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Efficacy Comparison of 16 Interventions for Myopia Control in Children

A Network Meta-analysis

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Purpose: To determine the effectiveness of different interventions to slow down the progression of myopia in children.

Methods: We 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.

Main Outcome Measures: The primary outcomes were mean annual change in refraction (diopters/year) and mean annual change in axial length (millimeters/year).

Results: 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 [0.52−0.84]; axial length change: −0.21 [−0.28 to −0.16]), moderate-dose atropine (refraction change: 0.53 [0.28−0.77]; axial length change: −0.21 [−0.32 to −0.12]), and low-dose atropine (refraction change: 0.53 [0.21−0.85]; axial length change: −0.15 [−0.25 to −0.05]) markedly slowed myopia progression. Pirenzepine (refraction change: 0.29 [0.05−0.52]; 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 [0.02−0.26]; axial length change: −0.04 [−0.09 to −0.01]) showed slight effects.

Conclusions: 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. *Ophthalmology 2016;123:697-708 © 2016 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Myopia has emerged as a worldwide public health issue and is 1 of the 5 ocular conditions identified as immediate priorities by the World Health Organization's Global Initiative for the Elimination of Avoidable Blindness.[1] In developed countries, myopia is the most common medical condition requiring treatment, with an adult prevalence varying from 15% to 49%.[2] Although myopia is often highlighted as an Asian problem, the UK 1958 birth cohort study[3] and Gutenberg Health Study[4] showed a high prevalence of myopia in Western countries. A study of university students in the United Kingdom showed no significant difference in myopia prevalence between Asian (53.4%) and white (50%) students.[4] Furthermore, the prevalence of myopia is increasing in both Asia and the West: in Singapore doubling between 1987 and 1992 and 2009 and 2010[5] and in the United States increasing from 25% to 41.6% over a 30-year period.[6]

In addition to the optical impact of myopia on vision and the associated costs of correction, myopia is a major risk factor for ocular disease.[7] Myopia increases the risk of eye

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diseases, including glaucoma, cataract, and retinal detachment.[8,9] The risks associated with myopia are significant even in low myopes (<−3 diopters [D]) and comparable to the risks of smoking and hypertension to cardiovascular health.[9] There is also a clear dose-response relationship with increased risks at higher levels of myopia. Myopia is the primary risk factor for myopic maculopathy,[10] which is now the second most common cause of low vision in Beijing.[11] Outside Asia, myopic maculopathy is 1 of the top 5 causes of blindness among working-age people in the United Kingdom,[12] Ireland,[12] and Israel.[13]

Standard clinical care currently treats only the optical and medical consequences of myopia rather than limiting its progression. Despite the lack of consensus on the causes of myopia, a range of potential interventions to reduce its progression have been tested. These have been based on clinical observations, animal models of myopia development, or both.[14–20] Trials of such treatments have provided a substantial evidence base, but most studies are of a single intervention versus control, lacking direct head-to-head comparison. Furthermore, there are inconsistencies among trials examining the same intervention. Three meta-analyses have shown the efficacy of multifocal spectacle lenses,[21] atropine,[22] and increasing time outdoors[23] on myopia control. Another composite meta-analysis[24] has assessed the effects of several interventions, including eye drops, spectacles, and contact lenses among children.

This article provides a network meta-analysis of interventions proposed to reduce myopia progression. This network approach is an extension of a traditional meta-analysis that allows for both direct and indirect comparisons, even when 2 strategies have not been directly compared.[25] A network meta-analysis integrates relevant data without losing the strength of randomization in individual randomized controlled trials (RCTs).[26] We conducted this network meta-analysis with the aim of deriving evidence-based clinical guidelines for myopia control in children.

Methods

Eligibility Criteria

Trials were eligible for our network meta-analysis if they (1) compared interventions for slowing the progression of myopia to control patients or other therapeutic interventions in children and (2) had a treatment duration of at least 1 year. We excluded trials if they (1) included patients aged more than 18 years when enrolled in trials, (2) included patients with less than 0.25 D of spherical equivalent myopia at baseline, (3) were a nonrandomized or noncomparative study, (4) did not have the required outcome measures, or (5) failed to provide data suitable for meta-analysis. We used mean annual change in refraction (diopters/year) and mean annual change in axial length (millimeters/year) as our primary outcomes. We specified tropicamide as a placebo at the outset, because a previous study by Shih et al[27] found that 0.5% tropicamide had a similar effect to placebo on myopia progression. Likewise, single vision spectacle lenses were prespecified as a control along with placebo. Furthermore, the concentration of atropine was classed into 3 groups: high-dose atropine (1% and 0.5%), moderate-dose atropine (0.1%), and low-dose atropine (0.01%).

Search Methods

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov databases (from inception to August 2014) for RCTs in any language. The search strategy is shown in the Appendix (available at www.aaojournal.org). We also examined reference lists from reports on clinical trials, meta-analyses, and systematic reviews to identify relevant studies.

Study Selection and Data Collection

Two investigators (D.Z.W., J.H.H.) independently reviewed the titles, abstracts, and full text articles for inclusion using standardized data extraction forms. They conducted a focused discussion to resolve any disagreements. When the same population was involved in multiple articles, we included only the primary report in the meta-analysis. We extracted the following information from each trial: (1) first author, (2) year of publication, (3) follow-up duration, (4) type of intervention, (5) sample size, (6) baseline characteristics (age, refraction, axial length, dropouts from total number), and (7) end points (mean change in refraction and axial length). For any missing data, we contacted the authors of trial reports or used GetData GraphDigitizer 2.24 (http://getdata-graph-digitizer.com) to read data from figures.

Risk of Bias Assessment

Study quality was assessed by Cochrane Collaboration's risk-of-bias method.[28] The methodology examined the following aspects of each trial: random sequence generation and allocation concealment (both items related to selection bias), blinding of participants and personnel (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. We graded each of the item domains at "low," "high," or "unclear" risk of bias.

Statistical Analysis

We conducted direct head-to-head comparisons using a random-effects model to estimate weighted mean differences and 95% confidence intervals (CIs),[29] and assessed heterogeneity with the I^2 statistic,[30] with I^2 values greater than 50% indicating substantial heterogeneity. We performed direct comparisons using STATA version 10.0 (StataCorp LP, College Station, TX). For all comparisons, the stated values represent the differences in final refraction or axial elongation between the first intervention and the second intervention. In terms of refractive error, a positive mean difference therefore indicates that the first intervention is better (less myopia progression). In terms of axial length, a negative mean difference indicates the first intervention is better (less axial elongation).

We performed a Bayesian random-effects network meta-analyses using WinBUGS version 1.4 (MRC Biostatistics Unit, Cambridge, UK) to estimate pooled weighted mean differences and 95% credible intervals (CrIs). We estimated the posterior densities for all unknown parameters using the Markov chain Monte Carlo method for each model. Each chain used 50 000 iterations with a burn-in number of 20 000, thin interval of 1, and updates varying between 80 and 110. The choice of burn-in was made according to the Gelman−Rubin approach.[31] The code is available from the authors on request. We ranked treatments on the basis of the relative treatment effects compared with placebo or single vision spectacle lenses and the analysis of ranking probabilities. We defined refraction change ≥0.50 D/year or axial length change ≥0.18 mm/year as a "strong" effect, refraction change from 0.25 D/year to 0.50 D/year or axial length change from 0.09 mm/year to 0.18 mm/year as a

"moderate" effect, and refraction change from 0 to 0.25 D/year or axial length change range from 0 to 0.09 mm/year as a "weak" effect. Inconsistency between direct and indirect evidence was assessed by "node-splitting."[32] Further sensitivity analyses were undertaken by removal of trials that caused high heterogeneity in direct comparisons. We also performed an additional network meta-analyses in 4 subgroups of studies: subgroups 1 (16 studies) and 2 (11 studies) examining trials with different ethnicity (Asian and white subjects), and subgroups 3 (20 studies) and 4 (17 studies) examining trials with different treatment durations (1 year from baseline and 2 years from baseline).

Results

Figure 1 shows the flowchart for the study analysis. We identified 2435 articles through the electronic literature searches, and 1727 remained after removal of duplicates. After review of the titles and abstracts of these articles, a further 1584 were excluded. On fully evaluating the remaining 143 citations, we found 30 primary articles (4 articles with a multi-arm design) that met the inclusion criteria in the network meta-analysis, comprising a total of 5387 people (5422 eyes) (the Appendix shows the full details of these 30 studies, available at www.aaojournal.org). Among the 30 trials contributing to the analysis, 4 main types of interventions were involved: 13 spectacle lens studies, 9 contact lenses studies, 1 outdoor activity study, and 7 pharmacologic studies. Nineteen studies reported both refraction and axial length outcomes, 9 studies only reported refraction, and 2 studies reported only axial length.

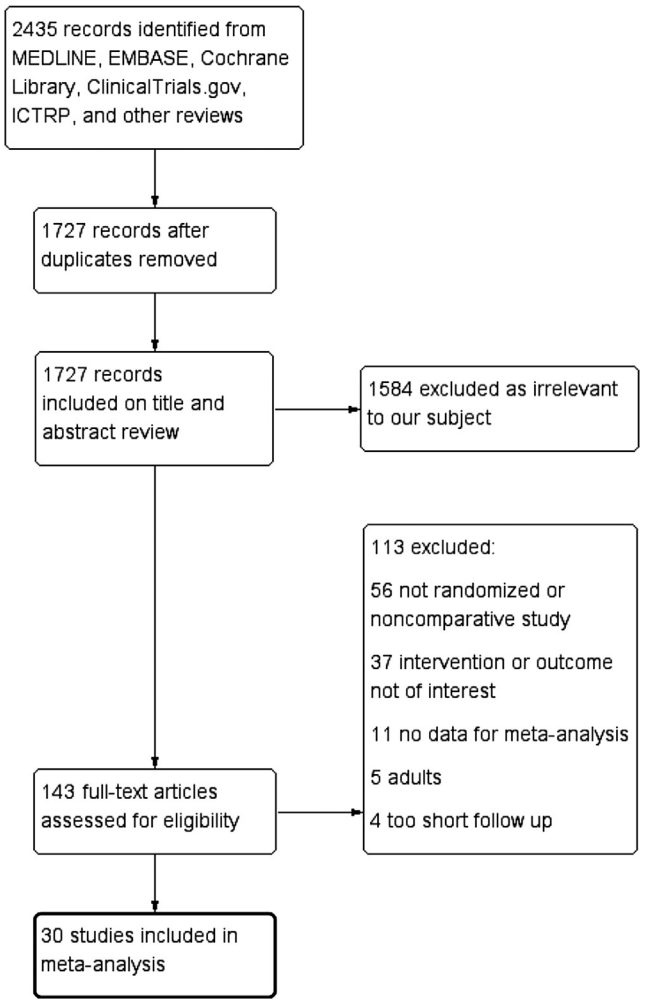

Figure 1. Flowchart for the study analysis. ICTRP = International Clinical Trials Registry Platform.

The quality of the included trials is shown in the Appendix (available at www.aaojournal.org). Overall, the trials that we included in this analysis seem to have a low to moderate risk of bias, with most of the trials reporting adequate random sequence generation, allocation concealment, and blinding of outcome assessment. However, participants in most studies could not be masked because of the physical nature of a treatment (e.g., contact lenses versus spectacles) or its effects (e.g., pupil dilatation with higher doses of atropine). Having unmasked participants could increase the risk of bias. For example, if participants receive a treatment perceived as useful, this may enhance their compliance and vice versa.

There are some issues that should be noted: Sankaridurg et al[33] reported the results of 3 designs of peripheral defocus modifying spectacle lenses, and only the most effective design (type III, an asymmetric design) was selected in our analyses. The study by Anstice and Phillips[34] was a cross-over trial with 2 periods, and we used only data from the first period (10 months) with 1-year treatment effects.

Figure 2 shows the network of direct comparisons for the interventions of myopia. Table 1 shows the results (refraction or axial length change per year) of conventional meta-analyses. In

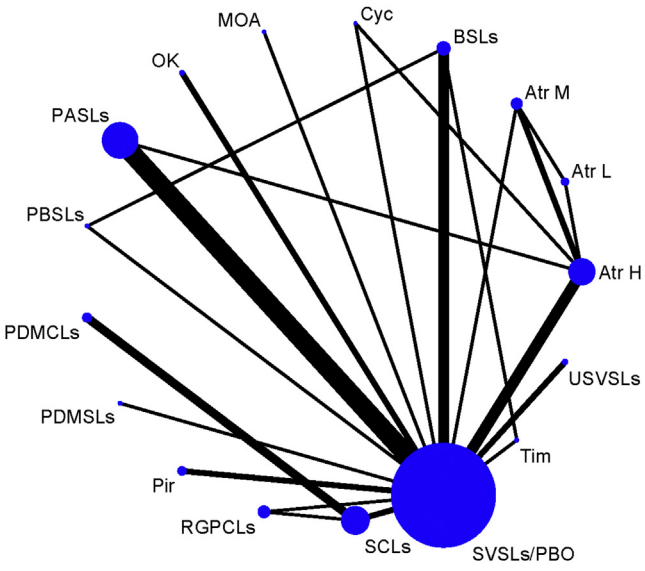

Figure 2. Network of direct comparison for the interventions of myopia. Each node represents 1 treatment. The size of the node is proportional to the number of participants randomized to that treatment. The edges represent direct comparisons, and the width of the edge is proportional to the number of trials. Atr = atropine; Atr H = high-dose atropine (1% or 0.5%); Atr L = low-dose atropine (0.01%); Atr M = moderate-dose atropine (0.1%); BSLs = bifocal spectacle lenses; Cyc = cyclopentolate; MOA = more outdoor activities (14–15 hrs/wk); OK = orthokeratology; PASLs = progressive addition spectacle lenses; PBO = placebo; PBSLs = prismatic bifocal spectacle lenses; PDMCLs = peripheral defocus modifying contact lenses; PDMSLs = peripheral defocus modifying spectacle lenses; Pir = pirenzepine; RGPCLs = rigid gas-permeable contact lenses; SCLs = soft contact lenses; SVSLs = single vision spectacle lenses; Tim = timolol; USVSLs = undercorrected single vision spectacle lenses.

Table 1. Changes in Refraction and Axial Length per Year from Direct Comparisons between Each Pair of Interventions

	Refraction Change, D/yr			Axial Length Change, mm/yr		
	No. of Studies	*Mean Difference (95% CI)*	I^2	*No. of Studies*	*Mean Difference (95% CI)*	I^2
Atr H	4	0.70 (0.42−0.99)	93.9%	2	−0.21 (−0.25 to −0.18)	5.8%
Atr M	1	0.59 (0.43−0.75)				
BSLs	4	0.09 (−0.05 to 0.24)	85.6%	2	−0.06 (−0.10 to −0.02)	0%
Cyc	1	0.33 (0.07−0.59)				
MOA	1	0.14 (0.06−0.22)				
OK				2	−0.14 (−0.19 to −0.10)	0%
PASLs	7	0.12 (0.07−0.18)	51.1%	5	−0.04 (−0.07 to −0.01)	51.5%
PBSLs	1	0.34 (0.22−0.46)		1	−0.09 (−0.14 to −0.04)	
PDMSLs	1	0.12 (−0.06 to 0.30)		1	−0.05 (−0.12 to 0.02)	
Pir	2	0.29 (0.13−0.44)	47.6%	2	−0.09 (−0.15 to −0.02)	0.0%
RGPCLs	1	−0.03 (−0.13 to 0.07)		1	0.02 (−0.04 to 0.08)	
SCLs	2	−0.06 (−0.10 to −0.02)	0.0%	1	0.01 (−0.01 to 0.03)	
Tim	1	−0.02 (−0.15 to 0.11)				
USVSLs vs. SVSLs/PBO	2	−0.11 (−0.22 to 0.00)	0.0%	1	0.03 (−0.02 to 0.08)	
Atr M	2	−0.23 (−0.61 to 0.15)	94.7%	1	0.00 (−0.03 to 0.03)	
Atr L	1	−0.10 (−0.19 to −0.01)		1	0.07 (0.03−0.11)	
Cyc	1	−0.36 (−0.61 to −0.11)				
PASLs vs. Atr H	1	−0.51 (−0.64 to −0.38)		1	0.18 (0.13−0.23)	
Atr M vs. Atr L	1	0.06 (−0.03 to 0.15)		1	−0.07 (−0.11 to −0.03)	
PBSLs	1	0.08 (−0.03 to 0.19)		1	−0.01 (−0.07 to 0.05)	
Tim vs. BSLs	1	−0.11 (−0.23 to 0.01)				
SCLs vs. PDMCLs	3	−0.31 (−0.60 to −0.02)	90.6%	3	0.12 (0.05−0.19)	82.3%
SCLs vs. RGPCLs	1	−0.21 (−0.34 to −0.08)		1	−0.02 (−0.09 to 0.05)	

Atr = atropine; Atr H = high-dose atropine (1% or 0.5%); Atr L = low-dose atropine (0.01%); Atr M = moderate-dose atropine (0.1%); BSLs = bifocal spectacle lenses; CI = confidence interval; Cyc = cyclopentolate; D = diopter; MOA = more outdoor activities (14−15 hrs/wk); OK = orthokeratology; PASLs = progressive addition spectacle lenses; PBO = placebo; PBSLs = prismatic bifocal spectacle lenses; PDMCLs = peripheral defocus modifying contact lenses; PDMSLs = peripheral defocus modifying spectacle lenses; Pir = pirenzepine; RGPCLs = rigid gas-permeable contact lenses; SCLs = soft contact lenses; SVSLs = single vision spectacle lenses; Tim = timolol; USVSLs = undercorrected single vision spectacle lenses.

direct comparison with single vision spectacle lenses/placebo, the following interventions were all found to be effective with statistically significant effect ($P < 0.05$): high-dose atropine (refraction change: 0.70 D, 95% CI, 0.42−0.99; axial length change: −0.21 mm, 95% CI, −0.25 to −0.18), moderate-dose atropine (refraction change: 0.59 D, 95% CI, 0.43−0.75), cyclopentolate (refraction change: 0.33 D, 95% CI, 0.07−0.59), more outdoor activities (refraction change: 0.14 D, 95% CI, 0.06−0.22), orthokeratology (axial length change: −0.14 mm, 95% CI, −0.19 to −0.10), progressive addition spectacle lenses (refraction change: 0.12 D, 95% CI, 0.07−0.18; axial length change: −0.04 mm, 95% CI, −0.07 to −0.01), prismatic bifocal spectacle lenses (refraction change: 0.34 D, 95% CI, 0.22−0.46; axial length change: −0.09 mm, 95% CI, −0.14 to −0.04), and pirenzepine (refraction change: 0.29 D, 95% CI, 0.13−0.44; axial length change: −0.09 mm, 95% CI, −0.15 to −0.02). On direct comparison, high-dose atropine was superior ($P < 0.05$) to low-dose atropine (refraction change: 0.10 D, 95% CI, 0.01−0.19; axial length change: −0.07 mm, 95% CI, −0.11 to −0.03), cyclopentolate (refraction change: 0.36 D, 95% CI, 0.11−0.61), and progressive addition spectacle lenses (refraction change: 0.51 D, 95% CI, 0.38−0.64; axial length change: −0.18 mm, 95% CI, −0.23 to −0.13). Direct comparison of peripheral defocus modifying contact lenses (refraction change: 0.31 D, 95% CI, 0.02−0.60; axial length change: −0.12 mm, 95% CI, −0.19 to −0.05) and rigid gas-permeable contact lenses (refraction change: 0.21 D, 95% CI, −0.08 to −0.34) showed superiority ($P < 0.05$) to soft contact lenses.

There was heterogeneity among some within-trial comparisons ($I^2 > 50\%$), for example, high-dose atropine (1% and 0.5%) versus placebo (refraction change: 0.70 D, 95% CI, 0.42−0.99, $I^2 = 93.9\%$), bifocal spectacle lenses versus single vision spectacle lenses (refraction change: 0.09 D, 95% CI, −0.05 to 0.24, $I^2 = 85.6\%$), progressive addition spectacle lenses versus single vision spectacle lenses (refraction change: 0.12 D, 95% CI, −0.07 to −0.18, $I^2 = 51.1\%$; axial length change: −0.04 mm, 95% CI, −0.07 to −0.01, $I^2 = 51.5\%$), high-dose atropine (1% and 0.5%) versus moderate-dose atropine (0.1%) (refraction change: 0.23 D, 95% CI, −0.15 to 0.61, $I^2 = 94.7\%$), and peripheral defocus modifying contact lenses versus soft contact lenses (refraction change: 0.31 D, 95% CI, 0.02−0.6, $I^2 = 90.6\%$; axial length change: −0.12 mm, 95% CI, −0.019 to −0.05, $I^2 = 82.3\%$). The forest plots demonstrating this heterogeneity are shown in the Appendix (available at www.aaojournal.org).

We also performed a random effects network meta-analysis combining the direct and indirect evidence to compare different interventions with single vision spectacle lenses/placebo (Fig 3) and with each other (Fig 4). As shown in Figure 3 and Table 2, in comparison with placebo or single vision spectacle lenses, high-dose atropine (refraction change: 0.68 D, 95% CrI, 0.52−0.84; axial length change: −0.21 mm, 95% CrI, −0.28

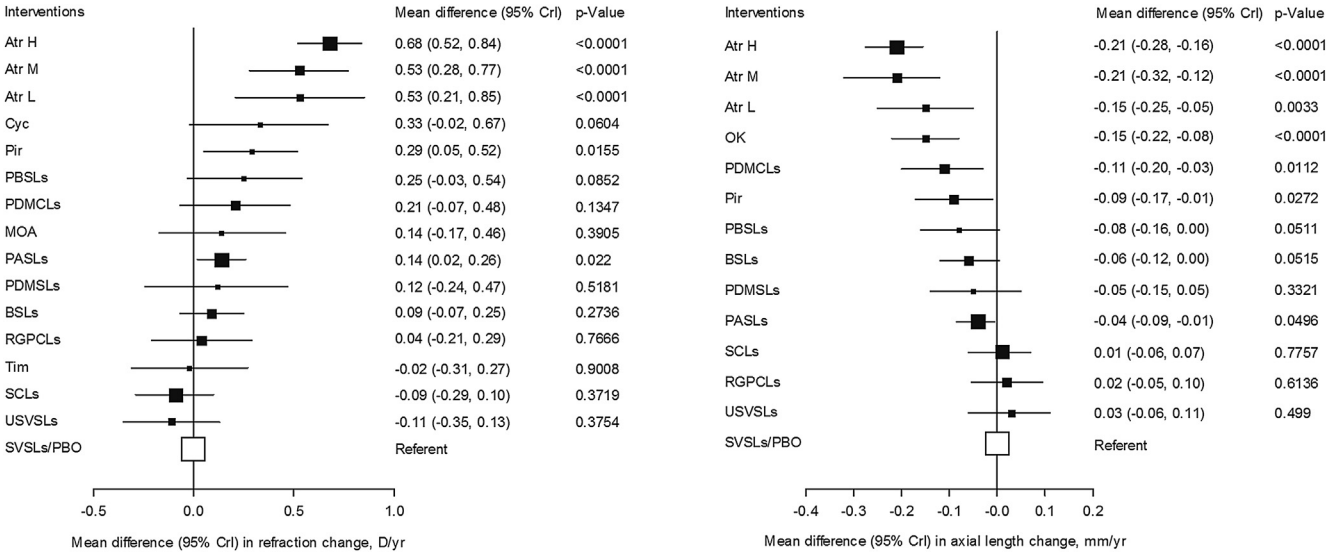

Figure 3. Results of network meta-analysis using single vision spectacle lenses/placebo as referent intervention. Atr = atropine; Atr H = high-dose atropine (1% or 0.5%); Atr L = low-dose atropine (0.01%); Atr M = moderate-dose atropine (0.1%); BSLs = bifocal spectacle lenses; CrI = credible interval; Cyc = cyclopentolate; MOA = more outdoor activities (14–15 hrs/wk); OK = orthokeratology; PASLs = progressive addition spectacle lenses; PBO = placebo; PBSLs = prismatic bifocal spectacle lenses; PDMCLs = peripheral defocus modifying contact lenses; PDMSLs = peripheral defocus modifying spectacle lenses; Pir = pirenzepine; RGPCLs = rigid gas-permeable contact lenses; SCLs = soft contact lenses; SVSLs = single vision spectacle lenses; Tim = timolol; USVSLs = undercorrected single vision spectacle lenses.

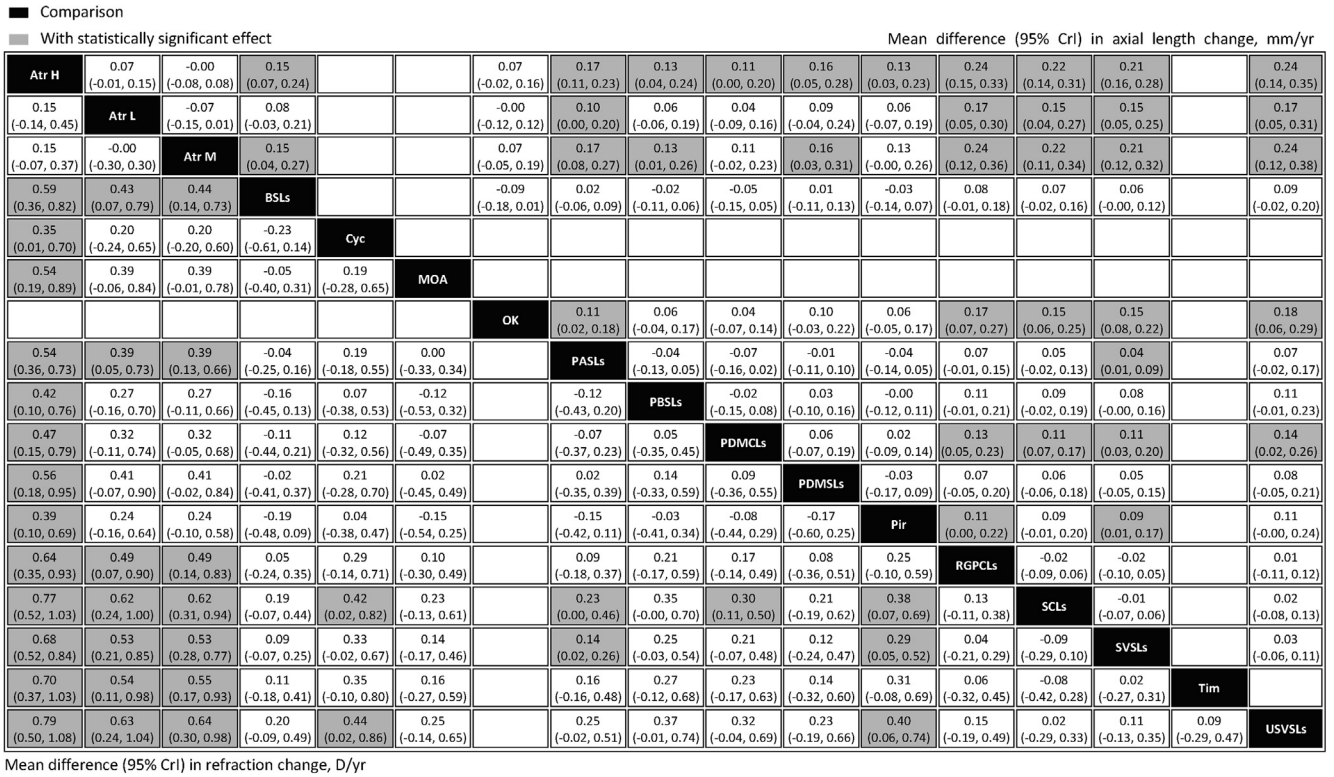

Figure 4. Network meta-analysis comparing all interventions of myopia. Atr = atropine; Atr H = high-dose atropine (1% or 0.5%); Atr L = low-dose atropine (0.01%); Atr M = moderate-dose atropine (0.1%); BSLs = bifocal spectacle lenses; CrI = credible interval; Cyc = cyclopentolate; MOA = more outdoor activities (14–15 hrs/wk); OK = orthokeratology; PASLs = progressive addition spectacle lenses; PBO = placebo; PBSLs = prismatic bifocal spectacle lenses; PDMCLs = peripheral defocus modifying contact lenses; PDMSLs = peripheral defocus modifying spectacle lenses; Pir = pirenzepine; RGPCLs = rigid gas-permeable contact lenses; SCLs = soft contact lenses; SVSLs = single vision spectacle lenses; Tim = timolol; USVSLs = undercorrected single vision spectacle lenses.

Table 2. Treatment Effect Relative to Single Vision Spectacle Lenses/Placebo Based on the Network Meta-analysis

	Ineffective R: ≤0 D/yr AL: ≥0 mm/yr	Weak R: 0 to 0.25 D/yr AL: 0 to −0.09 mm/yr	Moderate R: 0.25 to 0.50 D/yr AL: −0.09 to −0.18 mm/yr	Strong R: ≥0.50 D/yr AL: ≤ −0.18 mm/yr
Atr H				R: 0.68 (0.52−0.84) AL: −0.21 (−0.28 to −0.16)
Atr M				R: 0.53 (0.28−0.77) AL: −0.21 (−0.32 to −0.12)
Atr L			AL: −0.15 (−0.25 to −0.05)	R: 0.53 (0.21−0.85)
Pir		AL: −0.09 (−0.17 to −0.01)	R: 0.29 (0.05−0.52)	
PDMCLs		R: 0.21 (−0.07 to 0.48)	AL: −0.11 (−0.20 to −0.03)	
OK			AL: −0.15 (−0.22 to −0.08)	
PBSLs		AL: −0.08 (−0.16 to 0.00)	R: 0.25 (−0.03 to 0.54)	
Cyc			R: 0.33 (−0.02 to 0.67)	
PASLs		R: 0.14 (0.02−0.26) AL: −0.04 (−0.09 to −0.01)		
BSLs		R: 0.09 (−0.07 to 0.25) AL: −0.06 (−0.12 to 0.00)		
PDMSLs		R: 0.12 (−0.24 to 0.47) AL: −0.05 (−0.15 to 0.05)		
MOA		R: 0.14 (−0.17 to 0.46)		
RGPCLs	AL: 0.02 (−0.05 to 0.10)	R: 0.04 (−0.21 to 0.29)		
Tim	R: −0.02 (−0.31 to 0.27)			
SCLs	R: −0.09 (−0.29 to 0.10) AL: 0.01 (−0.06 to 0.07)			
USVSLs	R: −0.11 (−0.35 to 0.13) AL: 0.03 (−0.06 to 0.11)			

AL = axial length change; Atr = atropine; Atr H = high-dose atropine (1% or 0.5%); Atr L = low-dose atropine (0.01%); Atr M = moderate-dose atropine (0.1%); BSLs = bifocal spectacle lenses; Cyc = cyclopentolate; D = diopter; MOA = more outdoor activities (14−15 hrs/wk); OK = orthokeratology; PASLs = progressive addition spectacle lenses; PBO = placebo; PBSLs = prismatic bifocal spectacle lenses; PDMCLs = peripheral defocus modifying contact lenses; PDMSLs = peripheral defocus modifying spectacle lenses; Pir = pirenzepine; R = refraction change; RGPCLs = rigid gas-permeable contact lenses; SCLs = soft contact lenses; SVSLs = single vision spectacle lenses; Tim = timolol; USVSLs = undercorrected single vision spectacle lenses.
The underlined data indicate that there are statistically significant effects ($P < 0.05$). A 0.18-mm axial length change is estimated to produce a 0.50 D change in refraction.

to −0.16), moderate-dose atropine (refraction change: 0.53 D, 95% CrI, 0.28−0.77; axial length change: −0.21 mm, 95% CrI, −0.32 to −0.12), and low-dose atropine (refraction change: 0.53 D, 95% CrI, 0.21−0.85; axial length change: −0.15 mm, 95% CrI, −0.25 to −0.05) markedly slowed myopia progression. Pirenzepine (refraction change: 0.29 D, 95% CrI, 0.05−0.52; axial length change: −0.09 mm, 95% CrI, −0.17 to −0.01), orthokeratology (axial length change: −0.15 mm, 95% CrI, −0.22 to −0.08), and peripheral defocus modifying contact lenses (axial length change: −0.11 mm, 95% CrI, −0.20 to −0.03) showed moderate effects. Progressive addition spectacle lenses (refraction change: 0.14 D, 95% CrI, 0.02−0.26; axial length change: −0.04 mm, 95% CrI, −0.09 to −0.01) showed weak effects, and rigid gas-permeable contact lenses, soft contact lenses, undercorrected single vision spectacle lenses, and timolol were ineffective in slowing myopia progression. The pairwise comparisons of all interventions (Fig 4) shows that high-dose atropine (1% and 0.5%) was significantly superior ($P < 0.05$) to other interventions in refraction change or axial length change, with the exception of moderate-dose atropine (0.1%) (refraction change: 0.15 D, 95% CrI, −0.07 to 0.37; axial length change: −0.00 mm, 95% CrI, −0.08 to 0.08), low-dose atropine (0.01%) (refraction change: 0.15 D, 95% CrI, −0.14 to 0.45; axial length change: −0.07 mm, 95% CrI, −0.15 to 0.01), and orthokeratology (axial length change: −0.07, 95% CrI −0.16 to 0.02). There were no significant differences ($P > 0.05$) among bifocal spectacle lenses, cyclopentolate, more outdoor activities, orthokeratology, progressive addition spectacle lenses, prismatic bifocal spectacle lenses, peripheral defocus modifying contact lenses, peripheral defocus modifying spectacle lenses, and pirenzepine in pairwise comparisons, with the exception of orthokeratology versus progressive addition spectacle lenses (axial length change: −0.11 mm, 95% CrI, −0.18 to −0.02). Rigid gas-permeable contact lenses, soft contact lenses, timolol, and undercorrected single vision spectacle lenses were inferior to most other interventions, with no significant differences in these pairwise comparisons. The resulting ranking probabilities are shown in the Appendix (available at www.aaojournal.org). Node-splitting analysis of inconsistency indicates no significant discrepancies between direct and indirect estimates (range of P values: 0.18−0.97; the Appendix shows more details, available at www.aaojournal.org).

In sensitivity analyses (Table 3) using control as the reference intervention, 4 trials (Shih et al,[32] Parssinen et al,[35] Leung and Brown,[36] and Aller and Wildsoet[37]) contributed high levels of heterogeneity in the analysis and were subsequently removed. As expected, the effects of most interventions compared with control became a little less pronounced, but the ranking of interventions of the network meta-analysis did not significantly change. Subgroup analyses (Table 4) using single vision spectacle lenses/placebo as the reference intervention showed that in some interventions (bifocal spectacle lenses, progressive addition spectacle lenses, and pirenzepine) Asian children appeared to benefit more from treatment than white children, especially in the treatment with bifocal spectacle lenses versus single vision spectacle lenses. In that comparison, Asian children (refraction change: 0.26 D, 95% CrI, −0.13 to 0.65; axial length change: −0.08 mm, 95%

Table 3. Results of Sensitivity Analyses Performed by Removal of Trials That Caused High Heterogeneity Across Studies Based on the Network Meta-analysis

	Original Data		Sensitivity Analyses	
	Mean Difference (95% CrI) in Refraction, D/yr	*Mean Difference (95% CrI) in Axial Length, mm/yr*	*Mean Difference (95% CrI) in Refraction, D/yr*	*Mean Difference (95% CrI) in Axial Length, mm/yr*
Atr H	0.68 (0.52–0.84)	−0.21 (−0.28 to −0.16)	0.55 (0.45–0.68)	−0.21 (−0.26 to −0.17)
Atr M	0.53 (0.28–0.77)	−0.21 (−0.32 to −0.12)	0.51 (0.33–0.71)	−0.21 (−0.28 to −0.14)
Atr L	0.53 (0.21–0.85)	−0.15 (−0.25 to −0.05)	0.45 (0.27–0.66)	−0.14 (−0.22 to −0.07)
BSLs	0.09 (−0.07 to 0.25)	−0.06 (−0.12 to 0.00)	0.16 (0.05–0.26)	−0.06 (−0.11 to −0.01)
Cyc	0.33 (−0.02 to 0.67)	NA	0.26 (0.00–0.52)	NA
MOA	0.14 (−0.17 to 0.46)	NA	0.14 (−0.02 to 0.30)	NA
OK	NA	−0.15 (−0.22 to −0.08)	NA	−0.14 (−0.20 to −0.08)
PASLs	0.14 (0.02–0.26)	−0.04 (−0.09 to −0.01)	0.10 (0.03–0.17)	−0.03 (−0.06 to −0.00)
PBSLs	0.25 (−0.03 to 0.54)	−0.08 (−0.16 to 0.00)	0.28 (0.12–0.45)	−0.08 (−0.14 to −0.02)
PDMCLs	0.21 (−0.07 to 0.48)	−0.11 (−0.20 to −0.03)	0.07 (−0.10 to 0.25)	−0.08 (−0.15 to −0.02)
PDMSLs	0.12 (−0.24 to 0.47)	−0.05 (−0.15 to 0.05)	0.12 (−0.11 to 0.35)	−0.05 (−0.13 to 0.03)
Pir	0.29 (0.05–0.52)	−0.09 (−0.17 to −0.01)	0.28 (0.13–0.43)	−0.09 (−0.16 to −0.01)
RGPCLs	0.04 (−0.21 to 0.29)	0.02 (−0.05 to 0.10)	0.04 (−0.10 to 0.17)	0.02 (−0.03 to 0.08)
SCLs	−0.09 (−0.29 to 0.10)	0.01 (−0.06 to 0.07)	−0.08 (−0.19 to 0.01)	0.01 (−0.04 to 0.05)
Tim	−0.02 (−0.31 to 0.27)	NA	0.02 (−0.15 to 0.19)	NA
USVSLs	−0.11 (−0.35 to 0.13)	0.03 (−0.06 to 0.11)	−0.11 (−0.26 to 0.04)	0.03 (−0.04 to 0.10)

Atr = atropine; Atr H = high-dose atropine (1% or 0.5%); Atr L = low-dose atropine (0.01%); Atr M = moderate-dose atropine (0.1%); BSLs = bifocal spectacle lenses; CrI = credible interval; Cyc = cyclopentolate; D = diopter; MOA = more outdoor activities (14–15 hrs/wk); NA = not available; OK = orthokeratology; PASLs = progressive addition spectacle lenses; PBO = placebo; PBSLs = prismatic bifocal spectacle lenses; PDMCLs = peripheral defocus modifying contact lenses; PDMSLs = peripheral defocus modifying spectacle lenses; Pir = pirenzepine; RGPCLs = rigid gas-permeable contact lenses; SCLs = soft contact lenses; SVSLs = single vision spectacle lenses; Tim = timolol; USVSLs = undercorrected single vision spectacle lenses.
All mean difference use SVSLs/PBO as the referent intervention.

CrI, −0.23 to 0.07) and white children (refraction change: 0.03 D, 95% CrI, −0.09 to 0.17; axial length change: −0.04 mm, 95% CrI, −0.22 to 0.13) differed by 0.23 D in refraction change and 0.05 mm in axial length change. These differences did not reach statistical significance, and additional trial data are required to adequately address the question of whether race has an impact on the efficacy of myopia control treatments. Further subgroup analyses stratified by different treatment durations showed that most interventions lose their early effect in the second year, especially in the protection of axial length change.

Discussion

Our study is a network meta-analysis aimed specifically at investigating the efficacy or comparative effectiveness of different interventions to slow myopia progression. In addition, the present study updates previous evidence-based reviews.[24,38,39] A previous review by Saw et al[39] and a more recent Cochrane review[29] both concluded that the evidence from randomized clinical trials of that time does not provide sufficient information to support interventions to slow down the progression of myopia. The increased availability of high-quality clinical trials combined with the network meta-analysis techniques used in this article can now provide some guidance regarding the management of myopic progression.

The main findings of our analysis are as follows:

1. High-dose atropine (1% and 0.5%), moderate-dose atropine (0.1%), and low-dose atropine (0.01%) showed clear effects in myopia control (all with statistically significant effect); pirenzepine, orthokeratology, peripheral defocus modifying contact lenses, cyclopentolate, and prismatic bifocal spectacle lenses showed moderate effects (all with statistically significant effect except for cyclopentolate and prismatic bifocal spectacle lenses); progressive addition spectacle lenses, bifocal spectacle lenses, peripheral defocus modifying spectacle lenses, and more outdoor activities showed weak effects (only progressive addition spectacle lenses with statistically significant effect); rigid gas-permeable contact lenses, soft contact lenses, undercorrected single vision spectacle lenses, and timolol were ineffective (all with no statistically significant effect).
2. High-dose atropine (1% and 0.5%) was significantly superior to other interventions except moderate-dose atropine (0.1%) and low-dose atropine (0.01%). Among bifocal spectacle lenses, cyclopentolate, more outdoor activities, orthokeratology, progressive addition spectacle lenses, prismatic bifocal spectacle lenses, peripheral defocus modifying contact lenses, peripheral defocus modifying spectacle lenses, and pirenzepine, pairwise comparisons showed no significant differences apart from a benefit of orthokeratology over progressive addition spectacle lenses. Rigid gas-permeable contact lenses, soft contact lenses, timolol, and undercorrected single vision spectacle lenses were inferior to most other interventions, with no significant differences within this group.

Table 4. Results of Subanalyses Using Single Vision Spectacle Lenses/Placebo as Referent Intervention Based on the Network Meta−analysis

	Different Ethnicity				Different Treatment Duration			
	Asian Children		*White Children*		*1 Yr from Baseline*		*2 Yrs from Baseline*	
	Mean Difference (95% CrI) in Refraction Change, D/yr	*Mean Difference (95% CrI) in Axial Length Change, mm/yr*	*Mean Difference (95% CrI) in Refraction Change, D/yr*	*Mean Difference (95% CrI) in Axial Length Change, mm/yr*	*Mean Difference (95% CrI) in Refraction Change, D*	*Mean Difference (95% CrI) in Axial Length Change, mm*	*Mean Difference (95% CrI) in Refraction Change, D*	*Mean Difference (95% CrI) in Axial Length Change, mm*
Atr H	0.68 (0.49−0.88)	−0.22 (−0.33 to −0.12)	NA	NA	0.76 (0.47−1.03)	−0.34 (−0.49 to −0.19)	1.40 (0.76−2.05)	−0.40 (−0.77 to −0.04)
Atr M	0.53 (0.23−0.82)	−0.22 (−0.40 to −0.04)	NA	NA	0.61 (0.15−1.07)	−0.32 (−0.53 to −0.10)	1.07 (0.30−1.84)	−0.39 (−0.92 to 0.12)
Atr L	0.53 (0.13−0.91)	−0.15 (−0.33 to 0.03)	NA	NA	0.49 (0.03−0.96)	−0.21 (−0.43 to −0.00)	1.09 (0.08−2.11)	−0.26 (−0.78 to 0.27)
BSLs	0.26 (−0.13 to 0.65)	−0.08 (−0.23 to 0.07)	0.03 (−0.09 to 0.17)	−0.04 (−0.22 to 0.13)	0.16 (−0.03 to 0.35)	−0.12 (−0.29 to 0.05)	0.21 (−0.26 to 0.68)	−0.21 (−0.58 to 0.16)
Cyc	0.33 (−0.07 to 0.73)	NA		NA	0.36 (−0.03 to 0.75)	NA	NA	NA
MOA	0.14 (−0.25 to 0.52)	NA		NA	NA	NA	0.28 (−0.66 to 1.22)	NA
OK	NA	−0.14 (−0.26 to −0.04)		NA	NA	−0.19 (−0.32 to −0.08)	NA	−0.29 (−0.55 to −0.03)
PASLs	0.17 (−0.00 to 0.34)	−0.05 (−0.15 to 0.03)	0.06 (−0.09 to 0.22)	−0.04 (−0.17 to 0.08)	0.19 (−0.02 to 0.40)	−0.08 (−0.19 to −0.00)	0.28 (−0.18 to 0.75)	−0.10 (−0.35 to 0.09)
PBSLs	0.34 (−0.06 to 0.73)	−0.09 (−0.24 to 0.06)		NA	0.40 (0.05 to 0.76)	−0.18 (−0.35 to −0.01)	0.65 (−0.19 to 1.52)	−0.21 (−0.58 to 0.17)
PDMCLs	NA	NA	0.50 (0.21−0.80)	−0.18 (−0.44 to 0.06)	−0.10 (−0.68 to 0.50)	−0.15 (−0.40 to 0.12)	−0.40 (−2.05 to 1.22)	−0.09 (−0.73 to 0.56)
PDMSLs	0.12 (−0.29 to 0.54)	−0.05 (−0.21 to 0.11)		NA	0.12 (−0.26 to 0.51)	−0.05 (−0.20 to 0.11)	NA	NA
Pir	0.37 (−0.04 to 0.77)	−0.13 (−0.31 to 0.05)	0.21 (−0.03 to 0.45)	−0.06 (−0.24 to 0.13)	0.32 (0.06 to 0.58)	−0.08 (−0.21 to 0.04)	0.41 (−0.57 to 1.36)	−0.12 (−0.51 to 0.27)
RGPCLs	−0.03 (−0.42 to 0.35)	0.02 (−0.13 to 0.17)	0.15 (−0.13 to 0.42)	0.03 (−0.22 to 0.27)	−0.02 (−0.39 to 0.34)	0.02 (−0.15 to 0.19)	−0.05 (−1.01 to 0.88)	0.05 (−0.32 to 0.42)
SCLs	NA	NA	−0.06 (−0.21 to 0.09)	0.01 (−0.16 to 0.18)	−0.42 (−0.96 to 0.13)	−0.01 (−0.25 to 0.23)	−0.59 (−1.94 to 0.74)	0.04 (−0.48 to 0.57)
Tim	NA	NA	−0.06 (−0.26 to 0.16)	NA	−0.04 (−0.38 to 0.30)		−0.04 (−0.89 to 0.82)	NA
USVSLs	−0.11 (−0.40 to 0.18)	0.03 (−0.12 to 0.18)	−0.11 (−0.38 to 0.16)	NA	−0.01 (−0.29 to 0.28)	0.05 (−0.10 to 0.20)	−0.23 (−1.19 to 0.71)	0.06 (−0.31 to 0.43)

Atr = atropine; Atr H = high-dose atropine (1% or 0.5%); Atr L = low-dose atropine (0.01%); Atr M = moderate-dose atropine (0.1%); BSLs = bifocal spectacle lenses; CrI = credible interval; Cyc = cyclopentolate; D = diopter; MOA = more outdoor activities (14−15 hrs/wk); NA = not available; OK = orthokeratology; PASLs = progressive addition spectacle lenses; PBSLs = prismatic bifocal spectacle lenses; PDMCLs = peripheral defocus modifying contact lenses; PDMSLs = peripheral defocus modifying spectacle lenses; Pir = pirenzepine; RGPCLs = rigid gas-permeable contact lenses; SCLs = soft contact lenses; Tim = timolol; USVSLs = undercorrected single vision spectacle lenses.

3. Asian children appeared to benefit more from treatment than white children, and most interventions lose their early effect in the second year.

Certain trials caused high heterogeneity across studies, but removal of them only introduced less pronounced effects of most interventions, without a significant change in the results, and we did not find any statistically significant inconsistencies in the network. This implies that the results are relatively reliable.

The major advantage of our current meta-analytic approach over individual trials is the larger sample size that results from incorporating both direct and indirect evidence. This approach also differs from traditional meta-analyses in that traditional meta-analyses are characterized by a series of smaller meta-analyses of different active comparisons and thus provides less robust information. Although comparisons between specific classes of interventions for myopia control have been investigated in multiple studies, others have been performed only in a single trial or have never been performed. Thus, a network meta-analysis makes it possible to both validate previous empirical evidence of direct comparisons and provide evidence regarding comparisons for which no direct empirical evidence exists.[40]

Previous trials suggested that, with the exception of timolol, drug treatments (especially atropine) showed the highest efficacy, which is consistent with our results.[41] It remains unclear how atropine slows down myopia progression. Earlier studies have suggested that this may be due to the effects of atropine on lens accommodation, whereas subsequent studies have shown that atropine's effects on myopia is via a nonaccommodative pathway in the retina or sclera.[18,19] However, the inevitable side effects of higher doses of atropine (i.e., glare, photophobia, and near vision blur) and the rebound phenomenon after stopping treatment have restricted its widespread clinical use.[42,43] There appears to be a differential dose-dependent sensitivity to atropine's impact on myopia progression, pupil size, and accommodation. Low-dose atropine (0.01%) is still one of the most effective interventions identified in this analysis and has been found to induce minimal clinical symptoms.[44] Furthermore, this lower dose does not display the same rebound effect that has been seen in higher doses. This makes low-dose atropine a definite candidate treatment for myopia progression, although this result needs to be replicated in other populations.

Alternatively, pirenzepine, a selective antimuscarinic agent, represents a viable alternative to atropine for the control of myopia progression. Pirenzepine is less likely to produce pupillary dilatation and cycloplegia with moderate effects in myopia control.[45,46] Of note, the analysis of pirenzepine was limited by involvement of only 2 articles; thus, further trials with larger sample sizes are required to confirm its effect.

Multifocal spectacle lenses have been tested in controlling the progression of myopia for several years, but their efficacy is controversial.[47,48] A previous meta-analysis[21] indicated that multifocal spectacle lenses slowed myopia progression by a mean of 0.25 D in school-aged children compared with single vision spectacle lenses. In the current study, our results suggest only modest effects of bifocal spectacle lenses and progressive addition spectacle lenses. Furthermore, there was no significant difference between bifocal spectacle lenses and progressive addition spectacle lenses in pairwise comparison. As for specifically designed multifocal spectacle lenses (prismatic bifocal spectacle lenses), our meta-analysis showed that they have a moderate effect in myopia control, but this was not statistically significant with wide CrIs. This is partly because only 1 relevant RCT was included, so further trials are warranted. Overall, multifocal spectacle lenses do not seem to be a viable option for controlling progression of myopia.

In terms of contact lenses, orthokeratology has been shown to be an effective treatment in controlling progression of myopia.[49,50] Orthokeratology flattens the central cornea while steeping the midperipheral cornea to reduce relative peripheral hyperopia, which may slow the elongation of the axial length.[51,52] However, orthokeratology is not in widespread use because of a variety of possible issues, such as the additional skills required by practitioners for fitting these lenses, the discomfort during overnight wear, the cost, and the risks of infective keratitis.[53–55] In recent years, soft contact lenses with myopia control features that create additional myopic defocus on the retina have generated great interest in myopia control.[33] Our results showed that peripheral defocus modifying contact lenses were superior to peripheral defocus modifying spectacle lenses. Similar to other interventions, the limited relevant RCTs included in this meta-analysis showed wide CrIs thus, more RCTs are required to demonstrate its efficacy. In comparison, other contact lenses such as standard rigid gas-permeable contact lenses and conventional soft contact lenses showed no effect on myopia control in our study.

A previous review has indicated that increasing outdoor activities may be a simple strategy to reduce the risk of myopia progression.[23] However, in the current study, only 1 RCT of outdoor activities contributed to the analysis, and the effect was modest. Further trials are required to elucidate the value of this intervention.

Some epidemiologic studies have reported racial differences between childhood myopia prevalence in Asians and white subjects within the same country, highlighting the potential role of ethnicity.[56,57] In accordance with previous studies,[21] we found that Asians appeared to benefit more from treatment than white patients. This finding may be explicable on the basis of an increased genetic susceptibility of Asians to myopia or a faster rate of progression in Asians. Also similar to previous studies,[58,59] our study found that most interventions lose their early effect in the second year, which may be due to increased age.

Study Limitations

There are some inherent limitations in this analysis that should be highlighted. Optical interventions vary for each individual patient. For example, multifocal spectacle lenses have different refractive powers for each patient, and the off-axis effects of orthokeratology vary with refractive correction. Both placebo and single vision spectacle lenses are used as

controls. The quality of trials conducted and reporting varied (some studies were not double-blind). There was a wide variation in subject age (mean age range, 8.3−14.0 years), but because studies reported only the age range or mean, data were insufficient to determine how treatment varies with age. Our study provides information on the efficacy but not the safety of different treatment options because of lack of data within the included articles. Clinical decisions on any intervention require information on efficacy, short-term/long-term benefits, and the risks of side effects, so additional examination of the safety of these interventions is important. In addition, high heterogeneity was found in some combinations, and most interventions are based on indirect comparisons (113 pairs). More trials are required to confirm the results from these indirect comparisons.

The fundamental challenge in this analysis is the lack of sufficient data on some treatments, which results in wide CrIs. Future trials with larger sample sizes are required to provide better-quality data to help establish the effect of various interventions in controlling myopia. In addition, the possible additive or even synergistic effects of different combinations (e.g., combined atropine and contact lens treatments) have not, to date, been adequately addressed. This is certainly a worthy question for future studies and may help to provide treatments for myopic progression that are both effective and easily tolerated by the patient.

Notwithstanding these limitations, it is unlikely that the number of head-to-head trials necessary to address all these clinical questions will be conducted. At least 136 trials are needed to compare all interventions of myopia control, and in their absence, our network meta-analysis provides a valuable approach to the issue.

In conclusion, on the basis of evidence from the available RCTs used in this analysis, the following evidence-based guidelines might be proposed. (1) Rigid gas-permeable contact lenses, conventional soft contact lenses, timolol, and undercorrected single vision spectacle lenses are ineffective in slowing the progression of myopia in children. (2) Atropine, pirenzepine, orthokeratology, soft contact lenses with myopia control features (peripheral defocus modifying designs), and progressive addition spectacle lenses are effective and produce a statistically significant reduction of myopia progression in terms of refraction or axial length. (3) The introduction of myopia treatments into clinical practice may be limited by side effects (e.g., atropine 1%), cost and complexity (e.g., orthokeratology), and limited effectiveness (e.g., progressive add spectacle lenses). This leaves low-dose atropine (0.01%), pirenzepine, and soft contact lenses with myopia control features (e.g., peripheral defocus modifying designs) as viable options for the active management of myopia progression.

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Abbreviations and Acronyms:
CI = confidence interval; **CrI** = credible interval; **D** = diopter; **RCT** = randomized controlled trial.

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