 3 were two-arm parallel studies (Table 1).[15,24–34] There were seven comparisons of atropine eyedrops (three against tropicamide, one against cyclopentolate, and three against lenses), two comparisons of timolol eyedrops (against bifocals and single-vision spectacles); there were also seven comparisons of bifocals with various adds, one of multifocal lens alone and in conjunction with 0.5% atropine, and one of contact lenses (all against single-vision spectacles). All studies reported per protocol comparisons on subjects who completed the study. In seven studies the numbers analyzed were at least 80% (average, 91%; range, 83%–98%) of those randomized, with no significant differential dropout rates among treatment groups. The three remaining studies analyzed fractions of 38%, 60%, and 74%, also with no significant differences across groups.[24,31,34] The follow-up period varied from 1 to 3.5 years, with seven studies having at least 2 years of follow-up (Table 2). Frequency of follow-up visits varied from every 3 months to yearly (most common was every 6 months). We grouped the studies according to the interventions: cycloplegic eyedrops, pressure-lowering eyedrops, bifocal lenses, or contact lenses. We report on each separately.

Cycloplegic Eyedrops

An early study using a matched-pair design in 26 twins tested the combination of 1% tropicamide with bifocals against single-vision spectacles and found no significant difference (Table 2, Fig 1).[27] A range of atropine concentrations was tested in Taiwan; 1% atropine was quickly rejected from the experience of the Yen study (side effects of atropine included photophobia resulting in children stopping gymnastic classes and spending less time outdoors). Shih noted in a 1999[26] and a 2000 study (Proceedings of the

Table 2. Study Outcomes and Results of the 10 Randomized Clinical Trials

Study	Intervention	Cycloplegia?	Follow-up (years)	Group rates (Diopter/year)	Evidence*
Eyedrops					
Yen 1989[24]	1% atropine	Yes	1.0	−0.22 (0.54)†	B, I
	1% cyclopentolate			−0.58 (0.49)†	
	Normal saline‡			−0.91 (0.58)	
Shih 1999[26]	0.5% atropine	Yes	2.0	−0.04 (0.63)†	B, I
	0.25% atropine			−0.45 (0.55)†	
	0.1% atropine			−0.47 (0.91)†	
	0.5% tropicamide‡			−1.06 (0.61)	
Shih 2000§	0.5% atropine	Yes	1.5	−0.28 (0.05)†	B, I
	Multifocals			−0.79 (0.05)	
	Single vision‡			−0.93 (0.06)	
Schwartz 1981[27]	1% tropicamide	Yes	3.5	Paired analysis	C, I
	Single vision‡				
Bifocal lenses					
Grosvenor 1987[34]	Bifocals + 2 D	Yes	3.0	−0.32	C, I
	Bifocals + 1 D			−0.34	
	Single vision‡			−0.32	
Parssinen 1989[25]	Bifocals + 1.75 D	Yes	3.0	−0.56 (0.3)	C, I
	Single vision (distance only)			−0.59 (0.3)	
	Single vision‡			−0.49 (0.3)	
Jensen 1991[13]	Bifocals + 2 D	Yes	2.0	−0.48 (0.28)	C, I
	Single vision + 0.25% timolol			−0.59 (0.30)	
	Single vision‡			−0.57 (0.36)	
Fulk 1996[29]	Bifocals + 1.25 D	Yes	1.5	−0.39 (0.12)	C, I
	Single vision‡			−0.57 (0.11)	
Fulk 2000[30]	Bifocals + 1.50 D	Yes	2.5	−0.40 (0.27)†	C, I
	Single vision‡			−0.50 (0.26)	
Contact lenses					
Horner 1999[31]	Soft contact lenses	No§	3.0	−0.36 (0.03)	C, II‖
	Single vision‡			−0.30 (0.03)	

*Importance to clinical outcome, strength of evidence.

†2 $P < 0.05$ for difference in myopia progression rates between the intervention and control group.

‡Control group.

§By Shih and colleagues (Proceedings of the VIII International Conference on Myopia, 352–6, 2000).

‖Noncycloplegic refractive measurements.

B = moderately important recommendation; C = relevant but not critical recommendation; D = diopters; I = strong evidence supporting recommendation; II = substantial evidence supporting recommendation but lacking some qualities required for strong support.

VIII International Conference on Myopia, 352-6, 2000) that a series of lower atropine concentrations were effective; the 0.5% atropine-bifocals group showed remarkably slow progression of myopia of −0.04 D per year compared with an average rate of −0.46 D per year for the 0.25% and 0.1% atropine groups.[26] Two children given 0.5% atropine in the Shih 1999[26] study complained of intolerable photophobia, but there were no notable side effects in the children given 0.25% and 0.1% atropine. Overall there is some evidence that regular application of atropine eyedrops can at least halve a baseline myopia progression of −1 D per year and halve the proportion of fast myopia progressors (progression at least −0.25 or −0.5 D per year). These studies need to be replicated in other countries with similarly high baseline myopia progression rates and in the West, where baseline rates seem to be less than half those recorded in the Taiwanese studies. Further studies on the short-term and long-term side effects of the varying concentrations of atropine eyedrops are also needed.

Timolol Trial

The Danish study of 0.25% timolol maleate (a β-adrenergic blocking agent) against single-vision spectacles was reported twice and showed no retardation of progression (Table 2).[15,32] Five children reported stinging sensations and discomfort of the eye; and one boy developed bronchial asthma.

Bifocal Lens Trials

A range of near vision additions (+1.00 to +2.00 D) was tested, but only the +2.00 D intervention was replicated[13,34]; control group progression rates were similar among all studies (−0.32 to −0.57 D/year) (Table 2, Fig 1).[32,34]

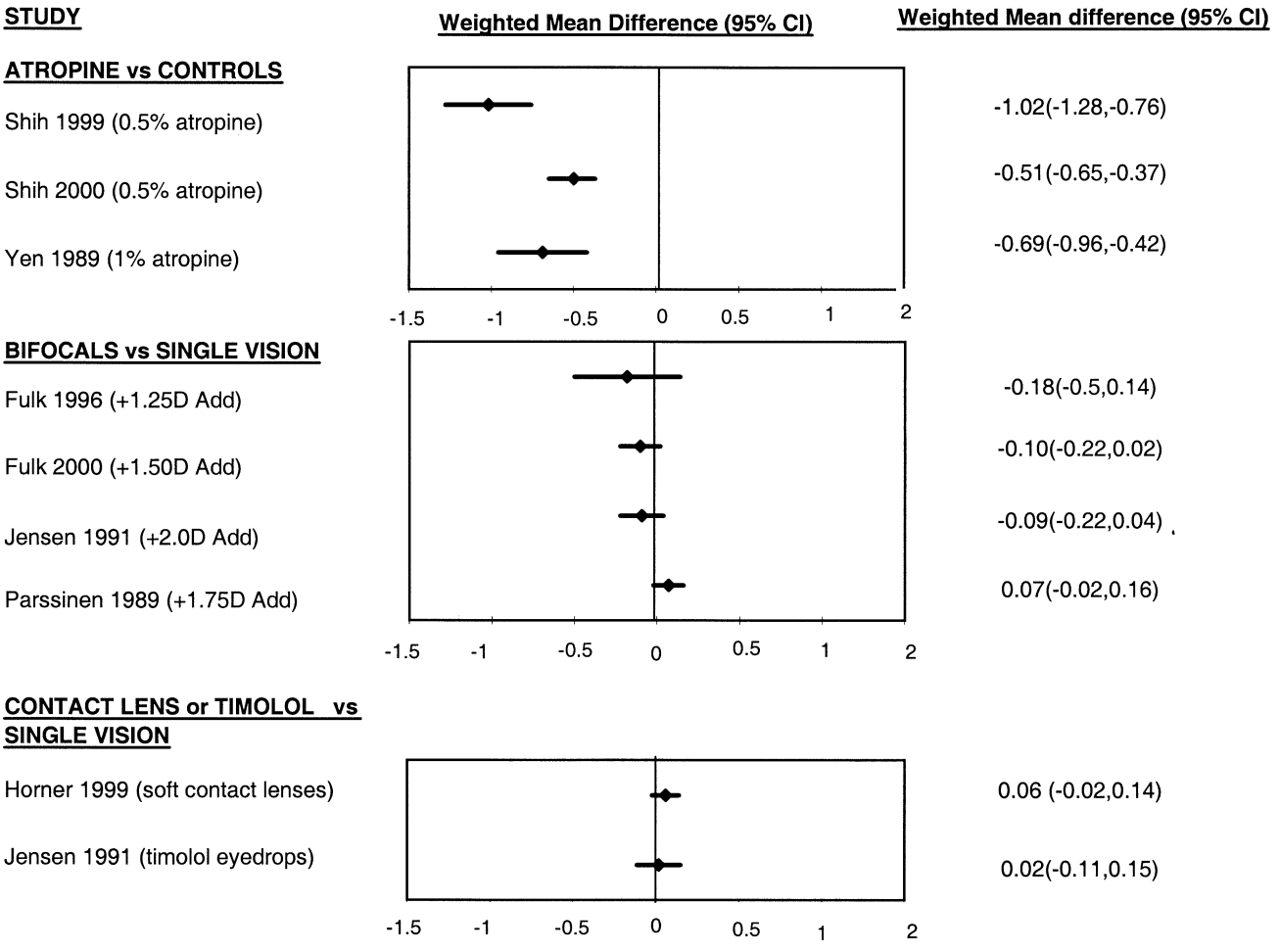

Figure 1. Forest-plot of randomized clinical trials. The Grosvenor study[34] is not included, because standard deviations of the myopia progression rates are not available. CI = confidence interval.

Note this is about half that in the Taiwanese studies. The Finnish study compared bifocal lenses with +1.75 D to two alternative single-vision spectacle-wearing regimens, continuous and distance-use only.[25,33] Fulk et al[29,30] compared bifocal lenses + 1.25 D in a small study of 32 subjects and later + 1.50 D in a larger study of 75 esophoric children. The latter study was barely significant (rate difference of 0.1 D/year, $P = 0.04$); the axial length increase was 0.16 mm/year in the bifocal lens group and 0.20 mm/year in the single-vision group.[30] The bifocal lens groups in the Jensen[32] and two Fulk studies[29,30] exhibited a trend in the direction of slower progression compared with single-vision spectacles. The latest study by Shih and colleagues (Proceedings of the VIII International Conference on Myopia, 352-6, 2000) showed an insignificant effect in favor of multifocals (−0.79 D per year versus −0.93 D per year, difference 0.12 D, 95% confidence interval, −0.01, 0.29). No side effects of bifocal or multifocal lenses were found.

Contact Lens Trial

Soft contact lenses were evaluated in one single-masked randomized clinical trial in the United States.[31] There was no statistically significant difference in myopia progression rates in the contact lens group (−0.36 D/year) compared with the single-vision lens group (−0.30 D/year) (Table 2, Fig 1). The refractive error measurements were, however, noncycloplegic, and 26% of the randomized subjects were dropped from the analysis. No side effects of contact lenses were reported.

In summary, three randomized clinical trials have demonstrated that 0.5% atropine eyedrops may lower the rate of progression of myopia; however, the long-term side effects are largely unknown. There is no evidence to suggest that bifocal lenses, pressure-lowering eyedrops, or soft contact lenses retard the progression of myopia, and further studies are needed.

Clinical Recommendations

The evidence for clinical recommendations is based on a systematic and comprehensive search of relevant articles and a consolidation of the best available evidence. Only

Table 3. Clinical Recommendations for the Different Interventions

Intervention	Recommendation	Evidence Rating
Atropine eyedrops	The routine use of atropine in children to reduce myopia is not recommended.	B, I
Bifocal lenses	Bifocal lenses are not recommended to retard myopia progression in children.	C, I
Soft contact lenses	Soft contact lenses are not recommended for retardation of myopia progression in children.	C, II

B = moderately important recommendation; C = relevant but not critical recommendation; I = strong evidence supporting recommendation; II = substantial evidence supporting recommendation but lacking some qualities required for strong support.

randomized clinical trials were included, because this "gold standard" study design provides the strongest evidence for efficacy of an intervention and a safeguard against biases. In randomized clinical trials, the nonpredictability of the treatment assignment for the next patient eliminates any selection bias on the part of investigators or patients. If the clinical trials were single- or double-masked, the results of the study would be even more rigorous. Because all studies evaluated were randomized clinical trials, the "strength of the evidence" for all recommendations was considered as I, except for soft contact lenses (II) (one small trial did not yield conclusive results) (Table 3). Recommendations regarding the use of atropine eyedrops were considered level B, moderately important to outcome. Bifocal lenses and soft contact lenses were considered to be level C, relevant but not critical to current patient care, because the interventions have not been clearly efficacious.

There is some evidence that atropine eyedrops retard myopia progression in three randomized clinical trials (B, I). The beneficial effects of atropine eyedrops have also been shown in retrospective studies, noncontrolled trials, and nonrandomized controlled studies.[35,36] The efficacy of atropine is supported by animal experiments, demonstrating that muscarinic acetylcholine receptors may affect eye and scleral growth.[37,38] However, there is little information on the exact mechanisms of action of atropine. Atropine eyedrops may not be recommended for all myopic children, because the possible long-term side effects such as cataract formation and retinal toxicity, are largely unknown. Few studies have evaluated the possible adverse effects and complications of the use of anticholinergic agents in growing eyes, especially over long periods of time. Thus, data on the safety of the drug are sparse. The possibility of reversal of myopia progression rates after termination of atropine eyedrops is still undetermined. Further randomized clinical trials are needed before considering the use of atropine in young children with rapid myopia progression rates (at least 1.0 D/year).

Bifocal lenses are not generally recommended for the retardation of the progression of myopia in children (C, I). Despite several negative reports, we noted that Fulk and colleagues[30] reported significant results and no side effects from a recent randomized clinical trial. If the parents of a young child with progressive axial myopia request treatment with bifocal lenses, the parents should be counseled regarding the lack of evidence and possible side effects before bifocal lenses are prescribed. This hypothesis has to be confirmed by evidence from future well-designed randomized clinical trials. Alternatives to bifocal lenses include multifocal progressive lenses, which may be more acceptable cosmetically, and allow children to have clear vision at all distances. However, as the experience with pseudophakic adults has shown, adapting to the use of multifocal lenses is not always easy.

We do not recommend soft contact lenses for the retardation of the progression of myopia, because the evidence suggests that there is no significant retardation of the progression of myopia (C, II). Soft contact lenses are associated with a higher risk of ocular complications compared with rigid gas-permeable lenses. Soft contact lens wear is not without attendant risks such as ocular infections; the maintenance and care of contact lenses may be an inconvenience as well.

Other interventions, namely, part-time spectacle wear and hydrogel lenses, have been evaluated in retrospective case studies, nonrandomized controlled trials, and uncontrolled clinical trials.[19,39] In addition, programs designed to decrease possible environmental risk factors such as near-work or night lights have not been evaluated in a systematic fashion. Evidence is lacking, and well-designed randomized clinical trials with low dropout rates are needed to answer the question: Do these interventions really retard the progression of myopia in children?

The best available evidence for myopia intervention in children is not conclusive, because the magnitude of effect of the intervention compared with the control group is small, dropout rates may be high, and compliance rates may be low. Use of 1% and 0.5% atropine eyedrops in children is associated with major side effects. Not all interventions have been evaluated using the "gold standard" study design of randomized clinical trials. Often, the primary purpose of the trials was not to evaluate the long-term retardation of the progression of myopia, but to evaluate short-term, possibly transient, effects. Several controlled trials did not use rigorous randomization techniques, such as random number tables, but opted for other means of treatment allocation such as "even" and "odd" number assignments or matching.[40] New research in this area should focus on large double-masked randomized clinical trials with optimal optical refraction data and adequate follow-up time. Long-term follow-up studies of atropine eyedrop instillation in humans or animals to determine the possible long-term side effects of atropine eyedrops are strongly advocated. Ongoing clinical trials of the efficacy of pirenzepine, a subtype-selective M1 antimuscarinic antagonist with possibly

fewer side effects compared with atropine, may provide useful and valuable information.

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