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Interventions to slow progression of myopia in children (Review)

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[Intervention Review]

Interventions to slow progression of myopia in children

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Editorial note: This Cochrane Review has been superseded by Interventions for myopia control in children: a living systematic review and network meta-analysis (https://doi.org/10.1002/14651858.CD014758).

ABSTRACT

Background

Nearsightedness (myopia) causes blurry vision when one is looking at distant objects. Interventions to slow the progression of myopia in children include multifocal spectacles, contact lenses, and pharmaceutical agents.

Objectives

To assess the effects of interventions, including spectacles, contact lenses, and pharmaceutical agents in slowing myopia progression in children.

Search methods

We searched CENTRAL; Ovid MEDLINE; Embase.com; PubMed; the LILACS Database; and two trial registrations up to February 2018. A top up search was done in February 2019.

Selection criteria

We included randomized controlled trials (RCTs). We excluded studies when most participants were older than 18 years at baseline. We also excluded studies when participants had less than -0.25 diopters (D) spherical equivalent myopia.

Data collection and analysis

We followed standard Cochrane methods.

Main results

We included 41 studies (6772 participants). Twenty-one studies contributed data to at least one meta-analysis. Interventions included spectacles, contact lenses, pharmaceutical agents, and combination treatments. Most studies were conducted in Asia or in the United States. Except one, all studies included children 18 years or younger. Many studies were at high risk of performance and attrition bias.

Spectacle lenses: undercorrection of myopia increased myopia progression slightly in two studies; children whose vision was undercorrected progressed on average -0.15 D (95% confidence interval [CI] -0.29 to 0.00; n = 142; low-certainty evidence) more than those wearing fully corrected single vision lenses (SVLs). In one study, axial length increased 0.05 mm (95% CI -0.01 to 0.11) more in the

undercorrected group than in the fully corrected group (n = 94; low-certainty evidence). Multifocal lenses (bifocal spectacles or progressive addition lenses) yielded small effect in slowing myopia progression; children wearing multifocal lenses progressed on average 0.14 D (95% CI 0.08 to 0.21; n = 1463; moderate-certainty evidence) less than children wearing SVLs. In four studies, axial elongation was less for multifocal lens wearers than for SVL wearers (-0.06 mm, 95% CI -0.09 to -0.04; n = 896; moderate-certainty evidence). Three studies evaluating different peripheral plus spectacle lenses versus SVLs reported inconsistent results for refractive error and axial length outcomes (n = 597; low-certainty evidence).

Contact lenses: there may be little or no difference between vision of children wearing bifocal soft contact lenses (SCLs) and children wearing single vision SCLs (mean difference (MD) 0.20D, 95% CI -0.06 to 0.47; n = 300; low-certainty evidence). Axial elongation was less for bifocal SCL wearers than for single vision SCL wearers (MD -0.11 mm, 95% CI -0.14 to -0.08; n = 300; low-certainty evidence). Two studies investigating rigid gas permeable contact lenses (RGPCLs) showed inconsistent results in myopia progression; these two studies also found no evidence of difference in axial elongation (MD 0.02mm, 95% CI -0.05 to 0.10; n = 415; very low-certainty evidence). Orthokeratology contact lenses were more effective than SVLs in slowing axial elongation (MD -0.28 mm, 95% CI -0.38 to -0.19; n = 106; moderate-certainty evidence). Two studies comparing spherical aberration SCLs with single vision SCLs reported no difference in myopia progression nor in axial length (n = 209; low-certainty evidence).

Pharmaceutical agents: at one year, children receiving atropine eye drops (3 studies; n = 629), pirenzepine gel (2 studies; n = 326), or cyclopentolate eye drops (1 study; n = 64) showed significantly less myopic progression compared with children receiving placebo: MD 1.00 D (95% CI 0.93 to 1.07), 0.31 D (95% CI 0.17 to 0.44), and 0.34 (95% CI 0.08 to 0.60), respectively (moderate-certainty evidence). Axial elongation was less for children treated with atropine (MD -0.35 mm, 95% CI -0.38 to -0.31; n = 502) and pirenzepine (MD -0.13 mm, 95% CI -0.14 to -0.12; n = 326) than for those treated with placebo (moderate-certainty evidence) in two studies. Another study showed favorable results for three different doses of atropine eye drops compared with tropicamide eye drops (MD 0.78 D, 95% CI 0.49 to 1.07 for 0.1% atropine; MD 0.81 D, 95% CI 0.57 to 1.05 for 0.25% atropine; and MD 1.01 D, 95% CI 0.74 to 1.28 for 0.5% atropine; n = 196; low-certainty evidence) but did not report axial length. Systemic 7-methylxanthine had little to no effect on myopic progression (MD 0.07 D, 95% CI -0.09 to 0.24) nor on axial elongation (MD -0.03 mm, 95% CI -0.10 to 0.03) compared with placebo in one study (n = 77; moderate-certainty evidence). One study did not find slowed myopia progression when comparing timolol eye drops with no drops (MD -0.05 D, 95% CI -0.21 to 0.11; n = 95; low-certainty evidence).

Combinations of interventions: two studies found that children treated with atropine plus multifocal spectacles progressed 0.78 D (95% CI 0.54 to 1.02) less than children treated with placebo plus SVLs (n = 191; moderate-certainty evidence). One study reported -0.37 mm (95% CI -0.47 to -0.27) axial elongation for atropine and multifocal spectacles when compared with placebo plus SVLs (n = 127; moderate-certainty evidence). Compared with children treated with cyclopentolate plus SVLs, those treated with atropine plus multifocal spectacles progressed 0.36 D less (95% CI 0.11 to 0.61; n = 64; moderate-certainty evidence). Bifocal spectacles showed small or negligible effect compared with SVLs plus timolol drops in one study (MD 0.19 D, 95% CI 0.06 to 0.32; n = 97; moderate-certainty evidence). One study comparing tropicamide plus bifocal spectacles versus SVLs reported no statistically significant differences between groups without quantitative results.

No serious adverse events were reported across all interventions. Participants receiving antimuscarinic topical medications were more likely to experience accommodation difficulties (Risk Ratio [RR] 9.05, 95% CI 4.09 to 20.01) and papillae and follicles (RR 3.22, 95% CI 2.11 to 4.90) than participants receiving placebo (n=387; moderate-certainty evidence).

Authors' conclusions

Antimuscarinic topical medication is effective in slowing myopia progression in children. Multifocal lenses, either spectacles or contact lenses, may also confer a small benefit. Orthokeratology contact lenses, although not intended to modify refractive error, were more effective than SVLs in slowing axial elongation. We found only low or very low-certainty evidence to support RGPCLs and sperical aberration SCLs.

PLAIN LANGUAGE SUMMARY

Interventions to slow progression of nearsightedness in children

What was the aim of this review?
To find out if there are treatments that can slow the progress of nearsightedness (myopia) in children. Myopia is a vision condition in which people can see close objects clearly, but objects farther away appear blurred.

Key message
Eye drop medication, such as atropine, probably slows myopia progression in children. Children taking these eye drops may have blurred near vision, sensitivity to light, and some itching and discomfort. Multifocal lenses, either spectacles or contact lenses, may also confer a small benefit.

What did we study in this review?
During childhood and adolescence, the eyeballs can grow too long and can develop myopia. Treatments can slow growth of the eye, thereby slowing down the progression of myopia.

Cochrane researchers assessed how certain the evidence was for each review finding, factoring in problems such as the ways studies were done, inclusion of very small studies, and inconsistent findings across studies. They also looked for factors that can make the evidence more certain, including very large effects. They graded each finding as very low, low, moderate, or high certainty.

What were the main results of this review?
Cochrane researchers found 41 studies of treatments to slow myopia progression. These studies included a total of 6772 children. The review found that the following treatments may slow the progression of myopia, compared with wearing ordinary spectacles.

• Eye drops, in particular antimuscarinic drugs such as atropine, pirenzepine gel, and cyclopentolate (moderate-certainty evidence).

• Multifocal spectacles (either bifocal or progressive addition lenses) (moderate-certainty evidence).

• Bifocal soft contact lenses (low-certainty evidence).

• Orthokeratology contact lenses (moderate-certainty evidence).

• Combinations of eye drops and multifocal spectacles (moderate-certainty evidence).

The review found that the following treatments may have a small effect, or no effect, on myopia progression.

• Spherical aberration soft contact lenses (low-certainty evidence).

• Systematic adenosine antagonists (moderate-certainty evidence).

Children who wear undercorrected spectacles may have an increased chance of myopia progression compared with children who wear fully corrected spectacles (low-certainty evidence). Only very low-certainty evidence on rigid gas permeable contact lenses was available.

Antimuscarinic eye drops may result in blurred near vision, sensitivity to light, some discomfort and itching, and medication residue on the eyelids or eyelashes. Some children may develop small nodules or bumps under the eyelid. Spectacles and contact lenses, if used properly, are safe and effective.

How up-to-date is the review?
Cochrane researchers reviewed studies published up to February 2018.

SUMMARY OF FINDINGS

Summary of findings 1. Interventions to slow progression of myopia in children

Interventions to slow progression of myopia in children

Population: children with myopia (nearsightedness)

Settings: ophthalmology or optometry clinics

Outcome: c**hange in refractive error, measured in diopters (D), from baseline to 1-year follow-up**

Comparison (intervention vs comparator)	Mean difference (95% CI) Positive values represent slower progression of myopia in the treatment group than in the comparison group	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
Undercorrected vs fully corrected spectacles	-0.15 D (-0.29 to 0.00)	142 (2)	⊕⊕⊖⊖ **low**[a,b]	A third study did not report this outcome at 1 year
Multifocal vs single vision lens spectacles	0.14 D (0.08 to 0.21)	1463 (9)	⊕⊕⊕⊖ **moderate**[b]	Five studies not included in the meta-analyses also showed mostly favorable effects of multifocal lenses for slowing myopia progression
Peripheral plus spectacles vs single vision lens spectacles	See comment	597 (3)	⊕⊕⊖⊖ **low**[b,c]	No meta-analysis was conducted because of clinical and methodological heterogeneity among the 3 studies; furthermore, the results from these studies were inconsistent
Bifocal vs single vision soft contact lenses	0.20 D (-0.06 to 0.47)	300 (4)	⊕⊕⊖⊖ **low**[b,c]	-
Rigid gas permeable contact lenses vs spectacles or soft contact lenses	See comment	420 (2)	⊕⊖⊖⊖ **very low**[a,b,c]	No meta-analysis was conducted due to differences among 2 studies that reported inconsistent results
Orthokeratology contact lenses vs single vision lenses	See comment	-	-	Because orthokeratology contact lenses temporarily reduce myopia, their myopia control treatment effect can be measured only by axial elongation. We did not analyze the changes in refractive error for this comparison
Spherical aberration soft contact lenses vs single vision soft contact lenses	See comment	209 (2)	⊕⊕⊖⊖ **low**[b,d]	No meta-analysis was conducted because 1 of the studies did not provide effect estimates; however, 2 studies comparing spherical aberration SCLs with single vision SCLs reported no difference in myopia progression

Antimuscarinic agents vs placebo	Atropine: 1.00 D (0.93 to 1.07) Pirenzepine: 0.31 D (0.17 to 0.44) Cyclopentolate: 0.34 D (0.08 to 0.60)	629 (3) 326 (2) 64 (1)	⊕⊕⊕⊖ **moderate[b]**	We stratified the analysis by types of antimuscarinic agents due to statistical inconsistency
Atropine vs tropicamide	Atropine 0.1%: 0.78 D (0.49 to 1.07) Atropine 0.25%: 0.81 D (0.57 to 1.05) Atropine 0.5%: 1.01 D (0.74 to 1.28)	196 (1)	⊕⊕⊕⊖ **low[b]**	-
Systemic 7-methylxanthine vs placebo	0.07 D (-0.09 to 0.24)	77 (1)	⊕⊕⊕⊖ **moderate[a]**	-
Timolol drops vs no drops	-0.05 D (-0.21 to 0.11)	95 (1)	⊕⊕⊖⊖ **low[a,b]**	-
Atropine plus multifocal spectacles vs placebo plus SVLs	0.78 D (0.54 to 1.02)	191 (2)	⊕⊕⊕⊖ **moderate[b]**	-
Atropine plus bifocal spectacles vs cyclopentolate plus SVLs	0.36 D (0.11 to 0.61)	64 (1)	⊕⊕⊕⊖ **moderate[b]**	-
Bifocal spectacles vs SVLs with timolol drops	0.19 D (0.06 to 0.32)	97 (1)	⊕⊕⊕⊖ **moderate[b]**	-
Tropicamide plus bifocal spectacles vs SVLs	See comment	50 (1)	-	No estimate of effect was reported

Outcome: c**hange in axial length, measured in millimeters (mm), from baseline to 1-year follow-up**

Comparison **(intervention vs comparator)**	**Mean difference (95% CI)** **Negative values represent less axial elongation in the treatment group than in the comparison group**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
Undercorrected vs fully corrected spectacles	0.05 mm (-0.01 to 0.11)	94 (1)	⊕⊕⊖⊖ **low[a,b]**	Two studies did not report this outcome at 1 year
Multifocal vs single vision lens spectacles	-0.06 mm (-0.09 to -0.04)	896 (4)	⊕⊕⊕⊖ **moderate[b]**	Four studies (not included in the meta-analysis) showed mostly favorable effects of multifocal lenses and 6 studies did not report this outcome
Peripheral plus spectacles vs single vision lens spectacles	See comment	597 (3)	⊕⊕⊖⊖ **low[b,c]**	-

Bifocal vs single vision soft contact lenses	-0.11 mm (-0.14 to -0.08)	300 (4)	⊕⊕⊖⊖ **low[b,c]**	-
Rigid gas permeable contact lenses vs spectacles or soft contact lenses	0.02 mm (-0.05 to 0.10)	415 (2)	⊕⊕⊖⊖ **low[a,b]**	-
Orthokeratology contact lenses vs single vision lenses	-0.28 mm (-0.38 to -0.19)	106 (2)	⊕⊕⊕⊖ **moderate[b]**	One other study reported this outcome; however, the study did not report sufficient data for analysis
Spherical aberration soft contact lenses vs single vision soft contact lenses	See comment	209 (2)	⊕⊖⊖⊖ **very low[a,b,d]**	No meta-analysis was conducted due to clinical, methodological, and statistical differences between the 2 studies; however, 2 studies comparing spherical aberration SCLs with single vision SCLs reported no difference in axial length
Antimuscarinic agents vs placebo	Atropine: -0.35 mm (-0.38 to -0.31) Pirenzepine: -0.13 mm (-0.14 to -0.12)	502 (2) 326 (2)	⊕⊕⊕⊖ **moderate[c]**	We did not combine results for all antimuscarinic agents due to statistical inconsistency; outcome was not reported by 2 studies
Atropine vs tropicamide	See comment	196 (1)	-	Outcome was not reported
Systemic 7-methylxanthine vs placebo	-0.03 mm (-0.10 to 0.03)	77 (1)	⊕⊕⊕⊖ **moderate[a]**	-
Timolol drops vs no drops	See comment	95 (1)	-	Outcome was not reported
Atropine plus multifocal spectacles vs placebo plus SVLs	-0.37 mm (-0.47 to -0.27)	127 (1)	⊕⊕⊕⊖ **moderate[b]**	One study did not report this outcome
Atropine plus bifocal spectacles vs cyclopentolate plus SVLs	See comment	64 (1)	-	Outcome was not reported
Bifocal spectacles vs SVLs with timolol drops	See comment	97 (1)	-	Outcome was not reported
Tropicamide plus bifocal spectacles vs SVLs	See comment	50 (1)	-	Outcome was not reported
Adverse effects				
No serious adverse events were reported across all interventions. Two studies showed that participants receiving antimuscarinic topical medications (n=259) were more likely to experience accommodation difficulties (Risk Ratio 9.05, 95% CI 4.09 to 20.01), papillae and follicles (RR 3.22, 95% CI 2.11 to 4.90) than participants receiving placebo (n=128), but no difference in medication residue on the eyelids or eyelashes (RR 0.91, 95% CI 0.73 to 1.12). Certainty of a body of evidence was moderate, downgraded for imprecision of results (-1).				

GRADE Working Group grades of evidence.
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

CI: confidence interval; D: diopters.
[a]Downgraded for imprecision (i.e. wide confidence interval).
[b]Downgraded for risk of bias among included trials.
[c]Downgraded for inconsistency.
[d]Downgraded for indirectness due to averaging values over time assuming linear change (e.g. reporting the change per year using data collected at baseline and at 2 years of follow-up).

BACKGROUND

Description of the condition

Myopia, also known as nearsightedness, occurs because the cornea or the lens is too powerful or the eyeball is longer than normal; this causes distant objects to be focused in front of the retina instead of on it, as occurs in nonmyopic individuals. In myopia, near objects are seen clearly but distant objects appear blurred.

Epidemiology

Myopia is an important cause of reduced vision in populations throughout the world and is one of the five immediate priorities for the "Vision 2020" initiative of the World Health Organization (WHO) (Pararajasegaram 1998). Approximately 33% of persons in the United States are myopic, reflecting an increase from approximately 25% in the early 1970s (Vitale 2009). It is estimated that half of the world's population will be myopic by 2050 (Holden 2016). Racial and ethnic differences in the magnitude and prevalence of myopia have been observed (Garner 1999; Lin 1999; Maul 2000; Voo 1998; Zhan 2000), with both greater in Asia than in other parts of the world (Lin 1999; Zhan 2000).

Juvenile-onset myopia in the United States typically develops at approximately six to eight years of age and progresses at a rate of approximately 0.50 D (diopters) per year through 15 to 16 years (COMET Study 2003; Fulk 2002; Goss 1987; Perrigin 1990). The progression of myopia is typically faster at younger ages (Braun 1996; Goss 1987; Goss 1990; Pärssinen 1989; Saw 2000), but myopia onset, progression, and stabilization vary widely among individuals (Braun 1996; Pärssinen 1989; Saw 2000). Similar proportions of boys and girls are affected by myopia, and the degree of myopia is similar between the two genders (Zadnik 2003).

Etiology and risk factors

Several factors have been suggested to have a role in the development of myopia. Many models estimate greater genetic effects than environmental effects for myopia (Chen 1985; Hammond 2001). Children with two myopic parents have greater axial lengths; this indicates higher risk of myopia than for children with one or no myopic parents (Zadnik 1994). Environmental influences are related to prolonged reading or near work, which has inconsistently been associated with increased myopia prevalence (Saw 2001; Young 1969). Fewer hours spent outdoors has also been associated with myopia (Dirani 2009; Guggenheim 2012; Guo 2013; Jones 2007; Rose 2008). Children randomly assigned to additional outdoor time exhibit a lower incidence of myopia onset but do not exhibit slowed progression of myopia after onset (He 2015; Wu 2010).

Presentation and diagnosis

The primary symptom of myopia is blurred distance vision. Children often present to an eye care practitioner after they have failed a vision screening at school or after a parent or teacher has noticed the child squinting or having difficulty seeing distant objects.

An eye care practitioner using autorefraction or retinoscopy may confirm the diagnosis of myopia objectively, or the practitioner can confirm the diagnosis by performing a subjective refraction, which requires responses from the child. To diagnose myopia in a child, cycloplegic drops should be placed in the child's eyes, hindering his or her ability to focus the eyes, so that an accurate prescription can be determined.

Description of the intervention

Spectacles are often the initial treatment for children with myopia because they provide clear vision with few potential side effects. Spectacles for myopia correction use concave lenses that focus light more posteriorly, resulting in a clear image focused on the retina.

Contact lenses are typically a secondary treatment option for children because they require greater dexterity and responsibility when compared to spectacles. They also bear greater risks than spectacles, which range from innocuous redness of the eyes to severe pain and vision loss due to corneal ulcers (Fonn 1988; MacRae 1991; Schein 1989). However, young children are at lower risk for problems associated with contact lens wear than are college-age adults (Chalmers 2011; Wagner 2011). There are different types of contact lenses. Soft contact lenses are made of gel-like, water-containing, flexible plastics that allow oxygen to pass through the cornea. Spherical aberration soft contact lenses aims to correct an optical problem that occurs when incoming light rays end up focusing at different points after passing through a spherical surface (in this case the ocular system). Rigid gas permeable contact lenses (RGPCLs) are rigid, more durable and less likely to tear compared to soft contact lenses, and resistant to deposit buildup; however, they may be less comfortable to wear initially. Orthokeratology is a lens fitting procedures that uses specially designed RGPCLs to change the curvature of the cornea to temporarily improve the eye's ability to focus on objects. Most orthokeratology lenses are worn at night and then removed during the day. When orthokeratology is discontinued, the cornea will return to its original curvature and the eye to its original amount of nearsightedness.

Lastly, both spectacles and contact lenses can contain more than one power zone; they are called bifocal, multifocal, or progressive addition lenses.

There are currently no pharmaceutical agents approved by the US Food and Drug Administration for use as myopia treatments, although antimuscarinic agents, such as atropine, pirenzepine, tropicamide, and scopolamine, as well as 7-methylxanthine (7-mx), a non-antimuscarinic agent, have been used off-label and targeted in recent clinical trials.

Laser refractive surgery, such as laser in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK), causes permanent flattening of the central corneal curvature resulting from removal of stromal tissue with a laser once myopia has developed (Duffey 2003; Shortt 2006), but it is not routinely performed in children.

Other forms of myopia correction, such as placement of a lens inside the eye and clear rings into the cornea, also are not used routinely in children because of the risk of potential myopia progression (Barsam 2010).

How the intervention might work

In terms of slowing myopia progression, use of multifocal spectacles and undercorrection of myopic refractive error are thought to reduce accommodative error, which may act as a stimulus for increased eye growth. Myopic patients exhibit greater

accommodative lag than nonmyopic patients (COMET Study 2003; Mutti 2006). Accommodative lag results in light focused behind the retina during near work, which may act as a signal to increase eye growth and may result in myopia. If the accommodative error can be reduced with bifocals or myopic undercorrection, then the stimulus for eye growth will be reduced, and this may slow myopia progression.

Antimuscarinic agents were thought to reduce myopic progression by eliminating accommodation, but this has been shown to be a local retinal effect that slows myopia progression (Troilo 1987). Antimuscarinic receptor binding may lead to a biochemical change that slows eye growth, but the exact mechanism is unknown.

Multifocal contact lenses provide myopic defocus of light in the periphery while allowing clear vision by focusing light on the central retina (Charman 2006; Kang 2011; Moore 2017; Ticak 2013). The myopic defocus (light focused in front of the retina) may act as a signal to slow eye growth and reduce myopia progression (Smith 2009). Orthokeratology works by flattening the center cornea to temporarily improve the eye's ability to focus on objects.

Why it is important to do this review

Myopia has been reported to have reached epidemic proportions in parts of the world (Park 2004). Strategies to control progression of myopia gain importance in the context of the "Vision 2020" initiative by the WHO, which seeks to eliminate preventable causes of blindness, including risks associated with high myopia, by the year 2020 (Pararajasegaram 1998). Interventions that have been explored for this purpose include bifocal spectacles, cycloplegic eye drops, intraocular pressure–lowering drugs, muscarinic receptor antagonists, and contact lenses. In this review, we systematically assessed the effectiveness of strategies to control progression of myopia in children.

OBJECTIVES

To assess the effects of interventions, including spectacles, contact lenses, and pharmaceutical agents, such as muscarinic receptor antagonists, cycloplegic eye drops, and intraocular pressure–lowering medications, in slowing myopia progression in children.

METHODS

Criteria for considering studies for this review

Types of studies

This review included randomized controlled trials (RCTs).

Types of participants

We included trials in which participants were treated with spectacles, contact lenses, or pharmaceutical agents for controlling progression of myopia. We excluded trials in which most participants were older than 18 years at the start of the trial. We also excluded trials that included participants with less than -0.25 D spherical equivalent myopia at baseline. (The spherical equivalent is an optical measurement based on a mathematical calculation: the sum of the spherical power plus half the cylindrical power of the refractive error.)

Types of interventions

We included trials in which any of the following interventions for slowing the progression of myopia were compared with a control treatment of single vision spectacle lenses, single vision soft contact lenses (SVSCLs), or placebo treatment, or with each other.

- Undercorrection of myopia, bifocal lenses (spectacles), progressive addition lenses (PALs), and other modifications to spectacle lenses.
- Bifocal soft contact lenses (BSCLs), RGPCLs, and corneal reshaping (orthokeratology) contact lenses.
- Pharmaceutical agents (e.g. atropine, pirenzepine).

Types of outcome measures

Primary outcomes

- Progression of myopia assessed as the mean change in refractive error (spherical equivalent) from baseline to each year of follow-up and measured by any method

Secondary outcomes

- Mean change in axial length, measured by any method
- Mean change in corneal radius of curvature, measured by any method

We analyzed the secondary outcomes for each year of follow-up when sufficient data were available.

Adverse effects

We summarized reported adverse effects related to the interventions as described in the included studies, including but not limited to blurry vision, red eyes, infection, and conjunctival reactions.

Economic data

We documented reported cost analyses and other data on economic outcomes when reported by the included trials.

Quality of life measures

We documented any quality of life information when reported by the included trials.

Follow-up

We reported outcomes for follow-up at one year, at two years, and as available throughout the study periods. We imposed no restrictions based on length of follow-up.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the following electronic databases for RCTs and controlled clinical trials, with no language or publication year restrictions up to Febrary 2018 (and all relevant studies up to Febrary 2018 were included in the current version). A top up search was done on February 26, 2019. We listed potentially relevant studies from the top up search in the tables for "Characteristics of studies awaiting classification" and "Characteristics of ongoing studies".

- Cochrane Central Register of Controlled Trials (CENTRAL; Issue 2, 2019) (which contains the Cochrane Eyes and Vision Trials Register), in the Cochrane Library (searched February 26, 2019) (Appendix 1).
- MEDLINE Ovid (1946 to February 26, 2019) (Appendix 2).
- Embase (1947 to February 26, 2019) (Appendix 3).
- PubMed (1948 to February 26, 2019) (Appendix 4).
- Latin American and Caribbean Health Science Information Database (LILACS) (1982 to February 26, 2019) (Appendix 5).
- International Standard Randomized Controlled Trials Number (ISRCTN) registry (www.isrctn.com/editAdvancedSearch; searched February 26, 2019) (Appendix 6).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicalTrials.gov; searched February 26, 2019) (Appendix 7).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched February 26, 2019) (Appendix 8).

Searching other resources

We searched the reference lists of identified trial reports to find additional trials. We used the Science Citation Index (last assessed April 12, 2013) to find studies that had cited the identified trials. We contacted the primary investigators of identified trials for details of other potentially relevant trials not identified by the electronic searches, and of recently completed or ongoing trials. We did not conduct manual searches of abstracts of conference proceedings and optometry literature specifically for this review, as these sources are searched by the Cochrane Eyes and Vision Group and are listed in CENTRAL.

Data collection and analysis

Selection of studies

Two review authors, including at least one clinician and one methodologist, independently assessed the titles and abstracts of records identified by electronic and manual searches as per the Criteria for considering studies for this review. We classified records as (1) definitely relevant, (2) possibly relevant, or (3) definitely not relevant. We obtained and assessed the full-text reports of records classified as (1) or (2) by at least one review author. After assessing the full-text reports, we classified studies as (A) include, (B) awaiting assessment, or (C) exclude. A third review author resolved disagreements. Review authors were unmasked to report authors, authors' institutions, and trial results during this assessment. We included and further assessed studies identified as (A) for study design and risk of bias. We contacted the authors of studies classified as (B) for clarification and reassessed these studies as per the inclusion criteria, as further information became available. We excluded studies identified as (C) and documented the reasons for exclusion in this review.

We initially included Cheng 2010, but after data extraction and risk of bias assessment, we assessed this study to be quasi-randomized and thus deemed it ineligible for the review. However, as we initially included the study, we did not exclude it post hoc but instead conducted sensitivity analyses for inadequate randomization when applicable.

Data extraction and management

Two review authors independently extracted the data for primary and secondary outcomes on two paper data collection forms developed by the Cochrane Eyes and Vision Group. We resolved discrepancies by discussion. We contacted primary investigators for data reported unclearly or incompletely. One review author entered the data into Review Manager 5 (RevMan 5) (Review Manager 2014), and a second review author verified the data entered.

Assessment of risk of bias in included studies

Two review authors independently assessed potential sources of bias in trials according to the methods described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We resolved disagreements between authors through discussion.

We considered the following parameters.

- Selection bias (random sequence generation, quality of allocation concealment).
- Performance bias (masking of participants).
- Detection bias (masking of outcome assessors and data analyzers).
- Attrition bias (completeness of follow-up, intention-to-treat [ITT] analysis).
- Reporting bias (selective outcome reporting, incomplete reporting of results).
- Other potential sources of bias (e.g. funding source).

For attrition bias, we considered whether or not reasons for losses to follow-up were comparable between treatment arms, and whether or not all participants were analyzed as randomized. If studies reported that an ITT analysis was performed, we assessed whether (1) all randomized participants were included in the analysis, even when no outcome data were collected, and (2) participants were analyzed in the intervention groups to which they were randomized, regardless of the intervention they actually received. We interpreted a true ITT analysis to have been undertaken only when both of these criteria were fulfilled.

We classified the risk of bias for each parameter as "low risk of bias," "unclear risk of bias," or "high risk of bias." For example, we considered studies using allocation concealment by centralized randomization and use of sequential opaque envelopes (which provided reasonable confidence that participating eye care providers and patients were not aware of the randomization sequence) to be at low risk of bias. We contacted the authors of trials when we needed additional information to assess risk of bias. If trial authors did not respond within an eight-week period, we classified the trial based on available information.

Measures of treatment effect

We reported mean differences (MDs) for continuous outcome measures and risk ratios (RRs) for dichotomous outcomes.

Unit of analysis issues

When only one eye per participant was randomized, the unit of analysis was the individual eye (and participant). When both eyes from the same participant were randomized (either to the same

intervention or to different interventions), we used estimates that had accounted for the correlation between the two eyes. For cross-over design and cluster-randomized design, we analyzed only estimates that had accounted for the design.

Dealing with missing data

We contacted the authors of trial reports for any missing data. When we did not receive a response within eight weeks, we analyzed the studies based on available information. We will include any new information in future updates of the review.

Assessment of heterogeneity

We assessed methodological and clinical heterogeneity by examining the characteristics and design of included studies. We assessed statistical heterogeneity by using the Chi^2 test and the I^2 statistic. We considered a P value less than 0.1 as significant for the test of heterogeneity. We assessed the inconsistency of effect estimates across studies using the I^2 statistic. An I^2 value greater than 50% was an indication of substantial statistical heterogeneity.

Assessment of reporting biases

We assessed reporting biases based on communications with trial authors regarding any outcomes assessed but not reported.

Data synthesis

We used a fixed-effect model for meta-analyses including fewer than three studies, and a random-effects model for meta-analyses including three or more studies. Change-from-baseline data were combined in meta-analyses with mean outcome data at annual measurement time points based on the generic inverse variance (unstandardized) MD method, as outlined in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017). When we assessed substantial clinical, methodological, or statistical heterogeneity, we did not combine individual trials in meta-analysis but instead reported study results separately.

Subgroup analysis and investigation of heterogeneity

We undertook subgroup analyses for types of intervention modalities (i.e. bifocals, PALs, and specific pharmaceutical agents). In the future, if sufficient evidence becomes available, we will also conduct subgroup analyses according to age, degree of myopia at baseline, and type of contact lens (soft vs rigid gas permeable).

Sensitivity analysis

We conducted a sensitivity analysis for meta-analyses in which more than three studies were included and when change-from-baseline outcomes were combined in analysis with mean outcomes at annual measurement time points. We combined studies using autorefraction in analysis with subjective refraction or when analyses included the Cheng 2010 study.

"Summary of findings"

We prepared a "Summary of findings" table including all comparisons for each of the following outcomes: change in refractive error, change in axial length, change in corneal curvature, and adverse effects. Additionally, we presented adverse effects by intervention in the Additional tables section, as the data were insufficient for quantitative analysis. We used the GRADE approach to assess the overall certainty of evidence for each outcome based on five criteria: risk of bias, imprecision, inconsistency, indirectness, and publication bias (Guyatt 2011).

RESULTS

Description of studies

Results of the search

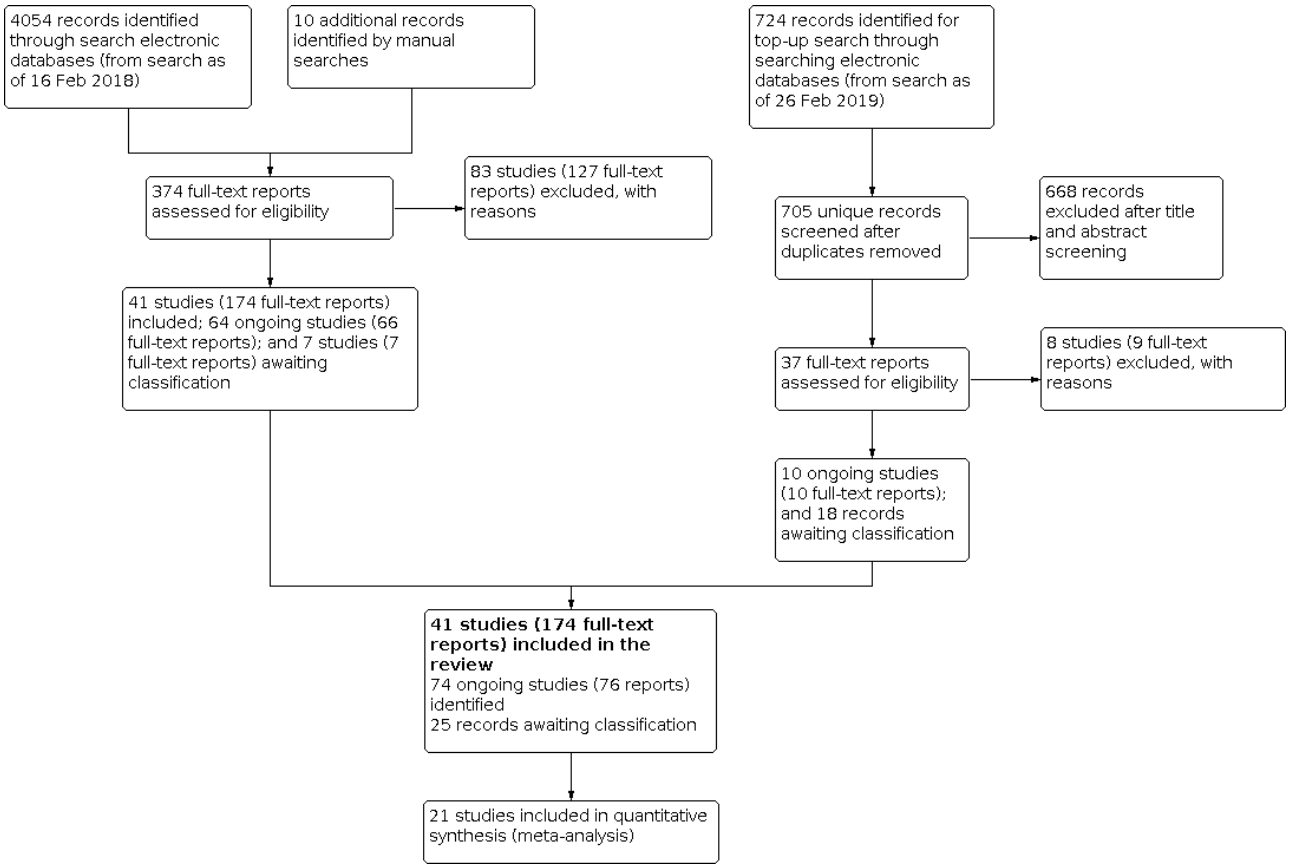
Details of results of the 2011 version of this review were published previously (Walline 2011). Briefly, we included 89 records (from 23 studies), excluded 82 records (from 61 studies), identified four records awaiting classification (from three studies: Anstice 2011; ATOM 2 Study 2012; COMET2 Study 2011), and identified one ongoing study (STAMP Study 2012).

In February 2018, we conducted an update of the electronic literature search, handsearched the reference lists of included studies, and used the Science Citation Index to identify additional studies. We identified 4064 additional records, 10 of which we identified by manual searching. After omitting duplicates and screening 4052 titles and abstracts, we excluded 3678 records and obtained full-text reports of 374 records for further review. Upon full-text review, we excluded 127 reports. Of them, six excluded reports belonged to a study previously assessed as awaiting classification because it did not include a single vision control group (ATOM 2 Study 2012). We also identified 66 reports for studies listed as ongoing. We listed seven reports as awaiting classification. We included the remaining 174 reports: 27 reported 15 newly included studies (Cambridge Anti-Myopia Study 2013; Charm 2013; Cheng 2016; DISC Study 2011; Fujikado 2014; Han 2018; Hasebe 2014; Koomson 2016; Lu 2015; ROMIO Study 2012; Swarbrick 2015; Trier 2008; Wang 2005; Wang 2017; Yi 2015), six reported results for the previously assessed ongoing study (STAMP Study 2012), two reported results for studies previously assessed as awaiting classification (Anstice 2011; COMET2 Study 2011), 50 reported new results for studies already included in the review, and 89 reported results included in the previously published review (Walline 2011).

In an additional top-up search conducted on February 26, 2019, we screened 724 titles and abstracts, of which we excluded 668 records. We excluded nine reports upon full-text review. We identified 10 reports of 10 studies listed as ongoing and 18 records as awaiting assessment.

Overall, we included 41 studies (174 reports), excluded 91 studies (136 reports), identified 74 ongoing studies (76 reports), and 25 records awaiting classification (Figure 1).

Figure 1. Study flow diagram.



Included studies

We included 41 studies (6772 total participants) in this review. The studies evaluated varying interventions, including spectacles, contact lenses, and pharmaceutical agents (Table 1). With the exception of interventions, study characteristics and outcomes were comparable among the included studies. Except one study (Cambridge Anti-Myopia Study 2013; n=147), all other studies included children 18 years or younger. No participant had myopia less than 0.25 D. Progression of myopia, measured as the change in refractive error, was assessed as the primary outcome in 37 studies, and as a secondary outcome in three studies (Charm 2013; Swarbrick 2015; Trier 2008). ROMIO Study 2012 was the only study that did not report refractive error as an outcome. Thirty-eight studies measured refraction under cycloplegia, of which 33 used autorefraction. No study reported quality of life or economic outcomes. Outcomes by intervention are summarized in Table 2 Table 3 and Table 4.

The most common methods of handling unit of analysis issues were to use the average of both eyes (15 studies); to use data from the right eye only (15 studies); and to use data from the eye with more severe myopia (one study) (Table 5). Nine studies were funded primarily by industry, were conducted by employees of the manufacturer of the intervention, or both (Anstice 2011; Cheng 2010; Cheng 2016; CONTROL Study 2016; Fujikado 2014; Hasebe 2014; PIR-205 Study 2004; Tan 2005; Trier 2008). An additional 14 studies were funded partially by industry or received materials from the manufacturer (Adler 2006; ATOM Study 2006; Charm 2013; CLAMP Study 2004; COMET Study 2003; COMET2 Study 2011; Edwards 2002; Hasebe 2008; ROMIO Study 2012; Sankaridurg 2010; Schwartz 1981; STAMP Study 2012; Swarbrick 2015; Yang 2009).

Spectacles

Undercorrected versus fully corrected spectacles

Three studies compared the use of undercorrected spectacles versus fully corrected spectacles. In two studies, one in Israel and one in Ghana, children up to 15 years old were randomized to receive spectacles blurred by +0.50 D or spectacles with full correction (Adler 2006; Koomson 2016). In the third study, 106 Malay and Chinese children were evenly randomized to receive spectacles undercorrected by approximately +0.75 D or fully corrected spectacles (Chung 2002). Study follow-up periods were 18 months in Adler 2006 and two years in Chung 2002 and Koomson 2016.

Multifocal versus single vision lenses

Fourteen studies included in the review compared multifocal spectacles versus single vision lenses (SVLs) (spectacles) for slowing progression of myopia in children: six used bifocal lenses (Cheng 2010; Fulk 1996; Fulk 2002; Houston Study 1987; Jensen 1991; Pärssinen 1989), and eight used progressive addition lenses (PALs) (COMET Study 2003; COMET2 Study 2011; Edwards 2002; Hasebe 2008; MIT Study 2001; STAMP Study 2012; Wang 2005; Yang 2009). All studies enrolled children from 6 to 15 years of age, used a plus addition lens from +1.00 D to +2.00 D, and had at least 18 months of follow-up (maximum three years). All bifocal studies were conducted outside of Asia (Canada, Denmark, Finland,

or USA), although the Canadian study included only children of Chinese ancestry (Cheng 2010); five PAL studies were conducted in Asia (China, Hong Kong, Japan, or Taiwan), and three in the USA (COMET Study 2003; COMET2 Study 2011; STAMP Study 2012).

Of the six bifocal studies, two were two-arm trials that directly compared bifocal spectacles to SVLs for slowing the progression of myopia in children. One study, conducted in Tahlequah, Oklahoma, USA, randomized 32 children to receive bifocals with +1.25 D addition or SVLs (Fulk 1996). The children were 6 to 13 years old and were followed for 18 months. Following this pilot study, study authors initiated a larger study with slight modifications to the study design (Fulk 2002). For their second study, study authors added another study center in Tulsa, Oklahoma, USA; enrolled 82 children aged 6 to 12 years; changed the bifocal addition to +1.50 D; and extended the follow-up period to 30 months.

The remaining four bifocal studies were three-arm trials with at least one bifocal group and one SVL group. In the Houston Myopia Control Study (Houston Study 1987), 207 children ages 6 to 15 years were randomized to one of three treatment groups and were followed for three years. Treatment groups included two intervention groups that received bifocals with either +1.00 D or +2.00 D addition and a standard treatment group that received SVLs. A three-arm trial including interventions of bifocals, timolol maleate, and SVLs was completed in Odense, Denmark (Jensen 1991). For two years, 159 schoolchildren with a mean age of 10.9 years were followed after they were randomized to one of three treatment groups. The bifocal group received bifocal lenses with +2.00 D addition for constant wear. The timolol group received one drop of 0.25% timolol maleate (an intraocular pressure [IOP]-reducing beta-blocker) in each eye twice daily in addition to SVLs for constant wear. The control group received only SVLs for constant wear. Another study compared the effects of bifocal lenses (+1.50 D) with or without three-prism diopters of base-in prism in the near segment with single vision distance lenses for slowing the progression of myopia over two years in 150 Chinese Canadian children (aged 8 to 13 years) (Cheng 2010). A study from central Finland enrolled myopic schoolchildren referred by local doctors and nurses after routine vision check-ups (Pärssinen 1989). In all, 240 children with a mean age of 10.9 years were randomized to one of three treatment groups and were followed for three years. The first intervention group, the distant use group, received full myopic correction and were advised to use glasses for distance vision only and to read at the greatest distance possible. The second intervention group, the bifocal group, received bifocal lenses with +1.75 D addition for continuous use. The third group was the control group and received minus lenses with full correction for continuous use.

All eight PAL studies directly compared use of PALs (multifocal lenses with gradual and progressive changes in power) to SVLs. The three USA-based studies used +2.00 addition PALs, and four of the five Asia-based studies used +1.50 addition PALs (the fifth Asian study did not specify the addition power). The Correction of Myopia Evaluation Trial (COMET) was a three-year, multicenter trial conducted in four major US cities (COMET Study 2003). In all, 469 children aged 6 to 11 years were randomized to receive either PALs or SVLs. The COMET 2 study was conducted to evaluate effectiveness in slowing myopia progression among children (n = 118) aged 8 to 11 years with low baseline myopia, high accommodative lag, and near esophoria (COMET2 Study 2011). Follow-up was provided for three years. In the third USA-based study, 85 children aged 6 to 11 years between -0.75D and -4.50 D of myopia, high accommodative lag, and near esophoria wore either PALs or SVLs for one year; all children wore SVLs in the second year of the study (STAMP Study 2012). A Japanese cross-over trial followed up children aged 6 to 12 years for 18 months after randomization to PALs or SVLs (Hasebe 2008). After 18 months, each child was switched to receive the alternate type of lens and was followed up for another 18 months. The Myopia Intervention Trial (MIT) included 227 Taiwanese children and investigated SVLs, PALs, and PALs in combination with atropine drops for controlling the progression of myopia (MIT Study 2001). The children, who were between 6 and 13 years of age, were randomized to one of three treatment groups and were followed up for 18 months: (1) SVLs and placebo eye drops; (2) PALs and placebo eye drops; and (3) PALs and 0.5% atropine instilled once a day at bedtime. Studies of 298 children from 7 to 10.5 years of age and of 178 children from 7 to 13 years of age were completed in Hong Kong and China (Edwards 2002; Yang 2009), respectively. The children in both studies were randomized to receive PALs or SVLs and were followed up for two years. Finally, another Chinese study, reported only in the form of a conference abstract, enrolled 104 children aged 6 to 15 years; the addition power used in the PAL lenses was not reported (Wang 2005).

Peripheral plus spectacles versus single vision lenses

Four studies compared various types of peripheral plus spectacles versus SVLs (Han 2018; Hasebe 2014; Lu 2015; Sankaridurg 2010). Peripheral plus spectacles are designed to reduce peripheral hyperopic defocus (peripheral vision farsightedness). As such they consist of lenses that correct for central vision as SVLs do, as well as for peripheral vision using positively aspherized and increasing peripheral power. The addition of the peripheral plus spectacles in these three trials ranged from +1.00 D to +2.50 D. All trials were conducted in China (Hasebe 2014 was a multicenter trial with additional sites in Japan and South Korea) and enrolled children aged 6 to 14 years. Hasebe 2014 randomized 197 children to one of three treatment groups: peripheral plus spectacles with +1.00 D addition, peripheral plus spectacles with +1.50 D addition, and SVLs. Lu 2015 randomized 80 children to either peripheral plus spectacles with up to +2.50 D addition or SVLs. Sankaridurg 2010 randomized 210 children to lens designs that had (1) a symmetrical, clear central aperture (20 mm) with increasing peripheral power to +1.00 D; (2) a symmetrical, clear central aperture (14 mm) with increasing peripheral power to +2.00 D; (3) an asymmetrical, clear central aperture with increasing peripheral power to +1.90 D; or (4) SVLs. The study was planned for two years of follow-up but was terminated at year one because the older age of participants resulted in slower than expected myopia progression among all study participants. Study follow-up periods were one year in Lu 2015 and two years in Hasebe 2014. Finally, Han 2018 included 240 children who were randomized to (1) peripheral defocus-reducing spectacles, (2) single vision lenses, or (3) orthokeratology lenses.

Contact lenses

Bifocal soft contact lenses versus single vision soft contact lenses

Four studies compared bifocal soft contact lenses (BSCLs) to single vision soft contact lenses (SVSCLs) for controlling myopia progression; one each was conducted in China (DISC Study 2011), Japan (Fujikado 2014), New Zealand (Anstice 2011), and the USA (CONTROL Study 2016). The age of children included in all trials

ranged from 6 to 18 years. The addition powers for BSCLs ranged from +0.50 to +2.50 D across trials.

The New Zealand study was a paired-eye, cross-over study in which one eye of each child aged 11 to 14 years was randomized to receive +2.00 D addition BSCLs or SVSCLs. Fellow eyes received the other type of lens. After 10 months, the types of lenses worn in each eye were switched and children were followed for another 10 months. The Japanese study also was a cross-over trial in which children aged 6 to 16 years were randomized to wear +0.50 D addition BSCLs or SVSCLs in both eyes for one year, then were switched to the other type of lens for the second year. The remaining two studies were parallel-group trials. In the first, children aged 8 to 13 years wore either +2.50 D addition BSCLs or SVSCLs for two years. In the second parallel-group study, 78 children from California, USA, ages 8 to 18 years with eso (convergent) fixation disparity, were randomized to wear BSCLs or SVSCLs every day for one year; the BSCL power prescribed was that needed to eliminate the child's eso fixation disparity while looking at near.

Rigid gas permeable contact lenses versus single vision lenses

Two studies included in the review compared rigid gas permeable contact lenses (RGPCLs) to either SVSCLs or spectacles (SVLs). The Contact Lens and Myopia Progression (CLAMP) study was a three-year trial that compared RGPCLs to SVSCLs for controlling myopia in school-aged children (CLAMP Study 2004). All participants had to complete a run-in period successfully before enrollment to exclude those who could not adapt to wearing rigid contact lenses. After the run-in period, 116 children aged 8 to 12 were randomized to RGPCL or SVSCL treatment groups. A study of 564 children aged 6 to 12 years in Singapore compared RGPCLs to SVL spectacles for controlling myopia over a two-year period (Katz 2003). After a three-month adaptation period, 383 participants remained in the study.

Orthokeratology contact lenses versus single vision lenses

Four studies investigated overnight orthokeratology contact lenses for controlling myopia progression. Studies enrolled children from 6 to 16 years of age with East Asian ethnicity; two studies were conducted in Hong Kong (Charm 2013; ROMIO Study 2012), one in China (Han 2018), and one in Australia (Swarbrick 2015). Charm 2013 evaluated high myopia (-5.00 D or worse), whereas ROMIO Study 2012 and Swarbrick 2015 included children with low to moderate myopia (no worse than -4.50 D). Axial length was the primary outcome in three studies (Charm 2013; ROMIO Study 2012; Swarbrick 2015).

The two studies from Hong Kong compared orthokeratology contact lenses worn overnight versus single vision spectacles. In Charm 2013, 26 of 52 children randomized were assigned to wear partial reduction orthokeratology contact lenses (target 4.00 D) and single vision spectacles during the daytime if needed. In ROMIO Study 2012, 51 of 102 children randomized were assigned to wear orthokeratology contact lenses (target not reported). The Australian study was a paired-eye, cross-over study in which one eye of each child was randomized to wear orthokeratology contact lenses during the night and the other eye to wear an RGPCL during the day. After six months, the type of contact lens worn in each eye was switched and children were followed for another six months. In Han 2018, 90 of 240 children were randomized to wear orthokeratology lenses with a "four-district seven-arc reverse geometric design."

Spherical aberration soft contact lenses versus single vision soft contact lenses

Two studies compared SVSCLs with or without an additional design to alter spherical aberration. The Cambridge Anti-Myopia Study 2013 was a 2 × 2 factorial trial testing a spherical aberration design and vision training against SVSCLs in 147 British participants aged 14 to 22 years. Although this trial included adults, most participants were 18 years of age or younger, thus we decided to include it in this review. We did not include in the analysis the two groups with vision training as an intervention because the review is limited to devices and pharmaceuticals. In Cheng 2016, 127 children aged 8 to 11 years were randomized to receive soft daily disposable contact lenses either with positive spherical aberration or without positive spherical aberration. The trial was conducted in the USA and enrolled mostly Asian children (91%). Both studies were planned for two years, but Cheng 2016 was stopped early and reported only one-year data.

Pharmaceutical agents

Antimuscarinic agents versus placebo

Use of three different topical antimuscarinic agents was compared with use of placebo for control of myopia progression in six studies: three studies evaluated atropine eye drops (ATOM Study 2006; MIT Study 2001; Yi 2015); two evaluated pirenzepine gel (PIR-205 Study 2004; Tan 2005); and one evaluated both atropine and cyclopentolate eye drops (Yen 1989). All studies were conducted in Asia, except for PIR-205 Study 2004, which was conducted in the USA. Studies included children from 6 to 14 years of age at enrollment who had low to moderate myopia (up to -6.00 D). The atropine studies used one of two doses, 0.5% or 1.0%; the pirenzepine studies used a 2% gel formulation; and the cyclopentolate study used a dosage of 1%.

Two studies compared daily 1% atropine with placebo. The Atropine in the Treatment of Myopia (ATOM) Study enrolled 400 Singaporean children aged 6 to 12 years (ATOM Study 2006). Once each child was randomized to a treatment group, one eye of each child was randomized to receive treatment and the other eye served as a natural control. Follow-up for this study was two years. In Yi 2015, 140 children with low myopia (-0.50 D to -2.00 D) instilled either 1% atropine or placebo drops in both eyes every night for one year.

One study compared daily 0.5% atropine with placebo (Wang 2017); 126 children aged 5 to 10 years with myopia ranging from -0.5 D to -2.00 D were randomized to the two interventions. In both groups, the intervention was administered once daily at night for one year.

Two three-arm studies investigated using atropine in conjunction with wearing multifocal lenses. The Myopia Intervention Trial, described above in the "Spectacles" section, evaluated SVLs, PALs, and PALs in combination with 0.5% atropine drops for controlling progression of myopia (MIT Study 2001). Yen 1989 randomized 247 Taiwanese children aged 6 to 14 years to one of three treatment groups: (1) 1% atropine eye drops every other night and bifocal spectacles prescribed after two weeks of treatment; (2) 1% cyclopentolate eye drops every night and SVLs prescribed if necessary; and (3) normal saline eye drops every night and SVLs as prescribed if necessary. Follow-up was at one year for Yen 1989 and at 18 months for the MIT Study 2001.

Two studies compared pirenzepine gel (an antimuscarinic) to placebo gel for control of myopia progression. The first was a multicenter US study that enrolled 174 children 8 to 12 years old and followed them up for one year (PIR-205 Study 2004). Children were randomized at a 2:1 ratio to 2% pirenzepine ophthalmic gel or placebo gel twice a day. An additional year of follow-up was provided for children who completed the first year. The final study was a three-arm, multicenter trial from Singapore, Hong Kong, and Thailand (Tan 2005). For one year, 353 children aged 6 to 13 years were randomly treated with (1) 2% pirenzepine gel applied twice daily (gel/gel); (2) placebo once daily and 2% pirenzepine gel once daily (placebo/gel); or (3) placebo gel twice daily (placebo/placebo).

Antimuscarinic agents versus tropicamide

One study, completed in Taiwan, investigated the effectiveness of low concentrations of atropine for controlling progression of myopia in children aged 6 to 13 years (Shih 1999). Two hundred children were randomized to one of three atropine groups or to a control group: (1) daily drop of 0.5% atropine and advised to wear bifocal spectacles; (2) daily drop of 0.25% atropine and advised to wear slightly undercorrected SVLs; (3) daily drop of 0.1% atropine and advised to wear fully corrective SVLs; or (4) daily drop of 0.5% tropicamide.

Systemic adenosine antagonists versus placebo

One study investigated the effectiveness of systemic 7-mx, an adenosine receptor antagonist, for slowing axial elongation and thus controlling the progression of myopia (Trier 2008). In the first year of this Danish study, 83 children aged 8 to 13 years were randomized to take a 7-mx or placebo tablet once daily. After one year, all children had the option to receive 7-mx and to continue follow-up for two more years.

Combinations of interventions

Tropicamide plus bifocal spectacles versus single vision lenses

In a study of 26 twin pairs, the combined use of bifocal lenses and tropicamide ophthalmic solution for controlling myopia progression was compared to the use of SVLs over a 3½-year period (Schwartz 1981). This Washington DC area study included monozygotic twin pairs between the ages of 7 and 14 with similar myopia. From each twin pair, one twin was randomized to receive combined treatment of bifocal spectacles with a +1.25 D addition and two drops of 1% tropicamide ophthalmic solution (a short-acting cycloplegic) instilled into each eye nightly; the other twin received a standard myopic spectacle correction.

Other combinations of interventions

The following combinations of interventions were compared by studies described in the previous sections.

- Atropine plus multifocal spectacles versus placebo plus SVLs (MIT Study 2001 Yen 1989).
- Atropine plus bifocal spectacles versus cyclopentolate plus SVLs (Yen 1989).
- Bifocal spectacles versus SVLs with timolol eye drops (Jensen 1991).

Ongoing studies

We identified 74 ongoing studies, which are described under Characteristics of ongoing studies. These studies compared multifocal contact lenses, orthokeratology lenses, progressive addition lenses, spectacle lenses, full correction, and undercorrection. We will incorporate their findings in future updates of this review.

Excluded studies

We excluded 91 studies from this review after full-text assessment. The complete list of studies and reasons for exclusion are provided in the Characteristics of excluded studies table. Our reasons for exclusion were based on four categories: (1) the study was not an RCT (58 studies); (2) study interventions were not intended to control myopia progression (13 studies); (3) study interventions were not within the scope of this review (13 studies); and (4) the study population was not eligible for this review (seven studies).

We excluded from this review two RCTs comparing SVSCLs with spectacles in myopic children and adolescents because SVSCLs and spectacles are not meant to control the progression of myopia (ACHIEVE Study 2008; Horner 1999). The purpose of the ACHIEVE study was to compare the effects of contact lens wear versus spectacle wear on children's self-perception.

Risk of bias in included studies

Allocation

Thirty-three (81%) of the 41 included studies described the randomization procedure used to allocate participants to treatment groups; we judged them as having adequate sequence generation and thus low risk of allocation bias (Figure 2). Methods employed for adequate sequence generation included using block randomization schemes, computer-generated randomization lists, or independently prepared randomization lists or tables, and flipping coins or drawing lots. Seven studies stated that children were randomized but did not report other details on how randomization was implemented, and we judged unclear risks of bias for sequence generation (Charm 2013; Cheng 2016; Lu 2015; Wang 2005; Yang 2009; Yi 2015; Han 2018). This review included RCTs only; however, we included one study that was reported to be an RCT but was confirmed to be a quasi-randomized study based on information provided by the study author (Cheng 2010). The first 50 numbers pulled out were assigned to the control group, the second 50 to the bifocal group, and the remaining 50 to the bifocal plus prism group. This method of sequence generation was inadequate because participants did not have equal chances of being assigned to all treatment groups once the first 50 numbers were drawn. In addition, because treatment assignments were consecutive, allocation concealment was inadequate. We judged this study as having inadequate sequence generation and allocation concealment because treatment assignment was determined by selecting from a container pieces of paper with patient numbers written on them.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

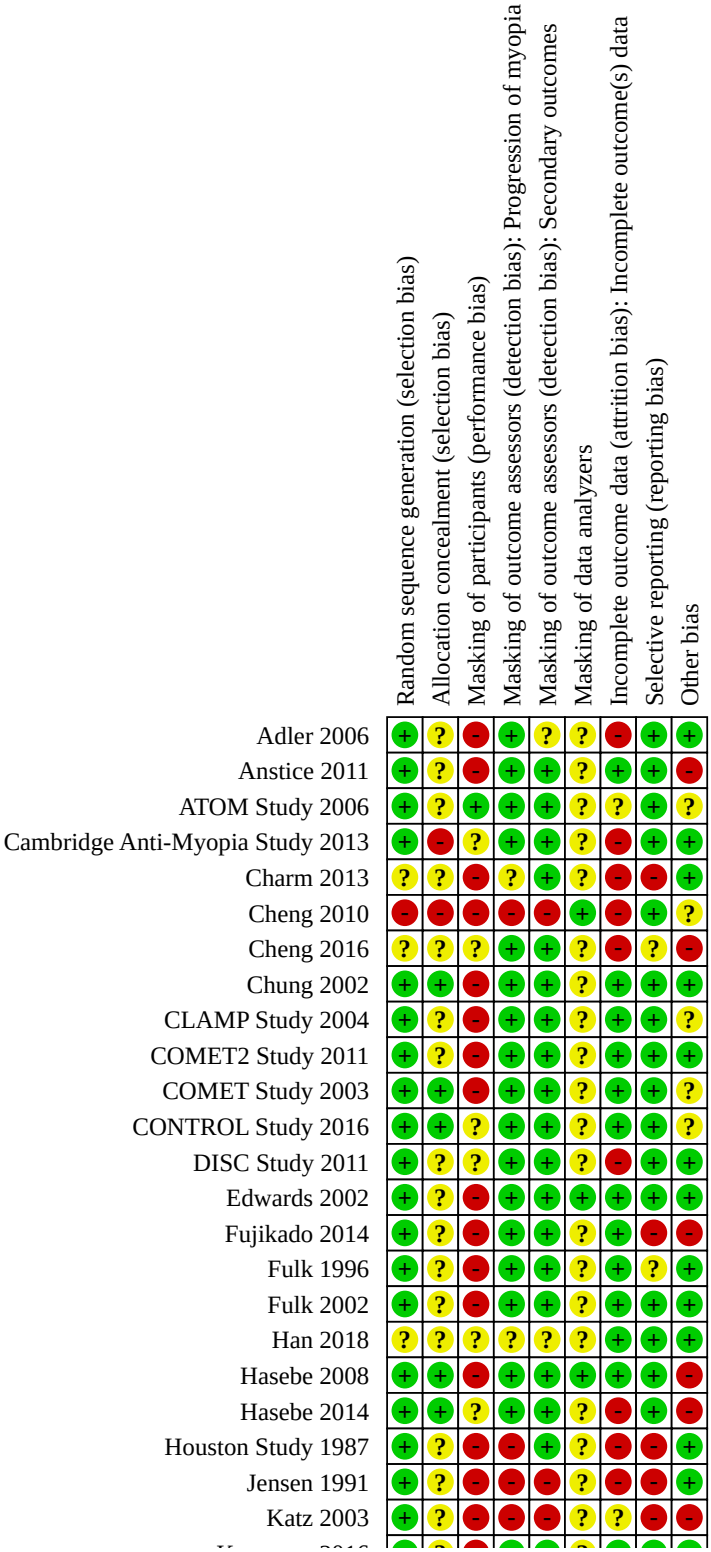
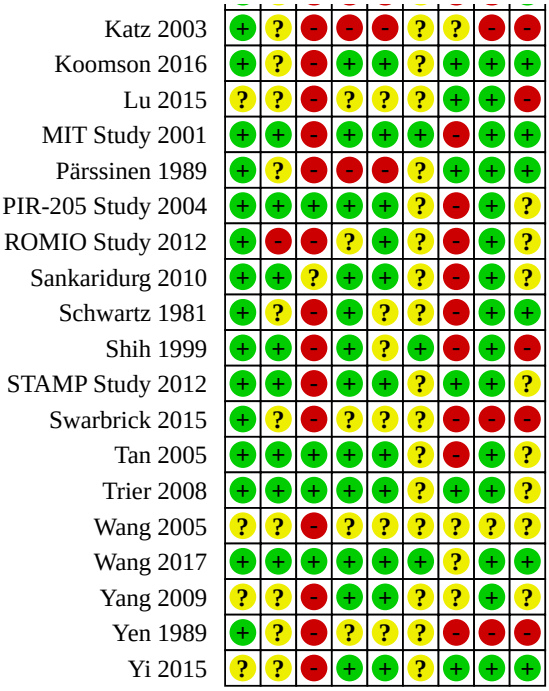


Figure 2. (Continued)



We judged 13 studies to have adequate allocation concealment. Methods considered to be at low risk of bias for this domain included using sequentially numbered, sealed, and opaque envelopes, and calling a centralized coordinating center. Twenty-five studies did not provide sufficient information on whether and how allocation was concealed. These studies were judged to be unclear risk of bias for allocation concealment. Two studies stated that the person assigning participants to treatment groups was aware of the allocation sequence (ROMIO Study 2012; Cambridge Anti-Myopia Study 2013), and they were judged as high risk of bias for this domain.

Masking (performance bias and detection bias)

We assessed the use of masking (blinding) for three types of roles: study participants, outcome assessors, and data analysts (Figure 2). Furthermore, we considered separately the masking of outcome assessors for primary (change in refractive error) and secondary (changes in axial length and corneal radius of curvature) outcomes.

Due to the interventions under investigation, masking of participants was not feasible for many of the studies included in this review. Interventions from 34 (83%) of the 41 included studies had significant physical (e.g. contact lenses vs spectacles), functional (e.g. multifocal lenses vs SVLs), or performance (e.g. undercorrected vs fully corrected spectacles) differences between control interventions. Despite these differences, six studies reported masking participants, but we judged them as having unclear risk of bias because it was not clear whether masking was effective (Cambridge Anti-Myopia Study 2013; Cheng 2016; CONTROL Study 2016; DISC Study 2011; Hasebe 2014; Sankaridurg 2010). Of six studies evaluating pharmaceutical agents exclusively, four studies masked participants adequately by distributing identically packaged and coded bottles or tablets (ATOM Study 2006; PIR-205 Study 2004; Tan 2005; Trier 2008), and two did not implement masking of participants (Shih 1999; Yi 2015).

Adequate methods of masking outcome assessors involved having participants examined by an investigator who was unaware of treatment assignments. This method was implemented for spectacle or contact lens studies by having participants remove contact lenses and spectacles before they were examined or distributing SVLs for all participants to wear during office visits. Use of coded, identical packaging was considered adequate masking for pharmaceutical studies. Overall, masking of primary outcome assessors was done for 28 (72%) of the 39 included studies. Of the 28 studies that masked primary outcome assessors, 25 were masked similarly for secondary outcome assessors and three did not measure secondary outcomes related to this review. ROMIO Study 2012 did not assess change in refractive error as an outcome but masked assessments for our review's secondary outcomes. We assessed Charm 2013 as having unclear risk of bias for not reporting masking of primary outcome assessment and low risk for masking of secondary outcomes.

We judged five included studies as being at high risk of bias for not masking primary outcome assessors adequately. In a three-armed study comparing bifocal lenses or timolol with SVLs, there was only one study investigator, who therefore could not be masked to treatment assignments (Jensen 1991). Refractive errors for this study were measured by cycloplegic autorefraction. In another three-armed trial comparing bifocals or distance-use spectacles versus continuous-use single vision spectacles, it was reported that the examining ophthalmologist did not look at group assignments before the examination, but often for different reasons group assignments were revealed (Pärssinen 1989). However, three-year follow-up examinations were conducted by two different ophthalmologists, one of whom did not know the

group assignments. Refractive errors for this study were measured by subjective cycloplegic refraction. The Houston Myopia Control Study included a team of masked observers (evaluation team) and a team of unmasked observers (patient care team) to measure outcomes in a trial of bifocal lenses versus SVLs (Houston Study 1987). Results presented in the final analysis of the primary outcome were derived from the nonmasked group; therefore we judged the study as having inadequate masking of primary outcome assessors. Refractive errors for this study's results were measured by subjective noncycloplegic refraction. Two included studies did not attempt to mask primary outcome assessors; one measured refractive errors by cycloplegic autorefraction (Cheng 2010), and the other measured refractive errors by subjective cycloplegic refraction (Katz 2003). With the exception of the Houston study, secondary outcome assessors were the same as primary outcome assessors. Data for secondary outcomes in the Houston study were collected by the masked evaluation team; therefore we considered these studies to have low risk of bias.

Five studies did not report masking of primary or secondary outcome assessors; we judged them to have unclear risk of bias (Han 2018; Lu 2015; Swarbrick 2015; Wang 2005; Yen 1989).

The final assessments for masking were applied to study data analysts. How data were handled and whether or not data analysts were masked to treatment groups were not reported in 26 (63%) of the 41 included studies. Two studies explicitly stated that masked investigators analyzed the data independently (Edwards 2002; Hasebe 2008). Additionally, study authors contacted for clarification replied that data analysts were masked for Cheng 2010, MIT Study 2001, and Shih 1999. Although three studies stated that data were analyzed independently after the conclusion of the trial, we considered masking of data analysts to be unclear because treatment assignments may have been accessible in the data (Adler 2006; Chung 2002; Yang 2009). One study could not be masked because only one investigator was involved (Jensen 1991). Study authors for five studies informed us that data analysts were not masked (via email communications) (CLAMP Study 2004; COMET Study 2003; Katz 2003; PIR-205 Study 2004; Tan 2005). We assessed studies in which data analysts were not masked or in which masking of data analysts was not reported to have unclear risk of bias for this parameter.

Incomplete outcome data

Attrition rates reported by the included studies varied from 0% to 61%. Seven studies followed the intention-to-treat (ITT) analysis as defined by this review: (1) participants were analyzed in the intervention groups to which they were randomized, regardless of the intervention they actually received; and (2) all randomized participants were included in the analysis, even participants for whom no outcome data were collected. Three studies provided follow-up data for all participants at the final follow-up visit (CLAMP Study 2004; Lu 2015; Han 2018), and four used statistical methods to account for all randomized patients by imputing values for missing data (COMET Study 2003; COMET2 Study 2011; Fulk 2002; Koomson 2016).

A total of 14 studies analyzed participants in the intervention groups to which they were randomized but did not include all randomized participants in the analysis due to attrition. In none of these studies were participants excluded from the analysis due to noncompliance, switching of intervention groups, or failure to adhere to treatment protocols. In 11 of these studies, outcome data were missing for both intervention groups but dropouts were balanced across groups and participants who dropped out were similar to those who remained (Anstice 2011; Chung 2002; CONTROL Study 2016; Edwards 2002; Fujikado 2014; Fulk 1996; Hasebe 2008; Pärssinen 1989; STAMP Study 2012; Trier 2008; Yi 2015). The attrition rate for each of these studies was between 6.5% and 15%. For these considerations, we judged these 11 studies as having low risk of bias due to minimal quantities of incomplete outcome data. The other three studies had unclear risk of attrition bias due to unbalanced dropout rates between treatment groups, or because there were statistically significant differences between participants who dropped out compared with those who remained in the study (ATOM Study 2006; Katz 2003; Yang 2009). One additional study included all randomized participants in the analyses but did not report the methods used to address missing data.

One study published only as an abstract reported the number of patients included in the analyses, but it is not clear whether this number represents the total number initially enrolled in the study and randomized to treatment (Wang 2005).

We judged the remaining 18 studies to have high risk of bias due to incomplete outcome data. The percentage of missing data ranged from 4% to 61%. In all of these studies, a proportion of participants were excluded after randomization for not adhering to the treatment protocol, for having adverse events, or for withdrawing consent. In a study evaluating undercorrected spectacles with full correction spectacles, participants were excluded for not wearing spectacles continuously (Adler 2006). Two studies comparing bifocal lenses with SVLs excluded children from the analysis: one study excluded children who were randomized to receive SVLs but dropped out because their parents wanted them to receive bifocals (Cheng 2010), and another study dismissed noncompliant patients and patients who were fitted with contact lenses without informing study personnel, along with patients who were fitted with contact lenses without informing study personnel (Houston Study 1987). Two studies that investigated peripheral plus spectacles excluded participants for committing protocol violations, withdrawing because of an adverse event, or withdrawing consent (Hasebe 2014; Sankaridurg 2010). One study of BSCLs versus SVSCLs excluded 42% of participants because they did not want to wear the contact lenses (DISC Study 2011). All three orthokeratology studies excluded participants due to issues with wearing the orthokeratology lenses (Charm 2013; ROMIO Study 2012; Swarbrick 2015). Both studies of spherical aberration soft contact lenses excluded 17%—Cheng 2016—or 33%—Cambridge Anti-Myopia Study 2013—of participants from analyses. The other seven studies evaluated a pharmaceutical agent in at least one treatment arm (seven of the eight pharmaceutical studies included in this review). Five of these studies excluded participants for not using the eye drops or gel, or for not using them consistently (MIT Study 2001; PIR-205 Study 2004; Shih 1999; Tan 2005; Yen 1989). Another study evaluating timolol plus SVLs versus bifocals or SVLs excluded patients for switching to contact lenses, or because they could not adapt to bifocal lenses (Jensen 1991). The last study, a co-twin study in which one twin received bifocal spectacles and 1% tropicamide ophthalmic solution and the other twin received SVLs, excluded one twin pair from the study for noncompliance (Schwartz 1981).

In addition to excluding participants for nonadherence, two studies reported an imbalance in dropout rates (PIR-205 Study 2004; Tan 2005). The PIR-205 Study 2004 reported that there were significantly more dropouts in the pirenzepine arm compared with the placebo arm, although three additional analytical methods used to impute missing values for those who discontinued the study revealed similar or more beneficial treatment effects for pirenzepine compared with the analysis censoring dropouts. Tan 2005 also reported more dropouts in the pirenzepine-treated groups than in the placebo-only group. Although differences were not statistically significant, all participants who dropped out because of adverse events were included in the pirenzepine group.

Two studies excluded participants for lack of efficacy of treatment (MIT Study 2001; Tan 2005). The MIT study excluded two children for having myopic progression greater than 2.00 D per year: one child was from the SVL group and the other child was from the PAL group (none were from the atropine plus PAL group). One child was dropped from the placebo group of the Tan 2005 study for inadequate efficacy.

Finally, the study with the highest percentage of missing data enrolled 247 children, but data were missing for 151 (61%) children (Yen 1989). Reasons for missing data were not reported. Study authors stated that "patients who used the eye drops continuously for one year received another complete ophthalmologic examination," and "96 such patients were collected for evaluation, 32 in each group." It is not clear whether the 96 patients analyzed included all children who were examined at one year or a subset of those examined.

Selective reporting

We assessed 31 (76%) studies as having low risk of bias for selective reporting: 16 studies reported results for study outcomes defined a priori (i.e. in a design and methods publication, baseline report, or clinical trial registry), and 15 studies reported results for outcomes described in the methods section of each paper (Figure 2).

We assessed three studies as having unclear risk of reporting bias. One study had unclear risk of bias due to inadequate reporting for one of the two outcomes measured (Fulk 1996). For this study, the refractive error outcome was reported by treatment assignment; however, the axial length outcome was presented only as it correlated with myopia progression and results by treatment groups were not given. One study was planned for two years but was terminated early and reported results for only one year of follow-up; 18.9% of children completed two years of follow-up before the study was terminated early (Cheng 2016). Another study was published as a conference abstract only (Wang 2005).

We considered seven studies to have high risk of reporting bias. One study reported results for only one intervention group (Charm 2013). Another study stated in its methods section that results would be discussed only if they were exceptional (Jensen 1991). In one study, not all outcomes described in the methods section were reported (Yen 1989), and in another study, all outcomes identified in the study methods were reported but the numbers of participants included in the analyses were not consistent between outcomes (Katz 2003). Two studies showed differences between outcomes specified in the clinical trial registration and in the journal publication: one study switched a secondary outcome in the clinical trial registration record to the primary outcome of the journal publication (Fujikado 2014), and the other study did not report results for secondary outcomes listed in the clinical trial registration record (Swarbrick 2015). The final study did not report results for evaluation team (masked observers) measurements nor for other secondary outcomes outlined in the design paper (Houston Study 1987). The methods paper stated that an evaluation team report would be based on (1) cycloplegic retinoscopy, (2) noncycloplegic autorefraction, and (3) cycloplegic autorefraction performed by masked examiners. However, findings from masked examinations were not reported in the outcomes paper; instead results from the patient team were reported (unmasked observers). Also, secondary outcomes such as change in axial length were not reported.

Other potential sources of bias

We assessed 18 (44%) studies as free of other potential sources of bias, 13 (33%) studies as having unclear risk of bias, and 10 (26%) studies as having high risk of bias (Figure 2).

We assessed all four cross-over trials as having high risk of bias because data were not analyzed according to the cross-over design, carry-over effects were not investigated, and some participants who completed the first period dropped out during the second period (Anstice 2011; Fujikado 2014; Hasebe 2008; Swarbrick 2015). Thus, we used only data from the first period to estimate treatment effects. Additionally, three of these studies reported financial conflicts of interest.

We assessed two additional studies as having high risk of bias due to unit of analysis issues (i.e. not accounting for the nonindependence of eyes) (Hasebe 2014; Lu 2015), and two studies as having unclear risk of bias for not reporting the unit of analysis (Wang 2005; Yang 2009).

Two studies planned for two years' duration were terminated early. We assessed one study as having high risk of bias because it was the funder's decision to stop early based on its own interests (Cheng 2016), and the other study as having unclear risk of bias because the decision to stop was made by investigators because they observed lower than expected progression in myopia among all study participants (Sankaridurg 2010).

One study reported imbalances at baseline between treatment groups in gender, corneal curvature, and refractive error (Katz 2003). This study reported unequal losses to follow-up between treatment groups and by gender. In addition to these considerations, and because 32% of participants dropped out of the study between randomization and the end of the adaptation period, we judged this study to have high risk of bias. Two other studies incorporated prerandomization administration of an intervention into their study design (ATOM Study 2006; CLAMP Study 2004). Run-in periods may enhance or diminish the effects of a subsequent randomized intervention; thus we assessed these studies as having unclear risk of bias.

The remaining two of 10 studies that we judged to be at high risk of other sources of bias were Shih 1999 and Yen 1989. In Shih 1999, participants in different treatment groups were advised to wear different types of spectacle lenses depending on the concentration of atropine received. The rationale for recommending different types of spectacles for different atropine doses (bifocals in the 0.5% group; undercorrected lenses in the 0.25% group; and fully

corrective lenses in the 0.1% group) was not explained. In Yen 1989, it was unknown why equal numbers of participants dropped out of each group, or how equal numbers of participants per group were selected for analysis ("96 such patients were collected for evaluation, 32 in each group").

Eight other studies were fully or partially funded by companies with financial interests in at least one of the interventions being studied. We considered these studies to have unclear risk of bias (Cheng 2010; COMET Study 2003; CONTROL Study 2016; PIR-205 Study 2004; ROMIO Study 2012; STAMP Study 2012; Tan 2005; Trier 2008).

Effects of interventions

See: **Summary of findings 1** Interventions to slow progression of myopia in children

We compared several interventions to SVLs (spectacles) or SCLs to determine which treatments are effective in slowing the progression of myopia in children. We meta-analyzed results for prespecified outcomes when appropriate; otherwise we reported study-specific results. For the primary outcome of this review, progression of myopia assessed as the mean change in refractive error (spherical equivalent) from baseline for each year of follow-up, negative mean differences (MDs) represented faster progression of myopia in the treatment group compared with progression in the control group. Thus, point estimates to the left of null on the forest plots favor the control group for this outcome. For axial length, negative MDs represent less axial elongation for treatment group participants compared with control group participants (point estimates to the left of null on the forest plots favor the treatment group for this outcome). The unit of analysis reported by each study is shown in Table 5.

Spectacles

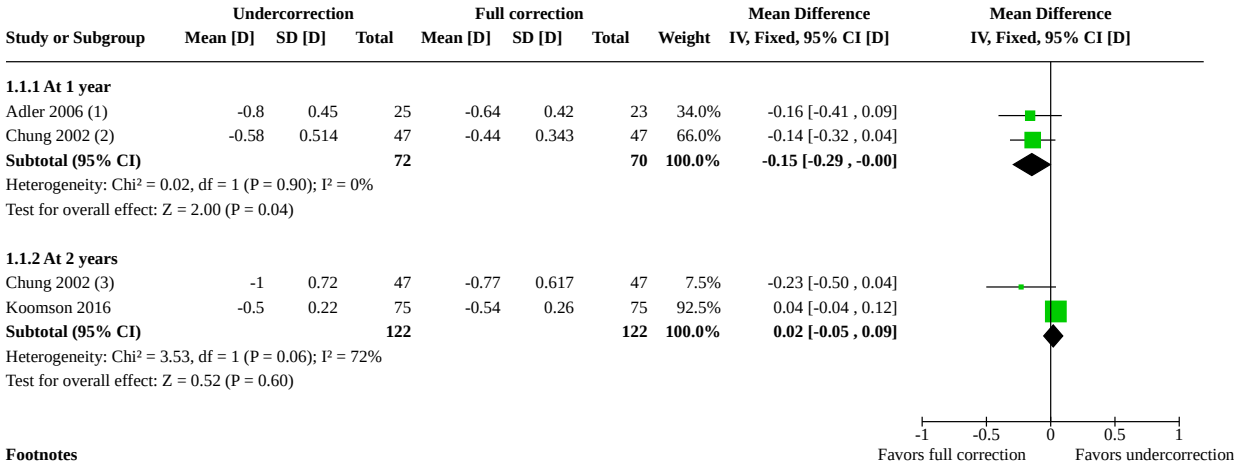
1. Undercorrected versus fully corrected spectacles

Three studies with a total of 292 participants compared spectacles that undercorrected myopia by approximately -0.50 to -0.75 D with SVLs that fully corrected myopia (Adler 2006; Chung 2002; Koomson 2016).

Change in refractive error (Analysis 1.1)

At one year, two studies reported that 72 children who were undercorrected progressed, on average, by -0.15 D (95% CI -0.29 to 0.00) more than the 70 SVL wearers (Figure 3). At two years, progression of myopia from baseline for the undercorrection group was 0.02 D (95% CI -0.05 to 0.09) compared with the full correction group in two studies with 244 children. We graded the certainty of evidence for refractive error as low, downgrading for imprecision (-1) and risk of bias (-1).

Figure 3. Forest plot of comparison: 1 Undercorrection vs full correction spectacles, outcome: 1.2 Change in refractive error from baseline (1 year).



Footnotes

(1) Data provided by study author.
(2) Data estimated from graph.
(3) Data estimated from graph (although reported as statistically significant in the article).

Change in axial length (Analysis 1.2)

Changes in axial length were measured by Chung 2002 and Koomson 2016. The undercorrected group showed greater axial elongation than the fully corrected group in one study at one year (MD 0.05 mm, 95% CI -0.01 to 0.11), and the studies showed no difference at two years (MD -0.01 mm, 95% CI -0.06 to 0.03). We graded the certainty of evidence for axial length as low, downgrading for imprecision (-1) and risk of bias (-1).

Change in corneal radius of curvature

Changes in corneal radius of curvature were not measured by Adler 2006 nor Koomson 2016, and were reported to be statistically nonsignificant during the two-year study by Chung 2002.

Adverse effects

Two participants who were undercorrected complained of blurred vision in the study by Adler 2006. No other adverse effects were reported by any study.

2. Multifocal spectacles versus single vision lens spectacles

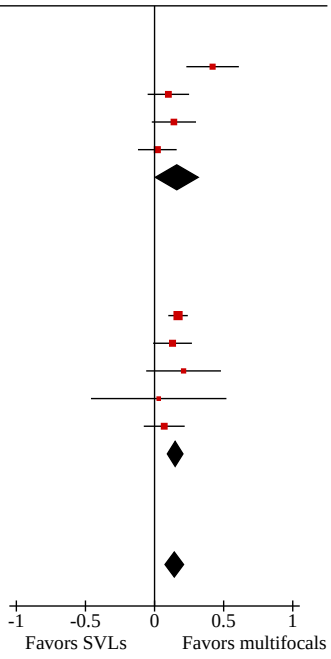
Fourteen studies compared multifocal spectacles versus single vision lens spectacles to slow the progression of myopia in children. Six studies evaluated bifocal lenses (Cheng 2010; Fulk 1996; Fulk 2002; Houston Study 1987; Jensen 1991; Pärssinen 1989), and eight studies used progressive addition lenses (PALs) (COMET Study 2003; COMET2 Study 2011; Edwards 2002; Hasebe 2008; MIT Study 2001; STAMP Study 2012; Wang 2005; Yang 2009). Ten studies were included in the quantitative analysis, and four studies did not provide adequate data for meta-analysis: two studies did not report data for each year of follow-up (Hasebe 2008; Wang 2005), and two studies reported outcomes as rates of change per year based on varying follow-up times (Fulk 1996; Houston Study 1987). Of the 10 studies that we analyzed quantitatively, eight reported mean changes from baseline and two reported only final values (Edwards 2002; MIT Study 2001). Because the studies were randomized with no significant imbalance in potential confounders between groups at baseline, we combined MDs based on changes from baseline with MDs based on final measurements, given the assumption that these measures address the same underlying between-group effects. With the exception of Pärssinen 1989, which measured refractive error by subjective cycloplegic refraction, studies included in the analysis used cycloplegic autorefraction for refraction measurements. We included Cheng 2010 in the review following full-text assessment, but we subsequently classified it as not adequately randomized; we examined the impact of excluding this study from meta-analysis by performing a sensitivity analysis when appropriate.

Change in refractive error (Analysis 2.1; Analysis 2.2; Analysis 2.3)

At one-year follow-up, the average progression was 0.14 D slower (95% CI 0.08 to 0.21; I^2 = 40%) for 729 multifocal (+1.50 D to +2.00 D near addition) spectacle wearers than for 734 SVL wearers in nine studies (Figure 4). The effect, from subgroup analysis based on type of lens, was similar among PAL wearers (MD 0.15 D, 95% CI 0.09 to 0.21; five studies) and bifocal lens wearers (MD 0.16 D, 95% CI 0.01 to 0.32; four studies). One study with quantitative data did not report data at one year (Yang 2009). Excluding from the analysis the two studies with MDs based on final values did not influence the results substantively (MD 0.14 D, 95% CI 0.07 to 0.22). Excluding Pärssinen 1989, which used subjective refraction, from the analysis did not influence the result substantively (MD 0.16 D, 95% CI 0.10 to 0.23). Excluding Cheng 2010, which was not randomized adequately, from the analysis did not influence the overall result substantively (MD 0.13 D, 95% CI 0.08 to 0.18); however, when Cheng 2010 was excluded from the analysis, the I^2 was reduced from 40% to 0%.

Figure 4. Forest plot of comparison: 2 Multifocal lenses vs single vision lenses, outcome: 2.1 Change in refractive error from baseline (1 year).

Study or Subgroup	MD	SE	Multifocal lenses Total	SVLs Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 Bifocal lenses						
Cheng 2010 (1)	0.42	0.0969	48	41	8.8%	0.42 [0.23 , 0.61]
Fulk 2002	0.1	0.0765	37	36	12.1%	0.10 [-0.05 , 0.25]
Jensen 1991	0.14	0.0816	51	49	11.1%	0.14 [-0.02 , 0.30]
Pärssinen 1989	0.02	0.0714	80	79	13.1%	0.02 [-0.12 , 0.16]
Subtotal (95% CI)			**216**	**205**	**45.1%**	**0.16 [0.01 , 0.32]**
Heterogeneity: Tau² = 0.02; Chi² = 11.45, df = 3 (P = 0.010); I² = 74%						
Test for overall effect: Z = 2.03 (P = 0.04)						
2.1.2 Progressive addition lenses						
COMET Study 2003	0.17	0.036	235	234	22.8%	0.17 [0.10 , 0.24]
COMET2 Study 2011	0.13	0.0716	55	58	13.0%	0.13 [-0.01 , 0.27]
Edwards 2002 (2)	0.21	0.138	121	133	5.1%	0.21 [-0.06 , 0.48]
MIT Study 2001 (2)	0.03	0.25	61	61	1.8%	0.03 [-0.46 , 0.52]
STAMP Study 2012	0.07	0.0755	41	43	12.2%	0.07 [-0.08 , 0.22]
Subtotal (95% CI)			**513**	**529**	**54.9%**	**0.15 [0.09 , 0.21]**
Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 4 (P = 0.75); I² = 0%						
Test for overall effect: Z = 5.18 (P < 0.00001)						
Total (95% CI)			**729**	**734**	**100.0%**	**0.14 [0.08 , 0.21]**
Heterogeneity: Tau² = 0.00; Chi² = 13.41, df = 8 (P = 0.10); I² = 40%						
Test for overall effect: Z = 4.18 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%						



Footnotes

(1) Data provided by study author.

(2) Mean differences based on final measurements.

Eight of the ten studies with meta-analyzable data followed up participants for at least two years; of these, four evaluated bifocal lenses and four evaluated PALs. At two years, average progression was 0.19 D slower (95% CI 0.08 to 0.30; I^2 = 55%) for 696 multifocal (+1.50 to +2.00 near addition) spectacle wearers than for 705 SVL wearers. Excluding from the analysis Pärssinen 1989, which used

subjective refraction and was the only study that favored SVLs, did not influence the result substantively (MD 0.22 D, 95% CI 0.15 to 0.29); however, when Pärssinen 1989 was excluded from the analysis, the I^2 was reduced from 55% to 0%.

Three of the ten studies with quantitative data followed up participants for three years (COMET Study 2003; COMET2 Study 2011; Pärssinen 1989). We did not combine these studies in an overall meta-analysis due to statistical heterogeneity (I^2 = 84.4%). For the PAL subgroup, average progression was 0.21 D slower (95% CI 0.08 to 0.34; I^2 = 0%) for 287 multifocal (+2.00 D near addition) spectacle wearers than for 292 SVL wearers. Pärssinen 1989 reported a nonsignificant MD in the opposite direction for bifocal wearers compared with SVL wearers (MD -0.19, 95% CI -0.47 to 0.09).

Four studies not included in the meta-analyses showed mostly favorable effects of multifocal lenses for slowing myopia progression. In a cross-over study of +1.50 D PALs versus SVLs, children wearing PALs during the first 18-month treatment period showed significantly less progression than children wearing SVLs (MD 0.31 D, 95% CI 0.11 to 0.51); however, no difference between groups was evident for the second 18-month period (MD 0.02 D, 95% CI -0.17 to 0.21) (Hasebe 2008). In an 18-month study reported only by a conference abstract, children wearing PALs showed significantly less progression than children wearing SVLs (MD 0.39 D, 95% CI 0.21 to 0.57; 104 children) (Wang 2005). In another 18-month study of 14 children assigned to wear +1.25 D bifocal lenses and 14 children assigned to wear SVLs, bifocal wearers progressed by -0.39 D per year and SVL wearers progressed by -0.57 D per year (P = 0.26) (Fulk 1996). Trial authors noted that during the first year of the study, the rate of progression was equal between groups, but during the last six months of the study, the SVL group progressed more rapidly than the bifocal group. In a three-arm trial of +1.00 D bifocals, +2.00 D bifocals, and SVLs, no significant differences were observed between groups after three years of follow-up (Houston Study 1987). The reported average change in refraction error per year during the three-year study for +1.00 D bifocals was -0.36 D per year (n = 41), for +2.00 D bifocals was -0.32 D per year (n = 44), and for SVLs was -0.34 D per year (n = 39).

We graded the certainty of evidence for refractive error as moderate, downgrading for risk of bias (-1).

Change in axial length (Analysis 2.4; Analysis 2.5; Analysis 2.6)

Eight studies reported axial length outcomes, four of which reported results for one-year follow-up (Cheng 2010; COMET Study 2003; Edwards 2002; STAMP Study 2012). At one year, the summary MD was -0.06 mm (95% CI -0.09 to -0.04) for 445 PAL wearers compared with 451 SVL wearers. This was similar to the summary results after two years of follow-up (MD -0.05 mm, 95% CI -0.10 to -0.01) for two of these studies (COMET Study 2003; Edwards 2002). After three years of follow-up, participants in the COMET study wearing PALs continued to have less axial elongation compared with participants wearing SVLs (MD -0.11 mm, 95% CI -0.17 to -0.05).

The four studies that did not report one-year data showed treatment effects in the same direction as the studies included in the meta-analysis, although results were not significant in two studies. In a three-arm trial of PALs with or without atropine compared with SVLs, a pairwise comparison showed that participants who wore PALs without atropine had on average 0.10 mm (95% CI 0.00 to 0.20) less axial elongation compared with participants who wore SVLs at 18-month follow-up (MIT Study 2001). In an 18-month study reported only by a conference abstract, children wearing PALs showed significantly less axial elongation than children wearing SVLs (MD -0.21 D, 95% CI -0.34 to -0.08; 104 children) (Wang 2005). In the cross-over trial Hasebe 2008, axial length was not measured at baseline; however, there was no significant difference in axial length between groups after the first 18-month study period (MD -0.08 mm, 95% CI -0.41 to 0.25), and no significant change in axial length was reported between groups after the second 18-month study period (MD -0.01 mm, 95% CI -0.09 to 0.07). In the third study, changes in axial length were not significantly different between bifocal wearers and SVL wearers after 30 months of follow-up (MD -0.09 mm, 95% CI -0.24 to 0.06) (Fulk 2002).

We graded the certainty of evidence for axial length as moderate, downgrading for risk of bias (-1).

Change in corneal radius of curvature (Analysis 2.7)

Changes in corneal radius of curvature outcomes were reported in four studies. Two studies stated only that differences were not significantly different between treatment and control groups (Edwards 2002; Hasebe 2008). In the COMET Study 2003, neither horizontal measurements nor vertical measurements differed between groups after three years of follow-up (MD 0.00 D, 95% CI -0.15 to 0.15; MD 0.00 D, 95% CI -0.14 to 0.14, respectively). In an 18-month study reported only by a conference abstract, children wearing PALs showed significantly greater change in horizontal corneal curvature when compared with children wearing SVLs (MD 0.03 D, 95% CI 0.01 to 0.05; 104 children) (Wang 2005).

Adverse effects

Only one study that compared multifocal lenses with SVLs reported adverse effects (COMET2 Study 2011). Three adverse effects were reported in the PAL group (one each of conjunctivitis, distance blur, and dizziness) and 14 in the SVL group (nine cases of dizziness, three of reduced visual acuity, and one each of floaters and eye pain).

3. Peripheral plus spectacles versus single vision lens spectacles

Three studies compared peripheral plus spectacles versus SVLs (Hasebe 2014; Lu 2015; Sankaridurg 2010). An additional study compared peripheral defocus-reducing spectacles versus SVLs. Three studies reported outcomes at only one-year follow-up —Han 2018 Lu 2015 Sankaridurg 2010—and one at only two-year follow-up—Hasebe 2014. All but one study reported using cycloplegic autorefraction; Han 2018 did not specify the method of measurement of refractive error. Due to differences in lens design and in follow-up across studies, we did not combine individual trial data in the meta-analysis.

Change in refractive error (Analysis 3.1; Analysis 3.2)

At one year, there were no significant differences in myopia progression among three peripheral plus lens types when compared with each other or with SVLs, as reported by Sankaridurg 2010. At one year, Lu 2015 reported a nearly 1.00-D difference between the peripheral plus group (mean change from baseline -0.35 D; SD 0.32; 80 eyes of 40 children) and the SVL group (mean change from baseline -1.32 D; SD 0.24; 80 eyes of 40 children) (MD 0.97, 95% CI 0.88 to 1.06). At two years, Hasebe 2014 reported

similar mean changes from baseline for the peripheral plus +1.00 D group compared with the SVL group (MD 0.06, 95% CI -0.09 to 0.21) but less myopia progression for the peripheral plus +1.50 D group compared with the SVL group (MD 0.19, 95% CI 0.05 to 0.33). At one year, Han 2018 reported estimates of change from baseline within groups, at -0.43 (SD 0.14) with peripheral defocus-reducing spectacles and -1.15 (SD 0.46) with SVLs. We graded the certainty of evidence for refractive error as low, downgrading for inconsistency (-1) and risk of bias (-1).

Change in axial length (Analysis 3.3; Analysis 3.4)

At one year, there were no significant differences in axial elongation among three peripheral plus lens types when compared with each other or with SVLs, as reported by Sankaridurg 2010, or between peripheral plus lenses compared with SVLs, as reported by Lu 2015 (MD 0.03, 95% CI -0.15 to 0.21). At two years, Hasebe 2014 reported similar mean changes from baseline for both the peripheral plus +1.00 D compared with SVL group (MD -0.05, 95% CI -0.16 to 0.06) and the peripheral plus +1.50 D compared with SVL group (MD -0.08, 95% CI -0.19 to 0.03). We graded the certainty of evidence for axial length as low, downgrading for inconsistency (-1) and risk of bias (-1).

Change in corneal radius of curvature

Corneal radius of curvature was not assessed by Hasebe 2014 Lu 2015 Sankaridurg 2010, or Han 2018.

Adverse effects

Sankaridurg 2010 conducted telephone questionnaires at one week post distribution of lenses. At this time, 2/50 participants in the type I group, 2/60 participants in the type II group, 5/50 participants in the type III group, and 1/50 participants in the SVL group reported blurred side vision. Three participants reported visual distortion—one in the type I group and two in the SVL group. Two participants in the type II group experienced dizziness; for one participant, dizziness resolved after one month; for the other participant, dizziness was accompanied by headaches causing the participant to withdraw from the study. Two falls were reported during the study period; both occurred in the type II lens group during the first weeks of the study. Hasebe 2014 reported that "no serious adverse events were reported during the 2-year follow-up," and that "children generally recognized the usability of wearing the study glasses as good (score 4) or very good (5). There was no difference in the median score in any of the questions among the study groups." Lu 2015 did not report adverse effects as an outcome.

Contact lenses

4. Bifocal soft contact lenses versus single vision soft contact lenses

Four studies compared bifocal soft contact lenses (BSCLs) versus single vision soft contact lenses (SVSCLs) (Anstice 2011; CONTROL Study 2016; DISC Study 2011; Fujikado 2014). Anstice 2011 was a paired-eye, cross-over study with two 10-month periods, and Fujikado 2014 was a cross-over study with two 12-month periods. Because data were not reported appropriately for within-person or cross-over designs, we included data for only the first phase of each trial, considered as one-year follow-up, and acknowledged that between-group estimates did not account for intraperson correlations for the paired-eye study. CONTROL Study 2016 followed children with myopia and eso fixation disparity at near vision for one year, and DISC Study 2011 followed children for two years. All trials used cycloplegic autorefraction.

Change in refractive error (Analysis 4.1)

At one year, myopia in the BSCL group (n = 149) progressed slightly slower than in the SVSCL group (n = 151) (MD 0.20 D, 95% CI -0.06 to 0.47; I^2 = 86%). Only one trial assessed change in refractive error at two years; DISC Study 2011 reported a similar effect between the BSCL group (n = 65) and the SVSCL group (n = 63) (MD 0.20 D, 95% CI 0.02 to 0.38). We graded the certainty of evidence for refractive error as low, downgrading for inconsistency (-1) and risk of bias (-1).

Change in axial length (Analysis 4.2)

At one year, axial elongation in the BSCL group was significantly less than in the SVSCL group (MD -0.11 mm, 95% CI -0.14 to -0.08; I^2 = 67%). At two years, DISC Study 2011 reported a similar effect between the BSCL group (n = 65) and the SVSCL group (n = 63) (MD -0.12 mm, 95% CI -0.20 to -0.04). We graded the certainty of evidence for axial length as low, downgrading for inconsistency (-1) and risk of bias (-1).

Change in corneal radius of curvature (Analysis 4.3)

At one year, in CONTROL Study 2016, the corneal radius of curvature in the BSCL group showed similar change compared with the SVSCL group (MD -0.05 D, 95% CI -0.15 to 0.05). Corneal radius of curvature was not assessed by the other three trials.

Adverse effects

Six (15%) of 40 children in the Anstice 2011 study—three from each group—did not complete follow-up; four children withdrew due to difficulties handling the contact lenses, one due to negative publicity on contact lens solutions, and one due to dislike of cycloplegia. The other three studies did not report any adverse effect.

5. Rigid gas permeable contact lenses versus spectacles or soft contact lenses

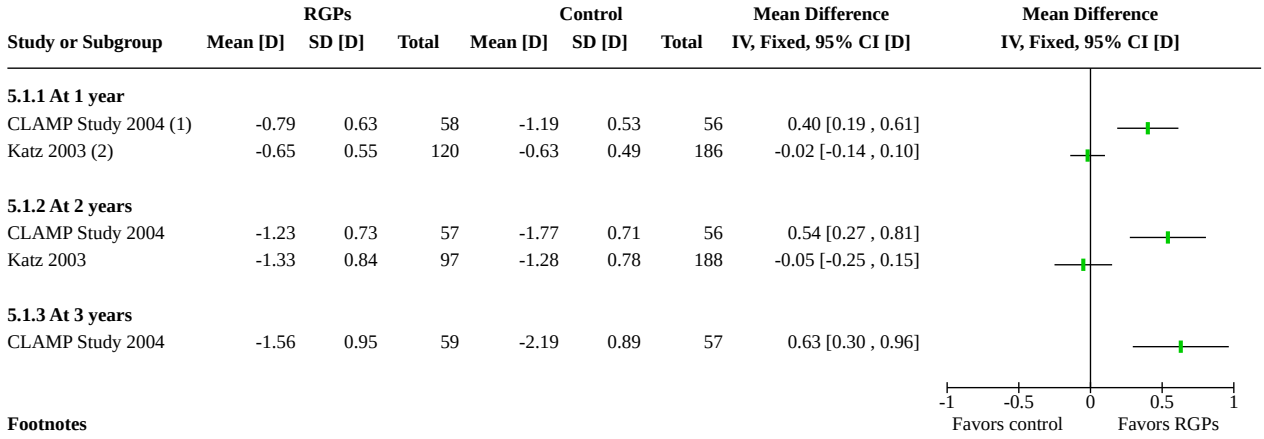
Two studies investigated the use of rigid gas permeable contact lenses (RGPCLs) in slowing the progression of myopia in children. RGPCLs were compared with soft contact lenses (SCLs) in one study (CLAMP Study 2004), and they were compared with SVLs in the other group (Katz 2003). The CLAMP Study 2004 followed up participants for three years, and the Katz 2003 study followed up participants for two years. We assessed the CLAMP Study 2004 as having generally low risk of bias, and the Katz 2003 study as having generally high risk of bias.

Change in refractive error (Analysis 5.1)

The CLAMP Study 2004 evaluated the use of RGPCLs to slow the progression of myopia in children compared with SCLs. At one (MD 0.40 D, 95% CI 0.19 to 0.61), two (MD 0.54 D, 95% CI 0.27 to 0.81), and three (MD 0.63 D, 95% CI 0.30 to 0.96) years of follow-up, participants wearing RGPCLs had significantly less progression of myopia compared with participants wearing SCLs (Figure 5). After one year and two years of follow-up, no difference in myopia progression was observed between RGPCL wearers and SVL wearers in Katz 2003 (MD -0.02, 95% CI -0.14 to 0.10; MD -0.05 D, 95% CI -0.25 to 0.15, respectively). Data were not pooled for these studies due to statistical heterogeneity (I^2 = 91% at one year and

92% at two years). We graded the certainty of evidence for refractive error as very low, downgrading for imprecision (-1), inconsistency (-1), and risk of bias (-1).

Figure 5. Forest plot of comparison: 5 Rigid gas permeable contact lenses vs control, outcome: 5.1 Change in refractive error from baseline [D].



Footnotes

(1) Control group wore soft contact lenses.

(2) Control group wore single vision spectacles.

Change in axial length (Analysis 5.2)

At one year, meta-analysis of the two studies showed that axial elongation was 0.02 mm (95% CI -0.05 to 0.10) greater for the 176 RGPCL wearers than for 239 control participants. After two years, it was 0.03 mm greater (95% CI -0.05 to 0.12) for the 154 RGPCL wearers than for 240 control participants who were followed up by the two studies. After three years, it was 0.05 mm greater (95% CI -0.12 to 0.22) for the 59 RGPCL wearers than for 57 SCL participants in the CLAMP Study 2004. We graded the certainty of evidence for axial length as low, downgrading for impression (-1) and risk of bias (-1).

Change in corneal radius of curvature (Analysis 5.3)

Data from the CLAMP Study 2004 suggest that use of RGPCLs may prevent increases in the corneal radius of curvature compared with SCLs. At one, two, and three years of follow-up, the MD between participants wearing RGPCLs and participants wearing SCLs was -0.24 D (95% CI -0.43 to -0.05), -0.38 D (95% CI -0.56 to -0.20), and -0.26 D (95% CI -0.48 to -0.04), respectively. After one year of follow-up, Katz 2003 also suggested that RGPCLs may be beneficial compared with SCLs (MD -0.08 D, 95% CI -0.14 to -0.01); however, these results were not statistically significant after two years of follow-up (MD -0.06 D, 95% CI -0.14 to 0.02). Data were not pooled for these studies due to statistical heterogeneity (I^2 = 60% for year one results and 90% for year two results).

Adverse effects

None were reported.

6a. Orthokeratology contact lenses versus single vision lenses

Four studies investigated orthokeratology contact lenses to slow the progression of myopia. Charm 2013 and ROMIO Study 2012 followed up participants wearing either orthokeratology contact lenses or SVLs for two years. Swarbrick 2015 compared orthokeratology contact lenses with RGPCLs in a paired-eye, cross-over study with two six-month periods. Analysis for this study did not account for the within-person, cross-over design of the study; therefore no data were included in any meta-analysis. While three studies had overall high risk of bias, one study had unclear risk of bias (Han 2018).

Change in refractive error

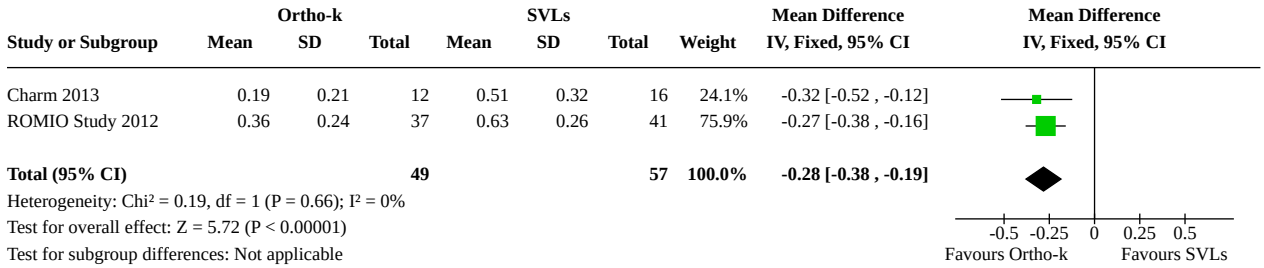
Because orthokeratology contact lenses temporarily reduce myopia, their myopia control treatment effect can be measured only by axial elongation. We did not analyze changes in refractive error for this comparison.

Change in axial length

Three of the four studies reported axial length as an outcome; however, as with outcomes of refractive error, Swarbrick 2015 did not report data eligible for analysis. A fourth study did not report data on axial length (Han 2018).

Summary estimates suggest that the change in axial length is significantly different in favor of the orthokeratology group at two-year follow-up (MD -0.28, 95% CI -0.38 to -0.19; Figure 6; Analysis 6.1).

Figure 6. Forest plot of comparison: 6 Orthokeratology contact lenses versus single vision lenses, outcome: 6.1 Change in axial length from baseline (2 years).



We graded the certainty of evidence for axial length as moderate, downgrading for risk of bias (-1).

Change in corneal radius of curvature

Neither Charm 2013 nor ROMIO Study 2012 reported outcomes related to changes in corneal radius of curvature; Swarbrick 2015 reported inconsistent findings at the end of each six-month cross-over period.

Adverse effects

All three studies reported adverse effects; however, these effects were different across studies. Of 26 participants assigned to wear orthokeratology contact lenses in Charm 2013 five withdrew from the study because they could not achieve a proper lens fitting despite repeated modifications, one withdrew due to lens discomfort, and another withdrew due to not wearing the lenses as instructed. Of the remaining 19 participants, six reported issues with lens binding at the beginning of the study and six showed pigmented corneal arc formation at one-month follow-up. Additionally, all participants wore SVLs to correct for residual refractive error during the daytime.

In ROMIO Study 2012, mild rhinitis (3/51 participants), increased conjunctival hyperemia (1/51 participants), and chalazion (1/51 participants) were observed in the orthokeratology group and one case of recurrent corneal inflammation was observed in the SVL group during two years of follow-up.

Swarbrick 2015 reported that one of 26 eyes in the orthokeratology group had lens adherence.

6b. Spherical aberration soft contact lenses versus single vision soft contact lenses

Two studies investigated spherical aberration soft contact lenses to slow the progression of myopia. The Cambridge Anti-Myopia Study 2013 followed up participants for two years. Quantitative results for this study were reported for the combined cohort of participants (not by treatment group) or were graphically represented in figures only. Thus, we were not able to calculate between-group effects for this study but instead describe the results as available. Cheng 2016 planned to follow participants for two years but ended the trial early and reported results for one year only. We identified issues impacting risk of bias in both studies.

Change in refractive error

Neither study reported clinically meaningful differences between treatment groups. Cheng 2016 reported that the least squares mean (LSM) difference in the mean change in refractive error was 0.137 D (95% CI -0.007 to 0.281) among 52 children in the spherical aberration group compared with 57 children in the SVSCL group at one-year follow-up. The Cambridge Anti-Myopia Study 2013 reported, "The mean progression was found to be 0.33 Dioptres (D) over the 2 years of the study," and "There was no significant treatment effect of either Vision Training or Contact Lens Spherical Aberration control on myopia progression." We graded the certainty of evidence for refractive error as low, downgrading for risk of bias (-1) and indirectness (-1).

Change in axial length

At one year, Cheng 2016 reported that axial elongation was 0.143 mm (95% CI -0.188 to -0.098) less for children in the spherical aberration group compared with control participants. The Cambridge Anti-Myopia Study 2013 reported, "Axial length increased steadily over the 2 years of the study by 0.15 mm (SD 0.14) in both right and left eyes," and "There were no significant differences between axial length increases in the different groups." We graded the certainty of evidence for axial length as very low, downgrading for imprecision (-1), risk of bias (-1), and indirectness (-1).

Change in corneal radius of curvature

Corneal radius of curvature was not assessed by Cambridge Anti-Myopia Study 2013 nor by Cheng 2016.

Adverse effects

Adverse effects were not reported by Cambridge Anti-Myopia Study 2013. Cheng 2016 reported that one child in the spherical aberration group had allergic conjunctivitis and one child in the control group had contact dermatitis.

Pharmaceutical agents

7. Antimuscarinic agents versus placebo

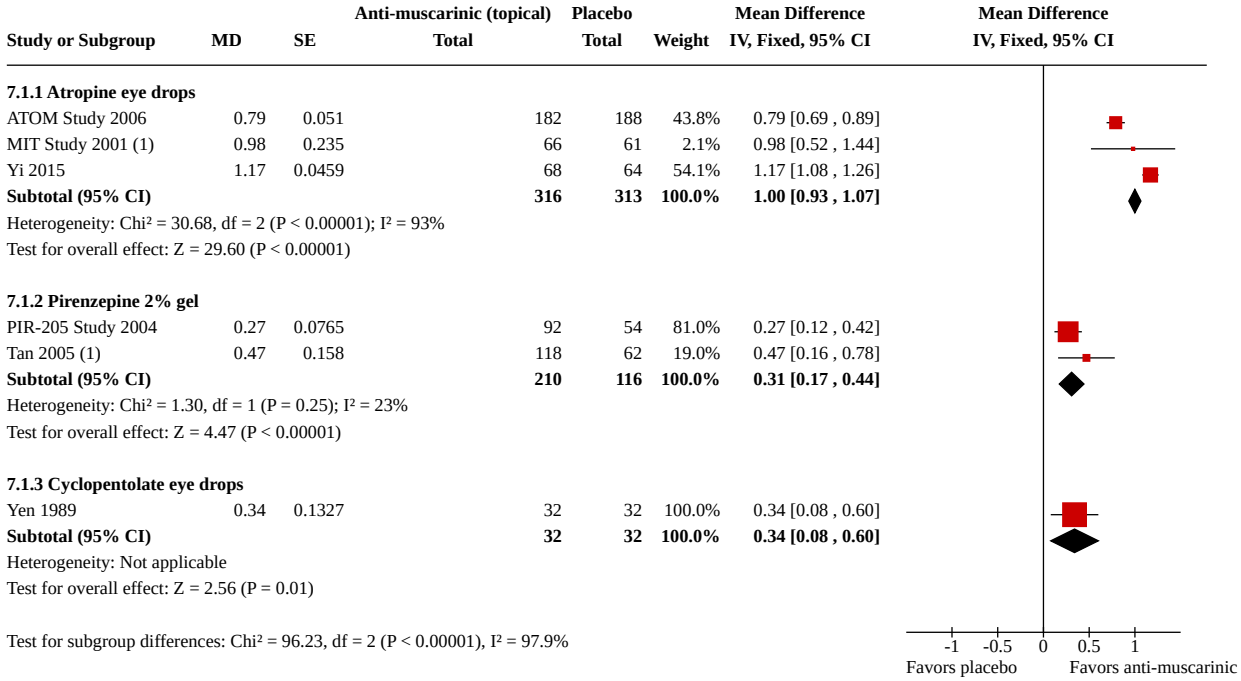
Six studies assessed topical antimuscarinic agents for slowing the progression of myopia in children. Three studies evaluated an atropine ophthalmic solution, one at 0.5% (MIT Study 2001), and two at 1% (ATOM Study 2006; Yi 2015), versus placebo; two studies evaluated 2% pirenzepine gel versus placebo (PIR-205 Study 2004; Tan 2005); and one study evaluated 1% cyclopentolate ophthalmic solution versus placebo (Yen 1989). Study participants included in these analyses from the MIT Study 2001 also were provided with PALs. With the exception of Yen 1989, which measured refractive error by subjective cycloplegic refraction, these studies used cycloplegic autorefraction for refraction measurements. We

did not include data from one study because it did not report data eligible for meta-analysis. Specifically, estimates of changes from baseline reported in the paper were of the same magnitude as those reported at baseline, suggesting that they were not, in fact, changes from baseline (Wang 2017).

Change in refractive error (Analysis 7.1; Analysis 7.2)

Due to statistical heterogeneity (I^2 = 98%), we did not combine results for all antimuscarinic agents but instead pooled the subgroups separately. At one-year follow-up, average progression was 1.00 D slower (95% CI 0.93 to 1.07) for participants treated with atropine, 0.31 D slower (95% CI 0.17 to 0.44) for participants treated with pirenzepine, and 0.34 D slower (95% CI 0.08 to 0.60) for participants treated with cyclopentolate (Figure 7). The difference in progression between groups continued among participants in the two studies with two years of follow-up (MD 0.92 D, 95% CI 0.75 to 1.09 for atropine; ATOM Study 2006 MD 0.41 D, 95% CI 0.13 to 0.69 for pirenzepine; PIR-205 Study 2004). We graded the certainty of evidence for refractive error as moderate, downgrading for risk of bias (-1).

Figure 7. Forest plot of comparison: 6 Antimuscarinic agents vs placebo, outcome: 6.1 Change in refractive error from baseline (1 year).



Footnotes

(1) Mean differences based on final measurements.

Change in axial length (Analysis 7.3; Analysis 7.4)

Four studies reported axial length outcomes; however, we did not combine results for all antimuscarinic agents due to statistical heterogeneity (I^2 = 99%). At one-year follow-up, the two atropine studies—ATOM Study 2006 and Yi 2015—reported significantly less axial elongation for participants assigned to atropine than for participants assigned to placebo (MD -0.35 mm, 95% CI -0.38 to -0.31). This effect persisted at the end of two years (MD -0.40 mm, 95% CI -0.48 to -0.32) in the ATOM Study 2006. In the pirenzepine gel studies, Tan 2005 reported that after one year, the mean increase in axial length was greatest in the placebo/placebo-treated group (0.33 mm) than in the placebo/gel (0.30 mm) and gel/gel (0.20 mm) groups. Although standard deviations (SDs) for mean changes in axial length were shown only on a graph, the paper reported that there was a statistically significant treatment effect at one year (repeated-measures analysis of variance; P = 0.008). No significant changes in axial length were observed at one year in the PIR-205 Study 2004 (MD -0.04 mm, 95% CI -0.15 to 0.07). We graded the certainty of evidence for axial length as moderate, downgrading for inconsistency (-1).

Change in corneal radius of curvature

Corneal radius of curvature outcomes were not assessed by studies comparing topical antimuscarinic agents versus placebo.

Adverse effects (Analysis 7.5)

Both of the studies evaluating pirenzepine documented ocular and systemic adverse events that occurred during the trials (Table 6). Both studies used a significance level of P < 0.15 for reporting adverse events. The three systemic adverse events most frequently reported were headache, common cold, and flu syndrome in the PIR-205 Study 2004, and increased cough, respiratory infection, and rhinitis in Tan 2005. In the PIR-205 Study 2004, events of common cold, rhinitis, and sinusitis differed statistically between groups (P < 0.15) and occurred more frequently in the placebo group than in the pirenzepine group. Tan 2005 reported more complaints of abdominal pain in the gel/gel group than in the placebo/placebo group (P = 0.065) and more incidents of rash in the placebo/gel group than in the placebo/placebo group (P = 0.104). The three ocular adverse events most frequently reported by

both studies (n=387) were symptoms of decreased accommodation (RR 9.05, 95% CI 4.09 to 20.01), papillae/follicles (RR 3.22, 95% CI 2.11 to 4.90), and medication residue on the eyelids or eyelashes (RR 0.91, 95% CI 0.73 to 1.12). Six ocular adverse events differed significantly (P < 0.15) between groups in the PIR-205 Study 2004; symptoms of decreased accommodation, papillae/follicles, decreases in visual acuity, eye discomfort, and mydriasis occurred more frequently in the pirenzepine-treated group, and medication residue on the eyelids or eyelashes occurred more frequently in the placebo group. Four ocular adverse events differed significantly (P < 0.15) between groups in Tan 2005: symptoms of decreased accommodation, papillae/follicles, and decreases in visual acuity occurred more frequently in the gel/gel and placebo/gel groups, and itchy eyes occurred more frequently in the placebo/gel group than in the placebo group. We graded the certainty of evidence for adverse effects as moderate, downgrading for imprecision of results (-1).

Five studies included in this review evaluated atropine in at least one study arm (ATOM Study 2006; MIT Study 2001; Shih 1999; Yen 1989; Yi 2015); however, only three studies compared atropine with placebo directly (ATOM Study 2006; MIT Study 2001; Yi 2015), and four studies reported adverse effect data. In the ATOM Study 2006, no serious adverse events were reported, although the four most common reasons for study withdrawal in the atropine group were allergic or hypersensitivity reactions or discomfort (4.5%), logistical difficulties (3.5%), glare (1.5%), and blurred near vision (1%). No instances of decreased visual acuity; intraocular pressure changes over 5.5 mmHg; or lenticular, optic disc, or macular changes were reported. Shih 1999 reported three adverse events, all of which occurred in the highest-dose atropine group (0.5%); two participants complained of photophobia and one participant had allergic blepharitis. Yen 1989 reported that all patients in the atropine (plus bifocal lenses) group had photophobia, which was not reported in the cyclopentolate (plus SVLs) or placebo (plus SVLs) groups. Yi 2015 reported that no adverse effects were observed for children in either atropine or placebo groups.

8. Antimuscarinic agents versus tropicamide

One study compared three doses of atropine versus tropicamide (Shih 1999). In the four-arm trial, participants were assigned to receive 0.5% atropine drops plus bifocals, 0.25% atropine drops plus slightly undercorrected lenses, 0.1% atropine drops plus fully corrected SVLs, or 0.5% tropicamide drops (control group).

Change in refractive error (Analysis 8.1; Analysis 8.2)

At one-year follow-up, myopia progression measured with cycloplegic autorefraction was significantly slowed for each atropine group compared with the tropicamide group, with the highest atropine dose showing the least progression (MD 0.78 D, 95% CI 0.49 to 1.07 for 0.1% atropine; MD 0.81 D, 95% CI 0.57 to 1.05 for 0.25% atropine; and MD 1.01 D, 95% CI 0.74 to 1.28 for 0.5% atropine). This effect was also observed at two-year follow-up for each atropine group compared with the tropicamide group (MD 1.95, 95% CI 1.60 to 2.30 for 0.1% atropine; MD 1.98, 95% CI 1.68 to 2.28 for 0.25% atropine; and MD 2.42, 95% CI 2.16 to 2.68 for 0.5% atropine). We graded the certainty of evidence as moderate, downgrading for risk of bias (-1).

Shih 1999 did not report on axial length, corneal radius of curvature, or adverse effects.

9. Systemic adenosine antagonists versus placebo

One study compared systemic 7-methylxanthine (7-mx), an adenosine receptor antagonist, versus placebo for one year (Trier 2008). Participants in both groups (35 in the 7-mx group and 42 in the placebo group) wore SVLs. Refractive error was measured by cycloplegic autorefraction.

Change in refractive error (Analysis 9.1)

At one-year follow-up, the mean difference in myopia progression when 7-mx was compared with placebo was 0.07 D (95% CI -0.09 to 0.24). We graded the certainty of evidence as moderate, downgrading for imprecision (-1).

Change in axial length (Analysis 9.2)

The 7-mx group showed less or the same amount of change in axial length compared with the placebo group at one-year follow-up (MD -0.03 mm, 95% CI -0.10 to 0.03). We graded the certainty of evidence as moderate, downgrading for imprecision (-1).

Change in corneal radius of curvature (Analysis 9.3)

The mean change in corneal radius of curvature between 7-mx and placebo groups was not significantly different at one-year follow-up (MD 0.02 D, 95% CI -0.03 to 0.07).

Adverse effects

Trial authors reported that "no subjective side effects were reported."

10. Timolol drops versus no drops

One study compared 0.25% timolol drops versus no drops for slowing the progression of myopia in children (Jensen 1991). Participants in both groups wore SVLs. Refractive error was measured by cycloplegic autorefraction.

Change in refractive error (Analysis 10.1)

There were no statistically significant differences in myopia progression for 46 participants who used timolol compared with 49 participants who did not, at one year (MD -0.05 D, 95% CI -0.21 to 0.11) and at two years (MD -0.04 D, 95% CI -0.30 to 0.22). We graded the certainty of evidence as low, downgrading for imprecision (-1) and risk of bias (-1).

Jensen 1991 did not report on axial length, corneal radius of curvature, or adverse effects.

Comparisons of combinations of interventions

11. Atropine plus multifocal spectacles versus placebo plus SVLs

Two studies compared atropine drops plus multifocal lenses versus placebo drops plus SVLs to slow the progression of myopia in children. The MIT Study 2001 used 0.5% atropine plus PALs, and Yen 1989 used 1% atropine plus bifocal lenses.

Change in refractive error (Analysis 11.1)

At one year, both studies showed less progression among atropine plus multifocal lens users compared with placebo plus SVL users (MD 0.78 D, 95% CI 0.54 to 1.02). We graded the certainty of evidence as moderate, downgrading for risk of bias (-1).

Change in axial length (Analysis 11.2)

At the end of the 18-month MIT Study 2001, participants in the atropine plus multifocal lens group had significantly less axial elongation compared with participants in the placebo plus SVL group (MD -0.37 mm, 95% CI -0.47 to -0.27). We graded the certainty of evidence as moderate, downgrading for risk of bias (-1).

Change in corneal radius of curvature

Neither the MIT Study 2001 nor Yen 1989 reported outcomes for corneal radius of curvature.

Adverse effects

Yen 1989 reported that all participants in the atropine plus bifocal lenses group had photophobia, which was not reported in the placebo plus SVLs group. The MIT Study 2001 did not report on adverse effects.

12. Atropine plus bifocal spectacles versus cyclopentolate plus SVLs

One study compared 1% atropine drops plus bifocal lenses versus 1% cyclopentolate drops plus SVLs (Yen 1989).

Change in refractive error (Analysis 12.1)

At one year, participants in the atropine plus bifocal lens group had significantly less myopia progression compared with participants in the cyclopentolate plus SVLs group (MD 0.36 D, 95% CI 0.11 to 0.61). We graded the certainty of evidence as moderate, downgrading for risk of bias (-1).

Axial length and corneal radius of curvature were not measured by Yen 1989. It was reported that all participants in the atropine plus bifocal lenses group had photophobia, which was not observed in the cyclopentolate plus SVLs group.

13. Bifocal spectacles versus SVLs with timolol drops

Change in refractive error (Analysis 13.1)

In a three-arm trial of +2.00 D bifocal lenses, 0.25% timolol drops plus SVLs, and SVLs (Jensen 1991), a pairwise comparison of bifocal and SVL plus timolol groups suggested that use of bifocals slowed the progression of myopia more effectively than SVLs plus timolol drops at one year (MD 0.19 D, 95% CI 0.06 to 0.32) and at two years (MD 0.23 D, 95% CI 0.00 to 0.46). Neither intervention when compared with the SVL-only group was statistically significant for this study (see Analysis 2.1; Analysis 2.2; Analysis 9.1). We graded the certainty of evidence as moderate, downgrading for risk of bias (-1).

Jensen 1991 did not report on axial length, corneal radius of curvature, or adverse effects.

Tropicamide plus bifocal spectacles versus SVLs

In a co-twin study, one twin from each twin pair was randomized to receive either 1% tropicamide once per day and +1.25 D bifocals or SVLs; follow-up was provided for 3.5 years (Schwartz 1981). No numerical results were presented in the paper. Study authors stated that control twins showed more progression in myopia than their co-twins who received tropicamide and bifocals, but that this difference was not statistically significant.

DISCUSSION

Summary of main results

Our review included 41 studies that investigated 15 comparisons of interventions to slow progression of myopia in children.

Our findings suggest that there is limited evidence favoring full correction of myopia over undercorrection. Trials have also shown a statistically significant but clinically unimportant benefit of multifocal spectacle lenses compared with single vision lenses (SVLs) for both myopia progression and axial elongation.

We found consistent evidence favoring antimuscarinic drugs compared with placebo for reducing progression of myopia and elongation of axial length in children with myopia. Atropine resulted in an effect of larger magnitude than was seen with pirenzepine or cyclopentolate. No trial directly compared the three different antimuscarinic drugs. These drugs are associated with frequent side effects, such as accommodation difficulties, papillae and follicles, sensitivity to light, and eye discomfort, which may lead to approximately 15% of children quitting therapy (ATOM Study 2006). One study directly compared atropine versus tropicamide and found a significant beneficial effect with atropine; however, the concentration of atropine (0.1% and 0.25%) was much lower than that used in other trials.

Studies investigating peripheral plus spectacle lenses, bifocal soft contact lenses, rigid gas permeable contact lenses, overnight orthokeratology contact lenses, spherical aberration soft contact lenses, systemic adenosine antagonists (7-methylxanthine), and topical timolol eye drops provided limited or inconclusive evidence as to the effectiveness of these interventions for slowing the progression of myopia compared with single vision lenses alone.

In summary, we found consistent evidence of meaningful benefit when antimuscarinic drugs were used for slowing progression of myopia in children. Neither the optimal dose of antimuscarinic drug nor the additional value of using an antimuscarinic drug along with spectacles or contact lenses has been adequately answered by available evidence. Evidence regarding beneficial effects of the other interventions included in this review is neither consistent nor confirmatory.

Overall completeness and applicability of evidence

Several interventions have been investigated by more than one reporting source (journal publication, conference abstract, trial registry, etc.), which provided sufficient evidence to determine the applicability of treatment for slowing myopia progression. However, reporting of results was inconsistent among studies, so grouping of findings was difficult. Antimuscarinic pharmaceutical agents hold the greatest promise for slowing myopia progression in children, but not all studies provided complete data for inclusion in the meta-analysis.

The included trials have been conducted across diverse geographic locations. The effects that we observed for antimuscarinic drugs were consistent across studies conducted in Caucasian populations as well as in Asian populations.

Evidence regarding the beneficial effects of various myopic control agents may be related to the ethnicity of participants and/or the comparator intervention in the included trials. For example, Asian

children are more likely to be myopic and their myopia progresses faster than that in Caucasian children (Lin 1999; Zhan 2000), so any myopia control agent may be more or less effective for Asian children than for Caucasian children because the cause of their myopia may be different.

The primary outcome for myopia progression studies typically has been change in refractive error over time; however, as new methods of assessing and treating myopia have become available, the primary outcome has been switched to axial growth of the eye. For example, all three studies evaluating orthokeratology lenses —Charm 2013 ROMIO Study 2012 Swarbrick 2015—and one study assessing systemic 7-methylxanthine—Trier 2008—defined axial length as their primary outcome. In some studies, both methods have been measured and reported, which may enhance confusion if the two methods yield differing information. For example, the rigid gas permeable contact lenses (RGPCLs) trial by Walline and colleagues found that RGPCLs significantly slowed myopia progression but did not slow axial eye growth (CLAMP Study 2004). The change in the primary outcome of myopia control studies also may lead to reporting bias, as was observed in one study that planned to report refractive error as the primary outcome but switched the primary outcome to axial length in the journal publication based on significant findings for axial length but not for refractive error (Fujikado 2014).

Quality of the evidence

Overall, the certainty of evidence ranged from very low to high across all comparisons and outcomes. In terms of the primary outcome for this review—change in refractive error—we assessed two comparisons (multifocal vs single vision lens spectacles and atropine plus multifocal spectacles vs placebo plus SVLs) to provide high-certainty evidence in favor of the treatment group, finding no reason to downgrade. We downgraded for imprecision, inconsistency, or risk of bias for most analyses. Imprecision and inconsistency may reflect comparisons with only one or two small trials and underlying differences among studies, respectively.

This review was limited to randomized controlled trials (RCTs), minimizing the chance of treatment selection bias based on participants' desires for a specific correction. However, not all biases were completely eliminated, and many children dropped out of studies due to dissatisfaction with the intervention received. For many interventions, participants could not be masked with regard to treatment when they were assigned randomly to spectacles versus contact lenses or to one of two types of contact lenses. Although it is unlikely that participants could influence the outcome of myopic eye growth, they may have been more likely to halt participation in a study if they received a treatment that did not interest them, which could potentially increase the risk of bias. Thus, high risk of performance bias, attrition bias, or both was the most common reason for downgrading the certainty of evidence when risk of bias was an issue.

Potential biases in the review process

We reduced the risk of bias during the review process by utilizing a thorough literature search and by not limiting reviewed studies on the basis of language or dates. Two review authors, including at least one clinician and one methodologist, independently assessed the search results for eligibility and extracted data. There is little reason to believe that investigations would have been missed by the search methods unless the study results were never reported.

Overall, despite improvement seen in trials following the CONSORT statement for RCTs (Schulz 2010), many studies still lack the required rigor of reporting necessary to allow the reader to assess the risk of bias in individual trials. The vast majority of studies either did not mask the person analyzing the study data or did not report whether this occurred. It is important for statisticians to make decisions based solely on available data that should not include treatment allocation to reduce or eliminate the potential for reporting bias.

Of the 25 records awaiting for classification, eight studies with published results are likely to be included in the future update of the review. Five of these eight studies are unlikely to contribute any quantitative data for synthesis because outcomes and timepoints for outcomes are out of the scope of the review (Cheung 2018; Lam 2018; Tan 2019; Tilia 2018; Wu 2018). The remaining three studies are likely to contribute quantitative data (Pärssinen 2017; Ren 2017; Wei 2017); however, because the findings in these three studies are consistent with what we report herein, we anticipate they will not change the effect sizes in any meaningful way.

Agreements and disagreements with other studies or reviews

Saw 2002a, Saw 2002b, and Gwiazda 2009 did not include a systematic and comprehensive literature search nor any meta-analyses. The conclusions of these three reviews are consistent with our observations in this systematic review. The 2017 report by the American Academy of Ophthalmology also concluded that there is "high-level evidence" to support the use of atropine to prevent myopia progression, although reports have described rebound of myopia after treatment is discontinued (Pineles 2017). Other treatments, such as undercorrection of myopia, multifocal spectacles, and RGPCLs, do not slow growth of the eye in a clinically meaningful manner (i.e. slowing growth of the eye by 50% or more).

AUTHORS' CONCLUSIONS

Implications for practice

Based on available evidence, antimuscarinic topical medications are effective in slowing myopia progression, but they lead to ocular adverse effects, such as reduced accommodation, papillae or follicles, and medication residue on the eyelids or eyelashes. Further investigations of myopia control must be conducted to find a treatment that is clinically meaningful and beneficial with fewer adverse effects.

Implications for research

Until recently, few RCTs have been conducted to investigate myopia control. Reporting of results from RCTs has been extremely variable. Investigators must compare results to those of previous investigations and must report findings according to the CONSORT statement to maximize the potential for combining results from a variety of studies. Future investigators should consider findings from this systematic review in determining the comparisons that should be examined and the patient populations that should be studied. We have not found conclusive evidence of the effects of most of the interventions included in this review despite our consistent findings on the effects of antimuscarinic drugs.

For example, there is limited evidence on an optimal dose of antimuscarinic drugs for use in children. The evidence that we examined was limited in several ways including the potential for bias. Future trials should be designed to reduce the potential for bias and should be reported in light of the potential for application of novel analytical methods such as multiple-treatment meta-analyses. The added value of using antimuscarinic drugs along with spectacles or contact lenses and the effects of other combinations of interventions in slowing the progression of myopia in children need to be clarified. If future investigators find a clinically and statistically significant treatment effect, they should determine whether the effect continues to be sustained after treatment is discontinued and should attempt to determine the true mechanism of the treatment effect.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adler 2006

Study characteristics	
Methods	Study design: parallel-group RCT Study center: urban private optometric practice in Jerusalem, Israel Number randomized: 62 children Study follow-up: 18 months Exclusions and losses to follow-up: 5 (8%) children who were randomized were excluded from the analyses; 9 (14.5%) were lost to follow-up
Participants	Age: mean = 10.08 years (range 6 to 15 years) Gender: 34 boys, 14 girls Culture: most children were orthodox Jews who attended school year-round and performed a study method of swaying back and forth while learning and reading Inclusion criteria: pediatric patients aged 6 to 15 years from study centers with early-onset myopia Exclusion criteria: (1) strabismus; (2) amblyopia; (3) VA < 6/9; (4) spherical equivalent > -6.00 D or < -0.50 D in either eye; (5) astigmatism > 1.50 D in either eye; (6) anisometropia > 1.50 D; (7) a difference between objective and subjective refraction findings ≥ 0.75 D; (8) any ocular pathological manifestations; and (9) premature birth
Interventions	Undercorrected group (n = 25): blurred by +0.50 D; glasses were to be worn continuously Fully corrected group (n = 23): glasses were to be worn continuously Note: changes in prescription were made if the subjective refraction had changed by ≥ 0.50 D for 1 or both eyes
Outcomes	Progression of early-onset myopia: • Objective refractions without cycloplegia: static retinoscopy (spherical equivalent) • Subjective refractions without cycloplegia: endpoint of maximum plus for best acuity • Near lateral phoria: alternating cover test using 6/9 size picture target held at 40 cm from eye Measurements taken at baseline, 6 months, 12 months, and 18 months Unit of analysis: average values of both eyes used for all results
Notes	Study dates: enrollment occurred over an 8-month period Trial registration: not reported Materials: free spectacle lenses were supplied by Einit Optical Clinic Additional data: study author provided unpublished data via email correspondence

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Adler 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	A coin was tossed to determine group assignments
Allocation concealment (selection bias)	Unclear risk	The assignment for each participant was determined after enrollment by tossing a coin, but it was unclear how the allocation was concealed
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to performance differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	The optometrist conducting the examination was masked to the treatment group and to previous results for each participant
Masking of outcome assessors (detection bias) Secondary outcomes	Unclear risk	N/A (study did not measure secondary outcomes of this review)
Masking of data analyzers	Unclear risk	Analysis of the results was carried out by the other member of the team only after all data had been collected
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	Of the 62 children recruited, 48 are included in the analysis; 5 were excluded (3 did not wear their glasses continually, 2 were twins born prematurely) and 9 were lost to follow-up
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Low risk	None was identified

Anstice 2011

Study characteristics	
Methods	Study design: paired-eye, cross-over RCT Study center: 1 Number randomized: 40 children Study follow-up: 20 months (10 months for each period) Exclusions and losses to follow-up: no exclusions; 5 (12.5%) and 6 (15.0%) were lost to follow-up at 10-month visit and 20-month visit, respectively
Participants	Age: mean = 13.4 years (range 11 to 14 years) Gender: 11 boys, 29 girls Culture: New Zealand, including East Asian ethnicity and others (European, Indian, and Maori/Pacifica) Inclusion criteria: (1) 11 to 14 years old at recruitment; (2) spherical equivalent between -1.25 and -4.50 D in the least myopic eye as determined by noncycloplegic subjective refraction; (3) myopia progression ≥ 0.50 D in the previous 12 months; (4) best-corrected spectacle visual acuity of Snellen 6/6 or better in each eye; (5) willingness to wear contact lenses for ≥ 8 hours per day during the study

Anstice 2011 *(Continued)*

	Exclusion criteria: history of (1) astigmatism ≥ 1.25 D; (2) anisometropia ≥ 1.00 D; (3) strabismus at distance or near as assessed by cover test; (4) ocular or systemic pathology likely to affect refractive development or successful contact lens wear; (5) birth weight ≤ 1250 g
Interventions	Group 1 (n = 21): 10 months wearing 2.00 D dual-focus (DF) contact lens in the dominant eye and SVSCL in the contralateral eye, followed by 10 months wearing the swapped lens assignment Group 2 (n = 19): 10 months wearing DF contact lens in the nondominant eye and SVSCL in the contralateral eye, followed by 10 months wearing the swapped lens assignment
Outcomes	Primary outcome: • Change in spherical equivalent refraction measured by cycloplegic autorefraction Secondary outcome: • Change in axial eye length measured by partial coherence interferometry Measurements taken at baseline and every 5 months for 20 months Unit of analysis: data analyzed by dominant eye
Notes	Study dates: 2005 to not reported Trial registration: ACTRN12605000633684 Funding source: Maurice and Phyllis Paykel Trust; New Zealand Optometric and Vision Research Foundation; Cornea and Contact Lens Society of New Zealand Notes: study is also known as the Dual-focus Inhibition of Myopia Evaluation in New Zealand (DIMENZ) study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Children were randomized into group 1 or group 2 using a permuted block design with a block size of 4"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants (performance bias)	High risk	"The participants and the optometrist responsible for clinical care were not masked to lens assignment"
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	The "investigating optometrists responsible for making outcome measures were masked"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	The "investigating optometrists responsible for making outcome measures were masked"
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	Six participants (15%)—3 from each group—were lost to followup and were excluded from the analysis: 4 children due to difficulties handling the contact lenses, 1 due to negative publicity on contact lens solutions, and 1 due to dislike of cycloplegia

Anstice 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes specified prospectively on a clinical trials registry were reported
Other bias	High risk	One of the study authors disclosed an inventor patent for the contact lens design. Data were not appropriately analyzed for paired-eye nor cross-over design

ATOM Study 2006

Study characteristics	
Methods	Study design: parallel-group RCT, with 2-week run-in period Study center: 1 Number randomized: 400 children Study follow-up: 2 years Exclusions and losses to follow-up: no exclusions; 54 (13.5%) were lost to follow-up
Participants	Age: mean = 9.2 years (range 6 to 12 years) Gender: 220 boys, 180 girls Culture: Chinese (94%) and Indian children (4%) in Singapore Inclusion criteria: (1) age 6 to 12 years; (2) myopia with spherical equivalent refractive error between -1.00 D and -6.00 D in each eye as measured by cycloplegic autorefraction; (3) distance vision correctable to logMAR 0.2 or better in both eyes; (4) normal ocular health; (5) good general health with no history of cardiac or significant respiratory disease; (6) normal binocular function and stereopsis; (7) willingness and ability to tolerate monocular cycloplegia and mydriasis Exclusion criteria: (1) astigmatism > -1.50 D by cycloplegic autorefraction; (2) IOP 21 mmHg or greater; (3) allergies to atropine, cyclopentolate, proparacaine, or benzalkonium chloride; (4) previous or current use of contact lenses, bifocals, PALs, or other forms of myopia treatment; (5) amblyopia or manifest strabismus, including intermittent tropia
Interventions	Atropine (n = 200): 1 eye was randomized to 1 drop of 1% atropine sulfate nightly; the other eye received nothing Placebo control (n = 200): 1 eye was randomized to 1 drop of vehicle nightly; the other eye received nothing Note: all children received single vision photochromatic lenses for correction of refractive errors
Outcomes	Primary efficacy outcome: • Progression of myopia defined as the change in spherical equivalent refractive error from baseline and measured by cycloplegic autorefraction Secondary efficacy outcome: • Change in axial length from baseline and measured by A-scan ultrasonography Primary safety outcome: • Occurrence of adverse events Secondary safety outcomes:

ATOM Study 2006 *(Continued)*

	• Best-corrected VA, IOP, slit-lamp biomicroscopy, fundus examination Measurements taken at baseline and annually for 2 years Note: baseline measurements recorded 2 weeks after treatment began to allow for stabilization of the cycloplegic effect of atropine Unit of analysis: only 1 eye per patient randomized to receive treatment (fellow eyes were controls)
Notes	Study dates: enrollment between April 1999 and September 2000 Trial registration: not reported Materials: vehicle drops were prepared by Alcon Laboratories; spectacles were SOLA Transitions SVLs Funding source: National Medical Research Council, Singapore Additional data: study author provided unpublished data via email correspondence

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Children were allocated to groups based on a computer-generated randomization list
Allocation concealment (selection bias)	Unclear risk	Methods section stated "allocated with concealment", but it was unclear how allocation concealment was conducted
Masking of participants (performance bias)	Low risk	Study was placebo-controlled, and identical appearing bottles with coded labels were distributed
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	Use of identical appearing bottles with coded labels and dilation of both pupils before examination
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Unclear risk	"All statistical analyses were based on the intention-to-treat principle" Study authors noted (via personal communication) that there was a typographical error in the publication (54 were lost to follow-up—34 from the atropine group and 20 from the placebo group); the paper reports that those who did not complete the study were characteristically similar to those who completed the study for each group
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Unclear risk	Pre-randomization administration of the intervention may have enhanced or diminished the effect of the intervention during the subsequent randomized evaluation period

Cambridge Anti-Myopia Study 2013

Study characteristics	
Methods	Study design: 2 × 2 factorial RCT Study center: 1 (Anglia Ruskin University) Number randomized: 147 children Study follow-up: 24 months Exclusions and losses to follow-up: 47 (33%) were excluded or lost to follow-up
Participants	Age: mean = 17 years (range 14 to 22 years) Gender: 69 boys, 78 girls Culture: British Inclusion criteria: (1) age 14 to 22 years; (2) myopia with cycloplegic spherical equivalent -0.75 to -10.00 D; (3) astigmatism ≤ 0.75 D; 0.0 logMAR or less visual acuity with spectacles in each eye; no strabismus or uncompensated phoria; no ocular pathology; no systemic pathology that may affect myopia progression; zero or positive spherical aberration at distance; able to wear soft contact lenses throughout trial; no previous myopia control in study participation
Interventions	SCLs + SA + VT group (n = 25): SCLs with design to alter spherical aberration (fourth order), with vision training (VT) consisting of lens flipper exercises VT-only group (n = 31): unaltered SCLs, with VT SCL + SA-only group (n = 41): SCLs with design to alter spherical aberration SCL group (n = 45): unaltered SCLs, without VT Note: SCLs were replaced when refractive error changed by 0.25 D or more
Outcomes	Primary outcome: • Change in spherical equivalent refractive error (cycloplegic autorefraction) Secondary outcome: • Change in axial length from baseline to 2-year visit Measurements taken at 6-month intervals for 2 years Unit of analysis: child-based (right eye)
Notes	Study dates: no dates provided; manuscript submitted October 2012 Trial registration: NCT00317551 Funding source: Australian government CRC Scheme via the Vision Cooperative Research Centre Disclosures: "the authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article"

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"When a participant was the first (and third etc.) member of a block, they were assigned by coin-toss to the control or treatment groups, and the second (and fourth etc.) member of a block were assigned to the alternate group"

Cambridge Anti-Myopia Study 2013 *(Continued)*

Allocation concealment (selection bias)	High risk	"One experimenter, who was unmasked, allocated participants to groups. Participants were referred to this experimenter by others who were enrolling participants in the trial"
Masking of participants (performance bias)	Unclear risk	"All participants wore contact lenses, either treatment or control, for the duration of the study. In order to mask the participants with regard to the treatment that they were getting, the participants were told that, in addition to wearing contact lenses, there were a range of possible things they might be required to do (including vision training), but this was not described in a way where they would see themselves as being in another treatment group or not for the purposes of the clinical trial"
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"The masked experimenters had no information about the way individual participants were allocated to treatment groups, and remained masked for the duration of the study"; "Completed data records for each visit were stored securely and were not available to the masked examiners. Clinical care records contained no information regarding the treatment assignments or data from the baseline or follow-up visits"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Same as for primary outcomes
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	"Over the course of the trial 33% of participants dropped out"; "Only participants with a full dataset are presented"; "There was no significant difference in the number of subjects who dropped out of the study from each treatment group (Chi square P = 0.81) or in the gender of participants who dropped out (Chi square P = 0.49)"
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper and in the clinical trial registry record
Other bias	Low risk	None was identified

Charm 2013

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (Hong Kong Polytechnic University) Number randomized: 52 children Study follow-up: 2 years Exclusions and losses to follow-up: 14 (27%) children who were randomized, 7 in each group, were excluded or lost to follow-up
Participants	Age: median = 10 years (range 8 to 11 years) Gender: not reported Culture: children "recruited via advertisements posted on local newspapers and leaflets in the Optometry Clinic of the School of Optometry"

Charm 2013 *(Continued)*

	Inclusion criteria: (1) age 8 to 11 years; (2) myopia with spherical equivalent refractive error ≥ -5.00 D by cycloplegic manifest refraction; (3) monocular Snellen VA 20/25 or better; (4) willingness to wear orthokeratology and to be available for monthly follow-up Exclusion criteria: (1) astigmatism > 1.25 D; (2) binocular vision problems; (3) any ocular or systemic condition that may affect vision or vision development; (4) contraindications for contact lens wear; (5) previous experience with refractive surgery, PALs, or orthokeratology
Interventions	Orthokeratology (n = 26): partial reduction orthokeratology contact lenses of target 4.00 D (DreamLite, Procornea Ltd, The Netherlands); "residual refractive errors were corrected by a pair of single vision spectacles to be worn during daytime" SVLs (n = 26): single vision spectacles Note: "spectacle prescription would be updated at any subsequent visit for either group of subjects if difference in residual refractive errors (sphere or astigmatism) obtained at that visit exceeded 0.50 D"
Outcomes	Primary outcome: • Change in axial length Secondary outcomes: • Objective and subjective cycloplegic refraction • Fundus examination • Visual acuity • Slit-lamp examination • Corneal topography Measurements taken every 6 months for 2 years Unit of analysis: child-based (right eye)
Notes	Study dates: not reported Trial registration: NCT00977236 Funding source: "this study was supported by a Collaborative Research Agreement between The Hong Kong Polytechnic University (PolyU) and Procornea Nederland B.V. and a Niche Area Funding (J-BB7P) from PolyU. We thank Menicon Company Limited for supplying Menicon O2 Care for the study" Conflict of interest: "the authors have no proprietary interest in any of the products used in the study"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment before randomization was not reported
Masking of participants (performance bias)	High risk	"Single-masked" study; participants were not masked
Masking of outcome assessors (detection bias) Progression of myopia	Unclear risk	This was not reported

Charm 2013 *(Continued)*

Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	"Measurements of AL were performed with the Zeiss IOLMaster (Carl Zeiss Meditec, Inc., USA) by masked examiners"; "This study was a single-masked design to eliminate any examiner bias on myopic progression. The masked examiner only measured and recorded the AL which was the primary outcome of the study"
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	"Seven subjects in the control group decided to quit the study after baseline examination. One PR ortho-k subject quitted after two days of lens wear due to lens discomfort, five were terminated due to poor lens fitting despite repeated lens modifications, and another was terminated after one week of lens wear due to noncompliance with aftercare schedule"
Selective reporting (reporting bias)	High risk	Results were reported for the intervention group only
Other bias	Low risk	None was identified

Cheng 2010

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (optometric practice in Mississauga, Ontario, Canada) Number randomized: 150 children Study follow-up: 2 years Exclusions and losses to follow-up: 15 (10%) children who were randomized were excluded from the analyses; 4 (3%) were lost to follow-up
Participants	Age: mean = 10 years (range 8 to13 years) Gender: 62 boys and 73 girls received treatment Culture: Chinese Canadian children were recruited by reviewing clinical records and mailing invitation letters addressed to their parents, or by responding to poster in the practice or during regular eye examinations Inclusion criteria: (1) Chinese Canadian children who were seen at the practice in the last 9 to 18 months; (2) age 8 to 13 years; (3) myopia between -1.00 D and -5.50 D; (4) myopia progression ≥ 0.50 D in the preceding year; (5) distance monocular visual acuity of 6/6 or better; (6) near monocular visual acuity of 6/6 or better; (7) stereoacuity ≤ 40 s of arc at 40 cm; (8) single vision distance lens wear; (9) consent of child and parent for study participation Exclusion criteria: (1) astigmatism > 1.50 D; (2) anisometropia > 1.50 D; (3) strabismus; (4) inability to respond to subjective testing; (5) history of systemic or ocular disease; (6) history of bifocal lens wear and/or contact lens use
Interventions	SVLs (n = 50): single vision distance lenses Bifocal lenses (n = 50): bifocal lenses with +1.50 D near addition Prismatic bifocal lenses (n = 50): prismatic bifocal lenses with +1.50 D addition and a 3-prism diopter base-in prism in the near segment

Cheng 2010 *(Continued)*

	Note: distance prescription changes were made if subjective refraction changed by ≥ 0.50 D in either eye
Outcomes	Primary outcome: • Myopic progression defined as difference between the mean cycloplegic spherical equivalent measured by an automated refractor at the baseline visit and subsequent 6-month visits for 24 months Secondary outcome: • Eye growth defined as difference between mean axial lengths measured by ultrasonography at the baseline visit and at subsequent 6-month visits for 24 months Measurements taken at baseline and every 6 months for 2 years Unit of analysis: child-based (right eye)
Notes	Study dates: April 2003 to April 2008 Trial registration: NCT00787579 Funding source: Essilor International of France Auxiliary data: parents and/or guardians completed questionnaires related to vision habits of the enrolled child and the child's birth parents' refractive errors. The number of years the children were myopic before entering the study was estimated from clinical records. Auxiliary data were used as covariates for regression statistics and to test the hypothesis that bifocal treatment is more effective with a shorter duration of myopia Additional data: study author provided unpublished data via email correspondence

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Randomization was implemented by putting the subjects' file numbers on slips of paper and drawing them from a container at random...The first 50 subjects drawn were assigned to the control group; the second 50 were assigned to the bifocal group, and so forth"
Allocation concealment (selection bias)	High risk	"The first 50 subjects drawn were assigned to the control group; the second 50 were assigned to the bifocal group, and so forth"
Masking of participants (performance bias)	High risk	"The subjects and the investigator were aware of the treatment assignments." Masking was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	High risk	"The subjects and the investigator were aware of the treatment assignments. Masking was difficult to achieve in a practice-based intervention, particularly when the lens treatments were visually very different." The primary study investigator dispensed lenses and performed examinations
Masking of outcome assessors (detection bias) Secondary outcomes	High risk	"...the primary and secondary outcome variables were measured by objective methods to minimize possible bias of the unmasked investigator"
Masking of data analyzers	Low risk	"The data analyst discerned the study investigated the effect of three types of lenses on ocular refraction, but he was masked to the possible effect of bifocal or prismatic bifocal lens on myopia control" (via email communication with study author)

Cheng 2010 *(Continued)*

Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	"The analysis of the data followed the intention-to-treat approach, and we used the last progression information (i.e. carry forward) method for subjects lost to follow-up". Although study authors stated that they used intention-to-treat analysis, 15 of the 150 children randomized were not included in the analysis: 9 children randomized to single vision lenses dropped out because their parents wanted them to receive bifocals; and 2 children in the bifocals group and 4 in the prismatic bifocals group were excluded due to adverse reactions following cycloplegia
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Unclear risk	This study was funded by a company that produces the types of lenses being investigated

Cheng 2016

Study characteristics	
Methods	Study design: parallel-group RCT Study center: Korb and Associates in Boston, Massachusetts Number randomized: 127 children Study follow-up: 12 months (planned for 24 months) Exclusions and losses to follow-up: 6 (4.7%) children who were randomized were excluded from the analyses; 15 (11.8%) were lost to follow-up
Participants	Age: mean = 9.7 years (range 8 to 11 years) Gender: 59 boys, 68 girls Culture: 90.6% were Asian and 8.7% were white Inclusion criteria: (1) ages 8 to 11 years; (2) myopia -0.75 to -4.00 D sphere by cycloplegic refraction; (3) 1.00 D or less astigmatism; (4) 1.00 D or less difference between eyes in spherical equivalent; (5) 20/25 + 2 or better visual acuity in each eye with spherocylindrical refraction; (6) 20/25 or better visual acuity with best sphere Exclusion criteria: (1) ocular or systemic pathology; (2) history of eye surgery; (3) history of myopia control
Interventions	SCL + SA group (n = 64): soft daily disposable contact lenses with positive spherical aberration (0.175 µm) SCL group (n = 63): soft daily disposable contact lenses without the positive spherical aberration Note: control and test lenses had identical material and appearance; spherical aberration was chosen to negate the negative spherical aberration that occurred in myopes during accommodation
Outcomes	Primary outcome: • Change in spherical equivalent cycloplegic autorefraction Secondary outcome:

Cheng 2016 *(Continued)*

- Change in axial length

Measurements taken every 6 months for 2 years

Unit of analysis: child-based (right eye)

Notes	Study dates: April 2008 to October 2011 Trial registration: NCT01829191; NCT01829230 Funding source: Johnson and Johnson Vision Care, Inc. Disclosures of interest: "Xu Cheng, Jing Xu, Khaled Chehab, and Noel Brennan are all paid employees of Johnson and Johnson Vision Care, Inc. Joan Exford of Korb & Associates is a contract principal investigator paid by Johnson and Johnson Vision Care, Inc."; "We thank Dr. Jichang He of New England College of Optometry and Dr. Victor Finnemore of Korb & Associates for collecting data for the study and Dr. Myles Jaffe of Innova Medical Communications, LLC, who is a contract medical writer paid by Johnson and Johnson Vision Care, Inc. for preparing this manuscript" Notes: "the study was terminated because sufficient data had been collected from concurrent internal studies of similar designs"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment before randomization was not reported
Masking of participants (performance bias)	Unclear risk	"Both the subjects and investigators involved in gathering data in the withdrawal phase continued to be masked as to the initial treatment assignment in the earlier double-masked component of this investigation"; "The test lenses were identical to the control lenses in every aspect except that they were designed with aspheric front surfaces incorporating +SA"
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"Both the subjects and investigators involved in gathering data in the withdrawal phase continued to be masked as to the initial treatment assignment in the earlier double-masked component of this investigation"; "Three investigators were involved in data collection. Two conducted lens fittings and provided ongoing care, and a separate masked investigator was responsible for refraction and AL measurements"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Same as for the primary outcome
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	Children who were randomized but who dropped out were excluded from analyses; "During the entire course of the treatment phase, a total of 21 (17%) subjects were discontinued from the study, among which 14 (22%) and 7 (11%) were from the test cohort and control cohort, respectively"
Selective reporting (reporting bias)	Unclear risk	Results were reported only for 12-month data; 24 (18.9%) children completed 24 months of follow-up before the study was terminated early

Cheng 2016 *(Continued)*

Other bias	High risk	This study was funded by a company that produces the types of lenses being investigated; the authors of the study are employees of the company; and "the study was terminated because sufficient data had been collected from concurrent internal studies of similar designs"

Chung 2002

Study characteristics	
Methods	Study design: parallel-group RCT Study center: patient care unit at the Department of Optometry, Faculty of Allied Health Science, National University of Malaysia Number randomized: 106 children Study follow-up: 2 years Exclusions and losses to follow-up: no exclusions; 12 (11%) were lost to follow-up
Participants	Age: mean = 11.56 years (range 9 to 14 years) Gender: 39 boys, 55 girls Culture: Malay and Chinese ethnic origin Inclusion criteria: (1) age 9 to 14 years; (2) myopia with spherical equivalent refractive error ≥ -0.50 D in both eyes, with no principal meridian being plano or having any amount of plus power; (3) corrected VA of 6/6 or better in each eye; (4) normal ocular health; (5) willingness to give written consent Exclusion criteria: (1) more than 2 diopters of astigmatism in each eye; (2) binocular vision problems, including anisometropia over 2.00 D, problems requiring refractive therapy, strabismus, and amblyopia; (3) previous contact lens wear; (4) family was planning to leave the area before the end of the study period
Interventions	Undercorrected group (n = 47): monocular VA blurred to 6/12 (approximately +0.75 D) in each eye with spectacles Fully corrected group (n = 47): monocular VA maintained at 6/6 or better in each eye with spectacles Note: in the fully corrected group, changes in prescription were made if subjective refraction had changed by ≥ 0.50 D for 1 or both eyes. For the undercorrected group, changes in prescription were made to maintain a vision of 6/12 in each eye
Outcomes	Progression of early-onset myopia: • Static retinoscopy without cycloplegia • Keratometry • Subjective cycloplegic refractions using the endpoint of maximum plus or minimum plus for best acuity • Ocular components measurements by means of A-scan ultrasonography Measurements taken at baseline and every 6 months for 2 years Unit of analysis: average values of both eyes used for all results
Notes	Study dates: not reported Trial registration: not reported

Chung 2002 *(Continued)*

	Funding source: IRPA grant Compliance in wearing glasses was monitored via questionnaires. Compliance was defined as wearing glasses for at least 8 hours a day (40 patients in the undercorrected group vs 41 in the fully corrected group). Partial compliance was defined as wearing glasses 6 to 8 hours a day (7 patients in the undercorrected group vs 6 in the fully corrected group)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization based on age, sex, race, and refractive error. Treatment and control pairings were made to complete cells based on 3 age categories, 4 refractive error categories, 2 racial groups, and 2 gender groups (3 x 4 x 2 x 2 = 48 cells). Patients were designated as subject 1 or subject 2 for each cell based on a predetermined randomization procedure
Allocation concealment (selection bias)	Low risk	Once the patients were paired, a coin toss determined which patient was assigned to the treatment or control group. Heads meant subject 1 was allocated to undercorrection and subject 2 received full correction. Tails meant subject 1 was allocated to full correction and subject 2 received undercorrection. A coin toss was performed for each pair
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to performance differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	During all evaluations, the examining optometrist was not aware of the group assignment
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	Results were analyzed only after the last reading of the last patient was collected
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	Of the 106 children recruited, 94 completed the study and were included in the analyses; 12 (11.3%) dropped out and were excluded from the analyses
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Low risk	None was identified

CLAMP Study 2004

Study characteristics

Methods	Study design: parallel-group RCT, with run-in period Study center: 1 (The Ohio State University College of Optometry) Number randomized: 116 children

CLAMP Study 2004 *(Continued)*

	Study follow-up: 3 years Exclusions and losses to follow-up: none
Participants	Age: mean = 10.7 years (range 8 to 12 years) Gender: 47 boys, 69 girls Culture: Columbus, Ohio, USA; 84.5% white (not of Hispanic origin), 8.6% Asian or Pacific Islander, 4.3% Black (not of Hispanic origin) Inclusion criteria: (1) 8 to 11 years old at time of randomization; (2) myopia with spherical equivalent refractive error between -0.75 D and -4.00 D in each eye, as measured by cycloplegic refraction; (3) corrected VA of 20/20 or better in each eye Exclusion criteria: (1) astigmatism > 1.50 DC in each eye by cycloplegic refraction or > 1.00 DC on manifest refraction; (2) previous or attempted history of contact lens wear; (3) anisometropia > 1.00 D between eyes; (4) eye disease and binocular vision problems; (5) systemic disease that may affect vision or vision development Note: all participants had to successfully complete a run-in period before enrollment into the study to exclude those who could not adapt to rigid contact lenses; 32 children did not complete the run-in period and were excluded. Success for the run-in period was defined as wearing the lenses at least 40 hours/week and stating that the lenses were "always comfortable" or "usually comfortable"
Interventions	(n = 59): RGPCLs worn during waking hours for 3 years (n = 57): SCLs worn during waking hours for 3 years Note: prescription changes were made by an unmasked examiner based on participant complaints and improvement in visual acuity
Outcomes	Primary outcome: • Change in cycloplegic autorefraction during 3 years (spherical equivalent) Secondary outcomes: • Change in axial length • Change in peripheral autorefraction • Change in crystalline lens curvatures • Change in corneal curvature and thickness • Change in accommodation • Change in IOP Measurements taken at baseline and every 6 months for 3 years Unit of analysis: data analyzed for right eye only
Notes	Study dates: enrollment July 8, 1998 to February 26, 2000 Trial registration: NCT00009529 Funding source: National Eye Institute, National Institutes of Health; Menicon Co, Ltd.; CIBA Vision Corporation; SOLA Optical; and Essilor

Risk of bias

Bias	Authors' judgement	Support for judgement

CLAMP Study 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomized participants were stratified by gender and in treatment blocks of 3. A list of randomized treatment assignments was prepared by an independent person before the study began
Allocation concealment (selection bias)	Unclear risk	Individual treatment assignments from the list were placed in sequentially numbered envelopes that were sealed. Envelopes were drawn from the pool in sequential order according to the participant's gender. It was unclear whether the envelopes were opaque.
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to material differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	Masked examiners conducted the primary outcome procedure and all secondary outcomes except visual acuity. When the masked examiner was in the room, participants wore only spectacle correction or no correction and were told not to mention any contact lens wear to the masked examiner. No assessment of masking was reported
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Outcome measures were performed by examiners masked to the mode of correction worn by the participant with the exception of visual acuity measurements
Masking of data analyzers	Unclear risk	This was not reported in the paper, but the persons conducting the analyses were not masked to treatment group allocation (JW). Outcome measures were not presented by treatment group until the conclusion of the trial. Data were managed via a dual-entry format
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	All data were analyzed according to the original result of the random assignment, and no data were missing. "We analyzed all data using intention-to-treat methods"
Selective reporting (reporting bias)	Low risk	All outcomes outlined in the study protocol were reported
Other bias	Unclear risk	Pre-randomization administration of the intervention may have enhanced or diminished the effect of the intervention during the subsequent, randomized evaluation period This study was partially funded by companies that produce the interventions being investigated

COMET2 Study 2011

Study characteristics	
Methods	Study design: parallel-group RCT Study centers: 8 (including 7 optometry colleges and schools and 1 community-based ophthalmology practice) Number randomized: 118 children Study follow-up: 3 years Exclusions and losses to follow-up: no exclusions; 8 (7%) were lost to follow-up

COMET2 Study 2011 *(Continued)*

Participants	Age: mean = 10.1 years (range 8 to 12 years) Gender: 54 boys, 64 girls Culture: USA Inclusion criteria: (1) age 8 to < 12 years; (2) refractive error determined by cycloplegic autorefraction, which meets all of the following: spherical equivalent -0.50 to -3.00 D in both eyes; astigmatism ≤ 1.5 D in both eyes; anisometropia ≤ 1.00 D difference between eyes in spherical equivalent; (3) visual acuity at least 20/20 with best subjective refraction in both eyes; (4) accommodative response at near vision (33 cm) is less than 2.0 D by noncycloplegic autorefraction; (5) near esophoria (≥ 2.0 PD) present by alternate prism and cover test (APCT) at near vision using best refractive correction determined from noncycloplegic subjective refraction Exclusion criteria: (1) history of strabismus; (2) current or prior use of PALs, bifocals, or contact lenses in either eye (prior or current use of SVLs was permitted)
Interventions	PAL group (n = 59): Varilux Ellipse progressive addition lenses with a +2.00 D near addition; worn during all waking hours for 3 years SVL group (n = 59): standard single vision lenses (spectacles); worn during all waking hours for 3 years Notes: the distance correction was changed if the endpoint of the noncycloplegic subjective refraction differed from the current prescription by 0.50 D or more in spherical equivalent. Prescription changes could be made for smaller differences at investigator discretion if the new prescription improved the patient's visual acuity by at least 1 line over that in their current correction
Outcomes	Primary outcome: • Change in spherical equivalent refractive error in diopters from baseline to 3-year visit measured by cycloplegic autorefraction Secondary outcomes: • Main axis astigmatism (J_0, dioptric power of a Jackson cross-cylinder with axis at 0°) and oblique astigmatism (J_{45}, dioptric power of a Jackson cross-cylinder with axis at 45°) by using the power vector approach Measurements taken at baseline and every 6 months for 3 years Unit of analysis: child-based (median for each eye averaged to obtain the spherical equivalent used for analysis)
Notes	Study dates: enrollment from April 2005 to March 2007 Trial registration: NCT00320593 Funding source: National Institutes of Health, Department of Health and Human Services, USA Materials: Essilor of America and Eyewear Designs provided spectacles at a reduced cost Study name: progressive addition lenses vs single vision lenses for slowing progression of myopia in children with high accommodative lag and near esophoria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"In a permuted block design stratified by site and by history of previous SVL wear, each subject was randomly assigned with equal probability to receive spectacles that were either PALs with a +2.00 D near addition or SVLs"

COMET2 Study 2011 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"All testing procedures were performed by a study-certified optometrist or ophthalmologist who was masked to the subject's lens assignment. To maintain masking of the investigators, the subject saw an unmasked coordinator before the examination who collected the subject's spectacles and told the optometrist or ophthalmologist performing the eye examination what distance refractive correction to use in trial frames for the examination"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	Masking of persons analyzing results was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	"All analyses followed the intent-to-treat principle. The Monte Carlo Markov Chain (MCMC) 18 method of multiple imputation was used to impute data for subjects who did not complete the 3-year visit. To evaluate the effect of imputation on the primary results, we also performed the primary analysis (1) using the last-observation carried-forward method and (2) using only data from subjects who completed the 3-year visit"; 1 (2%) and 7 (12%) children withdrew in SVLs and PALs groups, respectively; 3 were lost to follow-up, 1 moved to another state, and 4 withdrew by clinical site
Selective reporting (reporting bias)	Low risk	All outcomes specified prospectively on a clinical trials registry were reported
Other bias	Low risk	None was identified

COMET Study 2003

Study characteristics	
Methods	Study design: parallel-group RCT Study center: multicenter, including (1) a study chair, (2) a coordinating center, (3) 4 clinical centers, and (4) the National Eye Institute, USA Number randomized: 469 children Study follow-up: 3 years Exclusions and losses to follow-up: no exclusions; 7 (1.5%) were lost to follow-up
Participants	Age: mean = 9.3 years (range 6 to 11 years) Gender: 223 boys, 246 girls Culture: 4 major cities in the USA (Birmingham, Alabama: n = 133; Boston, Massachusetts: n =110; Philadelphia, Pennsylvania: n = 108; and Houston, Texas: n = 118) Inclusion criteria: (1) 6 to 11 years old; (2) myopia with spherical equivalent refractive error between -1.25 D and -4.50 D in both eyes, as measured by cycloplegic autorefraction; (3) astigmatism ≤ 1.50 D; (4) no anisometropia (difference in spherical equivalent < 1.00 D between eyes); (5) best-corrected VA of

COMET Study 2003 *(Continued)*

	20/32 or better; (6) no strabismus by cover test for far (4.0 m) and/or near (0.33 m) fixation; (7) willingness to not wear contact lenses for study duration Exclusion criteria: (1) strabismus detected by cover test; (2) any ocular, systemic, or neurodevelopmental conditions that could influence refractive development; (3) chronic medication use that might affect myopia progression or visual acuity; (4) birth weight < 1250 g; (5) previous use of bifocals, PALs, or contact lenses; (6) problems with adherence to the protocol or the follow-up period
Interventions	PAL group (n = 235): multifocal lenses (no-line bifocals) with gradual and progressive change toward less negative or more positive power from the distance portion to the near portion of the lens (power +2.00 D); worn during waking hours for 3 years SVL (n = 234): single vision lenses with same focal power throughout the lens area; worn during waking hours for 3 years Note: prescription changes were made if the subjective refraction had changed by at least 0.50 D for 1 or both eyes. Smaller prescription changes were made if clinically indicated. Both groups were offered single vision sports glasses to use while participating in sports activities
Outcomes	Primary outcome: • Change in refractive error Magnitude of change in spherical equivalent refractive error relative to baseline measured by cycloplegic autorefraction with 2 drops of 1% tropicamide Secondary outcomes: • Axial length (magnitude of change in axial length relative to baseline using average 3 to 5 measurements with the Sonomed A-scan) • Changes in ocular components, including lens thickness, anterior chamber depth, vitreous chamber depth • Accommodation and phoria by Maddox rod • Corneal curvature based on keratometry measured with the autorefractor • Normal reading distance for standardized age-appropriate text Measurements taken at baseline and every 6 months for 3 years Unit of analysis: child-based Average values of both eyes used if the correlation coefficient was > 0.85 between eyes and the mean difference was not statistically significant; otherwise the eye with greater myopic change used for each child
Notes	Study dates: enrollment was from September 1997 to September 1998; follow-up was designed for 3 years but continued for 7 years, including 5 years wearing original lens assignments and 2 years wearing either glasses or contact lenses Trial registration: NCT00000113 Funding source: NEI grants, Essilor of America, Marchon Eyewear, Marco Technologies, and Welch Allyn Sample of 150 children were followed up at 1 month to evaluate possible lens-induced phoria changes; no problems were detected in either group Compliance in wearing glasses was monitored via separate questionnaires for children and parents (93% compliance in PAL group, 96% compliance in SVL group). Attitude toward wearing glasses and self-esteem were also measured Additional data: study author provided unpublished data via email correspondence
Risk of bias	

COMET Study 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was derived by permuted block design with preset block size and was stratified by clinical center by the coordinating center
Allocation concealment (selection bias)	Low risk	Randomization assignments were allocated by the coordinating center after the eligibility of each participant was verified
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	Optometrists responsible for assessing study outcomes were unaware of lens assignments
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	"The data analysts were not masked to treatment assignment when analyzing the data" (via email communication with study author)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	"Follow-up data were analyzed by applying an intention-to-treat principle according to the child's original lens assignment and the last known value of the outcome measures. For the seven children lost to follow-up and thus without data at the third annual visit, progression information from the latest follow-up visit was used"
Selective reporting (reporting bias)	Low risk	All outcomes published a priori in the design paper (Hyman 2001) were reported in results papers
Other bias	Unclear risk	This study was partially funded by companies that produce the interventions being investigated

CONTROL Study 2016

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 Number randomized: 86 children Study follow-up: 1 year Exclusions and losses to follow-up: 8 children did not complete the study
Participants	Age: mean = 13 years (range 8 to 18 years) Gender: 26 boys, 60 girls Culture: California, USA Inclusion criteria: (1) myopia between -0.50 D and -6.00 D, with documented progression of -0.50 D or more since last examination; (2) eso fixation disparity at 33 cm with distance correction; (3) astigmatism 1.00 D or less; (4) anisometropia 2.00 D or less; (5) best-corrected visual acuity 20/20 or better in each eye; (6) ability to wear SCLs and attend follow-up visits

CONTROL Study 2016 *(Continued)*

	Exclusion criteria: (1) presence of ocular disease affecting eye growth or preventing wear of contacts; (2) prior ocular surgery; (3) history of wearing RGPs in previous 2 years or extended wear SCLs in previous 6 months: (4) pregnancy or nursing; (5) use of certain medications
Interventions	BSCL group (n = 39): Vistakon Acuvue Bifocal lenses (distance center, alternating 5-ring), worn on a daily basis SVSCL group (n = 40): Vistakon Acuvue 2, worn on a daily basis
Outcomes	Primary outcomes: • Changes in cycloplegic autorefraction at 1 year • Changes in cycloplegic subjective refraction at 1 year • Changes in axial length at 1 year Secondary outcomes: • Keratometric changes at 1 year • Changes in manifest refraction at 1 year • Relationship between residual fixation disparity and myopia progression Measurements taken at baseline, 6 months, and 12 months Unit of analysis: average values for both eyes
Notes	Study dates: start date was October 2003; study was completed in 2006 Trial registration: NCT00214487 Funding source: Vistakon Additional information: study author provided unpublished information via email correspondence

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Because of the relatively small group (sample) sizes involved, a modified covariate adaptive randomization approach was used to allocate treatments. Specifically, subjects were randomly assigned a treatment by the masked offsite clinical trial coordinator who used an adaptive biased coin toss design to increase the probability that successive subjects were assigned to the group with the smaller sample size with respect to age, refractive error, amount of eso-associated near phoria, sex, and Asian versus non-Asian ethnicity"
Allocation concealment (selection bias)	Low risk	Contact lens prescriptions for eligible participants were transmitted to an offsite research assistant for allocation (via email communication with study author)
Masking of participants (performance bias)	Unclear risk	"Masking was aided by the choice of lenses; both were 58% water, two-week disposable lenses, identical in appearance and supplied in masked packaging" "The study examiner, office staff, subjects, and parents were not aware of the lens assignments before the end of the study"
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"Masking was aided by the choice of lenses; both were 58% water, two-week disposable lenses, identical in appearance and supplied in masked packaging" "The study examiner, office staff, subjects, and parents were not aware of the lens assignments before the end of the study"

CONTROL Study 2016 *(Continued)*

Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	79/86 (92%) randomized participants were included in final analyses; attrition was balanced between groups
Selective reporting (reporting bias)	Low risk	All outcomes specified on a clinical trials registry and in a conference abstract were reported
Other bias	Unclear risk	This study was funded by a company that produces the types of lenses being investigated

DISC Study 2011

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (Hong Kong Polytechnic University) Number randomized: 221 children Study follow-up: 2 years Exclusions and losses to follow-up: 38 (34.2 %) in BSCL group and 36 (32.7%) in SVSCL group were excluded; 8 (7.2 %) in BSCL group and 11 (10.0%) in SVSCL group were lost to follow-up
Participants	Age: mean = 11 years (range 8 to 13 years) Gender: 85 boys, 136 girls Culture: Hong Kong, China Inclusion criteria: (1) age 8 to 13 years; (2) spherical equivalent -1.00 to -5.00 D; (3) astigmatism 1.00 D or less; (4) anisometropia 1.25 D or less; (5) spectacle-corrected monocular visual acuity 0.0 logMAR or better; (6) contact lens–corrected monocular visual acuity 0.1 logMAR or better; (7) willingness to wear contact lenses regularly and parents' understanding and acceptance of random allocation of intervention Exclusion criteria: (1) ocular or systemic abnormalities affecting visual function or refractive development; (2) prior use of PALs or bifocal contact lenses; (3) contraindication for contact lens wear
Interventions	BSCL group (n = 111): dual-focus incorporated soft contact (DISC) lenses, which were custom-made BSCLs with distance correction in the center and alternating rings of defocusing (+2.50 D addition) and distance correction zones SVSCL group (n = 110): single vision soft contact lenses Note: children were instructed to wear lenses for 5 to 10 hours per day and to wear spectacles with full prescription when not wearing contact lenses
Outcomes	Primary outcomes: • Refractive error (cycloplegic autorefraction)

DISC Study 2011 *(Continued)*

	• Axial length Secondary outcome: • Corneal curvature Measurements taken every 6 months over 2 years Unit of analysis: individual (right eye used for analysis)
Notes	Study dates: September 2007 and October 2009 Trial registration: NCT00919334 Funding source: "the study was supported by grants of RGC GRF (B-Q04G) and Niche Areas Fund (J-BB7P) from The Hong Kong Polytechnic University" Conflict of interest: reported "none"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Allocation was determined by a random software sequence in ex-cell"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment before randomization was not reported
Masking of participants (performance bias)	Unclear risk	"The children and their parents were not told which lens design was prescribed" It is unclear whether children would remain masked during the treatment period given the different designs of the lenses
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"One investigator was masked from grouping and was responsible for refracting and relevant ocular data measurement. The other investigator was unmasked and responsible for group allocation, lens fitting and aftercare, measuring lens performance, record keeping and compliance checking"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	"One investigator was masked from grouping and was responsible for refracting and relevant ocular data measurement. The other investigator was unmasked and responsible for group allocation, lens fitting and aftercare, measuring lens performance, record keeping and compliance checking"
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	46 (41.4%) in the BSCL group and 47 (42.7%) in the SVSCL group were not included in the final analyses. The most common reason for exclusion of children from the analyses—22 in the BSCL group and 22 in the SVSCL group—was that they did not want to wear the contact lenses
Selective reporting (reporting bias)	Low risk	All outcomes specified prospectively on a clinical trials registry were reported
Other bias	Low risk	None was identified

Edwards 2002

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (Centre for Myopia Research) Number randomized: 298 children Study follow-up: 2 years Exclusions and losses to follow-up: no exclusions; 44 (15%) were lost to follow-up
Participants	Age: mean = 9.09 years (range 7 to 10.5 years) Gender: 122 boys, 132 girls Culture: Hong Kong children, recruited through newspaper advertisements Inclusion criteria: (1) 7 to 10.5 years old; (2) spherical equivalent refractive error between -1.25 D and -4.50 D, as measured under cycloplegia; (3) best-corrected VA of 0.00 logMAR or better; (4) no previous use of contact lenses and willingness to not wear contact lenses; (5) willingness to wear glasses constantly; (6) parents' acceptance of randomization Exclusion criteria: (1) astigmatism > 1.50 D; (2) anisometropia > 1.50 D in spherical or cylindrical error; (3) any ocular or systemic condition that might affect refractive development; (4) previous use of bifocals or PALs; (5) problems with adherence to the protocol or the follow-up period
Interventions	PAL group (n = 138): SOLA MC progressive addition lenses (add +1.50 D); worn constantly for 2 years SVL (n = 160): SOLA single vision lenses; worn constantly for 2 years Note: prescription changes were made if there was a reduction in aided vision of ≥ 0.10 logMAR units
Outcomes	Primary outcomes: • Refractive error measured under cycloplegia (by autorefraction for data analysis and by subjective refraction for spectacle prescription) • Axial length measured under cycloplegia Secondary outcomes: • Aided visual acuity in each eye • Mean monocular and binocular distance and near PD • Noncycloplegic refraction • Horizontal and vertical heterophoria • Normal reading distance for standardized age-appropriate text Measurements taken at baseline and every 6 months for 2 years Unit of analysis: only data from right eyes reported
Notes	Study dates: not reported Trial registration: not reported Materials: lenses provided by Sola (Hong Kong) Ltd Funding source: Centre for Myopia Research (Area of Strategic Development), The Hong Kong Polytechnic University
Risk of bias	

Edwards 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Predetermined random sequence
Allocation concealment (selection bias)	Unclear risk	The investigator, who was involved in assigning children, was not aware of group allocation until a child was enrolled in the study. It was unclear how the allocation was concealed
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	The investigator measuring refractive error was masked to treatment assignment
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	The investigator measuring axial length was masked to treatment assignment
Masking of data analyzers	Low risk	Masked and unmasked investigators independently analyzed the data
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	There were no exclusions after randomization. There were 44 patients lost to follow-up: n = 17 in the PAL group, n = 27 in the SVL group. It was reported that whether or not a patient was retained in the study was not statistically associated with treatment allocation
Selective reporting (reporting bias)	Low risk	Results for study outcomes were reported at 2-year follow-up
Other bias	Low risk	None was identified

Fujikado 2014

Study characteristics	
Methods	Study design: cross-over RCT Study center: 1 (Osaka University School of Medicine) Number randomized: 24 children Study follow-up: 12 months for each phase Exclusions and losses to follow-up: "in the second year, two children dropped out from the study because their families moved to another city"
Participants	Age: mean = 14 years (range 6 to 16 years) Gender: 7 boys, 17 girls Culture: Japan Inclusion criteria: (1) 6 to 16 years of age; (2) myopic refractive error between -0.75 D and -3.50 D; (3) anisometropia ≤ 1.0 D; (4) astigmatism ≤ 1.0 D; (5) best-corrected visual acuity 20/20 or better; (6) willingness to wear lenses

Fujikado 2014 *(Continued)*

	Exclusion criteria: (1) amblyopia, strabismus, or other ocular disease other than refractive error; (2) history of orthokeratology, bifocal spectacles, or progression spectacles in past 12 months
Interventions	BSCL group (n = 11 in phase 1): progressive addition soft contact lenses (+0.50 D) with 8.6 mm base curve, 14.5 mm diameter, 3.25 mm central zone, and horizontal thick zones to prevent rotation (Mipafilcon A; Menicon, Nagoya, Japan) SVSCL group (n = 13 in phase 1): single vision soft contact lenses
Outcomes	Primary outcomes: • Axial length • Spherical equivalent at 12 and 24 months (cycloplegic autorefraction) Secondary outcomes: • Peripheral refraction • Compliance Measurements taken months 1, 3, 6, 9, and 12 in each phase Unit of analysis: individual (average of both eyes except for 1 child whose right eye was enrolled only)
Notes	Study dates: January 2011 to March 2013 Trial registration: JPRN-UMIN000007989 Funding sources: Menicon Corp., Itami Central Ophthalmology Clinic (Japan) Conflict of interest: "AS and MN are employees of Menicon. The authors report no other conflicts of interest in this work"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was done by a random-number table"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to performance differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"The outcome measurements were made by masked examiners"; "the measurements were taken by orthoptists masked to the type of CLs worn"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Same as for primary outcomes
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	No children were lost to follow-up in the first year; "the data for the children who attended at least the 12-monthly visit were included in the analysis of the progression of myopia"

Fujikado 2014 *(Continued)*

Selective reporting (reporting bias)	High risk	Axial length was listed as a secondary outcome in the clinical trial registry record, but it was stated as a primary outcome in the journal publication. Trials authors' main conclusion that "this pilot study suggests that low-addition soft CLs with decentered optical design can reduce the degree of axial elongation in myopic children after an initial transient phase of CL wear" does not correspond to the study's objective
Other bias	High risk	Study was funded by the manufacturers of the lenses under investigation. Inappropriate analysis of cross-over data was performed

Fulk 1996

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (Indian Health Service Hospital, Optometry Department, Tahlequah, Oklahoma, USA) Number randomized: 32 children Study follow-up: 18 months Exclusions and losses to follow-up: no exclusions; 4 (12.5%) were lost to follow-up
Participants	Age: range 6 to 13 years Gender: included boys and girls (numbers not reported) Culture: children with myopia and near point esophoria identified from medical records and referred by local optometrists Inclusion criteria: (1) at least 0.50 D of myopia in both principal meridians of both eyes; (2) ages 6 to 13.99 years for boys and 6 to 12.99 years for girls; (3) near point esophoria; (4) corrected acuity of at least 20/25 in each eye, distance and near, with SVLs; (5) ability to respond to subjective tests Exclusion criteria: (1) strabismus; (2) astigmatism greater than 2.00 D in either eye; (3) anisometropia greater than 2 D; (4) convergence insufficiency accompanied by symptoms; (5) diabetes or other systemic disease with potential effects on refractive error; (6) ocular disease other than mild inflammation of the adnexa
Interventions	Bifocals (n = 16): bifocal lenses with +1.25 D addition SVLs (n = 16): single vision lenses Note: prescription changes were made if the spherical equivalent in either eye had changed by 0.50 D
Outcomes	Primary outcomes: • Change in refractive error (spherical equivalent) measured by cycloplegic autorefraction • Change in axial length measured by Humphrey A/B Scan under cycloplegia Measurements taken at baseline and every 6 months for 18 months Unit of analysis: average values of both eyes
Notes	Study dates: not reported Trial registration: not reported

Fulk 1996 *(Continued)*

	Funding source: Northeastern State University Faculty Research Committee (Tahlequah, Oklahoma, USA)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization process was used with reference to Zelen
Allocation concealment (selection bias)	Unclear risk	"The optician kept envelopes containing the assignment and fitted the appropriate glasses at the end of the base-line examination" It was unclear if sequentially numbered, sealed, and opaque envelopes were used.
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"A research assistant who did not know what type of glasses the child wore, measured..." However, the success of masking the examiner was not addressed in the paper
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	32 participants were enrolled; 4 dropped out—2 from each treatment group; does not address reason for dropouts. Analysis is for the 28 remaining participants, so not “intention to treat” in terms of including all enrolled participants for analysis at the end; however, equal dropouts in each arm and patients were analyzed by the group to which they were randomized. It was not stated whether all 28 participants completed all 3 follow-up visits, although it was stated that they completed the study
Selective reporting (reporting bias)	Unclear risk	Refractive error outcome was reported. Axial length outcome (in mm) was plotted against myopia progression in D, but mean values by treatment groups were not given
Other bias	Low risk	None was identified

Fulk 2002

Study characteristics

Methods	Study design: parallel-group RCT and study of variables that may influence myopia progression in children Study centers: 2 (Tahlequah and Tulsa, Oklahoma, USA) Number randomized: 82 children Study follow-up: 30 months Exclusions and losses to follow-up: no exclusions; 7 (8.5%) were lost to follow-up
Participants	Age: mean = 10.7 years (range 6 to 12 years)

Fulk 2002 *(Continued)*

	Gender: 43 boys, 39 girls Culture: children with myopia and near point esophoria recruited locally and through clinics operated by the Cherokee Nation: 58% Caucasian, 29% American Indian, 5% Hispanic, 4% African American, 3% other, 1% Asian/Pacific Islander Inclusion criteria: (1) at least 0.50 D of myopia in both principal meridians of both eyes; (2) ages 6 to 12.99 years for boys and 6 to 11.99 years for girls; (3) near point esophoria; (4) corrected VA of at least 20/25 in each eye at distance and binocularly with SVLs; (5) corrected stereoacuity of at least 40 second arc with SVLs at 40 cm; (6) assent of child and consent to participate Exclusion criteria: (1) strabismus; (2) astigmatism or anisometropia greater than 2.00 D; (3) diabetes or other systemic disease with potential effects on refractive error; (4) ocular disease other than mild inflammation of the adnexa; (5) known history of allergic reaction to proparacaine or tropicamide; (6) history of use of RGPs; (7) current use of bifocals or use within the last year; (8) high myopia of -6.00 D or more for children younger than 9 years or -8.00 D or more for children 9 years or older; (9) inability to respond to subjective testing or hold fixation sufficiently to allow for study measurements
Interventions	Bifocals (n = 42): bifocal lenses with +1.50 D add SVLs (n = 40): single vision lenses Note: prescription changes were made if (1) the spherical equivalent in either eye had changed by 0.50 D, or (2) any combination of sphere or cylinder change could improve the distance acuity by 3 or more letters in either eye
Outcomes	Primary outcome: • Change in refractive error (spherical equivalent) (cycloplegic autorefraction) Secondary outcomes: • Change in axial length (A-scan ultrasonography) • Change in vitreous chamber depth (A-scan ultrasonography) • Changes in cylinder component (J_0 and J_{45}) • Variables associated with myopia progression: parental myopia, season, near point habits, and academic achievement Measurements taken at baseline and every 6 months for 30 months Unit of analysis: average values of both eyes
Notes	Study dates: enrollment between August 20 and October 15, 1996; original follow-up was for 30 months; some children remained for 54 months Trial registration: NCT00000128 Funding source: National Eye Institute, National Institutes of Health Notes: study was also known as the Myopia Progression Study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized permuted block design was used with separate number sequences for each of the 2 sites stratified by gender to assign participants in approximately equal allocation to the 2 treatments.

Fulk 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	"Sealed envelopes containing the treatment assignments were maintained at each site and opened by the optician after a subject was enrolled" It was unclear whether opaque envelopes were used.
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"A research assistant who did not know what type of glasses the child wore, measured..." However, the success of masking the examiner was not addressed in the paper
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	"This is an intention-to-treat analysis, with all subjects being classified according to their original treatment assignment - disregarding the fact that many discontinued that mode of correction during the last year" Seven participants did not complete the study: 6 of 42 were randomized to bifocals (2 died, 1 drowned, and 1 died in an auto accident; 4 were "unwilling"), and 1 of 40 were randomized to SVL (participant moved). "In a secondary analysis, estimates of myopia progression were imputed for children who did not complete the study; each subject who left the study prematurely was assumed to have myopia progression equal to that of mean progression observed in the SVL group for the time period for which their data were missing." This weakened the treatment effect
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were reported a priori
Other bias	Low risk	None was identified

Han 2018

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (Affiliated Yixing People Hospital of Jiangsu University) Number randomized: 240 children Study follow-up: 1 year Exclusions and losses to follow-up: none
Participants	Age: mean = 9.8 years (range 9 to 14 years) Gender: 117 boys, 123 girls Culture: China Inclusion criteria: children with myopia treated in the study authors' hospital Exclusion criteria: not reported

Han 2018 *(Continued)*

Interventions	OFG (n = 90): ordinary frame glasses M-OK lenses (n = 90): Mouldway orthokeratology lenses; described as "four-district seven-arc reverse geometric design. The main component is Boston XO (Bausch + Lomb, USA [Hexafocon A, main component fluorosiliconepropenylphenol ester]) and the standard piece was the Mouldway IV-DF type" ML (n = 60): Medcall lenses (ML) "fitted with a new paracentral defocus-reducing lens" Note: none
Outcomes	Primary outcome: • Outcomes not clearly specified as primary or secondary. Outcomes reported included "diopter, accommodative lag, and accommodative facility" Secondary outcome: • Not reported Measurements taken at 1 year Unit of analysis: individual (1 eye per person enrolled)
Notes	Study dates: between May 2013 and May 2015 Trial registration: not reported. Funding source: "the authors have no funding or conflicts of interest to disclose"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment before randomization was not reported
Masking of participants (performance bias)	Unclear risk	Masking of participants was not possible because of the nature of the interventions. Masking of study personnel was not reported
Masking of outcome assessors (detection bias) Progression of myopia	Unclear risk	Masking of outcome assessors was not reported
Masking of outcome assessors (detection bias) Secondary outcomes	Unclear risk	Masking of outcome assessors was not reported
Masking of data analyzers	Unclear risk	Masking of data analyzers was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	No details on attrition were provided; all participants seem to have been analyzed
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper

Han 2018 *(Continued)*

Other bias	Low risk	None was identified

Hasebe 2008

Study characteristics	
Methods	Study design: cross-over RCT Study center: 1 (Okayama University Medical School) Number randomized: 92 children Study follow-up: 3 years Exclusions and losses to follow-up: no exclusions; 6 (6.5%) were lost to follow-up
Participants	Age: mean = 9.85 years (range 6 to 12 years) Gender: 47 boys, 45 girls Culture: Okayama, Japan Inclusion criteria: (1) age 6 to 12 years; (2) spherical equivalent refractive error between -1.25 D and -6.00 D in both eyes, as measured by noncycloplegic autorefraction; (3) best-corrected VA of 20/20 or better in each eye; (4) no other eye disease; (5) experience wearing spectacles; (6) willingness to wear glasses constantly and attend follow-up visits; (7) acceptance of randomization Exclusion criteria: (1) astigmatism > 1.50 D in both eyes; (2) anisometropia > 1.50 D; (3) manifest strabismus; (4) birth weight < 1250 g; (5) heterotropia or severe ophthalmic disease that may affect refractive development; (6) previous use of PALs or contact lenses
Interventions	PALs (n = 46): 18 months wearing PALs (add +1.50 D), followed by 18 months wearing SVLs SVLs (n = 46): 18 months wearing SVLs, followed by 18 months wearing PALs (addition +1.50 D) Note: prescription changes were made if corrected distance visual acuity was less than 20/30 in at least 1 eye
Outcomes	Primary outcome: • Progression of myopia measured by cycloplegic autorefraction Secondary outcomes: • Noncycloplegic autorefraction • Noncycloplegic subjective refraction • Cycloplegic subjective refraction • Distant vision and myopia place • Corrected distant vision • Lags of accommodation measured by noncycloplegic, open-field autorefraction • Near point of accommodation • Reaction of accommodation by open-field autorefraction Measurements taken at baseline and every 6 months for 3 years Unit of analysis: child-based (mean of both eyes or right eye only)
Notes	Study dates: enrolled July 2002 to June 2003

Hasebe 2008 *(Continued)*

	Trial registration: ISRCTN28611140 Funding source: Japanese Ministry of Education, Culture, Sports, Science and Technology, and Megane Tanaka Chain, Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated to Group 1 or Group 2 by drawing lots. “Participants drew lots (number of 1-80 was described in each card) at initial inspection and participant number was randomly decided” (Hasebe 2002)
Allocation concealment (selection bias)	Low risk	Physicians conducting examinations did not know the allocation. Participants drew lots from numbered cards; then the principal investigator and 3 opticians determined allocation based on the number drawn (Hasebe 2002)
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	The examiners collecting data or prescribing spectacles were masked to lens assignment
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Low risk	Methods paper stated that the statistician was masked to lens assignments (Hasebe 2002)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	"Only six children, two in group 1 and four in group 2, failed to return for the final visit. The reasons for being lost to follow-up or excluded from the analysis included a problem in using cycloplegic eye drops (two children), moving to another prefecture (two children), desire to wear contact lenses (one child), or the occurrence of exotropia (one child)"
Selective reporting (reporting bias)	Low risk	All outcomes published a priori in the design paper were reported in the results papers
Other bias	High risk	Design-specific risk of bias: cross-over trial. Four children dropped out during the second study period The study was partially funded by a company that produces the types of lenses being investigated

Hasebe 2014

Study characteristics

Methods	Study design: parallel-group RCT Study centers: 3 (Okayama University Medical School, Japan; Eye Hospital of Wenzhou Medical College, China; Eulji University, South Korea) Number randomized: 197 children (120 from China and 77 from Japan) Study follow-up: 2 years

Hasebe 2014 *(Continued)*

	Exclusions and losses to follow-up: the trial in South Korea was terminated after 12 months due to protocol violation and the data were not included; 28/197 (14%) did not complete 2 years of follow-up
Participants	Age: mean = 10 years (range 6 to 12 years) Gender: 95 boys, 74 girls Culture: Chinese and Japanese children Inclusion criteria: (1) age 6 to 12 years; (2) spherical equivalent refractive error between -0.50 D and -4.50 D; (3) astigmatism ≤ 1.50 D; (4) anisometropia ≤ 1.50 in spherical or cylindrical error; (5) best-corrected visual acuity of 6/9 (20/30) or better in each eye; (6) normal ocular and general health; (7) willingness to wear spectacle lenses continuously; (8) willingness and ability to tolerate cycloplegia; (9) informed parental consent Exclusion criteria: (1) amblyopia or manifested squint; (2) history of rigid contact lens or bifocal contact lens wear; (3) use of bifocal or progressive lenses or other myopia treatment in previous 12 months; (4) abnormal binocular function; (5) vestibular disorders or motor imbalance; (6) any systemic condition affecting refractive development or vision, or any condition precluding adherence to the study protocol (e.g. not available for follow-up for 2 years)
Interventions	PA-PALs +1.0 D (n = 67): positively aspherized progressive addition lenses with +1.00 D add PA-PALs +1.5 D (n = 63): positively aspherized progressive addition lenses with +1.50 D add SVLs (n = 67) Note: all lenses are worn during normal waking hours
Outcomes	Primary outcomes: • Refractive error, measured by cycloplegic autorefraction • Axial length, measured by IOL Master (Carl Zeiss Meditec) Secondary outcome: peripheral refractive error, measured using an open field autorefractor Measurements taken at baseline and at 6, 12, 18, and 24 months Unit of analysis: eye (both eyes of each child analyzed)
Notes	Study dates: between July 2008 and June 2009 Trial registration: ACTRN12608000566336 Funding source: "supported by Carl Zeiss Vision" Conflict of interest: "S. Hasebe, Carl Zeiss Vision Australia Holdings Ltd. (F); J. Jun, Carl Zeiss Vision Australia Holdings Ltd. (F); S.R. Varnas, Carl Zeiss Vision Australia Holdings Ltd. (E), P"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"One of the authors (unmasked investigator) made a lens allocation table by using the Microsoft Excel (Microsoft, Redmond, WA, USA) function 'INT(RAND()*2.99),' which was used to generate random integers between 0 and 2. These numbers denote each lens design. This page was refreshed to change the seed of the RAND function until the allocation ratio was approximately 1:1:1"
Allocation concealment (selection bias)	Low risk	"The results were copied and pasted as values into a new spreadsheet (master allocation table). The masked investigator at each study center sent prescrip-

Hasebe 2014 *(Continued)*

		tions with the subject ID to the unmasked investigator who, in turn, assigned the lens design from the master allocation table according to the subject ID and placed the order with the Zeiss surfacing laboratory"
Masking of participants (performance bias)	Unclear risk	"Enrolled children and their parents were not told of their group allocation; we emphasized the importance of full-time proper wear of the assigned spectacles, as if they were wearing PA-PALs" "However, the rate of unmasking and its potential impact on the study results are not known"
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"All lenses had semivisible engravings indicating the lens design, but no masked investigator or optician having direct contact with the participants was allowed to check the engravings or was told their meaning. However, the rate of unmasking and its potential impact on the study results are not known"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Same outcome assessors as primary outcome
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	All children at 1 site were excluded. Only those who completed 2-year follow-up at the remaining 2 sites were included in the analysis; 9 (13.4%) children in PA-PALs +1.0 D group, 12 (19.0%) in the PA-PALs +1.5 D group, and 7 (10.4%) in the control group did not complete the study; 23 (19%) children from China and 5 (6%) from Japan discontinued due to complaint (10 children), moving to another city (4), refusal to undergo cycloplegia (2), loss to follow-up (2), inability to adapt the test lenses (1), or unknown (5)
Selective reporting (reporting bias)	Low risk	All outcomes specified prospectively on a clinical trials registry were reported
Other bias	High risk	Children were randomized and both eyes were analyzed without appropriate methods to account for within-person correlation. Study was funded by the manufacturers of the lenses under investigation

Houston Study 1987

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (University of Houston, Texas, USA) Number randomized: 207 children Study follow-up: 3 years Exclusions and losses to follow-up: 83 (40%) children were excluded from or dropped out of the study
Participants	Age: range 6 to 15 years Gender: 58 boys and 66 girls completed the study Culture: children were recruited from patients, from family members of faculty and staff, and from the racially diverse Houston community

Houston Study 1987 *(Continued)*

	Inclusion criteria: (1) myopia of -0.25 D in one or both eyes; (2) ages 6 to 15 years; (3) best corrected VA of 20/20 or 20/15; (4) normal ocular health; (5) ability to provide informed consent Exclusion criteria: (1) strabismus or amblyopia; (2) contact lens wearers; (3) astigmatism of 2.00 D or more; (4) particularly high or low gradient AC/A ratios
Interventions	Bifocals 1: bifocal lenses with +1.00 D addition Bifocals 2: bifocal lenses with +2.00 D addition SVLs Note: prescription changes were made if (1) there was a change in spherical power of 0.50 D or more in one or both eyes, or (2) there was an improvement of one line of visual acuity. One participant was allowed to wear contact lenses when playing basketball
Outcomes	Patient care team outcomes (unmasked): • Change in refractive error (spherical equivalent, noncycloplegic subjective refraction) • Characteristics of patients for whom bifocals were most effective in reducing the progression of myopia Evaluation team outcomes (masked): • Change in refractive error (cycloplegic retinoscopy, noncycloplegic autorefraction, and cycloplegic autorefraction) • Change in corneal refracting power • Change in anterior chamber depth • Change in lens radii of curvature and thickness • Change in vitreous chamber depth • Change in axial length of the eye Measurements taken at baseline and every 6 months for 3 years Unit of analysis: data from right eyes
Notes	Study dates: "subjects were admitted to the study over a period of 20 months, in five 'accrual groups.' The first group of subjects entered the study in February, 1981 and completed the study in February, 1984, whereas the last group of subjects entered the study in October, 1982," and completed the study in October, 1985 Trial registration: not reported Materials: bifocals were executive 1-piece lenses in CR-39 plastic (American Optical Corporation); SVLs were polycarbonate lenses (Gentex Corporation)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Placed in treatment group "on basis of a table of random numbers" via block randomization technique
Allocation concealment (selection bias)	Unclear risk	Allocation was done via a random numbers table, but it was unclear whether and how the allocation was concealed before randomization
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied

Houston Study 1987 *(Continued)*

Masking of outcome assessors (detection bias) Progression of myopia	High risk	This study involved a team of masked observers (evaluation team) and a team of unmasked observers (patient care team). The results presented in the final analysis are from the unmasked group
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Evaluation team members collecting the data were masked
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	Patients were dismissed for "noncompliance" and some were fitted with contact lenses without letting study personnel know, so they were also dropped. Participants who did not return and those who moved were dropped. Out of 207 enrolled, 83 (40%) dropped out. It is not clear from which treatment groups the dropouts came. Incomplete data were reported as only 60% remained in the study
Selective reporting (reporting bias)	High risk	Results were not reported for evaluation team measurements or for other secondary outcomes outlined in the design paper. The methods paper stated that an evaluation team report would be based on (1) cycloplegic retinoscopy, (2) noncycloplegic autorefraction, and (3) cycloplegic autorefraction performed by masked examiners. However, these were never reported in the outcome paper. Secondary outcomes, including axial length, were never reported in the outcome paper
Other bias	Low risk	None was identified

Jensen 1991

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (Odense University Hospital, Denmark) Number randomized: 159 children Study follow-up: 2 years Exclusions and losses to follow-up: 4 (2.5%) children who were randomized were excluded from the analyses; 16 (10%) were lost to follow-up
Participants	Age: mean = 10.9 years Gender: 87 boys, 72 girls Culture: medical records of children from schools in Odense, Denmark, were screened for myopia (n = 8769). Possible cases of myopia underwent a primary examination (n = 1216). Myopic children with at least -1.0 D in either eye, and in 2nd to 5th grades, were examined at the eye clinic (n = 361). Children meeting inclusion/exclusion criteria at the eye exam were mailed invitations to participate in the trial (n = 227) Inclusion criteria: (1) in 2nd to 5th grades at screening; (2) myopia with spherical equivalent refractive error between -1.25 D and -6.00 D in both eyes; (3) normal corrected vision; (4) Danish parents; (5) affirmative response to mailed invitation for study Exclusion criteria: (1) unilateral myopia; (2) eye disease or general illness, especially heart/lung disease; (3) experience in pilot study

Jensen 1991 *(Continued)*

Interventions	Bifocals (n = 57): constant wear of bifocals with +2.0 D addition to upper edge of reading segment Timolol (n = 51): 1 drop of 0.25% timolol maleate in each eye twice daily and constant wear of SVLs for corrected visual acuity ≥ 0.8 Control (n = 51): constant wear of SVLs for corrected visual acuity ≥ 0.8 Note: participants were permitted to wear their own SVLs if corrected visual acuity was ≥ 0.8
Outcomes	Primary outcomes: • Rate of myopia progression and changes in refractive components (spherical equivalent measured by cycloplegic autorefraction) • Prevention or delay of myopia with bifocals • Prevention or delay of myopia with pressure-lowering eye drops Secondary outcomes: • Changes in the fundus • Intraocular pressure • Phoria status • Accommodation • Close work • Body growth Measurements taken at baseline and every 6 months for 2 years Unit of analysis: right eyes and left eyes analyzed separately
Notes	Study dates: screening January to April 1983; eye clinic exams October 1984 to April 1985 Trial registration: not reported Notes: children who chose not to participate in the study (n = 44) did not statistically differ from those examined with regard to age and degree of myopia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization based on age, sex, and refractive error. Intervention and control groups were made by completing cells based on 3 age categories, 3 refractive error categories, and 2 gender groups (3 x 3 x 2 = 18 cells). Participants were assigned to each cell after baseline examinations
Allocation concealment (selection bias)	Unclear risk	For each cell, the children in groups of 3 were allocated to study groups by drawing numbers 1 to 6 for the first assignment. The second and third assignments were dependent on the first assignment. It was unclear how allocation was concealed before randomization.
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	High risk	Masking was not reported, but there was only 1 study investigator
Masking of outcome assessors (detection bias)	High risk	Primary and secondary outcomes were assessed by the same examiner

Jensen 1991 *(Continued)*
Secondary outcomes

Masking of data analyzers	Unclear risk	Data were analyzed by the study investigator
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	159 children were enrolled: 51 SVLs, 57 bifocals, 51 timolol. At the first year visit, 13 (8%) children were excluded or lost to follow-up: 1 patient given contact lenses was excluded and 1 patient dropped out from the control group; 6 patients dropped out from the bifocal group (3 because they could not adapt to the bifocals); and 2 patients were excluded and 3 dropped out from the timolol group. At the second year visit, an additional 7 (4.5%) children were excluded or lost to follow-up: 1 patient given contact lenses was excluded from the control group; 3 patients dropped out from the bifocal group because they could not adapt to the bifocals; and 3 dropped out from the timolol group
Selective reporting (reporting bias)	High risk	The methods section of the article described that results would be discussed only if exceptional
Other bias	Low risk	None was identified

Katz 2003

Study characteristics	
Methods	Study design: parallel-group RCT, with 3-month adaptation period Study center: 1 (Myopia Clinic of the Singapore Eye Research Institute) Number randomized: 564 children (428 children attended initial visit; 383 children completed the adaptation period) Study follow-up: 2 years Exclusions and losses to follow-up: 136 (24%) children who were randomized did not attend the initial visit, and 45 (8%) more did not complete the adaptation period; 86 (22%) of the 383 children who completed the adaptation period were lost to follow-up
Participants	Age: mean = 8.3 years (range 6 to 12 years) Gender: 204 boys, 179 girls Culture: Singaporean children with Chinese ethnicity Inclusion criteria: (1) age 6 to 12 years; (2) myopia with spherical equivalent refractive error between -1.0 D and -4.0 D; (3) Chinese ethnicity; (4) provided informed consent Exclusion criteria: (1) astigmatism > 2.0 D; (2) previous contact lens wear; (3) other ocular pathologies Note: all participants were provided a 3-month period to adapt to assigned intervention
Interventions	Contact lenses (n = 158): RGPCLs worn daily for at least 8 hours per day Spectacles (n = 225): SVLs worn daily for at least 8 hours per day Note: prescription changes were made if corrected visual acuity fell below 20/40
Outcomes	Primary outcome: • Change in refractive error (spherical equivalent) Measured by subjective cycloplegic refraction from post adaption through 2 years of follow-up

Katz 2003 *(Continued)*

	Secondary outcomes: • Change in keratometry (autokeratometry) • Change in axial length (A-scan ultrasonography) Measurements taken at baseline and every 3 months over a 24-month period Unit of analysis: only data from right eyes reported
Notes	Materials: Asian Design Lens, Baush and Lomb, Rochester, New York, USA Trial registration: not reported Adherence to treatment was measured for children and parents (agreement was almost 100%) and was defined as use of contact lenses or spectacle use for at least 8 hours per day, 7 days per week Notes: study is also known as the Contact Lens-Myopia Treatment Study (CL-MTS) Additional data: study author provided unpublished data via email correspondence

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization schedule of block size 6, generated from random number tables in Baltimore, USA
Allocation concealment (selection bias)	Unclear risk	Assignments were placed in sealed envelopes with sequential patient numbers. It was unclear whether the opaque envelopes were used.
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	High risk	Clinical observers were not masked to treatment group
Masking of outcome assessors (detection bias) Secondary outcomes	High risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	The data analyst was not masked (via email communication with study author)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Unclear risk	Of the 564 children randomized, 297 (53%) completed the study. There were 86 (22%) children who completed the adaptation period who were lost to follow-up or censored from the study for not attending the final study visit. Statistical comparisons between those lost to follow-up and those who completed the study showed "a higher proportion of girls in the contact lens (59%) than spectacle group (42%) completed the study (P = 0.004)." It was also reported that "axial length and astigmatism were similar between the treatment groups that completed the study, but the contact lens group that completed the study had 0.3 diopters more myopia at baseline than did those in the spectacle group that completed the study (P = 0.003)."
Selective reporting (reporting bias)	High risk	Although all outcomes identified in the study methods were reported, it is unclear why some participants were not included in the analyses. 105 RGPCL and 192 SVL wearers should be examined over 2 years, but only 97 RGPCL and 188 SVL wearers were included in the analyses

Katz 2003 *(Continued)*

Other bias	High risk	Unequal loss to follow-up; imbalance in gender, corneal curvature, and refractive error at baseline visit (controlled for in analyses); many participants lost from study before they were examined for outcomes

Koomson 2016

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (Kumasi, Ghana) Number randomized: 150 children Study follow-up: 24 months Exclusions and losses to follow-up: 1 child in the fully corrected group dropped out before the 24-month visit
Participants	Age: mean = 12.39 years (range 10 to 15 years) Gender: 60 boys, 90 girls Culture: recruited from "eight purposively chosen high socioeconomic schools in the Kumasi metropolis" in Ghana Inclusion criteria: (1) healthy children, ages 10 to 15 years; (2) spherical equivalent -1.25 to -4.50 D as measured by cycloplegic refraction; (3) visual acuity of 0.20 logMAR or worse with habitual spectacles and logMAR 0.00 or better with full correction; (4) willingness to wear study spectacles only and to wear them during waking hours Exclusion criteria: (1) strabismus; (2) amblyopia; (3) astigmatism over 1.25 D; (4) anisometropia over 1.00 D; (5) parental myopia; (6) allergy to cycloplegic agents; (7) use of multifocal optical lenses or pharmacological agents; (8) history of contact lens wear
Interventions	Undercorrected group (n = 75): SVLs blurred by +0.50 D Fully corrected group (n = 75): SVLs Note: changes in prescription were made if refraction had changed by at least 0.50 D for 1 or both eyes
Outcomes	Primary outcome: • Change in refractive error (spherical equivalent) measured by cycloplegic autorefraction at 24 months of follow-up Secondary outcomes: • Change in axial length at 24 months of follow-up • Correlation between baseline accommodative lag and SER changes at 24 months and between average lag (average of the 6th, 12th, 18th, and 24th months near lags) and SER changes at 24 months Measurements taken at 6-month intervals for 2 years Unit of analysis: child-based (right eye)
Notes	Study dates: enrollment September 2010 to March 2011 Trial registration: not reported Funding source: not reported

Koomson 2016 *(Continued)*

Disclosures of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Subjects for the study were matched in cells derived by using randomized block design based on three criteria (age, sex, and school) as suggested by Chung et al. The study design comprised three age groups (10-11, 12-13, and 14-15 years), created from the ages of the subjects recorded at baseline; two gender categories; and four schools. In total, 24 different cells of at most 10 members (due to the matched design, cells had even number of members starting from 4 to 10) were formed. In each block, numbers generated from random tables and placed in sealed envelopes with sequential patient identification numbers were used to pair the children. A coin was then tossed to separate each pair into either a control group (FC) or the treatment group (UC). After tossing the coin, if a head came up, the first subject in the pair was assigned to UC and the second to FC. On the contrary, if a tail came up, the first subject was allocated to FC and the second to UC"
Allocation concealment (selection bias)	Unclear risk	Used sealed envelopes and randomized subsequent to enrollment. It was unclear whether the opaque envelopes were used.
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to performance differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"During all examinations, the optometrist who took all measurements was not aware of the treatment group the child belonged and no child was supposed to discuss any problem on the spectacles with the optometrist"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	"During all examinations, the optometrist who took all measurements was not aware of the treatment group the child belonged and no child was supposed to discuss any problem on the spectacles with the optometrist"
Masking of data analyzers	Unclear risk	Masking of data analyzers was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	"Follow-up data were analyzed using an intent-to-treat principle according to the child's original lens assignment and the last measured value of the outcome measures"
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Low risk	None was identified

Lu 2015

Study characteristics

Methods	Study design: parallel-group RCT Study center: 1 (Guangzhou Red Cross Hospital, School of Medicine, Jinan University, China) Number randomized: 80 children Study follow-up: 1 year

Lu 2015 *(Continued)*

	Exclusions and losses to follow-up: not reported
Participants	Age: mean = 11.21 years (range 9 to 14 years) Gender: 43 boys, 37 girls Culture: Chinese Inclusion criteria: (1) age 9 to 14 years; (2) progressive (0.50 D or more change) myopia from -1.00 to -5.00 D; (3) astigmatism with 1.50 D or less with-rule, 0.75 D or less against-rule; (4) best-corrected visual acuity 1.0 or better in both eyes by Snellen chart; (5) ocular pressure less than 21 mmHg; (6) compliance with examination and treatment Exclusion criteria: (1) other ocular condition (glaucoma, cataract, iritis, congenital small cornea, keratoconus, fundus lesions, congenital amblyopia, dominant strabismus); (2) family history of hereditary eye disease (e.g. high myopia, Leber disease); (3) recent or current use of drugs that may affect myopia development; (4) previous RGP wear; (5) other systemic disease (diabetes, Marfan syndrome, albinism, severe sinusitis, etc.)
Interventions	Mid-periphery additional lenses (n = 40): addition up to +2.50 D and adjustment training SVLs (n = 40): frame glasses
Outcomes	Primary outcomes: • Change in visual acuity • Change in diopter • Change in axis length • Accommodation amplitude • Adjustment reaction index • AC/A value Secondary outcomes: • Not distinguished Measurements taken every 3 months for 1 year Unit of analysis: eye (both eyes of each child analyzed)
Notes	Study dates: January 2014 to July 2015 Trial registration: not reported Funding source: Guangdong Medical Science and Technology Research Foundation (No. A2014557); Department of Ophthalmology, Guangzhou Red Cross Hospital Affiliated to School of Medicine, Jinan University, China

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomly divided into two groups: treatment group and control group, 40 cases in each group"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment before randomization was not reported
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to functional differences between the interventions studied

Lu 2015 *(Continued)*

Masking of outcome assessors (detection bias) Progression of myopia	Unclear risk	Masking was not reported
Masking of outcome assessors (detection bias) Secondary outcomes	Unclear risk	Masking was not reported
Masking of data analyzers	Unclear risk	Masking was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	No attrition was reported
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	High risk	Children were randomized and both eyes were analyzed without appropriate methods to account for within-person correlation

MIT Study 2001

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (National Taiwan University Hospital vision care center) Number randomized: 227 children Study follow-up: 18 months Exclusions and losses to follow-up: 39 (17%) children were excluded or lost to follow-up
Participants	Age: range 6 to 13 years Gender: 105 boys, 122 girls Culture: school children in Taiwan with an average myopia of -3.27 D Inclusion criteria: (1) age 6 to 13 years; (2) provided informed consent; (3) willing to wear glasses; (4) available for follow-up period Exclusion criteria: (1) tropia or amblyopia; (2) increase of more than 2 D in any eye during the treatment period
Interventions	SVLs (n = 76): regular SVLs worn all the time and placebo drops PALs (n = 75): multifocal lenses with the near addition part for reading and placebo drops PALs plus atropine (n = 76): 0.5% atropine instilled once a day at bedtime, in addition to PALs Note: an intervention group given atropine and SVLs was omitted from the study design because difficulty while reading due to the intervention would have induced poor compliance. Prescription changes were made for any child whose refractive error increased by more than 0.75 D
Outcomes	Primary outcome:

MIT Study 2001 *(Continued)*

	• Myopic progression measured by cycloplegic autorefraction (spherical equivalent) Secondary outcomes: • Change in IOP (Tonopen) • Change in biometric axial length (A-scan ultrasonography) • Change in corneal radius (autorefraction) Measurements taken at baseline and every 3 months over an 18-month period Unit of analysis: data from right eyes analyzed
Notes	Study dates: 1997 to 2000 Trial registration: not reported Materials: HOYALUX3 plastic lenses were used for PALs; polycarbonate plastic lenses were used for SVLs Additional data: study author provided unpublished data via email correspondence

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratification was based on age (younger than 9.5 years or not), sex (boy or girl), and myopic severity (more than -4.0 D for both eyes or not) at the baseline visit. This resulted in the total of 8 strata. Each participant was categorized into 1 of the strata and then was randomized to receive 1 of the 3 treatments. A block size of 9 was used to balance the number of patients in the 3 treatment categories for each stratum (via email communication with study author)
Allocation concealment (selection bias)	Low risk	Group assignments were unknown to study personnel when participants were being enrolled by using coded bottles with sealed envelopes (via email communication with study author)
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	Ophthalmologists were masked, and it would be improbable to guess patients' treatment by examining the pupils because the ocular examination was performed only after the cycloplegic agent was given to each patient at each visit (via email communication with study author)
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Ophthalmologists (outcome assessors) were masked (via email communication with study author)
Masking of data analyzers	Low risk	Data analysts were masked (via email communication with study author)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	Attritions were reported by group: atropine, n = 10 (13%); PALs, n = 14 (19%); SVLs, n = 15 (20%). Reasons for attrition were poor follow-up, switching to contact lenses, poor compliance, myopic progression greater than 2.00 D per year (1 patient from the PAL group and 1 from the SVL group), and loss to follow-up with no specified reason
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Low risk	None was identified

Pärssinen 1989

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (outpatient clinic of the Central Hospital of Central Finland) Number randomized: 240 children Study follow-up: 3 years Exclusions and losses to follow-up: 1 (0.4%) child who was randomized was excluded from the analyses; 2 (0.8%) were lost to follow-up
Participants	Age: mean = 10.9 years (range 8.8 to 12.8 years) Gender: 119 boys, 121 girls Culture: schoolchildren with suspected myopia were referred by school nurses and doctors after routine vision check-ups Inclusion criteria: (1) in 3rd to 5th grade; (2) myopia with spherical equivalent refractive error between -0.25 D and -3.0 D in both eyes and ≥ -0.50 D in the worst eye; (3) corrected VA of 6/6 or better in both eyes Exclusion criteria: (1) astigmatism > 2.0 D; (2) anisometropia > 2.0 D; (3) manifest strabismus; (4) horizontal phorias more than -10 or +9 Δ or vertical more than 1 Δ; (5) previous use of spectacles for myopia; (6) eye disease or serious general disease; (7) plans to move out of the area in the near future or the child not wanting to have spectacles
Interventions	Distant use (n = 80): minus lenses with full correction to be used for distant vision only; advised to read at greatest distance possible Bifocals (n = 80): clear plastic bifocal lenses with +1.75 D addition for continuous use Continuous use (n = 79): minus lenses with full correction for continuous use; advised to remove spectacles only if there was danger of breaking them Note: prescription changes were made if corrected visual acuity fell below 20/40
Outcomes	Primary outcome: • Change in spherical equivalent (subjective cycloplegic refraction) Secondary outcomes: • Change in spherical refraction • Change in visual acuity • Change in astigmatism • Change in reading distance Measurements taken at baseline and annually for 3 years Unit of analysis: right eyes and left eyes analyzed separately
Notes	Study dates: enrollment March 1983 to April 1985 Trial registration: not reported Funding source: Academy of Finland

Pärssinen 1989 *(Continued)*

	Compliance was measured by questionnaires and patients were classified as compliant, partly compliant, or noncompliant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random, sex-stratified codes were used
Allocation concealment (selection bias)	Unclear risk	Treatment assignments were sealed in envelopes, but it was unclear whether opaque envelopes were used.
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	High risk	The ophthalmologist did not look at the group assignment before the examination, but often, for different reasons, the group was revealed. The 3-year examinations were conducted by 2 different ophthalmologists, 1 of whom did not know the group assignments
Masking of outcome assessors (detection bias) Secondary outcomes	High risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	"After allocation one of the boys in the continuous use group was excluded from comparison with the other treatment groups when we found that his sister has been included previously in a different group. Two children moved from the area, and their refraction values could not be obtained" The remaining participants were analyzed by their original treatment assignments
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in a study design paper
Other bias	Low risk	None was identified

PIR-205 Study 2004

Study characteristics

Methods	Study design: parallel-group RCT Study centers: 13 (US academic clinics and private practices) Number randomized: 174 children Study follow-up: 1 year (planned), plus 1 year extension Exclusions and losses to follow-up: 27 (15.5%) children who were randomized were excluded from the analyses; 2 (1%) were lost to follow-up
Participants	Age: mean = 9.9 ± 1.3 years (range 8 to 12 years) Gender: 71 boys, 103 girls

PIR-205 Study 2004 *(Continued)*

	Culture: children from US cities of study centers: 73% white, 7% black, 4% Asian, 12% Hispanic, 4% other Inclusion criteria: (1) age 8 to 12 years; (2) myopia of -0.75 D to -4.00 D; (3) best-corrected VA of 20/25 or better; (4) normal pupils; (5) good general health Exclusion criteria: (1) anisometropia or astigmatism greater than 1.00 D; (2) any manifest tropia; (3) current use of either contact lenses or bifocals; (4) history of ocular surgery, trauma, or chronic ocular disease, including allergic conjunctivitis; (5) disease requiring long-term or regular intermittent medication; (6) behavioral or neurological disorder that would interfere with the study; (7) participation in any study that involved an investigational drug within 1 month of enrollment; (8) intolerance or hypersensitivity to topical anesthetics, mydriatics, or components of the formulations; (9) contraindications to antimuscarinic agents; (10) pregnancy or planned pregnancy
Interventions	Pirenzepine (n = 117): 2% pirenzepine ophthalmic gel applied twice a day Control (n = 57): vehicle-placebo gel applied twice a day
Outcomes	Primary outcome: • Change in refractive error measured by cycloplegic autorefraction (spherical equivalent) Secondary outcome: • Change in axial length measured by A-scan ultrasonography Measurements taken at baseline and every 3 months for 1 year Unit of analysis: average of both eyes
Notes	Study dates: March 1, 2000 to February 28, 2002 Trial registration: not reported Funding source: Valley Forge Pharmaceuticals, Inc. Notes: study is also known as the Collaborative Assessment of Myopia Progression with Pirenzepine (CAMPP) study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible patients were randomized via a sponsor-prepared, computer-generated list stratified by site. Randomization was done at a 2:1 ratio of pirenzepine to placebo
Allocation concealment (selection bias)	Low risk	"Eligible patients were randomized via a sponsor-prepared, computer-generated list stratified by site...Study sites used coded lists to determine which tube of medication to administer to the next enrolled subject. The pirenzepine gels and placebo gels were packaged in identical tubes and the gels themselves appeared identical. Thus study personnel had no way of knowing which tubes had which medications, same for patients" (SC)
Masking of participants (performance bias)	Low risk	Study was placebo-controlled, and identical bottles with coded labels were distributed
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"Since the pirenzepine gels and placebo gels were packaged in identical tubes and the gels themselves appeared identical, the study personnel had no way of knowing which tubes had which medications" (SC)

PIR-205 Study 2004 *(Continued)*

Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	Data analyzers were not masked (personal communication with biostatistician)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	Screened 277 patients and enrolled 174. Attrition was reported: 145 of 174 patients completed the trial. There were significantly more dropouts in the pirenzepine arm: 26/117 (26%), compared with placebo arm: 3/57 (5%). Reasons for dropout included occurrence of adverse events, nonadherence, and loss to follow-up "Additional methods were used to impute missing values due to patients who discontinued the study. In all 3 methods used (last observation carried forward, visit-to-visit extrapolation using median of respective treatment, and visit-to-visit extrapolation using median of placebo group), the treatment effect was similar to or greater than in the primary analysis method"
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were chosen a priori and all were reported
Other bias	Unclear risk	Some study authors were employed by the pharmaceutical company funding the study

ROMIO Study 2012

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (Hong Kong Polytechnic University) Number randomized: 102 children Study follow-up: 2 years Exclusions and losses to follow-up: 24 (24%) children who were randomized (14 in the orthokeratology group and 10 in the control group) were excluded from the analyses, of whom, 9 (8.8%) were lost to follow-up
Participants	Age: mean = 9 years (range 6 to 10 years) Gender: 52 boys, 50 girls Culture: Hong Kong Inclusion criteria: (1) ages 6 to 10 years; (2) myopia between 0.50 D and 4.00 D in at least 1 eye and between 0.50 D and 4.50 D in both eyes; (3) astigmatism < 1.50 D, with-the-rule astigmatism (axes 180 ± 30) ≤ 1.25 D, astigmatism of other axes ≤ 0.50 D in both eyes; (4) anisometropia ≤ 1.50 D); (5) best-corrected logMAR visual acuity 0.10 or better in both eyes; (6) symmetrical corneal topography with corneal toricity < 2.00 D in either eye; (7) agree to randomization Exclusion criteria: (1) strabismus at distance or near; (2) history of contact lens wear or myopia control treatment; (3) contraindication for contact lens wear and orthokeratology; (4) history of ocular surgery, trauma, or chronic ocular disease; (5) concurrent use of medications that may affect tear quality; (6) systemic or ocular conditions that may affect tear quality or contact lens wear or that may affect refrac-

ROMIO Study 2012 *(Continued)*

	tive development; (7) poor compliance with tests; (8) lack of willingness to comply with allocated treatment and follow-up schedule
Interventions	Orthokeratology (n = 51): orthokeratology (ortho-k) lenses SVLs (n = 51): single vision spectacles Participants wore assigned treatment on a daily basis
Outcomes	Primary outcome: • Axial elongation Secondary outcome: • Adverse events Measurements taken at baseline and at 6, 12, 18, and 24 months Unit of analysis: child-based (right eye)
Notes	Study dates: enrollment March 2008 to November 2009 Trial registration: NCT00962208 Funding source: "supported by a collaborative agreement between The Hong Kong Polytechnic University and Menicon Co. Ltd., Japan; contact lenses and solutions and spectacles were sponsored by Menicon Co. Ltd., NKL Contactlenzen B.V., Alcon Hong Kong, Bausch & Lomb Hong Kong, Skyview Optical Co. Ltd., Hong Kong, and Hong Kong Optical Lens Co., Ltd.; and Niche Myopia Funding Grant J-BB7P for facilities at the Centre for Myopia Research"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed in blocks of two using a commercial spreadsheet random number generator (Excel; Microsoft, Redmond, WA)"
Allocation concealment (selection bias)	High risk	"The random allocation sequence was revealed to the unmasked examiner who would proceed to prescribe the assigned treatment to the subjects accordingly"
Masking of participants (performance bias)	High risk	Participants were not masked
Masking of outcome assessors (detection bias) Progression of myopia	Unclear risk	This was not assessed
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	"The primary outcome measure (i.e., the axial length) was masked in the study" Masking of persons measuring adverse events was not reported
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	24 (24%) children who were randomized (14 in the orthokeratology group and 10 in the control group) were excluded from the analyses: 5 children in the orthokeratology group and 1 in the control group due to ocular health problem; 9 children in the orthokeratology group due to poor correction or undercorrection; and 9 children in the control group due to loss to follow-up

ROMIO Study 2012 *(Continued)*

Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Unclear risk	Study was funded by a company producing the lenses under investigation in the study

Sankaridurg 2010

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (Zhongshan Ophthalmic Center, Sun Yet Sen University, China) Number randomized: 210 children Study follow-up: 12 months (study was originally planned to be 2 years in duration) Exclusions and losses to follow-up at 12-month visit: 2 children who were randomized were excluded from the analyses; 7 (3.3%) were lost to follow-up
Participants	Age: mean = 11 years (range 6 to 16 years) Gender: 110 boys, 100 girls Culture: Chinese children in Guangzhou, China Inclusion criteria: (1) age 6 to 16 years; (2) bilaterally myopic (spherical component range from -0.75 D to -3.50 D inclusive) with astigmatism not exceeding -1.50 D and maximum of 1.00 D of anisometropia; (3) vision correctable to 6/9.5 or better in each eye; (4) ocular findings considered to be normal; (5) willingness to wear study spectacles and adhere to the protocol schedule
Interventions	Novel spectacle lens type I (n = 50): a rotationally symmetrical design; featured a clear central aperture of 20 mm diameter, with maximum spherical equivalent of +1.0 D relative peripheral power achieved 25 mm from its axis Novel spectacle lens type II (n = 60): a rotationally symmetrical design; featured a clear central aperture of 14 mm diameter, with maximum spherical equivalent of +2.00 D relative peripheral power achieved 25 mm from its axis Novel spectacle lens type III (n = 50): an asymmetrical design; a clear central aperture extended approximately 10 mm either side of center along the horizontal meridian and a similar distance inferiorly, with positive additional peripheral power of 1.9 D 25 mm from the axis in that meridian SVLs (n = 50): conventional, single vision design Note: lenses were fitted to spectacle frames that ranged in eye-size from 45 mm to 55 mm with depths from 27 mm to 33 mm
Outcomes	Primary outcome: • Cycloplegic autorefraction assessed with an open-field autorefractor Secondary outcome: • Axial length Measurements taken at baseline, 6 months, and 12 months Unit of analysis: average of both eyes

Sankaridurg 2010 *(Continued)*

Notes	Study dates: recruitment October 2007 to January 2009 Trial registration: not reported Funding source: Australian Federal Government; Institute for Eye Research, Sydney, Australia; Vision CRC, Australia Lenses were provided by industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Subjects were randomized to a single treatment using the method of randomly permuted blocks of a constant size of 20" The website randomization.com was used
Allocation concealment (selection bias)	Low risk	Central allocation by web-based randomization was performed: "the four designs (3 novel and one standard) were coded A, B, C, and D and the randomization scheme generated using the website randomization.com (http://www.randomization.com)"
Masking of participants (performance bias)	Unclear risk	Although masking was reported for participants, study authors noted that the novel lenses were substantially different from SVLs. For this reason, 10 additional participants were enrolled for the group allocated to lens type II
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"Access to the study randomization table was restricted to the study optical dispenser who allocated the randomization and coordinated with the laboratory for the delivery of the spectacles. The dispenser was masked to the lens design. Also, the participants and investigators were masked to the spectacle lenses used in the study"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	"Access to the study randomization table was restricted to the study optical dispenser who allocated the randomization and coordinated with the laboratory for the delivery of the spectacles. The dispenser was masked to the lens design. Also, the participants and investigators were masked to the spectacle lenses used in the study"
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	Two children who were randomized were excluded from the analyses, and 7 (3.3 %) were lost to follow-up at 12 months (2 in type I, 1 each in type II and control, and 3 in type III). One child in type II withdrew due to an adverse event, and 1 in type III lenses withdrew consent. They were not included in the analysis, and there was no re-inclusion
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Unclear risk	Study originally was planned for 2 years but was stopped early at 1 year Lenses being investigated were provided by industry

Schwartz 1981

Study characteristics

Schwartz 1981 *(Continued)*

Methods	Study design: parallel-group RCT in twins Study center: 1 Number randomized: 52 children (26 twin pairs) Study follow-up: 3 years (planned), extended 6 months Exclusions and losses to follow-up: 2 (4%) children (1 twin pair) who were randomized were excluded from the study; none were lost to follow-up
Participants	Age: mean = 11.2 years (range 7 to 14 years) Gender: 26 boys (13 twin pairs) and 24 girls (12 twin pairs) completed the study Culture: pairs of monozygotic (MZ) twins identified from the Twin Registry of Eye Examinations from the Washington, DC area; all were Caucasian Inclusion criteria: (1) MZ twins with bilateral myopia; (2) ages 7 to 13 years; (3) shared domicile in local area; (4) good general health; (5) vision correctable to 20/20 or better; (6) third-degree fusion; (7) no other significant abnormality Exclusion criteria: (1) astigmatism or anisometropia greater than 1.00 D; (2) difference in refraction between co-twins of 1.50 D or more in the more advanced eye
Interventions	Treatment group (n = 26): combined treatment of bifocal spectacles with 1.25 D addition and 2 drops of 1% tropicamide ophthalmic solution instilled to each eye nightly Control group (n = 26): standard spectacle correction (SVLs) Note: full cycloplegic correction in the treatment group was sometimes reduced up to 0.50 D when it did not impair vision below 20/20
Outcomes	Primary outcome: • Change in refractive error (spherical equivalent) (cycloplegic refraction) Secondary outcome: • Compliance with treatment regimen (child and parent interviews) Measurements taken at baseline and every 6 months for 3 years Unit of analysis: average values of both eyes
Notes	Study dates: not reported Trial registration: not reported Materials: 1% tropicamide (Mydriacyl) ophthalmic solution supplied by Alcon Laboratories Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The assignment of special treatment or control status to members of each twinship was based on a strict randomization protocol"
Allocation concealment (selection bias)	Unclear risk	"Treatment or control status was randomly assigned only after the twin pair and the parents expressed willingness to accept the rigorous requirements and the desire to participate" does not explain how allocation was concealed.

Schwartz 1981 *(Continued)*

Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"All refractions were performed by the author, who was unaware of the treatment or control status of examinees" However, there was only 1 study investigator, and it was not reported who reviewed participants' activities when they came in for follow-up and how the examiner remained masked at follow-up visits
Masking of outcome assessors (detection bias) Secondary outcomes	Unclear risk	N/A (study did not measure secondary outcomes of this review)
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	Of 26 twin pairs enrolled, 25 pairs completed the study and 1 pair was excluded due to noncompliance after 1 year
Selective reporting (reporting bias)	Low risk	Outcomes were chosen a priori and presented in the methods and design paper
Other bias	Low risk	None was identified

Shih 1999

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (National Taiwan University Hospital) Number randomized: 200 children Study follow-up: 2 years Exclusions and losses to follow-up: 14 (7%) children who were randomized were excluded from the study; none were lost to follow-up
Participants	Age: mean = 9.2 years (range 6 to 13 years) Gender: included boys and girls Culture: children recruited from the vision care center at National Taiwan University Hospital Inclusion criteria: (1) age 6 to 13 years; (2) myopia with refractive error between -0.50 D and -6.75 D Exclusion criteria: (1) amblyopia or tropia; (2) astigmatism -2.00 D or greater; (3) anisometropia -2.00 D or greater
Interventions	Atropine 0.5% (n = 50): 1 drop of 0.5% atropine nightly; advised to wear bifocal spectacles Atropine 0.25% (n = 50): 1 drop of 0.25% atropine nightly; advised to wear slightly undercorrected spectacles Atropine 0.1% (n = 50): 1 drop of 0.1% atropine nightly; advised to wear fully corrective spectacles

Shih 1999 *(Continued)*

	Control (n = 50): 1 drop of 0.5% tropicamide nightly Note: all children were advised to wear sunglasses with UV protection in bright light
Outcomes	Primary outcome: • Change in refractive error measured by cycloplegic autorefraction (spherical equivalent) Measurements taken at baseline and every 3 months for 2 years Unit of analysis: average values of both eyes
Notes	Study dates: 1994 Trial registration: not reported Funding source: Department of Health grant (Taiwan) Additional data: study author provided unpublished data via email correspondence

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization: each participant was categorized into 1 of the strata and then was randomized to receive 1 of the 4 treatments. A block size of 12 was used to balance the number of patients in the 4 treatment categories for each stratum (via email communication with study author)
Allocation concealment (selection bias)	Low risk	Group assignments were unknown to study personnel when participants were being enrolled via coded bottles with sealed envelopes (via email communication with study author)
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to visual and functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	All study personnel, physicians, examiners, and data analysts were masked to treatment assignment (via email communication with study author)
Masking of outcome assessors (detection bias) Secondary outcomes	Unclear risk	N/A (study did not measure secondary outcomes of this review)
Masking of data analyzers	Low risk	All study personnel, physicians, examiners, and data analysts were masked to treatment assignment (via email communication with study author)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	14 (7%) children were excluded from the study: 9 from the 0.5% atropine group (4 had no patience for eye drops, 2 for photophobia, 2 from fear of drops, 1 for allergic blepharitis); 3 from the 0.25% atropine group (no patience for eye drops); 1 from the 0.1% atropine group (no patience for eye drops); and 1 from the 0.5% tropicamide group (no patience for eye drops)
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	High risk	Children were advised to wear different types of spectacle lenses depending on the concentration of atropine received

STAMP Study 2012

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (The Ohio State University College of Optometry) Number randomized: 85 children Study follow-up: 2 years Exclusions and losses to follow-up: 2 (2.3%) children did not complete the study
Participants	Age: mean = 9.8 years (range 6 to 11 years) Gender: 41 boys, 44 girls Culture: Ohio, USA: 20% Black, 68% White, 7% Asian, 5% other Inclusion criteria: (1) 6 to 11 years of age; (2) at least -0.75 D myopia in each meridian measured with cycloplegic autorefraction but not more than -4.50 D in each meridian in each eye; (3) ≥ 1.30 D accommodative lag (4 D stimulus) without correction; (4) esophoria at near if more than -2.25 D spherical equivalent; (5) astigmatism ≤ 2.00 DC in each eye; (6) anisometropia ≤ 2.00 D; (7) best-corrected VA of at least 20/32 logMAR equivalent; (8) birth weight ≥ 1250 g by parental report Exclusion criteria: (1) strabismus; (2) history of contact lens wear or previous bifocal wear; (3) diabetes mellitus
Interventions	PALs (n = 42): PALs with + 2.00 D addition (Varilux Ellipse; Essilor of America, Dallas, TX) SVLs (n = 43) Note: children were randomly assigned to wear either PALs or SVLs for the first year of the study; all children wore SVLs for the second year of the study
Outcomes	Primary outcome: • 1-year change in spherical equivalent refractive error (cycloplegic autorefraction) of the right eye after 1 and 2 years Secondary outcomes: • Axial length • Peripheral ocular shape • Central and peripheral aberrations • Accommodative lag • AC/A ratio • Corneal shape and thickness • Anterior chamber depth • Crystalline lens thickness and curvatures • Phoria • Intraocular pressure Measurements taken at baseline and at 6-month intervals for 2 years Unit of analysis: the individual (right eye only)
Notes	Study dates: study recruitment from December 2006 to May 2008 Trial registration: NCT00335049

STAMP Study 2012 *(Continued)*

	Funding source: National Eye Institute, National Institutes of Health, USA; Essilor of America, Inc.; American Optometric Foundation Ezell Fellowship
	Study name: study of theories about myopia progression (STAMP)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization sequence used random, even block sizes and was generated by the Optometry Coordinating Center at The Ohio State University"
Allocation concealment (selection bias)	Low risk	"Confirmation of eligibility and randomization of children to either SVLs or PALs was administered through a Web portal. A child's group assignment could not be accessed until all required baseline visit data were entered"
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"All outcome data were collected by an examiner masked to the treatment assignment"; "All outcome data were collected by an examiner masked to the treatment assignment. At each visit, subjects were reminded not to talk about their spectacles or vision when the examiner was in the room. The child's spectacles were removed and hidden from view before the examiner entered the room"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Same outcome assessors as for the primary outcome
Masking of data analyzers	Unclear risk	Masking of persons analyzing results was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	2 (2.3%) children did not complete the study and were excluded from the analysis
Selective reporting (reporting bias)	Low risk	Design and baseline data were published; results for all prespecified outcomes were reported
Other bias	Unclear risk	Study was funded by a company producing the PAL lenses under investigation in the study; trial authors were financially compensated by the company

Swarbrick 2015

Study characteristics

Methods	Study design: paired-eye, cross-over RCT
	Study center: 1 (School of Optometry and Vision Science, University of New South Wales, Australia)
	Number randomized: 32 children
	Study follow-up: 12 months (two 6-month periods)
	Exclusions and losses to follow-up: 6 (19%) during first period and 8 (25%) during 12-month study
Participants	Age: mean = 13.4 years (range 8 to 16 years)

Swarbrick 2015 *(Continued)*

	Gender: 14 boys, 12 girls Culture: East Asian ethnicity Inclusion criteria: (1) 8 to 16 years of age; (2) myopic refractive error between -1.00 D and -4.00 D in both eyes with < 0.75 D difference between eyes; (3) evidence of myopic progression in 12 months before enrollment; (4) with-the-rule astigmatism < 1.50 D and no against-the-rule astigmatism; (5) anisometropia ≤ 0.75 D; (6) best-corrected visual acuity of 6/9 or better; (7) East Asian ethnicity; (8) good general and ocular health Exclusion criteria: (1) contraindications for rigid contact lens wear; (2) history of previous rigid contact lens wear; (3) abnormal corneal topography; (4) abnormal binocular function; (5) ocular pathology or active ocular surface disease precluding contact lens wear
Interventions	Orthokeratology (n = 26): orthokeratology lens in 1 eye (overnight wear) RGP (n = 26): rigid gas permeable (RGP) contact lens in the other eye (daily or extended wear) Note: children were randomly assigned to wear the orthokeratology lens in 1 eye and the RGP lens in the other eye for 6 months; at 6 months, the lenses were switched for each eye. The clinical trial registry record also mentioned a matched control group of children who wore spectacles for 12 months; this group was not mentioned in the journal article
Outcomes	Primary outcome: • Axial length change at 6 months, measured by the IOLMaster ocular biometer Secondary outcomes: • Refractive error (noncycloplegic autorefraction) • Corneal curvature • Corneal epithelial cell exfoliation during gentle eye wash with sterile saline • Amount of bacterial binding • Peripheral refractive status Measurements taken at baseline and at 3, 6, 9, and 12 months Unit of analysis: the eye
Notes	Study dates: not reported Trial registration: ACTRN12608000007336 Funding sources: Australian Research Council (ARC) Linkage Project Grant Scheme, BE Enterprises Pty Ltd., Capricornia Contact Lens Pty Ltd. (Australia); Boston Products Group of Bausch & Lomb (USA) Disclosures of interest: "the authors have no proprietary or commercial interest in any materials discussed in this article"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"At study commencement, subjects were dispensed an OK lens for overnight wear only (with no lens wear during the day) in 1 eye chosen at random by coin toss (the “night” lens) and a conventional GP lens for the contralateral eye for daytime wear (the “day” lens)"
Allocation concealment (selection bias)	Unclear risk	Allocation of both eyes was determined at time of coin toss, but does not explain how the allocation was concealed.

Swarbrick 2015 *(Continued)*

Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Unclear risk	Masking of outcome assessors was not reported
Masking of outcome assessors (detection bias) Secondary outcomes	Unclear risk	Masking of outcome assessors was not reported
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	8 (25%) of 32 children were not included in the analyses: 4 due to inconvenience of study visits; 2 due to poor adaptation to GP lens wear; 1 due to persistent GP contact lens adherence; and 1 due to lenses not being consistently worn in the correct eye
Selective reporting (reporting bias)	High risk	Outcomes listed in the clinical trial registry record were not reported in the journal publication: corneal epithelial cell exfoliation during gentle eye wash with sterile saline, amount of bacterial binding, peripheral refractive status
Other bias	High risk	Data were not appropriately analyzed for paired-eye nor cross-over design

Tan 2005

Study characteristics	
Methods	Study design: parallel-group RCT Study centers: 7 (academic centers and clinical practices in Singapore, Hong Kong, and Thailand) Number randomized: 353 children Study follow-up: 1 year Exclusions and losses to follow-up: 55 (16%) children who were randomized were dropped from the analyses
Participants	Age: mean = 8.7 years (range 6 to 13 years) Gender: 177 boys, 176 girls Culture: 99.4% Asian Inclusion criteria: (1) age 6 to 12 years; (2) myopia of -0.75 D and -4.00 D; (3) good general health; (4) round pupils; (5) refractive to light; (6) best-corrected VA of 20/25 or better in each eye Exclusion criteria: (1) astigmatism greater than 1.00 D; (2) anisometropia greater than 1.00 D; (3) strabismus; (4) current use of either contact lenses or bifocals; (5) history of ocular surgery, trauma, or chronic ocular disease, including allergic conjunctivitis; (6) previous use of atropine for myopia; (7) disease requiring long-term or regular intermittent medication; (8) behavioral or neurological disorder that would interfere with the study; (9) participation in any study that involved an investigational drug within 1 month of enrollment; (10) intolerance or hypersensitivity to topical anesthetics, mydriatics, or components of the formulations; (11) contraindications to antimuscarinic agents; (12) pregnancy or planned pregnancy
Interventions	Gel/gel (n = 142): 2% pirenzepine ophthalmic gel applied twice a day

Tan 2005 *(Continued)*

	Placebo/gel (n = 140): 2% pirenzepine ophthalmic gel applied once a day and placebo gel applied once a day Placebo/placebo (n = 71): vehicle-placebo gel applied twice a day
Outcomes	Primary outcome: • Change in refractive error measured by cycloplegic autorefraction (spherical equivalent) Secondary outcome: • Change in axial length measured by A-scan ultrasonography Measurements taken at baseline and every 3 months for 1 year Unit of analysis: average of both eyes
Notes	Study dates: November 2000 to July 2002 Trial registration: not reported Funding source: Valley Forge Pharmaceuticals, Inc., and Novartis Ophthalmics AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible patients were randomized via a sponsor-prepared, computer-generated list stratified by site. Randomization was done at a 2:2:1 ratio of pirenzepine twice daily, pirenzepine once daily, and placebo
Allocation concealment (selection bias)	Low risk	Study sites used coded lists to determine which tubes of medication to administer to the next enrolled participant. The pirenzepine gels and placebo gels were packaged in identical tubes for morning and night applications, and the gels themselves appeared identical. All morning tubes had yellow labels, and all evening tubes had blue labels. Thus study personnel had no way of knowing which tubes had which medications; same for patients
Masking of participants (performance bias)	Low risk	Study was placebo-controlled, and identical appearing bottles with coded labels were distributed
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	Because the pirenzepine gels and placebo gels were packaged in identical tubes and the gels themselves appeared identical, study personnel had no way of knowing which tubes had which medications. The study reported that "no treatment code was unmasked for any subject during the study"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	Data analyzers were not masked (personal communication with biostatistician)
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	55 (16%) children were dropped from the study after randomization: 25 (18%) were gel/gel, 21 (15%) were placebo/gel, and 9 (13%) were placebo/placebo (this difference was not statistically different). Of these 55 patients, 31 discontinued the study because of adverse events (20 gel/gel, 11 placebo/gel, 0 placebo); 5 were not adherent to the study medication regimen; and 1 was dropped for inadequate efficacy (progression of myopia)

Tan 2005 *(Continued)*

		"We considered statistical methods to impute missing values due to patients who discontinued treatment. However, as the proportion of patients not completing the study was similar across treatment groups, any correction would apply similarly to all groups, and thus we did not conduct these analyses"
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were chosen a priori
Other bias	Unclear risk	Some study authors were employed by the pharmaceutical company funding the study

Trier 2008

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 Number randomized: 83 children Study follow-up: 3 years (intervention 12 months) Exclusions and losses to follow-up: 6 (7.2%), 9 (10.8%), and 7 (8.4%) were lost to follow-up during the first year, the second year, and the third year, respectively
Participants	Age: mean 11.3 years (range 8 to 13 years) Gender: not reported Culture: Denmark Inclusion criteria: (1) age 8 to 13 years; (2) minimum myopia of -0.75 D in 1 eye; (3) average axial length growth rate 0.075 to 0.39 mm per 6-month period Exclusion criteria: (1) severe general ailment (e.g. diabetes, epilepsy, psychiatric disease); (2) other eye disease (e.g. cataract, keratoconus, chronic iritis, glaucoma)
Interventions	Systemic 7-methylxanthine (n = 35): one 400 mg 7-methylxanthine (7-mx) tablet every morning Placebo (n = 42): 1 placebo tablet every morning Notes: children received either 7-mx or placebo for the first 12 months; all participants received 7-mx after 12 months (400 mg 7-mx tablet once or twice per day); "all children used single vision lenses"
Outcomes	Primary outcome: • Axial growth rate measured with noncontact, partial coherence interferometer (Zeiss IOL-Master) Secondary outcome: • Spherical equivalent measured with autorefractor (Retinomax, Nikon) 30 minutes after 1 drop of 1% cyclopentolate Measurements taken at -6, 0, 12, 24, and 36 months Unit of analysis: the individual (average of both eyes)
Notes	Study dates: October 2003 Trial registration: NCT00263471

Trier 2008 *(Continued)*

Funding source: "supported by grants from 'Jørgen Bagenkop Nielsens Myopi-Fond' and 'Generalkonsul Einar Høyvalds Fond', and by 'Øjenlæge Klaus Trier ApS'"

Declarations of interest: 2 authors affiliated with Trier Research Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The allocation sequence was generated in the pharmacy and sealed and numbered containers consecutively handed out to the participants"
Allocation concealment (selection bias)	Low risk	"The allocation sequence was generated in the pharmacy and sealed and numbered containers consecutively handed out to the participants"
Masking of participants (performance bias)	Low risk	"Outcomes were assessed unaware of group assignment at Trier Research Laboratories. No participants or investigators became unmasked during the first 12 months of the trial"
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"Outcomes were assessed unaware of group assignment at Trier Research Laboratories. No participants or investigators became unmasked during the first 12 months of the trial"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	"Outcomes were assessed unaware of group assignment at Trier Research Laboratories. No participants or investigators became unmasked during the first 12 months of the trial"
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	6 (7.2%), 9 (10.8%), and 7 (8.4%) children missed the first year, second year, and third year follow-up visits, respectively; reasons for missed visits were not reported
Selective reporting (reporting bias)	Low risk	Results of all outcomes prespecified in the clinical trial registry record were reported
Other bias	Unclear risk	Study was conducted by author's research company

Wang 2005

Study characteristics

Methods	Study design: parallel-group RCT Study center: 1 (Shanghai, China) Number randomized: 104 children Study follow-up: 18 months Exclusions and losses to follow-up: not reported
Participants	Age: mean = 11.6 years (range 6 to 15 years) Gender: 51 boys, 53 girls Culture: recruited from outpatient department of Eye & Ear, Nose, Throat Hospital in Shanghai, China

Wang 2005 *(Continued)*

	Inclusion criteria: (1) age 6 to 15 years; (2) myopia Exclusion criteria: not reported
Interventions	PAL group (n = 50): add not reported SVL (n = 54)
Outcomes	Primary outcomes: • Refractive error (cycloplegic autorefraction) • Axial length • Anterior chamber depth • Lens thickness • Corneal curve (vertical and horizontal) • Heterophoria (vertical and horizontal) Secondary outcomes: • Not distinguished Measurements taken at baseline and every 6 months for 18 months Unit of analysis: not reported
Notes	Study period: enrollment from April 1999 to April 2000 Trial registration: not reported Funding source: not reported We were not able to make contact with study authors for additional information; we report the data available in the conference abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"A randomized control trial (RCT) was conducted. Children were distributed into PALs group or control randomly"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment before randomization was not reported
Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Unclear risk	Masking was not reported
Masking of outcome assessors (detection bias) Secondary outcomes	Unclear risk	Masking was not reported
Masking of data analyzers	Unclear risk	Masking was not reported
Incomplete outcome data (attrition bias)	Unclear risk	Trial was reported only as a conference abstract with limited information to assess attrition bias

Wang 2005 *(Continued)*

Incomplete outcome(s) data		
Selective reporting (reporting bias)	Unclear risk	Trial was reported only as a conference abstract with limited information to assess outcomes
Other bias	Unclear risk	Reasons for trial authors not publishing full-length report of the study are not clear

Wang 2017

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (The People's Hospital of Yan'an and Affiliated Hospital of Yan'an Medical University) Number randomized: 126 children Study follow-up: 1 year Exclusions and losses to follow-up: 7 (11.1%) in intervention group and 5 (7.9%) in control group discontinued intervention; 2 (3.2%) in intervention group and 3 (4.8%) in control group were lost to follow-up
Participants	Age mean (SD): 9.1 (1.4) years in intervention group; 8.7 (1.5) years in control group Gender: 36 (57.1%) boys and 27 (42.9%) girls in intervention group; 31 (49.2%) boys and 32 (50.8%) girls in control group Culture: China Inclusion criteria: (1) diagnosis of low myopia (spherical equivalent between -0.50 and -2.00 D by cycloplegic autorefraction); (2) age 5 to 10 years; (3) normal intraocular pressure (IOP; < 21 mmHg); (4) not on any other treatment within 1 month before study enrollment; (5) provided informed consent Exclusion criteria: (1) abnormal binocular function or stereopsis; (2) other eye disease; (3) history of hemostatic or other systemic disorder; (4) contact lens or any other intervention for myopia; (5) allergy to atropine
Interventions	Atropine (n = 63): 0.5% eye drops once daily at night Placebo (n = 63): vehicle eye drops once daily at night Note: none
Outcomes	Primary outcome: • Progression of myopia, measured as a change in spherical equivalent Secondary outcome: • Axial length elongation Safety outcome: • Adverse events Measurements taken at 4, 8, and 12 months

Wang 2017 *(Continued)*

	Unit of analysis: individual (eye with more severe myopia used)
Notes	Study dates: January 2014 to December 2016 Trial registration: not reported Funding source: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The stratified randomization schedule was operated by a computerized number generated using SAS package (Version 9.1; SAS Institute Inc., Cary, NC)"
Allocation concealment (selection bias)	Low risk	"The information of all assignments and its allocation were concealed in sequentially numbered, opaque, sealed envelopes"
Masking of participants (performance bias)	Low risk	"The participants and investigators were not informed whether a participant was assigned to the intervention or control group"; "The placebo eyedrops had similar labels and appearances as the ATE"
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"We also blinded the outcome assessors and data analysts"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	"We also blinded the outcome assessors and data analysts"
Masking of data analyzers	Low risk	"We also blinded the outcome assessors and data analysts"
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Unclear risk	"Of those included participants, 17 were excluded because of the discontinued intervention (n = 12) and loss to contact (n = 5). Thus, 109 participants completed all treatment. Fortunately, we used ITT approach to analyze all outcome data" Unclear how ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Low risk	None was identified

Yang 2009

Study characteristics

Methods	Study design: parallel-group RCT Study center: 1 (Guangzhou City, China) Number randomized: 178 children Study follow-up: 2 years Exclusions and losses to follow-up: no exclusions; 29 (16%) were lost to follow-up

Yang 2009 *(Continued)*

Participants	Age: range 7 to 13 years Gender: 94 boys, 84 girls Culture: urban children from Guangzhou City, China Inclusion criteria: (1) age 7 to 13 years; (2) myopia with spherical equivalent refractive error between -0.50 D and -3.00 D in both eyes, as measured under cycloplegia; (3) astigmatism ≤ 1.50 D; (4) no anisometropia (difference in spherical equivalent ≤ 1.00 D between eyes); (5) best-corrected VA 6/6 or better; (6) no strabismus; (7) normal IOP; (8) willingness to wear glasses constantly for study duration; (9) understanding of random assignment and willingness to not use other medications Exclusion criteria: (1) any ocular or systemic condition known to influence refractive development; (2) use of medication that might affect refractive development; (3) moderately or highly myopic (< -3.00 D) parents; (4) birth weight ≤ 1250 g; (5) previous use of bifocals, PALs, or contact lenses
Interventions	PAL group (n = 89): multifocal lenses with +1.50 D near addition worn constantly SVL group (n = 89): single vision lenses worn constantly Note: prescription changes were made if subjective refraction had changed by at least 0.50 D for 1 or both eyes or if clinically indicated
Outcomes	Primary outcome: • Progression of myopia Change in spherical equivalent refractive error relative to baseline measured by cycloplegic autorefraction with 0.5% tropicamide + 0.5% phenylephrine hydrochloride Secondary outcomes: • Change in vitreous chamber depth by A-scan ultrasonography • Distance (5 m) and near (33 cm) horizontal heterophobia by cover test • Accommodative response by open-field autorefractor • Near workload, compliance, and adherence assessed by questionnaire Measurements taken at baseline and every 6 months for 2 years Unit of analysis: not reported
Notes	Study dates: enrollment was from July 2004 to March 2005 Trial registration: not reported Funding source: National Natural Science Grant, China Materials: lenses provided by Sola (China) Ltd. Compliance in wearing glasses was monitored with separate questionnaires for children and parents (87% overall compliance)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Enrolled subjects were assigned randomly to either the SV group or PAL group"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment before randomization was not reported

Yang 2009 *(Continued)*

Masking of participants (performance bias)	High risk	Masking of participants was not applicable due to functional differences between the interventions studied
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	Masked investigators were unaware of allocation groups during evaluation, although an unmasked investigator was available if clinical consultations were needed
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	Primary and secondary outcomes were assessed by the same examiners
Masking of data analyzers	Unclear risk	"All statistical analysis was carried out independently"
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Unclear risk	29 (16%) patients dropped out of the study: 15 in the PAL group and 14 in the SVL group. Statistical analyses comparing the retained participants to those lost to follow-up showed that dropouts had significantly worse myopia than those who remained in the study at baseline (P = 0.01)
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Unclear risk	Unit of analysis (i.e. average value of both eyes or right eye only) was not reported

Yen 1989

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (Refraction Clinic, Veterans General Hospital, Taipei, Taiwan) Number randomized: 247 children Study follow-up: 1 year Exclusions and losses to follow-up: 151 (61%) children were excluded or lost to follow-up
Participants	Age: mean = 9 years (range 6 to 14 years) Gender: 118 boys, 129 girls Culture: children with simple myopia were randomly selected from clinic records Inclusion criteria: (1) age 6 to 14 years; (2) myopia with refractive error between -0.5 D and -4.0 D Exclusion criteria: (1) amblyopia or tropia; (2) cylinder refraction greater than 1.0 D
Interventions	Atropine: 1% atropine drops every other night; bifocal spectacles prescribed 2 weeks after treatment began Cyclopentolate: 1% cyclopentolate drops every night; single vision spectacles prescribed if necessary Saline control: normal saline eye drops every night; single vision spectacles prescribed if necessary
Outcomes	Primary outcome: • Change in refractive error measured by cycloplegic refraction (spherical equivalent)

Yen 1989 *(Continued)*

	Secondary outcomes: • Changes in vision, fundoscopy, and IOP Measurements taken at baseline and every 3 months for 1 year Note: baseline for atropine group was measured 2 weeks after treatment began Unit of analysis: right eyes only
Notes	Study dates: enrollment from July 1, 1985 to October 31, 1986 Trial registration: not reported Funding source: not reported Additional data: study author provided unpublished data via email correspondence

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Ophthalmic examinations were done by 3 doctors. Each doctor got a random table. Patients were assigned to 3 groups according to the sequence on the random table (via email communication with study author)
Allocation concealment (selection bias)	Unclear risk	Allocation was done via a random numbers table, but it is not clear whether the allocation sequence was concealed
Masking of participants (performance bias)	High risk	Masking of participants was not reported for the pharmaceutical agents; however, 1 group received bifocal spectacles rather than single vision spectacles; therefore this was not masked
Masking of outcome assessors (detection bias) Progression of myopia	Unclear risk	No details were given
Masking of outcome assessors (detection bias) Secondary outcomes	Unclear risk	"To avoid deviation during retinoscopy, all examinations were done by three doctors"
Masking of data analyzers	Unclear risk	No details were given
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	High risk	"Patients who used the eye drops continuously for one year received another complete ophthalmologic examination...96 such patients were collected for evaluation, 32 in each group" Patients who discontinued using eye drops or who did not use them consistently were excluded from the study. Of the 247 children randomized in the study, 151 (61%) were not included in the analyses. The 96 patients analyzed included the first subset of children who followed the treatment protocol and were examined at 1 year (via email communication with study author)
Selective reporting (reporting bias)	High risk	Not all outcomes described in the methods section were reported (changes in vision, funduscopy, and IOP)
Other bias	High risk	"For statistical significance, each group should include at least 30 samples. Our aim was to evaluate the results after using the medication for 1 year. So, when we felt we had enough numbers of patients who had continuously used

Yen 1989 *(Continued)*

	the eye drops for 1 year, we decided to analyze the data. It happened to be 32 in each group" (via email communication with study author)

Yi 2015

Study characteristics	
Methods	Study design: parallel-group RCT Study center: 1 (The Third People's Hospital of Chongqing City) Number randomized: 140 children Study follow-up: 12 months Exclusions and losses to follow-up: 6 (8%) in treatment group and 2 (3%) in control group withdrew from the study
Participants	Age: mean = 9.8 years Gender: 65 boys, 67 girls Culture: China Inclusion criteria: (1) children with low myopia: refractive error between -0.50 and -2.00 D in both eyes as measured by cycloplegic autorefraction; (2) normal binocular function and stereopsis; (3) normal intraocular pressure less than 21 mmHg; (4) willingness and ability to tolerate cycloplegia and mydriasis Exclusion criteria: (1) astigmatism more than -1.00 D; (2) other ocular disease, such as amblyopia, strabismus, congenital cataract, glaucoma, corneal scar, optic neuropathy, traumatic ocular injury, uveitis, or ocular tumor; (3) history of any ocular surgery; (4) any systemic disease or condition that could affect visual function and development, including diabetes mellitus and/or chromosome anomaly; (5) previous or current use of contact lenses, bifocals, progressive addition lenses, or other forms of treatment (including atropine) for myopia
Interventions	Atropine (n = 70): 1% atropine sulfate once nightly in both eyes Placebo (n = 70): vehicle eye drops (Tears Naturale Free; Alcon, Fort Worth, TX) once nightly in both eyes
Outcomes	Primary outcomes: • Uncorrected distance visual acuity • Spherical equivalent of refractive status (cycloplegic autorefraction) • Axial length • Ophthalmoscopy • Slit-lamp biomicroscopy • Fundus examination • Adverse events Secondary outcomes: • Not distinguished Measurements taken at baseline and every 3 months up to 1 year Unit of analysis: individual (right eye)
Notes	Study dates: enrollment from January to October 2012 Trial registration: not reported

Yi 2015 *(Continued)*

Funding source: not reported

Declarations of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment before randomization was not reported
Masking of participants (performance bias)	High risk	"We could not make our study double-masked. We had to inform subjects about dilation and cycloplegia from atropine at the beginning"
Masking of outcome assessors (detection bias) Progression of myopia	Low risk	"To minimize observational bias, both pupils of every child were dilated fully and checked by nurses before being examined by the study investigators, who were kept masked to the assigned trial medications"
Masking of outcome assessors (detection bias) Secondary outcomes	Low risk	"To minimize observational bias, both pupils of every child were dilated fully and checked by nurses before being examined by the study investigators, who were kept masked to the assigned trial medications"
Masking of data analyzers	Unclear risk	This was not reported
Incomplete outcome data (attrition bias) Incomplete outcome(s) data	Low risk	Eight (6%) of 140 children who dropped out were not included in the analysis
Selective reporting (reporting bias)	Low risk	Results were reported for outcomes described in the methods section of the paper
Other bias	Low risk	None was identified

7-mx: 7-methylxanthine.
AC/A: accommodative convergence (in prism diopters) to the stimulus/accommodation ratio.
AL: axial length.
BSCL: bifocal soft contact lens.
D: diopters.
DC: diopter cylinder.
DF: dual focus.
DISC: dual-focus incorporated soft contact.
IOP: intraocular pressure.
logMAR: logarithm of the minimum angle of resolution.
MZ: monozygotic.
N/A: not applicable.
OFG: ordinary frame glasses.
PAL: progressive addition lens.
PD: pupillary distance.
PR: XXX.
RCT: randomized controlled trial.
RGPCL: rigid gas permeable contact lens.
SA: XXX.
SCL: soft contact lens.
SER: XXX.
SVL: single vision lens.

SVSCL: single vision soft contact lens.
VA: visual acuity.
VT: vision training.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abraham 1966	Not randomized: case report
ACHIEVE Study 2008	Not intended to control progression of myopia: glasses vs contacts for self-esteem in schoolchildren
Aller 2008	Interventional twin case series: included only 1 pair of twins: 1 randomized to wear bifocal SCLs and the other to wear SVSCLs for 1 year; both wore BSCLs for the second year
Andreo 1990	Not randomized: not intended to control progression of myopia; participants older than 18 were included
ATOM 2 Study 2012	Interventions not eligible: dosing study to compare doses of atropine, with no control group
Baldwin 1969	Not randomized: patients selected treatment assignment
Baltimore Myopia Project 1946	Interventions not eligible: vision training for myopia; interventions of vision training were not prespecified in the protocol
Baronet 1979	Not randomized: retrospective review of patients treated with atropine at a medical practice with no comparison group
Bedrossian 1979	Not randomized: method of allocation was not specified. Cross-over study of atropine in 1 eye for 1 year, with the fellow eye serving as the control, then alternated treatment after each year for 4 years
Berkeley OK Study 1983	Population not eligible: participants were 21 to 28 years old
Bier 1988	Not randomized: sequential assignment to groups
Brodstein 1984	Not randomized: "the lack of randomization permits a possibility for bias"
Chan 2014	Interventional twin case series: included only 1 pair of twins: 1 randomized to wear orthokeratology lens and the other to wear SVLs for 2 years
Chen 2012	Not randomized: allocation was done by parental decision
Chen 2014a	Not randomized: cohort study of children wearing SVLs with full correction or undercorrection
Chen 2016	Not randomized: treatment group included participants who chose to wear orthokeratology lenses; controls included participants who had never worn orthokeratology lenses
Cho 2012	Interventions not eligible: comparison of fenestrated orthokeratology lenses vs nonfenestrated orthokeratology lenses; interventions comparing types of orthokeratology lenses were not prespecified in the protocol
Cho 2017	Interventions not eligible: comparison of continuing vs discontinuing orthokeratology wear after 2 years; interventions comparing length of orthokeratology wear were not prespecified in the protocol

Study	Reason for exclusion
Choi 2005	Not randomized: study was reported only as a conference abstract and randomization was not specified ("We prescribed 1% atropine once a day with bifocal glasses to the treated group (41 patients) and prescribed only glasses to the control group (43 patients)")
Chou 1997	Not randomized: allocation was by parental decision
Dumbleton 1999	Interventions not eligible: lenses with different oxygen permeability; interventions comparing oxygen permeability not prespecified in the protocol
Dyer 1979	Not randomized: case-control study
Ebri 2007	Not intended to control progression of myopia: cycloplegic effect and pupillary dilation outcomes, as well as cost-effectiveness; follow-up 3 days
Eissa 2018	Interventions were not eligible
Filip 2000	Population was not eligible: myopia progression in adults
Gimbel 1973	Not randomized: comparison of patients vs an historical cohort
Goss 1984	Not randomized: treatment group included patients with overcorrection; controls included random patients selected retrospectively
Grosvenor 1991	Not randomized: historical control group
He 2016	Not randomized: retrospective cohort study; comparison of orthokeratology lenses vs SVLs
He 2018	Interventions were not eligible
Horner 1999	Not intended to control progression of myopia: comparison of soft spherical contact lenses vs spectacles; SCLs not expected to slow myopia progression. In fact, the study was conducted because researchers believed that SCLs may increase myopia progression
Hosaka 1982	Not randomized: interventional case series of children aged 6 to 14 years treated with labetalol ophthalmic solution
Hosaka 1988	Not randomized: interventional case series
Hua 2017	Interventions not eligible: cluster RCT of elevated light levels in classrooms to prevent myopia onset or progression; interventions of light levels were not prespecified in the protocol
Huffman 2002	Not intended to control progression of myopia: aspheric vs spheric lenses; outcome to decrease spherical aberration; adults were included
Jiang 2018	Not randomized
Kao 1988	Not randomized: children were enrolled in 2 separate series of patients
Keller 1996	Not randomized: all children wore RGPCLs
Kennedy 1995	Not randomized: treatment was atropine; controls were patients matched by medical records
Khoo 1999	Not randomized: study reported that "children were randomly selected from the various schools in Singapore. They were then randomly selected for contact lens wear"

Study	Reason for exclusion
	Children in the RGPCL cohort who completed 3 years of follow-up were compared with a cohort of children who wore spectacles
Kubena 2002	Not randomized: cohort study that compared spectacle lenses that filtered non-visible light vs conventional spectacle lenses
Lakkis 2006	Not intended to control progression of myopia: 2-week randomized cross-over trial to evaluate visual performance and satisfaction of clear and photochromic spectacle lenses in children aged 10 to 15 years wearing fully corrected spectacles
Lee 2016	Interventions not eligible: dosing study conducted to compare 0.125% or 0.25% atropine; controls were patients who preferred SVLs
Leung 1999	Not randomized: odd or even case numbers determined the 2 groups
Li 2005	Not randomized: experimental group received progressive multifocal lenses; control group wore common glasses; participants were 6 to 23 years old
Liang 2008	Interventions not eligible: RCT comparing atropine eye drops alone vs combined treatment with atropine and stimulation of the auricular acupoints in school-aged children with myopia
Lu 2010	Not randomized: case-control study comparing myopic children treated with seasonal doses of atropine vs nonmyopic children
Ma 2014	Interventions not eligible: cluster RCT with 3 groups: free spectacles provided in class; vouchers for free spectacles; and prescriptions for spectacles; interventions of accessibility to spectacles were not prespecified in the protocol
Mandell 1959	Not randomized: historical cohort, including adults
Meythaler 1971	Not randomized: interventional cases series (70 eyes in persons from 8 to 35 years of age were checked); 3 groups were based on age; youngest group was 8 to 19 years old
NCT00348166	Not randomized
NCT03372551	Wrong patient population
NCT03512626	Wrong patient population
Neetens 1985	Not randomized: control group consisted of participants who could not use bifocals
Nesterov 1990	Not randomized: comparison of a group using cycloplegics and ocular hypotensives vs a reference group for progression of myopia
Oakley 1975	Not randomized: control group consisted of children (or parents) who refused bifocals
Parker 1958	Not randomized: comparison of author's practice vs other practices
Perrigin 1990	Not randomized: treatment group was given silicone lenses; control consisted of an historical cohort
Pirenzepine 2003	Not randomized: review of pirenzepine studies and mechanism of action
Plowright 2015	Not intended to control progression of myopia: RCT to evaluate daily disposable contact lenses vs SVLs for 2 weeks

Study	Reason for exclusion
Pritchard 1999	Not intended to control progression of myopia: extended wear for low Dk vs high Dk lenses in adults
Rah 2002	Population not eligible: overnight orthokeratology in adults (LOOK study); not randomized
Rainey 2000	Interventions not eligible: vision therapy vs control; interventions for vision training were not pre-specified in the protocol
Ritchey 2005	Population not eligible: included adults aged 18 and older (COLM study)
Sankaridurg 2003	Not intended to control progression of myopia: RCT conducted to compare adverse events for SCLs vs SVLs (spectacles); participants were 16 to 35 years old
Santodomingo-Rubido 2012	Not randomized: allocation was done by parental decision
Savoliuk 1968	Not randomized: comparison of groups using SVLs continuously or for distance-use only vs no spectacles
Shen 2011	Allocation method not clear, randomization not specified: compared groups using 0.25% atropine vs no atropine
Shimmyo 2003	Allocation method not clear, randomization not specified: atropine vs control for 2 years
Shum 2003	Not randomized: comparison of groups using orthokeratology vs no orthokeratology
SightGlass 2018	Wrong patient population
SMART Study 2009	Not randomized: comparison of groups using orthokeratology lenses vs daily wear silicone hydrogel SCLs
Soni 2006	Not randomized: included adults
Stone 1976	Not intended to control progression of myopia: study authors state that "the research team is not purposely attempting to flatten the cornea in order to arrest the myopia"
Sun 2007	Not randomized: case-control study of spectacle users vs controls
Syniuta 2001	Not randomized: intervention group included patients whose parents requested treatment for myopic progression; control group comprised the next myopic child by alphabetical order after study child's record number
Takano 1964	Not randomized: cohort study comparing treatment with Mydrine (tropicamide + phenylephrine) eye drops with or without Neosynesin (phenylephrine) eye drops; included boys and girls with myopia ages 7 to 19 years; follow-up was 20 days
Tan 2012	Not randomized
Toki 1960	Not randomized: cohort study of patients receiving 5% Neosynesin (phenylephrine) eye drops; included boys and girls with myopia ages 7 to 21 years; follow-up was 14 to 28 days
Tokoro 1964	Not randomized: nonrandomized study of treatment with Mydrine (tropicamide + phenylephrine) eye drops + 5% Neosynesin (phenylephrine) eye drops + low-frequency electro stimulus in children ages 7 to 15 years; included children with hyperopia

Study	Reason for exclusion
Tokoro 1965	Not randomized: retrospective cohort comparing full correction spectacles vs undercorrection (< -1 D) spectacles or full correction in case of need in children ages 7 to 14 years; included children with hyperopia
TO-SEE Study 2013	Not randomized: prospective cohort study of children wearing orthokeratology lenses vs SVLs
Xiao 2009	Not randomized: observational study of 2 groups of children who wore RGPCLs vs spectacles
Yamada 2004	Not randomized: review article with some cohort data on children with high myopia
Yamaji 1967	Not randomized: observation of children treated with Mydrine-M; no control group
Yang 2017	Not intended to control progression of myopia: evaluated accommodative lag in groups using orthokeratology vs SVLs for 1 year
Yi 2011	Interventions not eligible: RCT to evaluate near- and middle-vision activities and outdoor activities in children with myopia; interventions of visual activities were not prespecified in the protocol
Young 1992	Not intended to control progression of myopia: comparison of overnight lenses for 12 months in adults only
Zeng 2009	Not intended to control progression of myopia: RCT to evaluate visual performance and satisfaction of ready-made spectacles vs custom spectacles in Chinese school-aged children with uncorrected refractive error
Zhou 2015	Not intended to control progression of myopia: evaluated accommodative lag in groups using RGPCLs vs SVLs for 1 year
Zhou 2016	Not randomized: 400 children wearing orthokeratology lenses or SVLs selected from patient records

BSCL: bifocal soft contact lens.
COLM: Comparison of Overnight Lens Modalities.
Dk: oxygen permeability.
LOOK: Lenses and Overnight Orthokeratology.
RCT: randomized controlled trial.
RGPCL: rigid gas permeable contact lens.
SCL: soft contact lens.
SVL: single vision lens.
SVSCL: single vision soft contact lens.

Characteristics of studies awaiting classification *[ordered by study ID]*

Anderson 2016

Methods	Randomized parallel-group design (participants were allowed to switch to intervention of their choice after 5 years)
Participants	Inclusion criteria: not reported Exclusion criteria: not reported
Interventions	Intervention: progressive addition lenses Comparison intervention: single vision lenses
Outcomes	Primary outcome: phoria magnitude

Anderson 2016 *(Continued)*

	Secondary outcomes: not reported Maximum follow-up: 10 years
Notes	Study name: Evaluation of progressive addition lens wear and age-related changes in phoria magnitude in myopic children

Bakaraju 2015

Methods	Randomized parallel-group design
Participants	Inclusion criteria: Chinese children, aged 8 to 13 years, with spherical equivalent refractive error between -0.75D and -3.50D Exclusion criteria: previous treatment for myopia and systemic or ocular disease
Interventions	Intervention: single vision control contact lenses Comparison intervention 1: extended depth of focus 1 prototype contact lenses Comparison intervention 2: extended depth of focus 2 prototype contact lenses
Outcomes	Primary outcome: cycloplegic autorefraction, axial length Secondary outcomes: not reported Maximum follow-up: 3 years
Notes	Study name: Extended depth-of-focus contact lenses can slow the rate of progression of myopia

BLINK Study 2017b

Methods	Not reported
Participants	Inclusion criteria: myopic children, aged 7 to 11, myopia (spherical component) of -0.75 D to -5.00 D (inclusive) and 1.00 D cylinder or less (corneal plane) Exclusion criteria: not reported
Interventions	Intervention: center-distance soft multifocal contact lens with a +2.50 D add Comparison intervention: spectacle correction
Outcomes	Primary outcome: visual acuity Secondary outcomes: not reported Maximum follow-up: not reported
Notes	Study name: Visual acuity and over-refraction in myopic children fitted with soft multifocal contact lenses in the BLINK Study

Cheung 2018

Methods	Observational
Participants	Inclusion criteria: not reported Exclusion criteria: not reported
Interventions	Intervention: orthokeratology lenses Comparison intervention: single-vision spectacles
Outcomes	Primary outcome: endothelial cell density, coefficient of variation in cell size, hexagonality Secondary outcomes: not reported Maximum follow-up: 2 years
Notes	Study name: Does a two-year period of orthokeratology lead to changes in the endothelial morphology of children?

ChiCTR1800018092

Methods	Randomized parallel-group design
Participants	Inclusion criteria: children with myopia were included in the randomized control, with no gender limitation, aged 7-12 years old, clear refractive media, equivalent spherical lens ≤-5.00D, 40.00D≤ corneal base curvature <45.50D, and corneal astigmatism ≤1.50D Exclusion criteria: rule out basic eye diseases that may affect vision, corneal plasticizer and potion
Interventions	Intervention: orthokeratology glass Comparison intervention: 0.01% atropine eye drops once per night
Outcomes	Primary outcome: axial length Secondary outcomes: spherical equivalent, corneal curvature Maximum follow-up: not reported
Notes	Study name: Comparison of myopia control effect between single use ortho-k and combined with 0.01% atropine eye drops in children

Diaz-Llopis 2018

Methods	Randomized parallel-group design
Participants	Inclusion criteria: aged 9 to 12 years, bilateral myopia of -0.5 to -2 D, less than 1.5 astigmatism Exclusion criteria: not reported
Interventions	Intervention: one drop of 0.01% atropine once a day in both eyes before going to bed Comparison intervention: no treatment
Outcomes	Primary outcome: progression of myopia, side effects

Diaz-Llopis 2018 *(Continued)*

	Secondary outcomes: not reported Maximum follow-up: 5 years
Notes	Study name: Superdiluted atropine at 0.01% reduces progression in children and adolescents. A 5 year study of safety and effectiveness

EUCTR2016-003340-37-IE

Methods	Randomized cross-over design
Participants	Inclusion criteria: spherical equivalent refractive error of -1.0D or worse with myopia progression of at least -0.50DS over the last year, based on refractive or clinical evidence; astigmatism less than or equal to -2.50D and an intraocular difference in spherical equivalent <= 1D; corrected visual acuity must be better or equal to logMAR 0.2 in both eyes and difference between non-cycloplegic and cycloplegic spherical refraction of less than 1.00 D; normal IOP (<= 21mmHg), normal ocular health and good general health with no history of cardiac/respiratory diseases; willingness to commit to the 2 year clinical trial as well as randomization to the placebo Exclusion criteria: ocular/systemic diseases/conditions affecting vision or refractive error; any ocular/systemic condition wherein atropine is contraindicated; known allergy to atropine, cyclopentolate hydrochloride and/or proxymetacaine hydrochloride; defective binocular vision, amblyopia or strabismus; any other conditions precluding adherence to the protocol including allergy to study eye drops (active agent or preservative); previous pharmaceutical or optical myopia control interventions; subjects (or parent/guardian) unable to provide written informed consent
Interventions	Intervention: atropine sulphate ophthalmic solution 0.01% Comparison intervention: placebo
Outcomes	Primary outcome: efficacy of treatment, the difference in QoL questionnaire scores between intervention and control groups, the occurrence of adverse events, proportion of participants needing bifocals, the drop-out rate Secondary outcomes: not reported Maximum follow-up: 24 months
Notes	Study name: Preventing the progression of shortsightedness in children using an eye drop called Atropine

EUCTR2018-001286-16-DK

Methods	Randomized parallel-group design
Participants	Inclusion criteria: children aged =6 years <9 years: myopia =-1 (spherical equivalent) in at least one eye; children aged =9 years <12 years: myopia =-2 (spherical equivalent) in at least one eye; cylinder less than 1.5 diopters Exclusion criteria: myopia related to retinal dystrophies; collagen syndromes (Ehlers-Danlos syndrome, Marfan syndrome and Stickler syndrome); other ocular pathology (e.g., amblyopia, strabismus); previous eye surgery; previous use of agents thought to affect myopia progression, e.g. atropine, pirenzepine or 7-methylxanthine (metabolite of caffeine and theobromine) and orthokeratology contact lenses; known allergy to atropine or any of the contents of the trial medication (active and in-active ingredients) used in the study; non-compliance to eye examinations; serious systemic health troubles (e.g., cardiac or respiratory illness) and developmental disorders and delays

EUCTR2018-001286-16-DK *(Continued)*

Interventions	Intervention 1: atropine 0.01% Comparison intervention 1: atropine 0.1% Comparison intervention 2: placebo eye drops
Outcomes	Primary outcome: axial length elongation; change in spherical equivalent Secondary outcomes: patient reported outcome; adverse effects and reactions; change in choroidal thickness; change in ocular biometry (i.e. keratometry, anterior chamber depth, lens thickness, vitreous axial distance); change in higher-order aberrations Maximum follow-up: 36 months
Notes	Study name: Low-dose atropine for the prevention of nearsightedness in Danish children

Jong 2015

Methods	Randomized parallel-group design
Participants	Inclusion criteria: children aged between 8 to 13 years (spherical refractive error between -0.75 D to -5.00 D, cylinder ≤ -1.00 D) Exclusion criteria: previous myopia treatment and no systemic or ocular disease
Interventions	Intervention: novel, daily disposable extended depth of focus (EDOF) contact lenses: EDOF1 Comparison intervention 1: novel, daily disposable extended depth of focus (EDOF) contact lenses: EDOF2 Comparison intervention 2: single vision (SV) contact lenses
Outcomes	Primary outcome: rate of increase in axial length Secondary outcomes: not reported Maximum follow-up: 6 months
Notes	Study name: A dose-response relationship between duration of daily lens wear and reduction in rate of axial elongation

Kinoshita 2017

Methods	Randomized parallel-group design
Participants	Inclusion criteria: children aged 8 to 12 years with spherical equivalent refractions of -1.00 to -6.00 diopters (D) and astigmatism of -1.50 D or less Exclusion criteria: not reported
Interventions	Intervention: orthokeratology with 0.01% atropine Comparison intervention: orthokeratology alone
Outcomes	Primary outcome: axial length Secondary outcomes: not reported

Kinoshita 2017 *(Continued)*

	Maximum follow-up: 1 year
Notes	Study name: Suppressive effect of combined treatment of orthokeratology and 0.01% atropine instillation on axial length elongation in childhood myopia

Lam 2018

Methods	Randomized parallel-group design
Participants	Inclusion criteria: healthy myopes, refractive errors between –4D to –5D sphere and astigmatism within –1.50D Exclusion criteria: long-term contact lens wearers and individuals with a history of ocular diseases
Interventions	Intervention: orthokeratology lens in one eye Comparison intervention: conventional rigid gas permeable lens in the other eye
Outcomes	Primary outcome: corneal curvature, biomechanics, and thickness Secondary outcomes: not reported Maximum follow-up: not reported
Notes	Study name: Influence of short-term orthokeratology to corneal tangent modulus: A randomized study

Maekawa 2016

Methods	Randomized parallel-group design
Participants	Inclusion criteria: not reported Exclusion criteria: not reported
Interventions	Intervention: ortho-k contact lenses made by Alpha Corp Comparison intervention: ortho-k contact lenses made by Technopia Co., Ltd
Outcomes	Primary outcome: objective cycloplegic refraction, axial length Secondary outcomes: not reported Maximum follow-up: 2 years and at 3-weeks post discontinuance of the ortho-k lens wear
Notes	Study name: Comparison of the correction effect to suppress the progression of myopia between two types of orthokeratology lenses

NCT02055378

Methods	Randomized parallel-group design

NCT02055378 *(Continued)*

Participants	Inclusion criteria: children aged from 6 to 12 years with myopia, defined as spherical equivalent (SE) of -0.5 diopter (D) or less, were recruited from the outpatient clinics from January 2011 to June 2012 Exclusion criteria: abnormal IOP (>21 mmHg) at presentation, astigmatism or anisometropia of more than 1.5 D, amblyopia or strabismus, the presence of any related eyelid diseases, ocular diseases, or auricular diseases, the presence of hemostatic disorders or other related major systemic diseases, history of allergy to atropine, previous or current use of contact lenses, bifocals, progressive lenses, or other forms of treatment for myopia
Interventions	Intervention: topical 0.125% atropine with auricular acupoint stimulation Comparison intervention: topical 0.125% atropine
Outcomes	Primary outcome: the change in spherical equivalent Secondary outcomes: axial length (AL) elongation, anterior chamber depth (ACD) and intraocular pressure(IOP) Maximum follow-up: 12 months
Notes	Study name: The effect of low-concentration atropine combined with auricular acupoint stimulation in myopia control

NCT02700139

Methods	Randomized parallel-group design
Participants	Inclusion criteria: myopia between 0.75 ~ - 4.50 D and with-the-rule astigmatism not more than 1.50 D; difference between eyes, no more than 1.25 spherical equivalent; best corrected visual acuity (VA) is equal to or better than 0.10 in logMAR scale (Snellen VA 6/7.5 or better); eyes straight at distance and near with best subjective correction; willing to be randomized and wear the study spectacles according to the instructions from practitioner; willing to come back for follow up; in the Optometry Clinic during the study period Exclusion criteria: abnormal ocular and general health; prior myopic treatment (e.g. refractive surgery and progressive lens wear for myopic control) before and during the study period; history of rigid contact lenses (including orthokeratology lenses) wearing; systemic condition which might affect refractive development (for example, Down syndrome, Marfan's syndrome); ocular conditions which might affect the refractive error (for example, cataract, ptosis)
Interventions	Intervention: aspheric lens Comparison intervention: single vision spheric/toric lens
Outcomes	Primary outcome: axial length Secondary outcomes: not reported Maximum follow-up: 1 year
Notes	Study name: Shamir aspheric ophthalmic lenses (MyLens) for myopic control clinical trial

NCT03519490

Methods	Randomized parallel-group design
Participants	Inclusion criteria: myopia: ≥ 0.5 D in least myopic meridian, < 12.0 D in most myopic meridian); Anisometropia (interocular difference in refractive error) ≤ 2D; astigmatism: ≤ 3D; myopia progression ≥ 0.5D in at least one eye based on available clinical records or based on habitual spectacle prescription; visual acuity: best corrected acuity of 20/20 or better in each eye; capable of proper handling, insertion and removal of hybrid contact lenses Exclusion criteria: ocular health: any pathology that may alter eye growth (e.g. history of retinal detachment & treatment for the same), and/or may adversely impact contact lens wear (e.g. chronic, poorly controlled allergic conjunctivitis) will be grounds for exclusion; strabismus, amblyopia; systemic disease that may affect vision, vision development or contact lens wear; chronic use of medications that may affect immunity, such as oral or topical corticosteroids rigid or hybrid contact lens wear within the preceding 3 months; prior ocular surgery, nursing or pregnant mothers; participants who cannot commit to the 24 month study period or who have a high likelihood of leaving the area within the 24 month study period
Interventions	Intervention: multifocal hybrid contact lens Comparison intervention: single vision hybrid contact lens
Outcomes	Primary outcome: myopia progress rate, axial length Secondary outcomes: subjective myopia progression rate, macular pigment optical density, tear film dynamics and meibomian gland health Maximum follow-up: 24 months
Notes	Study name: Can distance center and near center multifocal contact lenses control myopia progression in children?

Pärssinen 2017

Methods	Randomized parallel-group design
Participants	Inclusion criteria: spherical refraction (SR) >−3 D, astigmatism ≥−2 D, spherical equivalent (SE) ≥−3 D Exclusion criteria: other eye diseases and previous glasses for myopia
Interventions	Intervention: continuous use spectacles Comparison intervention 1: only for distant use spectacles Comparison intervention 2: bifocal spectacles with a 1.75 D add
Outcomes	Primary outcome: anisometropia of spherical equivalent and astigmatism Secondary outcomes: spherical equivalent, corneal refractive power, anterior chamber depth, axial length Maximum follow-up: 23 years
Notes	Study name: Anisometropia of spherical equivalent and astigmatism among myopes: a 23-year follow-up study of prevalence and changes from childhood to adulthood

Ren 2017

Methods	Randomized parallel-group design
Participants	Inclusion criteria: not reported Exclusion criteria: not reported
Interventions	Intervention: low concentration atropine Comparison intervention 1: orthokeratology Comparison intervention 2: spectacles
Outcomes	Primary outcome: refractive degree, ocular axial length Secondary outcomes: not reported Maximum follow-up: not reported
Notes	Study name: Effects of low concentration atropine and orthokeratology on myopia prevention and control

Sankaridurg 2017

Methods	Randomized parallel-group design
Participants	Inclusion criteria: myopic children with cycloplegic spherical equivalents (SE) between -0.75 to -4.25D Exclusion criteria: not reported
Interventions	Intervention: control group wearing single-vision, silicone hydrogel (SH) contact lens Comparison intervention 1: silicone hydrogel contact lens with a central treatment zone of relative +ve power of +1.00D combined with relative +ve powers of +2.50D Comparison intervention 2: silicone hydrogel contact lens with a central treatment zone of relative +ve power of +1.00D combined with relative +ve powers of +2.50D and +1.50D in the periphery Comparison intervention 3: hydrogel contact lens III Comparison intervention 4: hydrogel contact lens IV
Outcomes	Primary outcome: myopia progression Secondary outcomes: cycloplegic (1% tropicamide) autorefraction and axial length (AL) Maximum follow-up: 12 months
Notes	Study name: Novel contact lenses designed to slow progress of myopia: 12 month results

Tan 2019

Methods	Randomized parallel-group design
Participants	Inclusion criteria: aged 6 to <11 years; Chinese ethnicity; myopia between 1.00–4.00 D; astigmatism (negative cylinder) not more than 2.50 D of axes 180 ± 30; astigmatism with other axes not more

Tan 2019 *(Continued)*

	than 0.50 D; less than 1.00 D difference in spherical equivalent between the two eyes; best corrected logMAR visual acuity 0.10 or better in both eyes; symmetrical corneal topography with corneal toricity less than 2.00 D in either eye; normal ocular health other than myopia; agree to be randomized and to attend the scheduled and aftercare visits Exclusion criteria: contraindications to atropine: known allergies or cardiovascular disease, epilepsy; contraindications to contact lens wear and ortho-k: history of ocular inflammation or infection, strabismus or amblyopia; history of myopia control treatment (e.g., soft or rigid contact lenses, bifocal or multifocal spectacles, atropine eye drops); systemic condition which might affect refractive development (e.g., Down syndrome, Marfan's syndrome), or ocular conditions which might affect refractive error (e.g., cataract, ptosis)
Interventions	Intervention: combined atropine with orthokeratology Comparison intervention: orthokeratology alone
Outcomes	Primary outcome: lens performance, changes in refractive error, unaided vision, ocular adverse events, corneal staining, lens binding and centration, and axial length Secondary outcomes: not reported Maximum follow-up: 2 years
Notes	Study name: Combined atropine with orthokeratology for myopia control: study design and preliminary results

Tilia 2018

Methods	Randomized cross-over design
Participants	Inclusion criteria: myopic; between 7 and 18 years of age; be correctable to at least 0.3 logMAR distance high-contrast visual acuity (HCVA) at 6 m with spherical hydrogel contact lenses (power range -0.75 to -6.00 D); and have no ocular or systemic findings that would contraindicate contact lens wear Exclusion criteria: amblyopia or strabismus
Interventions	Intervention: single vision contact lens Comparison intervention 1: extended depth of focus contact lens low Comparison intervention 2: extended depth of focus contact lens high
Outcomes	Primary outcome: visual acuity, accommodative and binocular function, and objective static refraction Secondary outcomes: not reported Maximum follow-up: one week
Notes	Study name: Vision performance and accommodative/binocular function in children wearing prototype extended depth-of-focus contact lenses

Trier 2015

Methods	Randomized parallel-group design

Trier 2015 *(Continued)*

Participants	Inclusion criteria: not reported Exclusion criteria: not reported
Interventions	Intervention: 7-methylxanthine Comparison intervention: placebo
Outcomes	Primary outcome: myopia progression, safety Secondary outcomes: not reported Maximum follow-up: 8 years
Notes	Study name: 7-methylxanthine treatment

Wei 2017

Methods	Randomized parallel-group design
Participants	Inclusion criteria: myopic children with the diopter of -0.50 to -6.00 D Exclusion criteria: not reported
Interventions	Intervention: orthokeratology Comparison intervention: spectacles
Outcomes	Primary outcome: ocular peripheral refraction, relative peripheral refraction Secondary outcomes: not reported Maximum follow-up: not reported
Notes	Study name: A randomized controlled clinical trial on the effects of wearing orthokeratology and spectacles on ocular peripheral refraction in myopic children

Wu 2018

Methods	Randomized parallel-group design
Participants	Inclusion criteria: not reported Exclusion criteria: not reported
Interventions	Intervention: AC custom-made orthokeratology lens Comparison intervention: standard orthokeratology lens
Outcomes	Primary outcome: uncorrected visual acuity (UCVA), corneal topography, and the complications of corneal epithelium Secondary outcomes: not reported Maximum follow-up: 1 month

Wu 2018 *(Continued)*

Notes	Study name: Effectiveness of AC custom-made Ortho-K lens

Yam 2019

Methods	Randomized parallel-group design
Participants	Inclusion criteria: aged 4 to 12 years with myopic refraction of at least 1.0 D in both eyes, astigmatism of less than 2.5 D, and documented myopic progression of at least 0.5 D in the past 1 year Exclusion criteria: ocular diseases (e.g., cataract, congenital retinal diseases, amblyopia, and strabismus), previous use of atropine or pirenzepine, or orthokeratology lens or other optical methods for myopia control, allergy to atropine, or systemic diseases (e.g., endocrine, cardiac, and respiratory diseases)
Interventions	Intervention: 0.05% atropine eye drops Comparison intervention 1: 0.025% atropine eye drops Comparison intervention 2: 0.01% atropine eye drops Comparison intervention 3: placebo eye drops
Outcomes	Primary outcome: spherical equivalent Secondary outcomes: axial length, accommodation amplitude, mesopic and photopic pupil sizes, distant best corrected visual acuity, near visual acuity Maximum follow-up: 1 year
Notes	Study name: Low-concentration atropine for myopia progression (LAMP) study: a randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control

Zhao 2017

Methods	Randomized parallel-group design
Participants	Inclusion criteria: juveniles with ametropia and aged 11-15 years Exclusion criteria: glaucoma, cataract, retinal detachment or denaturation, and other ocular diseases affecting vision
Interventions	Intervention: blue-violet light filtering lenses Comparison intervention: ordinary aspherical lenses
Outcomes	Primary outcome: refractive power, axial length, contrast sensitivity (glare and non-glare under bright and dark conditions), accommodation, asthenopia, adverse reaction Secondary outcomes: not reported Maximum follow-up: 1 year
Notes	Study name: Role of short-wavelength filtering lenses in delaying myopia progression and amelioration of asthenopia in juveniles

N/A: not applicable.

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12605000633684

Study name	Trial of an experimental soft contact lens designed to inhibit the progression of axial myopia in children
Methods	Randomized cross-over design (within-person study)
Participants	**Inclusion criteria:** 40 children aged 11 to 14 years with progressing myopia, spherical equivalent refraction of -1.50 to -4.00, visual acuity of 6/6 or better **Exclusion criteria:** children with astigmatism > 0.75 D, anisometropia > 1.00 D, abnormal binocular vision, ocular pathology, systemic disease with ocular complications, active anterior surface disease that would preclude contact lens wear, inadequate fit of soft contact lenses
Interventions	**Intervention:** frequent replacement soft contact lens that both corrects vision and simultaneously produces myopic retinal defocus **Comparison intervention:** standard single vision frequent replacement soft contact lens
Outcomes	**Primary outcome:** myopia progression rate **Secondary outcomes:** refractive error, axial length **Maximum follow-up:** 20 months
Starting date	November 2005 **Estimated end date:** not reported
Contact information	http://www.anzctr.org.au/ ACTRN12605000633684 .aspx
Notes	

ACTRN12608000566336

Study name	Myopia control lens efficacy trial
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 300 children aged 6 to 12 years with spherical equivalent refractive error of –0.50 to -4.50 D, astigmatism of not more than -1.50 D, anisometropia of not more than -1.50 D in spherical or cylindrical error, best-corrected visual acuity of at least 6/9 (20/30) in each eye, normal ocular health other than myopia, no prior use of bifocal or progressive lenses in the last 12 months, no rigid contact lenses or bifocal contact lens experience, willingness not to wear contact lenses, in satisfactory health, willingness and ability to tolerate cycloplegia, informed parental consent **Exclusion criteria:** no availability for follow-up for at least 2 years, absence of parental consent to the random assignment of their child to 1 of 3 spectacle lens groups, any systemic condition that might affect refractive development or systemic disease that may affect vision or refractive error, previous use of contact lens/PALs or other treatment for myopia within the last 12 months, defective binocular function, amblyopia and or manifested squint, vestibular disorders or motor imbalance, any other conditions precluding adherence to the protocol
Interventions	**Intervention 1:** binocular progressive 1.00 D addition lenses

ACTRN12608000566336 *(Continued)*	
	Intervention 2: binocular progressive 1.50 D addition lenses **Comparison intervention:** single vision binocular lens
Outcomes	**Primary outcomes:** refractive error, axial length **Secondary outcome:** peripheral refractive error **Maximum follow-up:** 24 months
Starting date	September 2008 **Estimated end date:** September 2009
Contact information	https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=83124
Notes	

ACTRN12611000499987	
Study name	Duplex orthokeratology (DOK) and myopia progression in children
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** (1) 10 to 14 years of age; (2) spherical equivalent refractive error between -1.25 D and -4.00 D; (3) myopia progression of at least 0.50 D in previous 12 months; (4) astigmatism < 1.50 D; (5) anisometropia < 1.00 D; (6) best-corrected visual acuity of 6/6 or better in both eyes; (7) good general and ocular health; (8) parents and child able to communicate in English **Exclusion criteria:** (1) recent rigid contact lens wear; (2) history of corneal surgery; (3) active eye disease including keratoconus; (4) severe dry eye symptoms; (5) systemic disease affecting visual acuity; (6) taking medication that could affect ocular health
Interventions	**Intervention:** duplex (dual focus optic zone) orthokeratology lens in 1 eye (overnight wear) **Intervention comparison:** conventional orthokeratology lens in the other eye (overnight wear) Note: children were randomly assigned to wear the orthokeratology lens in the dominant eye or the nondominant eye
Outcomes	**Primary outcome:** change in vitreous chamber depth, measured by non-contact Optical Low-Coherence Reflectometry (Lenstar LS 900, Haag Streit, Switzerland) **Secondary outcomes:** magnitude of central and peripheral refractive error, amplitude of accommodation, contrast sensitivity
Starting date	May 2011 **Estimated end date:** not reported
Contact information	John Phillips, PhD, or Martin Loertscher Department of Optometry and Vision Science The University of Auckland 85 Park Road Grafton, Auckland 1023

ACTRN12611000499987 *(Continued)*

	email: j.phillips@auckland.ac.nz; m.loertscher@auckland.ac.nz http://www.anzctr.org.au/ACTRN12611000499987.aspx
Notes	

ACTRN12611000582954

Study name	Myopia control with progressive spectacle lenses trial (MCPAL-3)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 167 children aged 7 to 12 years with refractive error between -1.00 D and -4.50 D, best-corrected visual acuity of at least 6/9 or 20/30 in each eye, and anisometropia not more than -1.50 D, astigmatism not greater than -1.50 D, no other ocular conditions, no history of using bifocal or progressive lenses in 12 months preceding study, and tolerant to cycloplegia, with parental consent **Exclusion criteria:** systemic condition affecting vision or refractive errors, history of contact lens or other treatment for myopia in the preceding 12 months, impaired binocular function, history of amblyopia, manifest squint, vestibular disorders or motor imbalance, other conditions that prevent adherence to protocol
Interventions	**Intervention:** progressive addition lenses **Comparison intervention:** single vision lenses
Outcomes	**Primary outcome:** progression in refractive error (spherical equivalent using cycloplegic autorefraction) **Secondary outcome:** axial length **Maximum follow-up:** 24 months
Starting date	June 2011 **Date of last participant enrolment:** June 2012
Contact information	https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=343027
Notes	

ACTRN12611001148965

Study name	To determine the rate of refractive error change in children wearing multifocal soft contact lens as compared to those wearing single vision soft contact lenses
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 40 children aged 8 to 14 years with cycloplegic autorefraction: sphere -0.50 D to -4.00 D; cylinder 0 to -0.75 D; best-corrected visual acuity 6/9 or better; ability to safely wear contact lenses; distortion-free keratometric readings; no active corneal infection, inflammation, or infection of the anterior chamber, eye disease, injury or abnormality of the cornea; conjunctiva or eyelids affecting wearing of contact lenses; no previous ocular surgery; no severe insufficiency of lacrimal secretion; no evidence of corneal hypoesthesia; no systemic disease or use of medications that may affect the eye or produce an adverse response by the wearing of contact lenses

ACTRN12611001148965 *(Continued)*

	Exclusion criteria: binocular vision problems, strabismus, amblyopia, external ocular problems that may impact lens fit (i.e. lid ptosis, chalazia, swollen lids)
Interventions	**Intervention:** multifocal soft contact lenses **Comparison intervention:** single vision soft contact lenses
Outcomes	**Primary outcome:** rate of myopia progression **Secondary outcomes:** fitting characteristics of, and ocular response to, soft contact lenses **Maximum follow-up**: 3 years
Starting date	November 2005 **Estimated end date:** not reported
Contact information	https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=347659
Notes	

ACTRN12617000598381

Study name	A pilot study to evaluate the effectiveness of daily 0.01% atropine eye drop therapy in modifying the progression of myopia, in Australian children
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** aged 6 to 16 years, myopia with spherical equivalent refractive error greater or equal to -1.5 D in each eye, documented myopic progression of greater than or equal to -0.5 D over the previous 12 months in either eye, astigmatism less than -1.5 D, intraocular difference in spherical equivalent < 1 D, corrected visual acuity greater than logMar 0.2, normal IOP, normal ocular health, no history of cardiac/respiratory disease, willingness and ability to provide details of parents' country of origin, ability to provide appropriate parental/carer consent **Exclusion criteria:** astigmatism of 1.5 D or more; 1 D or more anisometropia; severe developmental delay (inability to participate in subjective refraction of testing); ocular comorbidities such as glaucoma, aphakia, pseudophakia, uveitis, keratoconus, or connective tissue disease (e.g. Marfan syndrome, vitreoretinal dystrophies); severe ocular surface disease; previous atropine treatment for amblyopia at any time in the past
Interventions	**Intervention:** 0.01% atropine eye drops **Comparison intervention:** placebo eye drops
Outcomes	**Primary outcome:** mean change in spherical equivalent refractive error **Secondary outcomes:** amplitude of accommodation, choroidal thickness, corneal curvature and axial length, Wilkins Rate of Reading test comparison, intraocular pressure, stereovision assessment, quality of life **Maximum follow-up:** 24 months
Starting date	January 2017 **Estimated end date:** December 2020
Contact information	https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372668

ACTRN12617000598381 *(Continued)*

Notes	

ACTRN12618000242224

Study name	Prospective, contralateral, randomized, cross-over dispensing clinical trial to compare the myopia progression rate between a myopia control contact lens and single vision contact lenses
Methods	Randomized cross-over design (within-person study)
Participants	**Inclusion criteria:** 45 participants aged 6 to 17 years, spherical equivalent -0.75 D to -3.50 D, cylinder no more than -1.00 D, anisometropia ≤ 0.75 D, vision correctable to 6/9.5 or better **Exclusion criteria:** preexisting ocular irritation precluding contact lens fitting, systemic or ocular condition or injury, corneal refractive surgery, keratoconus, allergy to cyclopentolate, astigmatism > 1.00 D in either eye, strabismus, amblyopia, any ocular or systemic disease associated with myopia, retinopathy of prematurity, current orthoptic treatment or vision training, eye injury or surgery within 12 weeks before enrollment, atropine treatment for myopia control, previously worn bifocal or progressive spectacles or antimyopia contact or orthokeratology lenses, anisometropic by > 0.75 D
Interventions	**Intervention:** experimental contact lens (lens type not reported) **Comparison intervention:** single vision contact lens
Outcomes	**Primary outcome:** change in cycloplegic autorefraction spherical equivalent **Secondary outcomes:** change in axial length **Maximum follow-up:** 12 months
Starting date	January 2018 **Estimated end date:** not reported
Contact information	https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374450
Notes	

BLINK Study 2017a

Study name	Bifocal lenses in nearsighted kids (BLINK)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 7 to 11 years of age, inclusive; at baseline examination, -0.75 to -5.00 D, inclusive; spherical component; cycloplegic autorefraction ≤ 1.00 DC; cycloplegic autorefraction; ≥ 2.00 D difference between sphere components of the 2 eyes (anisometropia); cycloplegic autorefraction; 0.1 logMAR or better best-corrected visual acuity in each eye; 0.1 logMAR or better visual acuity OU distance and near with a +2.50 D add contact lens; +2.50 D add lens provides adequate fit with respect to movement and centration **Exclusion criteria:** eye disease or binocular vision problems (e.g. strabismus, amblyopia, oculomotor nerve palsies, corneal disease); systemic disease that may affect vision, vision development, or contact lens wear (e.g. diabetes, Down syndrome); previous gas permeable, soft bifocal,

BLINK Study 2017a *(Continued)*

	or orthokeratology contact lens wear or bifocal/PAL spectacle wear (longer than 1 month of wear); chronic use of medication that may affect immunity
Interventions	**Intervention 1:** Biofinity Multifocal D +1.50 add **Intervention 2:** Biofinity Multifocal D +2.50 add **Comparison intervention:** Biofinity
Outcomes	**Primary outcomes:** ocular shape change, eye growth, peripheral defocus, axial length **Secondary outcomes:** not reported **Maximum follow-up:** 3 years
Starting date	September 2014 **Estimated end date:** July 2019
Contact information	https://clinicaltrials.gov/ct2/show/NCT02255474
Notes	Study author

ChiCTR1800016504

Study name	Clinical effect of vitamin B12 eye drops on myopia in children
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** age 6 to 12 years; the refractive power of the eyes after dilation is between -1.0 and -3.0d; no refractive error (binocular diopter within -1.0d); binocular astigmatism < -1.5d; far vision of the eyes can be corrected to at least 0.8; the intraocular pressure is lower than 21mmHg; no allergy to dilated pupils; no corneal plasticizer has been used to treat myopia; no amblyopia, squint, etc. **Exclusion criteria:** failing to meet the inclusion criteria; unwilling to participate in this study
Interventions	**Intervention:** vitamin B12 eye drop **Comparison intervention:** no intervention
Outcomes	**Primary outcome:** diopter **Secondary outcomes:** not reported **Maximum follow-up:** 12 months
Starting date	July 2018 **Estimated end date:** June 2019
Contact information	http://www.chictr.org.cn/showprojen.aspx?proj=26962
Notes	

ChiCTR1800017683

Study name	A double-masked comparative study of peripheral defocus lenses
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** age 8 to 13 years; spherical refractive error of -0.75 to -4.75 D in each eye, as measured by cycloplegic autorefraction; astigmatism of not more than 1.50 D; anisometropia of not more than 1.00 D; best corrected visual acuity of equal or better than 0.05 LogMAR (≥ 0.9 as Snellen) **Exclusion criteria:** history of PALs or bifocal use and no prior use of contact lenses; strabismus by cover test at near and distance; ocular disease with full ophthalmic examination, such as retinal disease, cataract and ptosis; systemic or neurodevelopmental conditions; ocular or systemic medicine, which might affect myopia progression or visual acuity through known effects on retina, accommodation or significant elevation of intraocular pressure
Interventions	**Intervention 1:** "defocus lenses" **Intervention 2:** "defocus lenses" **Comparison intervention:** single vision lenses
Outcomes	**Primary outcome:** refractive power; axial Length; contrast visual acuity **Secondary outcomes:** not reported **Maximum follow-up:** not reported
Starting date	July 2018 **Estimated end date:** November 2020
Contact information	http://www.chictr.org.cn/hvshowproject.aspx?id=13585
Notes	

ChiCTR1900021316

Study name	Clinical observation for auricular acupoint stimulation combined with low-concentration atropine in myopia control and its effect on accommodative microfluctuations
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** age 6 to 11 years children; male or female; with simple myopia; 0.5% tocarbamide mydriatic optometry: +0.5DS to-6.0DS; corneal topography Kmax: 42-44D; astigmatism of less than 1.50D, anisometropia of less than 1.00D, intraocular pressure of 10 to 21mmHg; patient with good compliance who volunteers to join the subject and signs informed consent **Exclusion criteria:** patient with other ocular diseases (e.g., cataract, congenital retinal disease, strabismus, amblyopia) or systemic diseases; patient with active eye lesions or undergo eye surgery; allergy to atropine;patient whose skin of the auricular acupoint area is broken or patient who has allergy to auricular plaster; guardians do not hold reasonable expectations
Interventions	**Intervention:** 0.01% atropine eyedrops combined with auricular acupoint stimulation **Comparison intervention:** 0.01% atropine eyedrops
Outcomes	**Primary outcome:** uncorrected distance visual acuity; diopter; axial length

ChiCTR1900021316 *(Continued)*

	Secondary outcomes: anterior chamber depth; accommodation amplitude; accommodative microfluctuations **Maximum follow-up:** not reported
Starting date	February 2019 **Estimated end date:** May 2020
Contact information	http://www.chictr.org.cn/hvshowproject.aspx?id=15141
Notes	

ChiCTR-INR-17013794

Study name	The effectiveness safety of corneal contact lens used to correct myopia: a multi-center, randomized, open and positive parallel control clinical trial
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 41 patients aged 8 to 40 years with myopia ≤ 4.00 D, astigmatism with-the-rule of < 1.75 D, and astigmatism against-the-rule of < 1.00 D; best-corrected visual acuity not less than 20/20; corneal curvature at 40.00 D to 46.00 D; diopter stay stability before trial; has not worn hard contact lenses in the past 2 months **Exclusion criteria:** systemic disease that causes low immunity or effects on corneal shape; corneal abnormality; corneal surgery; history of corneal or ocular trauma; hypocorneal sensory impairment; intraocular surgery; fundus lesions; ocular disease; pregnant or lactating; use of drugs that cause dry eyes or affect corneal curvature; allergy to contact lens or its solution; pupil diameter > 6.2 mm
Interventions	**Intervention:** corneal contact lens 2 (not specified) **Comparison intervention:** corneal contact lens 2 (not specified)
Outcomes	**Primary outcome:** visual acuity **Secondary outcomes:** not reported **Maximum follow-up:** not reported
Starting date	May 2017 **Estimated end date:** December 2018
Contact information	http://www.chictr.org.cn/showprojen.aspx?proj=23702
Notes	

ChiCTR-INR-17013853

Study name	Effects of orthokeratology and combined with 0.01% atropine on myopia control: a multicenter comparative study
Methods	Randomized parallel-group design

ChiCTR-INR-17013853 *(Continued)*

Participants	**Inclusion criteria:** 216 children aged 8 to 15 years; spherical degree without dilation ≥ -1.00 D and ≤ -5.50 D; equivalent spherical degree ≥ -1.00 D and ≤ -5.50 D; astigmatism ≤ -1.50 D; best-corrected visual acuity ≥ 1.0 D; no strabismus; no contact lens wearing history; no history of myopia control by optical or drug route; no active inflammation or ocular surface disease; no serious ocular appendage lesions and eye organic disease; cooperation with researchers **Exclusion criteria:** systemic connective tissue disease and autoimmune disease; history of ocular trauma or surgery; history of severe ocular infection
Interventions	**Intervention 1:** orthokeratology at night **Intervention 2:** orthokeratology at night and 0.01% atropine eye drops before sleep **Comparison intervention:** single vision spectacles
Outcomes	**Primary outcomes:** axial length, refraction, eyesight **Secondary outcomes:** IOP, corneal topography **Maximum follow-up:** 12 months
Starting date	December 2017 **Estimated end date:** June 2019
Contact information	http://www.chictr.org.cn/showprojen.aspx?proj=22940
Notes	

ChiCTR-IOR-17010432

Study name	Myopia progression with invisible round segment bifocal spectacle lenses
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** best-corrected vision of 6/9.5 or better with spectacles in each eye; normal ocular health; ability to comply with trial protocol; parental ability to understand English and Mandarin and parental consent **Exclusion criteria:** history of allergy to topical anesthetics; strabismus; eye surgery; ocular or systemic condition affecting vision; ocular injury; use of bifocals, spectacles, orthokeratology, vision training, orthoptic training, or conditions that affect ability to wear spectacles
Interventions	**Intervention:** bifocal spectacles **Comparison intervention:** single vision spectacles
Outcomes	**Primary outcome:** spherical equivalent **Secondary outcome:** axial length **Maximum follow-up**: not reported
Starting date	February 2017 **Estimated end date:** September 2018
Contact information	http://www.chictr.org.cn/showproj.aspx?proj=17727

ChiCTR-IOR-17010432 *(Continued)*

Notes	

ChiCTR-IOR-17011993

Study name	Prospective, masked, contralateral, randomized, cross-over dispensing clinical trial to compare the myopia progression rate between myopia control contact lenses and single vision contact lenses
Methods	Randomized cross-over design
Participants	**Inclusion criteria:** aged between 7 years and 13 years (7 years and 13 years inclusive); spherical component -0.75 D to -3.50 D with cylinder no more than -0.75 D; anisometropia ≤ 0.75 D; informed consent; parent or guardian who is able to read and comprehend Mandarin and give informed consent as demonstrated by signing a record of informed consent by both parent/guardian and participant; ocular health findings considered to be normal and that would not prevent patient from safely wearing contact lenses; vision correctable to 6/9.5 or better in each eye with study contact lenses **Exclusion criteria:** preexisting ocular irritation that would preclude contact lens fitting; any systemic or ocular condition or ocular injury that may preclude safe wearing of contact lenses; having undergone corneal refractive surgery; at baseline, astigmatism more than 0.75 D in either eye; past strabismus and/or current ongoing amblyopia; any ocular, systemic, or other condition or disease with possible associations with myopia or affecting refractive development; current orthoptic treatment or vision training; eye injury or surgery within 12 weeks immediately before enrollment for this trial; having undergone atropine treatment for myopia control, worn bifocal or progressive addition spectacles or antimyopia contact lenses previously; having worn orthokeratology lenses previously; requiring anticholinergic medication for gastrointestinal or other conditions; at baseline, anisometropic by more than 0.75 D
Interventions	**Intervention 1:** single vision contact lenses in both eyes **Intervention 2:** myopia control contact lens in 1 eye, and single vision contact lens in the other eye; contact lenses swapped between eyes after 6 months **Comparison intervention:** myopia control contact lens in 1 eye, and single vision contact lens in the other eye; contact lenses swapped between eyes after 6 months
Outcomes	**Primary outcome:** spherical equivalent, axial length **Secondary outcomes:** not reported **Maximum follow-up:** not reported
Starting date	Not reported **Estimated end date:** not reported
Contact information	http://www.chictr.org.cn/showprojen.aspx?proj=20301
Notes	

ChiCTR-IPD-16008844

Study name	Clinical study of low-concentration atropine in controlling child myopia
Methods	Randomized parallel-group design

ChiCTR-IPD-16008844 *(Continued)*

Participants	**Inclusion criteria:** 400 children aged 6 to 12 years; myopia spherical equivalent degree: -1.25 to -6.0; astigmatism less than 2.0; distance corrected visual acuity greater than or equal to 0.8, without significant skew and other eye disease; no ocular inflammation; no history of ocular trauma; no history of ocular surgery; no systemic and ocular implement qualitative sex pathological change **Exclusion criteria:** congenital myopia and pathological myopia; premature and low birth weight myopia patients, with no other related myopia drugs and training method in the past 6 months
Interventions	**Intervention 1:** 0.005% concentration atropine **Intervention 2:** 0.01% concentration atropine **Intervention 3:** 0.02% concentration atropine **Intervention 4:** 0.02% concentration atropine, once every 2 days **Comparison intervention:** spectacles
Outcomes	**Primary outcomes:** "myopia degree" **Secondary outcome:** not reported **Maximum follow-up:** not reported
Starting date	July 2016 **Estimated end date:** July 2020
Contact information	http://www.chictr.org.cn/com/25/hvshowproject.aspx?id=11127
Notes	

ChiCTR-TRC-07000029

Study name	Double-blinded, randomized controlled trial about the influence of new lenses on the progress of children's myopia
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 200 children aged 6 to 16 years; degree of myopia > -0.50 D and < -4.50 D; astigmatism degree < -1.50 D; binocular anisometropic degree < 1 D; healthy ocular region; visual acuity can be corrected to 6/9 (20/30) or higher **Exclusion criteria:** strabismus or amblyopia; history of allergy to tropicamide; any ophthalmopathy, previous ophthalmic surgery, systemic disease that may be related to myopia; using anticholinergic drugs; taking part in other myopia-controlled study; previous wearing of orthokeratology lenses in the last 2 weeks; accepted or are participating in orthophoria treatment or vision training
Interventions	**Intervention 1:** type A lenses **Intervention 2:** type B lenses **Intervention 3:** type C lenses **Comparison intervention:** routine lenses
Outcomes	**Primary outcomes:** axial length

ChiCTR-TRC-07000029 *(Continued)*

	Secondary outcome: "diopter" **Maximum follow-up:** not reported
Starting date	October 2007 **Estimated end date:** November 2009
Contact information	http://www.chictr.org.cn/showproj.aspx?proj=9496
Notes	

ChiCTR-TRC-07000044

Study name	Clinical randomized controlled trial of progressive addition lenses on control of myopia in Chinese adolescents
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 178 adolescents aged 7 to 18 years; computer optometry after cycloplegia; binocular myopia; spherical equivalent degree between -0.75 and -3.00 D; astigmatism degree less than -1.50 D; binocular anisometropic degree less than 1.00 D; bilateral corrected visual acuity more than 1.0; normal intraocular pressure: binocular intraocular pressure less than 21 mmHg, and difference less than 2 mmHg; no history of wearing contact lenses, bifocals, or multifocal lenses; term infants; birth weight more than 1250 g; agree to wear lenses and follow up for more than 2 years; understand the study objective and accept the randomized allocation **Exclusion criteria:** manifest strabismus or other ophthalmopathy; systematic disease; use of drugs that may influence the refractive status; myopia degree of either parent more than 3 D; use of contact lenses or other myopia treatment methods in the study
Interventions	**Intervention:** gradual focal lens **Comparison intervention:** routine single lens
Outcomes	**Primary outcomes:** myopic degree, eyeball biotest **Secondary outcome:** heterophoria **Maximum follow-up:** not reported
Starting date	July 2004 **Estimated end date:** May 2007
Contact information	http://www.chictr.org.cn/showproj.aspx?proj=9481
Notes	

ChiCTR-TRC-09000476

Study name	Novel spectacle lenses vs single vision spectacle lenses on progression of myopia in children: a randomized clinical trial
Methods	Randomized parallel-group design

ChiCTR-TRC-09000476 *(Continued)*

Participants	**Inclusion criteria:** children aged 6 to 12 years with spherical equivalent refraction between -0.75 D and -3.50 D; astigmatism less than or equal to -1.50 D; best-corrected vision of at least 6/9.5 with spectacles; ability to comply with study protocol; normal ocular health **Exclusion criteria:** anisometropia less than or equal to 1.00 D; history of allergy to topical anesthetics; strabismus; eye surgery; ocular or systemic conditions affecting vision; ocular injury; use of bifocals, spectacles, orthokeratology, vision training, orthoptic training, or conditions that affect ability to wear spectacles; concurrent participation in another clinical trial
Interventions	**Intervention:** not reported ("Iteration E") **Intervention:** not reported ("Iteration G") **Intervention:** not reported ("Iteration F") **Intervention:** not reported ("Iteration H") **Comparison intervention:** single vision spectacle lenses
Outcomes	**Primary outcomes:** cycloplegic autorefraction **Secondary outcome:** not reported **Maximum follow-up:** not reported
Starting date	August 2009 **Estimated end date:** December 2011
Contact information	http://chictr.org.cn/showprojen.aspx?proj=9058
Notes	

ChiCTR-TRC-10000914

Study name	Progression of refractive error in myopic Chinese children wearing commercially available single vision spectacles
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** children aged 7 to 14 years; spherical equivalent refraction between -0.50 D and -3.50 D; astigmatism less than or equal to 0.75 D; best-corrected vision in each eye of at least 6/9.5; ability to comply with protocol; parental ability to comprehend Mandarin; parental ability to consent **Exclusion criteria:** anisometropia not greater than 1.50 D; prior use of atropine for myopia control; prior use of bifocal or progressive addition spectacles or concurrent use of orthokeratology contact lenses in the previous 12 months; prior eye surgery or ocular trauma; history of ocular or systematic condition that affects refractive development
Interventions	**Intervention:** spherical profile spectacle lenses **Comparison intervention:** aspheric front surface spectacle lenses
Outcomes	**Primary outcomes:** spherical equivalent refraction, axial length **Secondary outcome:** not reported

ChiCTR-TRC-10000914 *(Continued)*

	Maximum follow-up: not reported
Starting date	July 2010 **Estimated end date:** September 2013
Contact information	http://www.chictr.org.cn/showprojen.aspx?proj=8624
Notes	

ChiCTR-TRC-11001463

Study name	Efficacy of MyoVision spectacle lenses for slowing the progression of myopia
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 200 children aged 6 to 12 years; myopic; spherical component -0.75 D to -3.50 D with astigmatism no more than -1.50 D; having at least 1 parent who is myopic; willingness to comply with wearing and visit schedule; having normal ocular health findings; having vision correctable to 6/9.5 or better in each eye with spectacles **Exclusion criteria:** allergy to tropicamide or topical anaesthetics; anisometropic by more than 1.00 D; strabismus or amblyopia; previous eye surgery; ocular or systemic disease with possible associations with myopia; any ocular injury or condition of the cornea or conjunctiva or eyelids; having worn bifocals or MyoVision spectacles in the last 12 months; having worn orthokeratology or bifocal contact lenses in the last 12 months; current orthoptic treatment or vision training
Interventions	**Intervention:** MyoVision spectacles **Comparison intervention:** single vision spectacles
Outcomes	**Primary outcome:** myopia progression **Secondary outcome:** axial length **Maximum follow-up:** not reported
Starting date	August 2011 **Estimated end date:** January 2014
Contact information	http://www.chictr.org.cn/hvshowproject.aspx?id=1096
Notes	

ChiCTR-TRC-11001746

Study name	Assessment of myopia progression rates in children wearing either a multifocal center near or single vision soft contact lens
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 100 children aged 10 to 17 years; Chinese ethnicity; myopic (short-sighted) up to -8.00 D of spherical equivalent; willingness to comply with wearing and clinical trial visit schedule as directed by the investigator; having ocular health findings considered to be “normal” and that

ChiCTR-TRC-11001746 *(Continued)*

	would prevent the patient from safely wearing contact lenses; having distance vision correctable to 6/9.5 or better in each eye with study contact lenses **Exclusion criteria:** preexisting ocular irritation, injury, or condition; any systemic disease that adversely affects ocular health; eye surgery within 12 weeks immediately before enrollment for this trial; previous corneal refractive surgery; keratoconus; known allergy to, or history of, intolerance to tropicamide or topical anaesthetics; past strabismus and/or amblyopia; any ocular, systemic, or other condition or disease with possible associations with myopia or affecting refractive development; current orthoptic treatment or vision training; having undergone atropine treatment for myopia control; having worn bifocal or progressive addition spectacles in the previous 12 months; having worn orthokeratology lenses in the previous 12 months; requiring anticholinergic medication for gastrointestinal or other conditions; pregnant or lactating females
Interventions	**Intervention 1:** multifocal silicone hydrogel contact lens **Intervention 2:** spherical silicone hydrogel contact lens
Outcomes	**Primary outcomes:** cycloplegic autorefraction, axial length **Secondary outcomes:** not reported **Maximum follow-up:** not reported
Starting date	December 2011 **Estimated end date:** December 2015
Contact information	http://www.chictr.org.cn/hvshowproject.aspx?id=1766
Notes	

ChiCTR-TRC-13003396

Study name	Myopia progression with sedentary use, small segment, concentric bifocals
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** children aged 6 to 12 years, with spherical equivalent of -0.75 D to -3.50 D; astigmatism not greater than -1.50 D; normal ocular health; parental willingness to comply with the protocol; ability to consent **Exclusion criteria:** anisometropia less than or equal to 1.00 D; history of allergy to topical anesthetics; strabismus; eye surgery; ocular or systemic conditions affecting vision; ocular injury; use of bifocals, spectacles, orthokeratology, vision training, orthoptic training, or condition that affects ability to wear spectacles; concurrent participation in another clinical trial
Interventions	**Intervention:** intermittent alternate use of spectacles with concentric bifocal lenses and single vision lenses **Comparison intervention:** single vision lens spectacles
Outcomes	**Primary outcome:** change in spherical equivalent **Secondary outcome:** change in axial length **Maximum follow-up:** not reported
Starting date	August 2013

ChiCTR-TRC-13003396 *(Continued)*

	Estimated end date: March 2015
Contact information	http://www.chictr.org.cn/hvshowproject.aspx?id=6324
Notes	

ChiCTR-TRC-13004032

Study name	Chinese University Low dose Atropine for Myopia Progression Study (CU-LAMP)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** age 4 to 12 years; myopia: SE -1 to -10 D; astigmatism: < 2.5 D; anisometropia: < 2.0 D; myopia progression > 1 D for BE in one year; informed parental consent **Exclusion criteria:** ophthalmic diseases other than refractive errors; previous use of treatment of atropine; allergy or intolerance to atropine; inability to attend regular follow up assessment
Interventions	**Intervention 1:** 0.05% atropine eye drops **Intervention 2:** 0.025% atropine eye drops **Intervention 3:** 0.01% atropine eye drops **Comparison intervention:** 0.9% normal saline eye drops
Outcomes	**Primary outcome:** spherical equivalent refraction (cycloplegic refraction); axial length **Secondary outcomes:** safety variable: best corrected visual acuity, pupil size, intraocular pressure **Maximum follow-up:** not reported
Starting date	January 2014 **Estimated end date:** not reported
Contact information	http://www.chictr.org.cn/hvshowproject.aspx?id=14749
Notes	

ChiCTR-TRC-14004227

Study name	Assessment rate of progression of myopia with contact lenses in Chinese children
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 450 children aged 8 to 12 years; Chinese ethnicity; myopic (short-sighted); -0.75 D to -3.50 D of cycloplegic spherical equivalent with astigmatism no more than 0.75 D; preferably progressive myopia; ocular health findings considered to be “normal”; vision correctable to 6/9.5 or better in each eye with study contact lenses **Exclusion criteria:** preexisting ocular irritation that would preclude contact lens fitting; any systemic or ocular condition or ocular injury that may preclude safe wearing of contact lenses; having undergone corneal refractive surgery; keratoconus; allergy to or history of intolerance to tropicamide or topical anesthetics; astigmatism more than 0.75 D in either eye; past strabismus and/or current ongoing amblyopia; any ocular, systemic, or other condition or disease with possible asso-

ChiCTR-TRC-14004227 *(Continued)*

	ciations with myopia or affecting refractive development; eye injury or surgery within 12 weeks immediately before enrollment for this trial; having undergone atropine treatment for myopia control; having worn bifocal or progressive addition spectacles or antimyopia contact lenses previously; having worn orthokeratology lenses previously; requiring anticholinergic medication for gastrointestinal or other conditions; anisometropic by more than 1.50 D; current enrollment in another clinical trial/research project
Interventions	**Intervention 1:** Clariti contact lenses **Intervention 2:** Aquamax contact lenses
Outcomes	**Primary outcome:** myopia progression **Secondary outcomes:** not reported **Maximum follow-up:** not reported
Starting date	February 5, 2014 **Estimated end date:** October 30, 2017
Contact information	http://www.chictr.org.cn/hvshowproject.aspx?id=8971
Notes	

ChiCTR-TRC-14004990

Study name	Low-concentration atropine to slow myopic progression in children
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 100 children aged 8 to 12 years with myopia of spherical equivalent -1 D to -6 D; astigmatism less than 1.5 D; anisometropia less than 2D; best-corrected visual acuity larger than 0.8; intraocular pressure less than 21 mmHg; myopia progression more than 0.5 D in 1 year **Exclusion criteria:** ophthalmic disease other than refractive error or systematic disease; previous use of treatment of atropine, RGP, or ortho-k; allergy or intolerance to atropine or tropicamide
Interventions	**Intervention:** 0.01% atropine eye drops **Comparison intervention:** placebo eye drops
Outcomes	**Primary outcome:** refraction **Secondary outcomes:** axial length, pupil size, residue accommodation **Maximum follow-up:** not reported
Starting date	July 2014 **Estimated end date:** not reported
Contact information	http://www.chictr.org.cn/showproj.aspx?proj=4584
Notes	

CTRI/2016/11/007450

Study name	Atropine eye drops to decrease myopia progression in children
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 40 children aged 6 to 12 years; refractive error of spherical equivalent between -2 D and -6 D in each eye; distance vision correctable to logMAR 0.2 or better in both eyes; normal ocular health other than myopia; informed consent; willingness to follow up **Exclusion criteria:** astigmatism more than -1.5 D; amblyopia; strabismus; allergy to atropine or homatropine; previous or concurrent use of contact lenses, bifocals, progressive addition lenses, or other forms of treatment for myopia; history of cardiac, neurological, or significant respiratory disease; unwillingness to give consent/follow-up
Interventions	**Intervention 1:** 0.01% atropine eye drop **Comparison intervention:** 0.5% carboxymethylcellulose eye drop
Outcomes	**Primary outcome:** myopia progression **Secondary outcomes:** side effects **Maximum follow-up:** 1 year
Starting date	January 2016 **Estimated end date:** not reported
Contact information	http://ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=15817&EncHid=&modid=&compid=%27,%2715817det%27
Notes	

IRCT20100414003714N3

Study name	Study of the effect of atropine eye drops with concentration of 0.1% & 0.01% and placebo in natural course of myopia progression in children 6 to 18 years old
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** aged 6 to 18 years; myopia or astigmatism (2 to 6 diopters); no amblyopia **Exclusion criteria:** strabismus
Interventions	**Intervention 1:** 0.1% atropine eye drops for 12 months **Intervention 2:** 0.11% atropine eye drops for 12 months **Comparison intervention:** artificial eye drops for 12 months
Outcomes	**Primary outcomes:** percentage of myopic power, axial length changes **Secondary outcomes:** not reported **Maximum follow-up:** 6 months
Starting date	June 2018 **Estimated end date:** December 2019

IRCT20100414003714N3 *(Continued)*

Contact information	http://en.irct.ir/trial/31944
Notes	

IRCT20180216038747N1

Study name	Controlling myopia progression
Methods	Not reported
Participants	**Inclusion criteria:** myopia -0.50 D to -6.00 D; astigmatism ≤ 0.75 D **Exclusion criteria:** myopic children with any ocular disease such as cataract, glaucoma, uveitis, strabismus; history of trauma; history of any ocular surgery systemic disease
Interventions	**Intervention 1:** 0.01% atropine eye drops for 1 year **Intervention 2:** 0.02% atropine eye drops for 1 year **Comparison intervention:** artificial tear drops for 1 year
Outcomes	**Primary outcomes:** axial length of the eye, accommodation amplitude, pupil size **Secondary outcomes:** not reported **Maximum follow-up:** 12 months
Starting date	April 2018 **Estimated end date:** May 2019
Contact information	https://www.irct.ir/trial/30096
Notes	

ISRCTN36732601

Study name	Efficacy, safety, and mechanisms of atropine eye drops in slowing the progression of shortsightedness (myopia) in children
Methods	Randomized cross-over design (within-person study)
Participants	**Inclusion criteria:** 250 children aged 6 to 16 years; myopia of -1.0 D or worse in each eye; astigmatism refractive error less than -1.50 D; progressive myopia of at least -0.50 D over the last year; intraocular difference in spherical difference equal to or less than 1.00 D; corrected visual acuity better than or equal to logMAR 0.2 in both eyes; normal IOP; normal ocular health **Exclusion criteria:** ocular or systemic disease affecting vision; allergy to study-related drugs; defective binocular vision; previous pharmaceutical or optical myopia control interventions
Interventions	**Intervention:** 0.01% atropine eye drops **Comparison intervention:** placebo eye drops
Outcomes	**Primary outcome:** spherical equivalent refraction

ISRCTN36732601 *(Continued)*

	Secondary outcomes: axial length, off-axis refraction, ocular growth, visual performance, ocular function, quality of life, adverse effects **Maximum follow-up:** 24 months
Starting date	October 2017 **Estimated end date:** May 2023
Contact information	http://www.isrctn.com/ISRCTN36732601
Notes	

JPRN-UMIN000005054

Study name	Clinical trial to evaluate effect of spectacle lens that reduces myopia progression
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 6 to 12 years of age; myopic refractive error between -1.50 D and -4.50 D; astigmatism < 1.5 D; best-corrected visual acuity 1.0 or better; father or mother with myopia **Exclusion criteria:** strabismus; having worn bifocals or progressive addition lenses in previous year; history of orthokeratology lens wear; prior participation in myopia trials; any eye disease other than myopia
Interventions	**Intervention:** eyeglasses that reduce myopic progression **Control:** normal eyeglasses
Outcomes	Not reported
Starting date	February 2011 **Estimated end date:** not reported
Contact information	Takeshi Morimoto Department of Applied Visual Science Osaka University School of Medicine 2-2 Yamadaoka, Suita, Osaka, Japan email: takeshi.morimoto@ophthal.med.osaka-u.ac.jp http://www.umin.ac.jp/ctr/index.htm
Notes	

JPRN-UMIN000007989

Study name	Clinical trial to prevent myopia progression by progressive additional soft contact lens compared with monofocal soft contact lens in children
Methods	Randomized cross-over design

JPRN-UMIN000007989 *(Continued)*

Participants	**Inclusion criteria:** 20 children age 6 to 16 years; refractive error -0.75 D to -3.5 D; corrected visual acuity by spherical Spectacle lens: better than (0.7) **Exclusion criteria:** anisometropia greater than 1.0 D; amblyopia; strabismus
Interventions	**Intervention:** wearing progressive additional soft contact lens **Comparison intervention:** wearing monofocal soft contact lens
Outcomes	**Primary outcome:** ocular refraction **Secondary outcome:** axial length **Maximum follow-up:** not reported
Starting date	January 2011 **Estimated end date:** not reported
Contact information	https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000009401&type=summary&language=E
Notes	

JPRN-UMIN000013698

Study name	Examination of the nearsighted progress depression effect of the low-concentrated atropine in the Japanese primary school child
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 90 children aged 6 to 12 years with no eye disease except refractive error **Exclusion criteria:** children with contact lens; history of myopia progress suppression treatment
Interventions	**Intervention 1:** 0.01% atropine eye drops **Intervention 2:** 0.025% cyclopentolate eye drops **Comparison intervention:** raw diet instillation
Outcomes	**Primary outcomes:** refractive error, axial length **Secondary outcomes:** not reported **Maximum follow-up:** not reported
Starting date	March 2014 **Estimated end date:** August 2017
Contact information	https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000015991&language=E
Notes	

JPRN-UMIN000014362

Study name	Examination of suppressive effect by combined treatment of orthokeratology and atropine 0.01% ophthalmic solution on myopia progression
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** cycloplegic spherical equivalent refractive error of -1.00 to -6.00 D in both eyes; astigmatism of less than 1.50 D in both eyes; anisometropia of less than 1.50 D; best corrected visual acuity of more than 1.0 in both eyes **Exclusion criteria:** eye disorders such as strabismus and amblyopia; systemic disorders such as cardiac or respiratory illness; birth weight of less than 1500 g; history of hypersensitivity to atropine 5) using of orthokeratology and/or atropine ophthalmic solutions
Interventions	**Intervention:** orthokeratology contact lens **Comparison intervention:** atropine 0.01% ophthalmic solution
Outcomes	**Primary outcomes:** axial length **Secondary outcomes:** corneal endothelial cell density; corneal endothelial cell density **Maximum follow-up:** 2 years
Starting date	June 2014 **Estimated end date:** March 2019
Contact information	https://rctportal.niph.go.jp/en/detail?trial_id=UMIN000014362
Notes	

JPRN-UMIN000018041

Study name	The efficacy of 0.01% atropine ophthalmic solution for controlling the progression of childhood myopia (ATOM-J Study)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 180 children aged 6 to 12 years; decrease in visual within the past year; cycloplegic objective spherical equivalent of -1.00 D to -6.00 D in each eye; anisometropia within 1.50 D; astigmatism within ± 1.50 D; corrected visual acuity of at least 1.0; no intraocular pressure abnormalities; capable of undergoing cycloplegia **Exclusion criteria:** abnormal visual function; amblyopia or manifest strabismus; difference in objective spherical equivalent with and without cycloplegia > 1.00 D in each eye; ocular disorders other than myopia; ocular or systemic disorders that potentially affect myopia or refractive power; previous treatment for myopia including atropine therapy, contact lenses, bifocal lenses, or progressive lenses with atropine therapy (does not apply to children who discontinued 0.4% tropicamide ophthalmic solution at least 3 months previously); history of cardiovascular or respiratory disease; children who have received pharmacotherapy for asthma in the past year; allergy to atropine, cyclopentolate, or benzalkonium; children who cannot instill medication into the eye, requiring contact lenses, bifocal lenses, or progressive lenses during the clinical study period
Interventions	**Intervention:** 0.01% atropine ophthalmic solution **Comparison intervention:** placebo ophthalmic solution
Outcomes	**Primary outcome:** change in objective spherical equivalent

JPRN-UMIN000018041 *(Continued)*

	Secondary outcome: none reported **Maximum follow-up:** 24 months
Starting date	July 2015 **Estimated end date:** not reported
Contact information	http://apps.who.int/trialsearch/Trial2.aspx?TrialID= JPRN-UMIN000018041
Notes	

JPRN-UMIN000019237

Study name	Effect of dual-focus soft contact lens wear on myopia progression
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 28 children aged 10 to 14 years; no previous wearing of contact lenses; -1.0 D to -6.0 D refraction in each eye under nonaccommodative palsy; total astigmatism diopter within -1.5 D in each eye; corrected visual acuity > 1.0 D in each eye; no eye misalignment; not a premature infant; no ocular or systemic maldevelopment; no drug use; ability to wear contact lens for 1 week **Exclusion criteria:** as deemed appropriate by study investigators
Interventions	**Intervention:** bifocal contact lenses **Comparison intervention:** spectacles
Outcomes	**Primary outcomes:** refractivity, optic axis length **Secondary outcomes:** not reported **Maximum follow-up:** not reported
Starting date	May 2015 **Estimated end date:** not reported
Contact information	https://rctportal.niph.go.jp/en/detail?trial_id=UMIN000019237
Notes	

JPRN-UMIN000023386

Study name	Clinical trial on the use of outdoor environment glasses for a suppressive effect on myopia progression
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 140 children, aged 6 to 12 years; paralysis of accommodation in both eyes; spherical equivalent of each is between -1.50 D and 4.50 D; at least 1 parent who has myopia; no eye disease other than refractive error **Exclusion criteria:** history of wearing bifocal or progressive power lenses; history of wearing orthokeratology lenses; unequal parallax exceeding 1.50 D; astigmatism exceeding 1.50 D; overt stra-

JPRN-UMIN000023386 *(Continued)*

	bismus; received refractive surgery in the past; keratoconus or herpes conjunctivitis; papillary proliferation; participating in other similar clinical research
Interventions	**Intervention:** wearing outdoor environment glasses **Comparison intervention:** wearing normal glasses
Outcomes	**Primary outcome:** change in axial length **Secondary outcome:** none reported **Maximum follow-up:** 24 months
Starting date	July 2016 **Estimated end date:** not reported
Contact information	https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000026874
Notes	

JPRN-UMIN000027940

Study name	Clinical study on the effect of multifocal contact lens on myopia progression in myopia school children
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 100 children aged 6 to 12 years; moderate myopia (objective equivalent spherical power -1.00 D to -6.00 D) **Exclusion criteria:** anisometropia; astigmatism beyond 1.5 D
Interventions	**Intervention:** multifocal contact **Comparison intervention:** normal contact
Outcomes	**Primary outcome:** refractive power change **Secondary outcome:** change in axial length **Maximum follow-up:** not reported
Starting date	August 2017 **Estimated end date:** not reported
Contact information	https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000032004
Notes	

Kinoshita 2018

Study name	Additive effects of orthokeratology and atropine 0.01% ophthalmic solution in slowing axial elongation in children with myopia: first year results

Kinoshita 2018 *(Continued)*

Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** aged 8 to 12; spherical equivalent refractive error of -1.00 to -6.00 diopters **Exclusion criteria:** not reported
Interventions	**Intervention:** orthokeratology (OK) and atropine 0.01% ophthalmic solution **Comparison intervention:** orthokeratology (OK)
Outcomes	**Primary outcome:** axial length **Secondary outcomes:** not reported **Maximum follow-up:** one year
Starting date	Not reported **Estimated end date:** not reported
Contact information	Nozomi Kinoshita, Department of Ophthalmology, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma-cho, Omiya-ku, Saitama-shi, Saitama, 330-8503, Japan. Email: nozomik@omiya.jichi.ac.jp
Notes	

Li 2013

Study name	The full correction and undercorrection of myopia evaluation trial (FUMET)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 7 to 15 years of age; 6/6 or better in each eye; spherical error between -1.5 and -6.0 D; astigmatism below 1.5 D in each eye; anisometropia below 1.0 D between the 2 eyes; no history of contact lens use, strabismus, amblyopia, or other ocular and systematic disease that influences refractive growth **Exclusion criteria:** inability to live close to study center for 2 years; inability to cooperate with examinations or surveys; allergy to mydriatic drugs; use of other treatments to prevent myopia progression
Interventions	**Intervention:** full correction **Intervention comparison:** undercorrection (blurred by +0.5 D)
Outcomes	**Primary outcomes:** change in cycloplegic autorefraction; change in axial length after 2 years **Secondary outcomes:** not specified **Maximum follow-up:** 2 years
Starting date	November 2010 **Estimated end date:** January 2013
Contact information	Professor Ning-Li Wang, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China. Email: wningli@vip.163.com
Notes	Registration number ChiCTR-TRC-10001122

Li 2013 *(Continued)*

	Funding source: grants from "Major State Basic Research Development Program of China ('973' Program, 2011CB504601) of the Ministry of Science and Technology"; "Major International (Regional) Joint Research Project (81120108807) of the National Natural Science Foundation of China"; "China Postdoctoral Science Foundation (20110490247)"; Research Foundation of Beijing Tongren Hospital Affiliated to Capital Medical University (2012-YJJ-019)"

MASS 2018

Study name	MiSight Assessment Study Spain (MASS)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** aged 8 to 12 with myopia (-0.75 to -4.00 D sphere) and astigmatism (< -1.00 D cylinder) **Exclusion criteria:** current or prior contact lenses wear; current or prior use of bifocals, progressive addition lenses, atropine, pirenzepine, or any other myopia control treatment; regular use of ocular medications and artificial tears; current use of systemic medications, which may significantly affect contact lens wear, tear film production, pupil size, accommodation, or refractive state; known allergy to fluorescein, benoxinate, proparacaine, or tropicamide; history of corneal hypoesthesia, corneal ulcer, corneal infiltrates, ocular viral or fungal infection, or other recurrent ocular infection; strabismus by cover test at far (4 m) or near (40 cm); wearing distance correction; systemic or ocular disease affecting ocular health; keratoconus or an irregular cornea; CCLRU grade ≥ 2 for any given anterior segment ocular clinical signs; having pathological myopia; connective tissue disorder
Interventions	**Intervention:** lens study group (MiSight) **Comparison intervention:** control group (single vision)
Outcomes	**Primary outcomes:** visual acuity, subjective refraction **Secondary outcomes:** axial length, anterior chamber, corneal power, cycloplegic autorefraction **Maximum follow-up:** 24 months
Starting date	September 2013 **Estimated end date:** June 2016
Contact information	Alicia Ruiz-Pomeda, Department of Pharmacy, Biotechnology, Optics and Optometry, European University of Madrid, C/Tajo s/n, Villaviciosa de Odón, 28670, Madrid, Spain. Email: alicia.ruiz@universidadeuropea.es.
Notes	

NCT00214487

Study name	Bifocal soft contact lenses and their effect on myopia progression in children and adolescents
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** myopia between -0.50 and -6.00; eso fixation disparity at 33 cm with distance correction; astigmatism 1.00 or less; ability to wear soft contact lenses

NCT00214487 *(Continued)*

	Exclusion criteria: presence of ocular disease preventing wear of contacts; pregnancy or nursing; use of certain medications
Interventions	**Intervention:** bifocal contact lenses **Comparison intervention:** single vision soft contact lenses
Outcomes	**Primary outcomes:** cycloplegic autorefraction, cycloplegic subjective refraction, axial length **Secondary outcomes:** keratometric changes, manifest refraction **Maximum follow-up:** 1 year
Starting date	October 2003 **Estimated end date:** March 2006
Contact information	https://clinicaltrials.gov/ct2/show/record/NCT00214487
Notes	

NCT00627874

Study name	Trial of myopia prevention using +3 D lenses (PLS)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 1200 children (age reported), with juvenile-onset myopia **Exclusion criteria:** hyperopia > +2.0 D; high myopia > -6.0 D; astigmatism > 1.5 D; anisometropia > 1.5 D; strabismus and amblyopia; any ocular, systemic, or neurodevelopmental conditions that could influence refractive development; chronic medication use that might affect myopia progression or visual acuity; already receiving other treatment for progressing myopia
Interventions	**Intervention:** +3 D lenses **Comparison intervention:** not reported
Outcomes	**Primary outcome:** axial length of eyes **Secondary outcome:** autorefraction **Maximum follow-up:** not reported
Starting date	April 2010 **Estimated end date:** April 2012
Contact information	https://clinicaltrials.gov/ct2/show/ NCT00627874
Notes	

NCT00762970

Study name	Controlling my;opia progression with soft contact lenses

NCT00762970 *(Continued)*

Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** myopic subjects between 8 and 12 years of age; best sphere contact lens correction must lie between -0.75 D (best of the 2 eyes) and -5.00 D (worst of the 2 eyes); astigmatism must be less than or equal to 1.00 D; 1.00 D or less difference in spherical equivalent between the 2 eyes; best-corrected visual acuity of 0.8 + 2 (20/25 + 2); spherical equivalent refraction visual acuity of 0.820/25 or better in both eyes; at least 8 D of accommodation **Exclusion criteria:** any ocular or systemic allergy or disease that may interfere with contact lens wear; systemic disease or autoimmune disease or use of medication (e.g. antihistamine) that may interfere with lens wear; clinically significant (grade 3 or 4) abnormality of the cornea that may contraindicate contact lens wear; clinically significant (grade 3 or 4) tarsal abnormalities or bulbar injection; any ocular infection; any corneal distortion; any infectious disease (e.g. hepatitis, tuberculosis) or immunosuppressive disease (e.g. HIV); diabetes; anisometropia greater than 1.00 D; astigmatism greater than 1.00 D in either eye; eye injury or surgery within 8 weeks immediately before enrollment for this study; previous refractive surgery; rigid contact lens wear; orthokeratology; keratoconus or other corneal irregularity in either eye; aphakia; strabismus; central corneal scar or pupil/lid abnormality in either eye; contraindications to contact lens; surgically altered eyes; ocular infection of any type; ocular inflammation; anterior chamber angle grade 2 or narrower
Interventions	**Intervention 1:** soft contact lens, Test Lens 1 **Intervention 2:** soft contact lens, Test Lens 2 **Comparison intervention:** spectacle lenses
Outcomes	**Primary outcomes:** spherical equivalent refraction, axial length **Secondary outcomes:** not reported **Maximum follow-up:** 2 years
Starting date	April 2007 **Estimated end date:** February 2010
Contact information	https://clinicaltrials.gov/ct2/show/NCT00762970
Notes	

NCT01704729

Study name	The children's WEAR trial (phases 1 & 2)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** aged 12 to 17 years; ≤ -1.00 D of myopic refractive error in each eye, with uncorrected vision ≤ 6/12 in at least 1 eye thought to be due to refractive error **Exclusion criteria:** significant strabismus or vision abnormality; vision deficiency
Interventions	**Intervention 1:** noncycloplegic self-refraction and conventional glasses **Intervention 2:** cycloplegic subjective refraction by experienced optometrist and conventional glasses **Intervention 3:** cycloplegic subjective refraction by rural refractionist program and conventional glasses

NCT01704729 *(Continued)*

	Comparison intervention: cycloplegic subjective refraction by experienced optometrist and ready-made glasses
Outcomes	**Primary outcome:** visual acuity **Secondary outcomes:** visual functioning, frequency of glasses-wear, accuracy of spectacles, value and satisfaction **Maximum follow-up:** 2 months
Starting date	September 2012 **Estimated end date:** January 2013
Contact information	https://clinicaltrials.gov/ct2/show/NCT01704729
Notes	

NCT01729208

Study name	An evaluation of the effectiveness of dual focus soft contact lenses in slowing myopia progression
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 300 children aged 8 to 12 years; best-corrected visual acuity by manifest refraction of +0.10 logMAR; spherical equivalent refractive error between =0.75 and -4.00 D inclusive; astigmatism < -0.75 D; anisometropia < 1.00 D; possess wearable and visually functional eyeglasses; agree to wear assigned contact lenses for a minimum of 10 hours per day at least 6 days per week, for the duration of the 3-year study **Exclusion criteria:** previously wore or currently wears contact lenses or rigid gas permeable contact lenses, including orthokeratology lenses; currently or within 30 days before this study has been an active participant in another clinical study; current or prior use of bifocals, progressive addition lenses, atropine, pirenzepine, or any other myopia control treatment; regular use of ocular medications, artificial tears, or wetting agents; current use of systemic medications that may significantly affect contact lens wear, tear film production, pupil size, accommodation, or refractive state; allergy to fluorescein, benoxinate, proparacaine, or tropicamide; strabismus; any ocular, systemic, or neurodevelopmental condition that could influence refractive development
Interventions	**Intervention:** dual focus soft contact lens **Comparison Intervention:** single vision soft contact lens
Outcomes	**Primary outcomes:** change in refractive error relative to baseline, change in axial length relative to baseline **Secondary outcomes:** incidence of adverse events **Maximum follow-up:** 3 years
Starting date	November 2012 **Estimated end date:** May 2019
Contact information	https://clinicaltrials.gov/ct2/show/NCT01729208
Notes	

NCT01787760

Study name	Controlling myopia progression with soft contact lenses
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** myopic subjects between 8 and 12 years of age; best sphere contact lens correction must lie between -0.75 D (best of the 2 eyes) and -5.00 D (worst of the 2 eyes); astigmatism must be less than or equal to 1.00 D; 1.00 D or less difference in spherical equivalent between the 2 eyes; best-corrected visual acuity of 0.8 + 2 (20/25 + 2); spherical equivalent refraction visual acuity of 0.820/25 or better in both eyes; at least 8 D of accommodation **Exclusion criteria:** any ocular or systemic allergy or disease that may interfere with contact lens wear; systemic disease or autoimmune disease or use of medication (e.g. antihistamine) that may interfere with lens wear; clinically significant (grade 3 or 4) abnormality of the cornea, which may contraindicate contact lens wear; clinically significant (grade 3 or 4) tarsal abnormalities or bulbar injection; any ocular infection; any corneal distortion; any infectious disease (e.g. hepatitis, tuberculosis) or immunosuppressive disease (e.g. HIV); diabetes; anisometropia greater than 1.00 D; astigmatism greater than 1.00 D in either eye; eye injury or surgery within 8 weeks immediately before enrollment for this study; previous refractive surgery; rigid contact lens wear; orthokeratology; keratoconus or other corneal irregularity in either eye; aphakia; strabismus; central corneal scar or pupil/lid abnormality in either eye; contraindications to contact lens; surgically altered eyes; ocular infection of any type; ocular inflammation; anterior chamber angle grade 2 or narrower
Interventions	**Intervention 1:** soft contact lens, Test Lens B **Intervention 2:** soft contact lens, Test Lens C **Comparison intervention:** spectacle lenses
Outcomes	**Primary outcomes:** spherical equivalent refraction, axial length **Secondary outcomes:** not reported **Maximum follow-up:** 3 years
Starting date	April 2007 **Estimated end date:** April 2010
Contact information	https://clinicaltrials.gov/ct2/show/NCT01787760
Notes	

NCT01829191

Study name	Controlling myopia progression with soft contact lenses (contact lens control)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** myopic subjects between 8 and 12 years of age; best sphere contact lens correction must lie between -0.75 D (best of the 2 eyes) and -5.00 D (worst of the 2 eyes); astigmatism less than or equal to 1.00 D; 1.00 D or less difference in spherical equivalent between the 2 eyes; best-corrected visual acuity of 0.8 + 2 (20/25 + 2); spherical equivalent refraction visual acuity of 0.820/25 or better in both eyes; at least 8 D of accommodation **Exclusion criteria:** any ocular or systemic allergy or disease that may interfere with contact lens wear; systemic disease or autoimmune disease or use of medication (e.g. antihistamine) that may

NCT01829191 *(Continued)*

	interfere with lens wear; clinically significant (grade 3 or 4) abnormality of the cornea, which may contraindicate contact lens wear; clinically significant (grade 3 or 4) tarsal abnormalities or bulbar injection; any ocular infection; any corneal distortion; any infectious disease (e.g. hepatitis, tuberculosis) or immunosuppressive disease (e.g. HIV); diabetes; anisometropia greater than 1.00 D; astigmatism greater than 1.00 D in either eye; eye injury or surgery within 8 weeks immediately before enrollment for this study; previous refractive surgery; rigid contact lens wear; orthokeratology; keratoconus or other corneal irregularity in either eye; aphakia; strabismus; central corneal scar or pupil/lid abnormality in either eye; contraindications to contact lens; surgically altered eyes; ocular infection of any type; ocular inflammation; anterior chamber angle grade 2 or narrower
Interventions	**Intervention 1:** soft contact lens, Test Lens A **Intervention 2:** soft contact lens, Test Lens C **Comparison intervention:** spectacle lenses
Outcomes	**Primary outcome:** spherical equivalent refractive error **Secondary outcomes:** axial length **Maximum follow-up:** 2 years
Starting date	April 2008 **Estimated end date:** May 2010
Contact information	https://clinicaltrials.gov/ct2/show/NCT01829191
Notes	

NCT01923675

Study name	The role of cone opsin mutations & glasses that control axial elongation
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** nearsightedness with refractive error of at least -0.5 diopters; myopia progression at least -.50 D per year in previous year; astigmatism and anisometropia not more than 1.5 D; distance monocular acuity 6/6 or better; near monocular acuity of 0.4 M or better; stereoacuity not more than 40 seconds of arc at 40 cm; no contact lens use during the study; willingness to donate a blood sample or a buccal swab for genetic analysis; can be refracted to 20/20 or 20/15 **Exclusion criteria:** glaucoma; amblyopia; strabismus; ocular disease; developmental delay; history of wearing bifocal lenses; many types of eye surgery; color vision deficiency
Interventions	**Intervention 1:** spectacles with red-blocking tint **Intervention 2:** spectacles with holographic diffuser and color neutral tint **Intervention 3:** spectacles with holographic diffuser and red-blocking tint **Comparison intervention:** spectacles with color neutral tint
Outcomes	**Primary outcome:** axial elongation **Secondary outcomes:** cycloplegic autorefraction **Maximum follow-up:** 18 months

NCT01923675 *(Continued)*

Starting date	September 2013 **Estimated end date:** November 2016
Contact information	https://clinicaltrials.gov/ct2/show/record/NCT01923675
Notes	

NCT02001415

Study name	Efficacy study of different lens treatments on Chinese adolescent myopia (DLTCAM)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 120 adolescent myopia patients aged 10 to 15; myopic refraction between -1.00 D and -4.50 D; astigmatism equal to or less than -1.50 D; normal break-up time of tear film **Exclusion criteria:** existence of any ocular disease except ametropia, hyperopia, severe dry eye
Interventions	**Intervention 1:** MyoVision spectacles **Intervention 2:** orthokeratology lenses at night **Comparison intervention:** spectacles
Outcomes	**Primary outcome:** ocular axial length **Secondary outcomes:** spherical equivalent refraction **Maximum follow-up:** 12 months
Starting date	November 2013 **Estimated end date:** September 2016
Contact information	https://clinicaltrials.gov/ct2/show/NCT02001415
Notes	

NCT02130167

Study name	Low-concentration atropine for myopia progression in schoolchildren
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 60 children aged 6 to 12 years with myopia of at least 0.5 diopters (D) and astigmatism of -1.50 D or less **Exclusion criteria:** children with strabismus, amblyopia, cataract, glaucoma, or any ocular disease; any ocular surgery; history of systemic disease
Interventions	**Intervention:** 0.01% atropine eye drops **Comparison intervention:** 0.05% atropine eye drops

NCT02130167 *(Continued)*

Outcomes	**Primary outcome:** cycloplegic spherical refraction **Secondary outcomes:** axial change, pupil size, accommodation, questionnaire **Maximum follow-up:** 1 year
Starting date	August 2012 **Estimated end date:** August 2017
Contact information	https://clinicaltrials.gov/ct2/show/ NCT02130167
Notes	

NCT02186184

Study name	Effect of orthokeratology vs spectacles on myopia progression in Chinese children: a crossover trial
Methods	Randomized cross-over design
Participants	**Inclusion criteria:** aged 7 to 14 years; visual acuity 20/20 or better in each eye; spherical error ranging from -0.5 D to -5.0 D and astigmatism less than 1.5 D in each eye; anisometropia less than 1.0 D between the 2 eyes; no strabismus, amblyopia, or any other ocular or systematic disease that may affect refractive development **Exclusion criteria:** currently using or history of using other interventions to control myopia progression (acupuncture, drugs, contact lenses, ear needles, and so on); inability to cooperate with the ocular examination; questionnaire survey; orthokeratology wearing
Interventions	**Intervention:** orthokeratology **Comparison intervention:** spectacles
Outcomes	**Primary outcomes:** refraction, axial length **Secondary outcomes:** tear film break-up time, self-evaluation of comfort, corneal endothelial cell density **Maximum follow-up:** 2 years
Starting date	June 2014 **Estimated end date:** June 2017
Contact information	https://clinicaltrials.gov/ct2/show/record/NCT02186184
Notes	

NCT02206217

Study name	Myopia control with the multisegment lens
Methods	Randomized parallel-group design

NCT02206217 *(Continued)*

Participants	**Inclusion criteria:** estimated 183 children aged 8 to 13 years with spherical equivalent refraction between -1.00 D and -5.00 D; anisometropia and astigmatism not greater than 1.50 D; best-corrected logMAR visual acuity of 0 or better using spectacles; parental understanding of random allocation **Exclusion criteria:** ocular or systemic condition affecting vision or refractive development; prior treatment with any intervention for control of myopia
Interventions	**Intervention:** multisegment spectacle lens **Comparison intervention:** single vision spectacle lens
Outcomes	**Primary outcome:** cycloplegic refraction **Secondary outcome:** axial length **Maximum follow-up:** 2 years
Starting date	August 2014 **Estimated end date:** July 2017
Contact information	https://clinicaltrials.gov/ct2/show/ NCT02206217
Notes	

NCT02544529

Study name	Echothiophate iodide for the prevention of progression of myopia
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** between 8 and 15 years of age; documentation of progression of myopia within the 12 months before enrollment **Exclusion criteria:** any history of retinopathy of prematurity, glaucoma, cataracts, corneal disease, uveitis, manifest strabismus, nystagmus,or ocular trauma; any history of unstable asthma, diabetes, or juvenile idiopathic arthritis; systemic muscarinic agents, steroids, or anticholinesterase agents; benzalkonium chloride preservative allergy; astigmatism > 0.75 D; anisometropia > 1.50 D; pregnancy or positive pregnancy test at the screening visit
Interventions	**Intervention:** echothiophate iodide 0.03% ophthalmic solution **Comparison intervention:** carboxymethylcellulose sodium (0.5%)
Outcomes	**Primary outcome:** cycloplegic refraction **Secondary outcomes:** axial length, choroidal thickness **Maximum follow-up:** 12 weeks
Starting date	June 2016 **Estimated end date:** June 2017
Contact information	https://clinicaltrials.gov/ct2/show/NCT02544529
Notes	

NCT02643342

Study name	A 2-year longitudinal study on the structural and optical effects of orthokeratology treatment on eye
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 90 children aged 6 to 10 years; myopia between 0.50 D and 4.00 D in both eyes; astigmatism < 1.50 D; ≤ 1.25 D for with-the-rule astigmatism (axes 180 ± 30); ≤ 0.50 D for astigmatism of other axes in both eyes; anisometropia ≤ 1.50 D; symmetrical corneal topography with corneal toricity < 2.00 D in both eyes; agree for randomization **Exclusion criteria:** contraindications for orthokeratology wear (e.g. limbus-to-limbus corneal cylinder, dislocated corneal apex); any type of strabismus or amblyopia; myopic treatment (e.g. refractive surgery, progressive lens wear for myopic control) before and during the study period; rigid contact lenses (including orthokeratology lenses); systemic condition that might affect refractive development (e.g. Down syndrome, Marfan's syndrome); ocular condition that might affect the refractive error (e.g. cataract, ptosis); poor compliance with lens wear to follow-up
Interventions	**Intervention 1:** orthokeratology with normal compression factor **Intervention 2:** orthokeratology with increased compression factor **Comparison intervention:** single vision glasses
Outcomes	**Primary outcome:** axial length **Secondary outcomes:** ocular aberration, corneal biomechanics, accommodation lag, choroidal thickness **Maximum follow-up:** 2 years
Starting date	June 2016 **Estimated end date:** December 2019
Contact information	https://clinicaltrials.gov/ct2/show/NCT02643342
Notes	

NCT02643758

Study name	Myopia control using soft bifocal lenses
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 97 children aged 6 to 12 years with refractive sphere -0.75 D to -4.50 D; refractive cylinder not to exceed 1.00 D; spherical equivalent: -0.75 D to -5.00 D; best-corrected distance VA (logMAR) 0.14 or better in each eye and 0.10 or better in both eyes; difference in refractive error (spherical equivalent) in the 2 eyes not to exceed 1.00 D **Exclusion criteria:** children with prior history of myopia control treatment; contraindication to contact lens wear; binocular anomalies (e.g. strabismus)
Interventions	**Intervention:** bifocal soft contact lenses **Comparison intervention:** single vision spectacles

NCT02643758 *(Continued)*

Outcomes	**Primary outcomes:** axial length, cycloplegic refractive error **Secondary outcomes:** wavefront aberrations, accommodation responses **Maximum follow-up:** 2 years
Starting date	January 2016 **Estimated end date:** September 2018
Contact information	https://clinicaltrials.gov/ct2/show/ NCT02643758
Notes	

NCT02955927

Study name	Combined atropine with orthokeratology in childhood myopia control (AOK): a randomized controlled trial
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 60 children aged 6 to 11 years; myopia between 1.00 and 4.00 D in both eyes; astigmatism ≤ 2.50 D; with-the-rule astigmatism (axes 180 ± 30) ≤ 2.50 D; astigmatism with other axes ≤ 0.50 D in both eyes; < 1.00 D difference in manifest spherical equivalent (SE); cycloplegic objective refraction between 1.00 and 4.00 D in sphere; astigmatism ≤ 2.50 D; < 1.00 D difference in manifest SE between the 2 eyes; best-corrected logMAR visual acuity 0.10 or better in both eyes; symmetrical corneal topography with corneal toricity < 2.00 D in either eye; normal ocular health other than myopia; agree to be randomized and to attend scheduled visits and aftercare **Exclusion criteria:** contraindications to atropine (known allergies or cardiovascular disease, epilepsy); contraindications to contact lens wear and ortho-k; strabismus or amblyopia; history of myopia control treatment; rigid contact lens (including ortho-k) wear experience; systemic condition that might affect refractive development; ocular condition that might affect refractive, poor response to lens wear including poor lens handling, poor vision and/ocular response after lens modifications, and poor compliance with scheduled visits
Interventions	**Interventions:** ortho-k and 0.01% atropine eye drops **Comparison intervention:** ortho-k
Outcomes	**Primary outcomes:** changes in axial length **Secondary outcomes:** none reported **Maximum follow-up:** 24 months
Starting date	November 2016 **Estimated end date:** April 2020
Contact information	https://clinicaltrials.gov/ct2/show/NCT02955927
Notes	

NCT03242226

Study name	The effect of +3.00 ADD on myopia progression in Chinese children
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 440 children aged 8 to 12 years; refractive error (cycloplegic autorefraction); spherical equivalent -1.00 to -6.00 D in both eyes; astigmatism ≤ 2.00 D in both eyes; spherical equivalent anisometropia ≤ 1.50 D; best-corrected visual acuity ≥ 6/9.5 **Exclusion criteria:** allergy to tropicamide or topical anesthetic drugs; eye disease causing visual impairment including strabismus, amblyopia, ocular surface–related disease, cataract, trauma, ocular fundus disease, ocular surgery; previous wearing of rigid gas permeable contact lenses, progressive addition lenses, bifocal spectacles lens, peripheral defocus modifying contact lenses; receiving visual function training
Interventions	**Intervention:** single vision spectacles (distant vision) and +3.00 ADD spectacles (near vision) **Comparison intervention:** single vision spectacles
Outcomes	**Primary outcome:** spherical equivalent refraction **Secondary outcomes:** axial length, corneal curvature, binocular vision **Maximum follow-up:** 3 years
Starting date	October 2016 **Estimated end date:** December 2018
Contact information	https://clinicaltrials.gov/ct2/show/NCT03242226
Notes	

NCT03246464

Study name	Clinical study of nearsightedness treatment with orthokeratology lenses (CONTROL)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 50 children aged 6 to 12 years; myopia -0.5 to -4.75 diopters spherical in 1 or both eyes; regular astigmatism ≤ -2.5 diopters in 1 or both eyes; anisometropia < 1.5 D spherical equivalent; best-corrected visual acuity 0.1 logMAR or better in both eyes; acceptance of treatment randomization **Exclusion criteria:** manifest or latent squint; contraindications to use of OKL comprising keratoconus, allergic conjunctivitis, and keratoconjunctivitis sicca; previous eye surgery; chronic eye disease demanding daily use of eye drops; noncompliance with eye examinations (unstable fixation or intolerance to OKL); 1 or both parents being ethnical Asian, African, Hispanic, or Spanish
Interventions	**Intervention:** orthokeratology lenses **Comparison intervention:** regular single vision spectacles
Outcomes	**Primary outcome:** axial length **Secondary outcomes:** quality of life, safety **Maximum follow-up:** 18 months

NCT03246464 *(Continued)*

Starting date	March 2017 **Estimated end date:** October 2020
Contact information	https://ichgcp.net/clinical-trials-registry/NCT03246464
Notes	

NCT03329638

Study name	A study assessing the efficacy and safety of DE-127 ophthalmic solution in subjects with mild or moderate myopia (APPLE)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 100 children aged 6 to 11 years; refractive error of spherical equivalent -1.0 diopter to -6.0 diopter in both eyes; anisometropia of spherical equivalent less than or equal to 1.50 diopters in both eyes; distance vision correctable to logMAR 0.2 or better in both eyes; normal intraocular pressure not greater than 21 mmHg in both eyes; no allergy to atropine, cyclopentolate, proparacaine, and benzalkonium chloride **Exclusion criteria:** amblyopia or manifest strabismus including intermittent tropia; ocular disorder that potentially affects myopia or refractive power; previous or current use of contact lenses, bifocal lenses, progressive addition lenses, or other forms of treatment (including atropine and pirenzepine) for myopia; systemic disorder that potentially affects myopia or refractive power
Interventions	**Intervention 1:** DE-127 ophthalmic solution low dose **Intervention 2:** DE-127 ophthalmic solution medium dose **Intervention 3:** DE-127 ophthalmic solution high dose **Comparison intervention:** placebo ophthalmic solution
Outcomes	**Primary outcome:** spherical equivalent **Secondary outcomes:** not reported **Maximum follow-up:** 12 months
Starting date	October 2017 **Estimated end date:** December 2019
Contact information	https://clinicaltrials.gov/ct2/show/NCT03329638
Notes	

NCT03334253

Study name	Low-dose atropine for treatment of myopia
Methods	Randomized parallel-group design

NCT03334253 *(Continued)*

Participants	**Inclusion criteria:** 186 children aged 5 to 12 years; myopia -1.00 D to -6.00 D spherical equivalent in both eyes; astigmatism ≤ 1.50 D in both eyes; anisometropia < 1.00 D spherical equivalent; gestational age ≥ 32 weeks; birth weight > 1500 g; understanding of the protocol and willingness to accept randomization to atropine or placebo by parents; willingness to participate in a 2- to 4-week run-in phase using daily artificial tear eye drops; ability to return in 2 to 4 weeks for possible randomization; accessible to phone; willingness to be contacted by Investigator's site staff **Exclusion criteria:** current or previous use of bifocals, progressive addition lenses, or multifocal contact lenses; current or previous use of orthoK, rigid gas permeable, or other contact lenses to reduce myopia progression; known atropine allergy; abnormality of the cornea, lens, central retina, iris, or ciliary body; current or prior history of manifest strabismus, amblyopia, or nystagmus; prior eyelid, strabismus, intraocular, or refractive surgery; Down syndrome or cerebral palsy; females who are pregnant, lactating, or intending to become pregnant within the next 30 months; negative urine pregnancy test (required for all females who have experienced menarche); current or previous myopia treatment with atropine, pirenzepine, or other antimuscarinic agent within 4 weeks of 13th birthday
Interventions	**Intervention:** 0.01% atropine eye drops **Comparison intervention:** placebo eye drops
Outcomes	**Primary outcome:** spherical equivalent refractive error **Secondary outcome:** spherical equivalent **Maximum follow-up:** 30 months
Starting date	June 2018 **Estimated end date:** October 2022
Contact information	https://clinicaltrials.gov/ct2/show/ NCT03334253
Notes	

NCT03350620

Study name	CHAMP: study of NVK-002 in children with myopia
Methods	Randomized cross-over design (within-person study)
Participants	**Inclusion criteria:** 483 children aged 3 to 17 years; myopia SER of at least -0.50 D and no greater than -6.00 D myopia in each eye **Exclusion criteria:** astigmatism more than -1.50 D in either eye; current or history of amblyopia or strabismus; history of any disease or syndrome that predisposes the patient to severe myopia; history in either eye of abnormal ocular refractive anatomy; serious systemic illness that, in the investigator's opinion, would render the patient ineligible; chronic use (more than 3 days per week) of any topical ophthalmic medication (prescribed or over-the-counter) other than the assigned study medication
Interventions	**Intervention 1:** NVK-002 concentration 1 **Intervention 2:** NVK-002 concentration 2 **Comparison intervention:** vehicle (placebo)
Outcomes	**Primary outcome:** myopia progression

NCT03350620 *(Continued)*

	Secondary outcomes: mean progression rates, proportion of patients who show < - 0.75 D progression, median time to change in myopia < - 0.75 D **Maximum follow-up:** 36 months
Starting date	November 2017 **Estimated end date:** November 2022
Contact information	https://clinicaltrials.gov/ct2/show/NCT03350620
Notes	

NCT03374306

Study name	Topical application of low-concentration (0.01%) atropine on the human eye with fast and slow myopia progression rate
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 80 children aged 7 to 10 years; good general health; no family history of ocular disease; no current or history of epilepsy or asthma; myopia -0.50 to -1.00 D (inclusive, both eyes); astigmatism ≤ 0.50 D; no hyperopia, amblyopia, or strabismus; no reported ocular eye disease or disorder or drug allergy **Exclusion criteria:** not reported
Interventions	**Intervention:** atropine 0.01% **Comparison intervention:** artificial tears
Outcomes	**Primary outcomes:** refractive errors **Secondary outcome:** axial length **Maximum follow-up:** 24 months
Starting date	January 2018 **Estimated end date:** June 2020
Contact information	https://clinicaltrials.gov/ct2/show/NCT03374306
Notes	

NCT03402100

Study name	Eye drops study for myopia control in schoolchildren
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 150 children aged 6 to 12 years with myopia diagnosed with spherical equivalent refraction at least -0.5 diopter (D); able to use eye drops

NCT03402100 *(Continued)*

	Exclusion criteria: children with astigmatism -1.50 D or greater; strabismus, amblyopia, cataract, glaucoma, any ocular disease, any ocular surgery; history of systemic disease; contact lens user; orthokeratology user
Interventions	**Intervention 1:** 0.01% atropine eye drops **Intervention 2:** 0.005% atropine eye drops **Intervention 3:** 0.25% ketorolac eye drops **Intervention 4:** 0.01% atropine plus 0.25% ketorolac eye drops **Intervention 5:** 0.005% atropine plus 0.25% ketorolac eye drops
Outcomes	**Primary outcome:** cycloplegic spherical refraction, axial length **Secondary outcome:** intraocular pressure, accommodation (diopter), pupil size, anterior chamber depth, posterior chamber depth **Maximum follow-up:** 1 year
Starting date	October 2014 **Estimated end date:** December 2019
Contact information	https://clinicaltrials.gov/ct2/show/ NCT03402100
Notes	

NCT03413085

Study name	To evaluate the efficacy and safety of multifocal soft contact lens in myopia control
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** 59 schoolchildren aged 6 to 15 years, with spherical equivalent refractive error between -1.00 D and -10.00 D; visual acuity with contact lens of 20/25 or better in each eye; astigmatism ≤ 1.50 D; anisometropia ≤ 1.00 D **Exclusion criteria:** eye disease interfering with contact lens wearing, use of bifocals, progressive addition lenses, rigid gas permeable contact lenses, orthokeratology lenses; myopia control treatment within 1 month before screening visit; systemic disease affecting vision or contact lens wearing; autoimmune disease, infectious disease, or immunosuppressive disease; surgically altered eyes; receiving medication for long-term use that interferes with contact lens wearing, tear film production, pupil size, accommodation, or refractive state; nasal decongestants, antihistamines, prednisolone, or methylphenidate
Interventions	**Intervention:** multifocal soft contact lens **Comparison intervention:** single vision soft contact lens
Outcomes	**Primary outcomes:** objective cycloplegic refractive error, axial length **Secondary outcomes:** myopia progression, axial elongation, patient self-assessment, average wearing hours across the study period, reasons and rates for discontinued wear during the study period **Maximum follow-up:** 48 weeks

NCT03413085 *(Continued)*

Starting date	May 2018 **Estimated end date:** March 2020
Contact information	https://clinicaltrials.gov/ct2/show/NCT03413085
Notes	

NCT03465748

Study name	Effectiveness of orthokeratology in myopia control
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** myopia progression more than -1.00 D in 1 year; prescription between -1.00 D and -6.00 D; best-corrected visual acuity 20/25 or better; at least 1 eye with refractive astigmatism < 1.50 D **Exclusion criteria:** contraindications for orthoK; refractive surgery; current gas permeable contact lens wearers
Interventions	**Intervention:** orthoK **Comparison intervention:** single vision spectacles
Outcomes	**Primary outcomes:** visual acuity, axial length, myopia progression **Secondary outcomes:** not reported **Maximum follow-up:** 2 years
Starting date	May 2017 **Estimated end date:** May 2019
Contact information	https://clinicaltrials.gov/ct2/show/record/NCT03465748
Notes	

NCT03508817

Study name	Atropine 0.01% eye drops in myopia study (AIMS)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** age 6 to 15 years; myopia ≥ 2.00 D (cycloplegic refraction; spherical equivalent); no prior or current treatment for preventing myopia progression (bifocals / progressive addition lenses / orthokeratology) **Exclusion criteria:** best corrected visual acuity < 0.5 (6/12); refractive myopia; astigmatism ≥ 1.5 D; amblyopia; ocular hypertension / glaucoma; prior intraocular surgery; allergy to atropine eye drops; systemic diseases associated with myopia such as Marfan syndrome, Stickler syndrome; history of cardiac or significant respiratory diseases; lack of consent for participating in the study
Interventions	**Intervention:** atropine sulfate 0.01% eye drops

NCT03508817 *(Continued)*

	Comparison intervention: control
Outcomes	**Primary outcomes:** spherical equivalent refractive error **Secondary outcomes:** axial length; adverse events **Maximum follow-up:** 2 years
Starting date	December 2018 **Estimated end date:** January 2022
Contact information	https://clinicaltrials.gov/ct2/show/NCT03508817
Notes	

NCT03538002

Study name	The effect of blue-light filtering spectacle lenses on myopia progression in schoolchildren
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** refraction: myopia of -1.00 diopters (D) to -5.00D; astigmatism: equal or less than -1.50D; anisometropia: equal or less than 1.00D; best corrected monocular visual acuity: 0.0 LogMAR or better after full correction; parents' understanding and acceptance of random allocation of grouping **Exclusion criteria:** any ocular and systemic abnormalities might affect visual functions or refractive development; prior treatment of myopic control, e.g. drugs, orthokeratology, progressive addition lenses, bifocal lenses, drugs (e.g. atropine), etc.
Interventions	**Intervention:** blue-light filtering spectacle lenses **Comparison intervention:** conventional anti-reflection coated spectacle lens
Outcomes	**Primary outcomes:** cycloplegic refraction **Secondary outcomes:** axial length **Maximum follow-up:** 2 years
Starting date	September 2018 **Estimated end date:** January 2021
Contact information	https://clinicaltrials.gov/ct2/show/NCT03538002
Notes	

NCT03552016

Study name	Evaluation of progression of myopia in children treated with vitamin B2 and outdoor sunlight exposure
Methods	Randomized parallel-group design

NCT03552016 *(Continued)*

Participants	**Inclusion criteria:** age 6 to12 years old with myopia more than 0.50 D and astigmatism no more than 1.5 D; caretakers who choose to enroll their child in the study must agree to participate in the study on their own will after knowledge of potential alternatives (spectacle correction, orthokeratology, atropine eye drops, etc.) are explained to the patient's caretaker **Exclusion criteria:** known allergy to riboflavin; birth history of premature birth; developmental delay or other neurological or mental conditions; major systemic health problems; significant anisometropia more than 1.5 Diopters; any other eye condition which may complicate interpretation of data including: congenital glaucoma, congenital cataract, ectatic corneal condition, amblyopia or strabismus
Interventions	**Intervention 1:** 200 mg Riboflavin (oral) **Intervention 2:** 400 mg Riboflavin (oral) **Comparison intervention:** 0 mg Riboflavin (oral)
Outcomes	**Primary outcomes:** cycloplegic refraction **Secondary outcomes:** axial length, keratometry values, uncorrected best visual acuity **Maximum follow-up:** 3 years
Starting date	October 2018 **Estimated end date:** October 2021
Contact information	https://clinicaltrials.gov/ct2/show/NCT03552016
Notes	

NCT03623074

Study name	Control of myopia using novel spectacle lens designs (CYPRESS)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** age 6 to 10 years (day prior to 10th birthday) at time of informed consent/assent; spherical equivalent refraction error between -0.75 and -4.50 D; spherical equivalent refraction power between the two eyes must be less than or equal to 1.50 D;willingness to participate in the trial for 3 years without content lens wear **Exclusion criteria:** previous or current use of contact lenses; previous or current use of bifocals, progressive addition spectacles lenses; previous or current use of myopia control treatment; astigmatism worse then -1.25 DC in either eye
Interventions	**Intervention:** novel spectacle lens design **Comparison intervention:** spectacle lenses
Outcomes	**Primary outcomes:** axial length; spherical equivalent refraction **Secondary outcomes:** not reported **Maximum follow-up:** 36 months
Starting date	July 2018

NCT03623074 *(Continued)*

	Estimated end date: January 2022
Contact information	https://clinicaltrials.gov/ct2/show/NCT03623074
Notes	

NCT03681366

Study name	Myopia control using optimized optical defocus RCTs
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** age at enrolment 8 to 13 years; Hong Kong Chinese; spherical equivalent refractions (SER): -1.00 to -5.00D; astigmatism: -1.00D or less; anisometropia: 1.25D or less; spectacle corrected monocular visual acuity (VA): 0.0 logMAR or better; contact lens corrected monocular VA: 0.1 logMAR or better; normal binocular function; willingness to wear contact lenses regularly; parents' understanding and acceptance of random allocation of grouping and masking **Exclusion criteria:** prior myopia control treatment, e.g. orthokeratology, defocus soft contact lenses, progressive addition lenses, bifocal lenses, drugs (e.g. atropine), etc.; strabismus or decompensated phoria (checked by cover test at far and near in screening); known contraindications for contact lens wear; have any ocular and systemic diseases and abnormalities that might affect visual function or refractive development
Interventions	**Intervention:** single vision soft contact lens **Comparison intervention:** DISC3.5 Plus lens
Outcomes	**Primary outcomes:** spherical equivalent **Secondary outcomes:** axial length **Maximum follow-up:** 12 months
Starting date	October 2018 **Estimated end date:** April 2021
Contact information	https://clinicaltrials.gov/ct2/show/NCT03681366
Notes	

NCT03690089

Study name	Low-dose atropine eye drops to reduce progression of myopia in children in the United Kingdom (CHAMP-UK)
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** age 6 to 12 years (at the time of consenting); myopia of -0.5 D or greater (spherical equivalent refractive error) in both eyes; best-corrected distance visual acuity (BCDVA) 0.20 logMAR or better in both eyes

NCT03690089 *(Continued)*

	Exclusion criteria: other ocular morbidities; myopia of -10 D or greater in either eye; astigmatism of 2 D or higher in either eye; amblyopia; significant health problems that can compromise the ability to attend research visits or complete the trial
Interventions	**Intervention:** atropine sulfate 0.01% eye drops **Comparison intervention:** placebo eye drops
Outcomes	**Primary outcome:** spherical equivalent refractive error **Secondary outcomes:** axial length, best-corrected distance visual acuity, near visual acuity, reading speed, pupil diameter, accommodation, spectacle correction, eye drop tolerability, adverse events, quality of life **Maximum follow-up:** 24 months
Starting date	April 2019 **Estimated end date:** December 2024
Contact information	https://clinicaltrials.gov/ct2/show/record/NCT03690089
Notes	

NCT03690414

Study name	Evaluation of short-term use of experimental eye drops BHVI2, 0.02% atropine, and BHVI2 plus 0.02% atropine eye drops
Methods	Randomized parallel-group design
Participants	**Inclusion criteria:** age 6 to 13 years; myopic; normal ocular findings; spherical equivalent between -0.50 diopter and -6.00 diopter; vision correctable to at least 20/25 or better in each eye with spectacles **Exclusion criteria:** preexisting ocular irritation, systematic disease, eye trauma, myopia control interventions
Interventions	**Intervention 1:** experimental BHVI2 **Intervention 2:** atropine sulfate 0.02% eye drops **Comparison intervention:** combination eye drops
Outcomes	**Primary outcomes:** pupillary diameter, accommodative amplitude **Secondary outcomes:** not reported **Maximum follow-up:** 1 month
Starting date	October 2018 **Estimated end date:** February 2019
Contact information	https://clinicaltrials.gov/ct2/show/NCT03690414
Notes	

PACT Study 2017

Study name	Personalized addition lenses clinical trial
Methods	Randomized controlled trial
Participants	**Inclusion criteria:** 7 to 12 years of age; myopic refractive error between -0.75 D and -4.00 D; cycloplegic spherical equivalent; astigmatism < 1.50 D; best-corrected visual acuity logMAR +0.05 or better in each; anisometropia < 1.00 D; at least 0.50 D progression by cycloplegic autorefraction over the past year **Exclusion criteria:** strabismus with or without add; ocular or systemic condition that may affect refractive error development
Interventions	**Intervention 1:** individualized add power **Intervention 2:** +2.00 D add power **Comparison intervention:** single vision
Outcomes	**Primary outcome:** change in cycloplegic spherical equivalent refractive error **Secondary outcome:** change in axial elongation **Maximum follow-up:** 2 years
Starting date	July 2014 **Estimated end date:** March 2017
Contact information	Eye Hospital of Wenzhou Medical University
Notes	None

D: diopters.
logMAR: logarithm of the minimum angle of resolution.

DATA AND ANALYSES

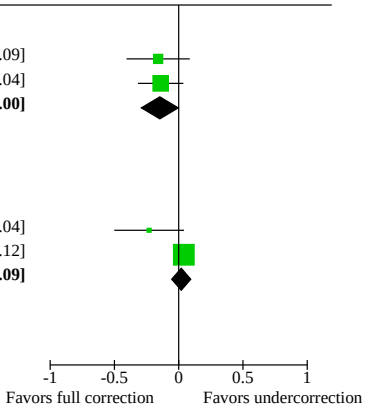
Comparison 1. Undercorrection vs full correction spectacles

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Change in refractive error from baseline	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 At 1 year	2	142	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.29, -0.00]
1.1.2 At 2 years	2	244	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.05, 0.09]
1.2 Change in axial length from baseline	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 At 1 year	1	94	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.01, 0.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.2 At 2 years	2	244	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.06, 0.03]

Analysis 1.1. Comparison 1: Undercorrection vs full correction spectacles, Outcome 1: Change in refractive error from baseline

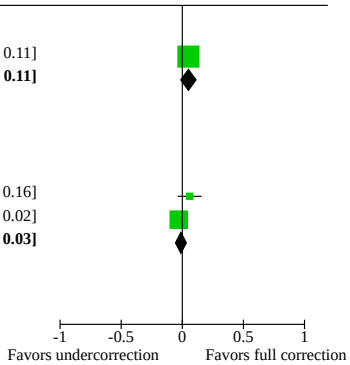
Study or Subgroup	Undercorrection Mean [D]	SD [D]	Total	Full correction Mean [D]	SD [D]	Total	Weight	Mean Difference IV, Fixed, 95% CI [D]
1.1.1 At 1 year								
Adler 2006 (1)	-0.8	0.45	25	-0.64	0.42	23	34.0%	-0.16 [-0.41 , 0.09]
Chung 2002 (2)	-0.58	0.514	47	-0.44	0.343	47	66.0%	-0.14 [-0.32 , 0.04]
Subtotal (95% CI)			**72**			**70**	**100.0%**	**-0.15 [-0.29 , -0.00]**
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%								
Test for overall effect: Z = 2.00 (P = 0.04)								
1.1.2 At 2 years								
Chung 2002 (3)	-1	0.72	47	-0.77	0.617	47	7.5%	-0.23 [-0.50 , 0.04]
Koomson 2016	-0.5	0.22	75	-0.54	0.26	75	92.5%	0.04 [-0.04 , 0.12]
Subtotal (95% CI)			**122**			**122**	**100.0%**	**0.02 [-0.05 , 0.09]**
Heterogeneity: Chi² = 3.53, df = 1 (P = 0.06); I² = 72%								
Test for overall effect: Z = 0.52 (P = 0.60)								



Footnotes
(1) Data provided by study author.
(2) Data estimated from graph.
(3) Data estimated from graph (although reported as statistically significant in the article).

Analysis 1.2. Comparison 1: Undercorrection vs full correction spectacles, Outcome 2: Change in axial length from baseline

Study or Subgroup	Undercorrection Mean [mm]	SD [mm]	Total	Full correction Mean [mm]	SD [mm]	Total	Weight	Mean Difference IV, Fixed, 95% CI [mm]
1.2.1 At 1 year								
Chung 2002 (1)	0.45	0.171	47	0.4	0.137	47	100.0%	0.05 [-0.01 , 0.11]
Subtotal (95% CI)			**47**			**47**	**100.0%**	**0.05 [-0.01 , 0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.56 (P = 0.12)								
1.2.2 At 2 years								
Chung 2002 (2)	0.65	0.274	47	0.59	0.206	47	20.5%	0.06 [-0.04 , 0.16]
Koomson 2016	0.21	0.14	75	0.24	0.17	75	79.5%	-0.03 [-0.08 , 0.02]
Subtotal (95% CI)			**122**			**122**	**100.0%**	**-0.01 [-0.06 , 0.03]**
Heterogeneity: Chi² = 2.57, df = 1 (P = 0.11); I² = 61%								
Test for overall effect: Z = 0.51 (P = 0.61)								



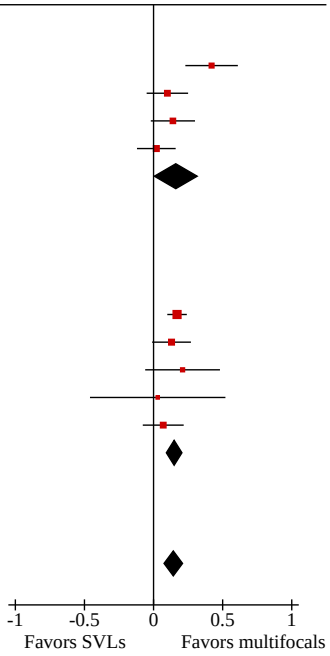
Footnotes
(1) Data estimated from graph.
(2) Data estimated from graph (reported as significant in text).

Comparison 2. Multifocal lenses vs single vision lenses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Change in refractive error from baseline (1 year)	9	1463	Mean Difference (IV, Random, 95% CI)	0.14 [0.08, 0.21]
2.1.1 Bifocal lenses	4	421	Mean Difference (IV, Random, 95% CI)	0.16 [0.01, 0.32]
2.1.2 Progressive addition lenses	5	1042	Mean Difference (IV, Random, 95% CI)	0.15 [0.09, 0.21]
2.2 Change in refractive error from baseline (2 years)	8	1401	Mean Difference (IV, Random, 95% CI)	0.19 [0.08, 0.30]
2.2.1 Bifocal lenses	4	416	Mean Difference (IV, Random, 95% CI)	0.20 [-0.09, 0.49]
2.2.2 Progressive addition lenses	4	985	Mean Difference (IV, Random, 95% CI)	0.20 [0.12, 0.28]
2.3 Change in refractive error from baseline (3 years)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.3.1 Bifocal lenses	1	158	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.47, 0.09]
2.3.2 Progressive addition lenses	2	579	Mean Difference (IV, Fixed, 95% CI)	0.21 [0.08, 0.34]
2.4 Change in axial length from baseline (1 year)	4	896	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.09, -0.04]
2.5 Change in axial length from baseline (2 years)	2	723	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.10, -0.01]
2.6 Change in axial length from baseline (3 years)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.7 Change in corneal radius of curvature from baseline, horizontal (3 years)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.7.1 At 3 years, horizontal	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.7.2 At 3 years, vertical	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Multifocal lenses vs single vision lenses, Outcome 1: Change in refractive error from baseline (1 year)

Study or Subgroup	MD	SE	Multifocal lenses Total	SVLs Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 Bifocal lenses						
Cheng 2010 (1)	0.42	0.0969	48	41	8.8%	0.42 [0.23 , 0.61]
Fulk 2002	0.1	0.0765	37	36	12.1%	0.10 [-0.05 , 0.25]
Jensen 1991	0.14	0.0816	51	49	11.1%	0.14 [-0.02 , 0.30]
Pärssinen 1989	0.02	0.0714	80	79	13.1%	0.02 [-0.12 , 0.16]
Subtotal (95% CI)			**216**	**205**	**45.1%**	**0.16 [0.01 , 0.32]**
Heterogeneity: Tau² = 0.02; Chi² = 11.45, df = 3 (P = 0.010); I² = 74%						
Test for overall effect: Z = 2.03 (P = 0.04)						
2.1.2 Progressive addition lenses						
COMET Study 2003	0.17	0.036	235	234	22.8%	0.17 [0.10 , 0.24]
COMET2 Study 2011	0.13	0.0716	55	58	13.0%	0.13 [-0.01 , 0.27]
Edwards 2002 (2)	0.21	0.138	121	133	5.1%	0.21 [-0.06 , 0.48]
MIT Study 2001 (2)	0.03	0.25	61	61	1.8%	0.03 [-0.46 , 0.52]
STAMP Study 2012	0.07	0.0755	41	43	12.2%	0.07 [-0.08 , 0.22]
Subtotal (95% CI)			**513**	**529**	**54.9%**	**0.15 [0.09 , 0.21]**
Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 4 (P = 0.75); I² = 0%						
Test for overall effect: Z = 5.18 (P < 0.00001)						
Total (95% CI)			**729**	**734**	**100.0%**	**0.14 [0.08 , 0.21]**
Heterogeneity: Tau² = 0.00; Chi² = 13.41, df = 8 (P = 0.10); I² = 40%						
Test for overall effect: Z = 4.18 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%						



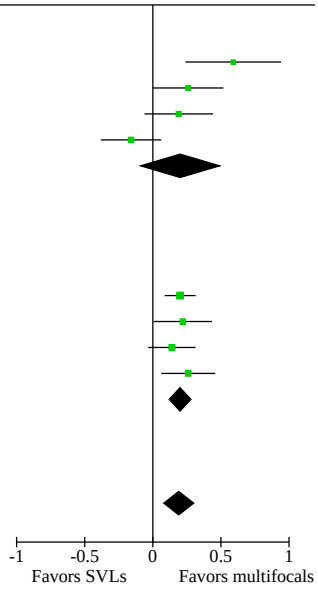
Footnotes

(1) Data provided by study author.

(2) Mean differences based on final measurements.

Analysis 2.2. Comparison 2: Multifocal lenses vs single vision lenses, Outcome 2: Change in refractive error from baseline (2 years)

Study or Subgroup	Multifocal lenses Mean	SD	Total	SVLs Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 Bifocal lenses								
Cheng 2010	-0.96	0.92	48	-1.55	0.77	41	6.9%	0.59 [0.24 , 0.94]
Fulk 2002	-0.76	0.55	34	-1.02	0.56	37	10.3%	0.26 [0.00 , 0.52]
Jensen 1991	-0.95	0.56	51	-1.14	0.71	49	10.6%	0.19 [-0.06 , 0.44]
Pärssinen 1989	-1.22	0.74	78	-1.06	0.67	78	12.1%	-0.16 [-0.38 , 0.06]
Subtotal (95% CI)			**211**			**205**	**39.9%**	**0.20 [-0.09 , 0.49]**
Heterogeneity: Tau² = 0.07; Chi² = 14.33, df = 3 (P = 0.002); I² = 79%								
Test for overall effect: Z = 1.36 (P = 0.17)								
2.2.2 Progressive addition lenses								
COMET Study 2003 (1)	-0.87	0.62	235	-1.07	0.64	234	19.1%	0.20 [0.09 , 0.31]
COMET2 Study 2011	-0.58	0.55	55	-0.8	0.61	58	12.5%	0.22 [0.01 , 0.43]
Edwards 2002	-1.12	0.67	121	-1.26	0.74	133	15.0%	0.14 [-0.03 , 0.31]
Yang 2009	-1.24	0.56	74	-1.5	0.67	75	13.5%	0.26 [0.06 , 0.46]
Subtotal (95% CI)			**485**			**500**	**60.1%**	**0.20 [0.12 , 0.28]**
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 3 (P = 0.84); I² = 0%								
Test for overall effect: Z = 4.91 (P < 0.00001)								
Total (95% CI)			**696**			**705**	**100.0%**	**0.19 [0.08 , 0.30]**
Heterogeneity: Tau² = 0.01; Chi² = 15.73, df = 7 (P = 0.03); I² = 55%								
Test for overall effect: Z = 3.40 (P = 0.0007)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%								

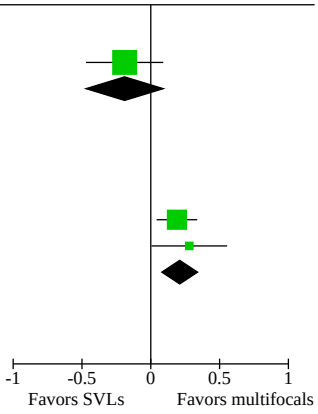


Footnotes

(1) Data provided by study authors.

Analysis 2.3. Comparison 2: Multifocal lenses vs single vision lenses, Outcome 3: Change in refractive error from baseline (3 years)

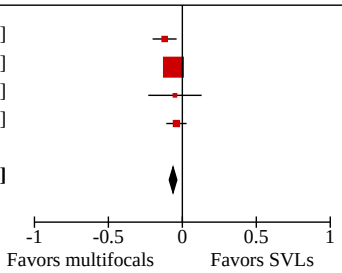
Study or Subgroup	Multifocal lenses Mean	SD	Total	SVLs Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.3.1 Bifocal lenses								
Pärssinen 1989	-1.67	0.9	79	-1.48	0.9	79	100.0%	-0.19 [-0.47 , 0.09]
Subtotal (95% CI)			**79**			**79**	**100.0%**	**-0.19 [-0.47 , 0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.33 (P = 0.18)								
2.3.2 Progressive addition lenses								
COMET Study 2003	-1.23	0.82	235	-1.42	0.81	234	77.6%	0.19 [0.04 , 0.34]
COMET2 Study 2011	-0.87	0.72	52	-1.15	0.75	58	22.4%	0.28 [0.01 , 0.55]
Subtotal (95% CI)			**287**			**292**	**100.0%**	**0.21 [0.08 , 0.34]**
Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%								
Test for overall effect: Z = 3.17 (P = 0.002)								



Analysis 2.4. Comparison 2: Multifocal lenses vs single vision lenses, Outcome 4: Change in axial length from baseline (1 year)

Study or Subgroup	MD	SE	Multifocal lenses Total	SVLs Total	Weight	Mean Difference IV, Random, 95% CI
Cheng 2010	-0.12	0.0414	48	41	9.8%	-0.12 [-0.20 , -0.04]
COMET Study 2003	-0.06	0.015	235	234	74.5%	-0.06 [-0.09 , -0.03]
Edwards 2002 (1)	-0.05	0.092	121	133	2.0%	-0.05 [-0.23 , 0.13]
STAMP Study 2012	-0.04	0.0349	41	43	13.8%	-0.04 [-0.11 , 0.03]
Total (95% CI)			**445**	**451**	**100.0%**	**-0.06 [-0.09 , -0.04]**

Heterogeneity: Tau² = 0.00; Chi² = 2.39, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 4.86 (P < 0.00001)
Test for subgroup differences: Not applicable

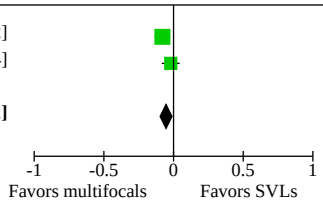


Footnotes
(1) Mean differences based on final measurements.

Analysis 2.5. Comparison 2: Multifocal lenses vs single vision lenses, Outcome 5: Change in axial length from baseline (2 years)

Study or Subgroup	Multifocal lenses Mean	SD	Total	SVLs Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
COMET Study 2003 (1)	0.45	0.31	235	0.53	0.31	234	56.5%	-0.08 [-0.14 , -0.02]
Edwards 2002	0.61	0.24	121	0.63	0.28	133	43.5%	-0.02 [-0.08 , 0.04]
Total (95% CI)			**356**			**367**	**100.0%**	**-0.05 [-0.10 , -0.01]**

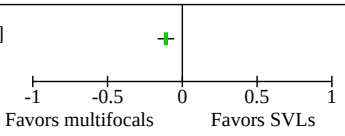
Heterogeneity: Chi² = 1.91, df = 1 (P = 0.17); I² = 48%
Test for overall effect: Z = 2.50 (P = 0.01)
Test for subgroup differences: Not applicable



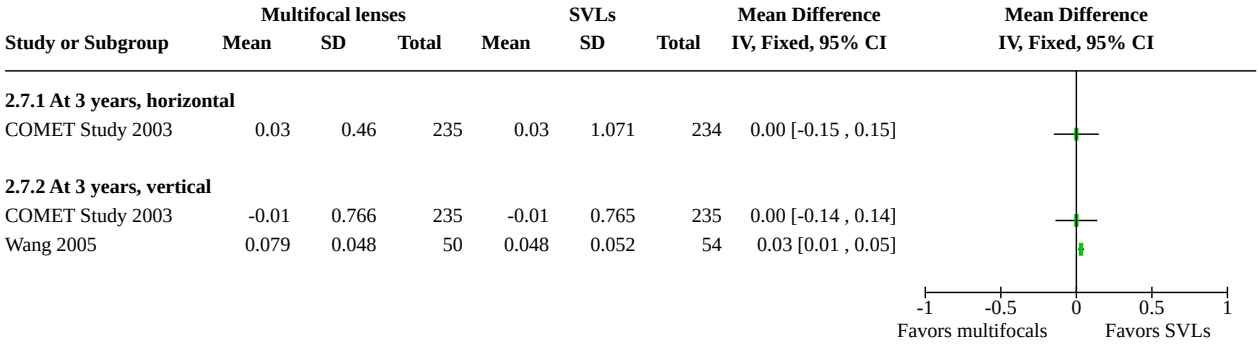
Footnotes
(1) Data estimated from graph.

Analysis 2.6. Comparison 2: Multifocal lenses vs single vision lenses, Outcome 6: Change in axial length from baseline (3 years)

Study or Subgroup	Multifocal lenses Mean	SD	Total	SVLs Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
COMET Study 2003	0.64	0.307	235	0.75	0.306	234	-0.11 [-0.17 , -0.05]



Analysis 2.7. Comparison 2: Multifocal lenses vs single vision lenses, Outcome 7: Change in corneal radius of curvature from baseline, horizontal (3 years)

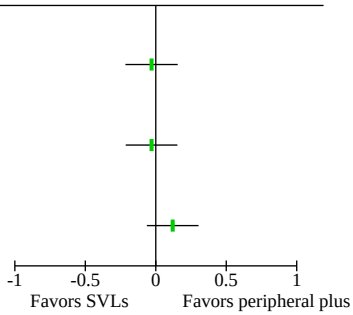


Comparison 3. Peripheral plus spectacles vs single vision lenses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Change in refractive error from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1.1 Type I	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1.2 Type II	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1.3 Type III	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.2 Change in refractive error from baseline (2 years)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.2.1 +1.0 Diopters	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.2.2 +1.5 Diopters	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.3 Change in axial length from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.3.1 Type I	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.3.2 Type II	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.3.3 Type III	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4 Change in axial length from baseline (2 years)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4.1 +1.0 Diopters	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4.2 +1.5 Diopters	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: Peripheral plus spectacles vs single vision lenses, Outcome 1: Change in refractive error from baseline (1 year)

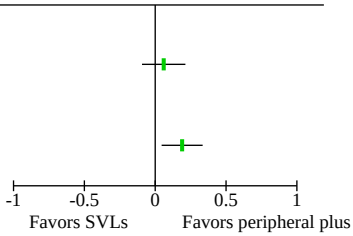
Study or Subgroup	Peripheral plus spectacles Mean	SD	Total	SVLs Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.1.1 Type I							
Sankaridurg 2010 (1)	-0.81	0.43	48	-0.78	0.5	49	-0.03 [-0.22 , 0.16]
3.1.2 Type II							
Sankaridurg 2010 (1)	-0.81	0.46	58	-0.78	0.5	49	-0.03 [-0.21 , 0.15]
3.1.3 Type III							
Sankaridurg 2010 (1)	-0.66	0.41	46	-0.78	0.5	49	0.12 [-0.06 , 0.30]



Footnotes
(1) SD for novel lens estimated from graph.

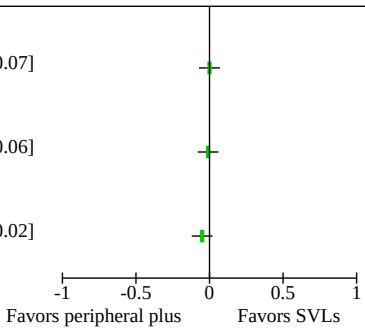
Analysis 3.2. Comparison 3: Peripheral plus spectacles vs single vision lenses, Outcome 2: Change in refractive error from baseline (2 years)

Study or Subgroup	Peripheral plus spectacles Mean	SD	Total	SVLs Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.2.1 +1.0 Diopters							
Hasebe 2014	-1.32	0.59	116	-1.38	0.61	120	0.06 [-0.09 , 0.21]
3.2.2 +1.5 Diopters							
Hasebe 2014	-1.19	0.49	102	-1.38	0.61	120	0.19 [0.05 , 0.33]



Analysis 3.3. Comparison 3: Peripheral plus spectacles vs single vision lenses, Outcome 3: Change in axial length from baseline (1 year)

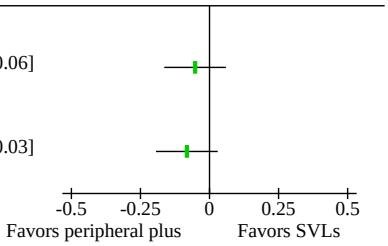
Study or Subgroup	Peripheral plus spectacles Mean	SD	Total	SVLs Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.3.1 Type I							
Sankaridurg 2010 (1)	0.36	0.13	48	0.36	0.22	49	0.00 [-0.07 , 0.07]
3.3.2 Type II							
Sankaridurg 2010 (1)	0.35	0.13	58	0.36	0.22	49	-0.01 [-0.08 , 0.06]
3.3.3 Type III							
Sankaridurg 2010 (1)	0.31	0.12	46	0.36	0.22	49	-0.05 [-0.12 , 0.02]



Footnotes
(1) SD for novel lens estimated from graph.

Analysis 3.4. Comparison 3: Peripheral plus spectacles vs single vision lenses, Outcome 4: Change in axial length from baseline (2 years)

Study or Subgroup	Peripheral plus spectacles Mean	SD	Total	SVLs Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.4.1 +1.0 Diopters							
Hasebe 2014	0.634	0.4847	116	0.686	0.3834	120	-0.05 [-0.16 , 0.06]
3.4.2 +1.5 Diopters							
Hasebe 2014	0.604	0.4545	102	0.686	0.3834	120	-0.08 [-0.19 , 0.03]



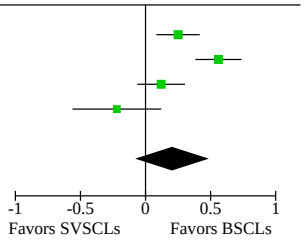
Comparison 4. Bifocal soft contact lenses vs single vision soft contact lenses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Change in refractive error from baseline (1 year)	4	300	Mean Difference (IV, Random, 95% CI)	0.20 [-0.06, 0.47]
4.2 Change in axial length from baseline (1 year)	4	300	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.14, -0.08]
4.3 Change in corneal radius of curvature from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

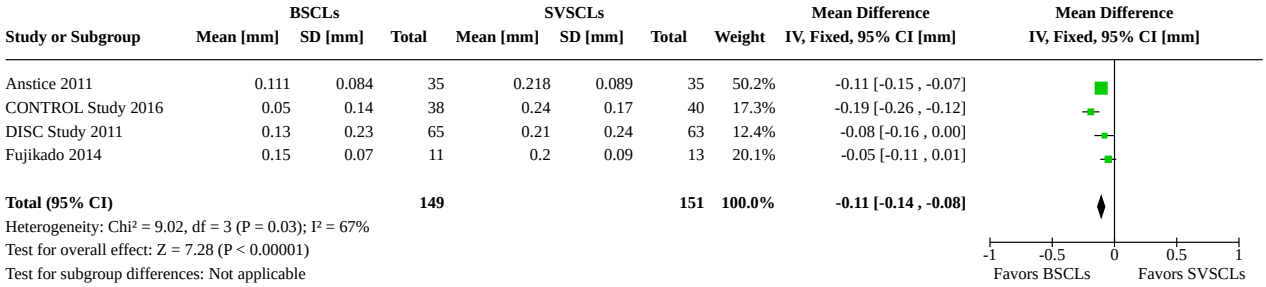
Analysis 4.1. Comparison 4: Bifocal soft contact lenses vs single vision soft contact lenses, Outcome 1: Change in refractive error from baseline (1 year)

Study or Subgroup	BSCLs Mean [D]	SD [D]	Total	SVSCLs Mean [D]	SD [D]	Total	Weight	Mean Difference IV, Random, 95% CI [D]
Anstice 2011	-0.44	0.33	35	-0.69	0.38	35	26.9%	0.25 [0.08 , 0.42]
CONTROL Study 2016	-0.22	0.34	38	-0.78	0.45	40	26.6%	0.56 [0.38 , 0.74]
DISC Study 2011	-0.36	0.49	65	-0.48	0.56	63	26.4%	0.12 [-0.06 , 0.30]
Fujikado 2014	-0.84	0.42	11	-0.62	0.43	13	20.2%	-0.22 [-0.56 , 0.12]
Total (95% CI)			**149**			**151**	**100.0%**	**0.20 [-0.06 , 0.47]**

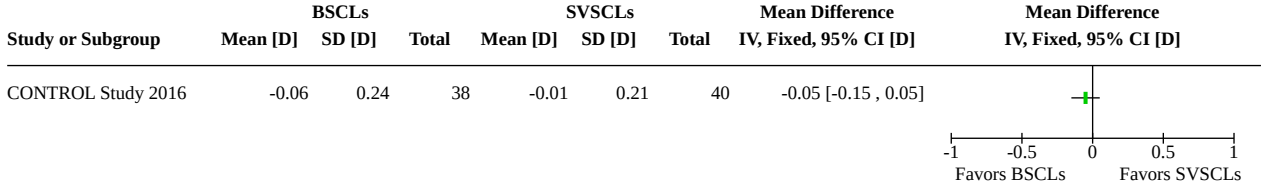
Heterogeneity: Tau² = 0.06; Chi² = 20.96, df = 3 (P = 0.0001); I² = 86%
Test for overall effect: Z = 1.49 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Bifocal soft contact lenses vs single vision soft contact lenses, Outcome 2: Change in axial length from baseline (1 year)



Analysis 4.3. Comparison 4: Bifocal soft contact lenses vs single vision soft contact lenses, Outcome 3: Change in corneal radius of curvature from baseline (1 year)



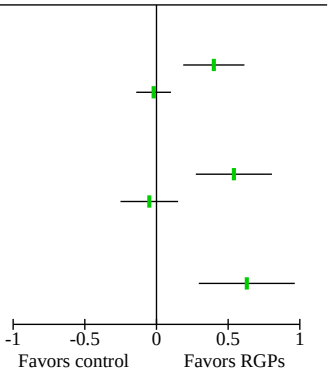
Comparison 5. Rigid gas permeable contact lenses vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Change in refractive error from baseline	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1.1 At 1 year	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1.2 At 2 years	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1.3 At 3 years	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.2 Change in axial length from baseline	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.2.1 At 1 year	2	415	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.05, 0.10]
5.2.2 At 2 years	2	394	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.05, 0.12]
5.2.3 At 3 years	1	116	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.12, 0.22]
5.3 Change in corneal radius of curvature from baseline	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.3.1 At 1 year	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.3.2 At 2 years	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3.3 At 3 years	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5: Rigid gas permeable contact lenses vs control, Outcome 1: Change in refractive error from baseline

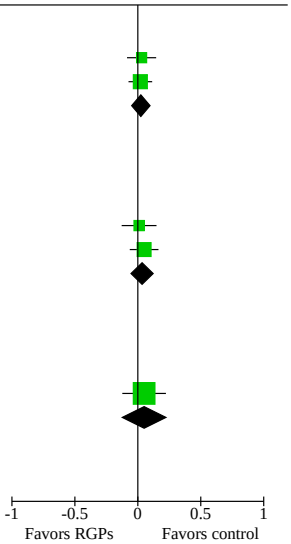
Study or Subgroup	RGPs Mean [D]	RGPs SD [D]	RGPs Total	Control Mean [D]	Control SD [D]	Control Total	Mean Difference IV, Fixed, 95% CI [D]
5.1.1 At 1 year							
CLAMP Study 2004 (1)	-0.79	0.63	58	-1.19	0.53	56	0.40 [0.19 , 0.61]
Katz 2003 (2)	-0.65	0.55	120	-0.63	0.49	186	-0.02 [-0.14 , 0.10]
5.1.2 At 2 years							
CLAMP Study 2004	-1.23	0.73	57	-1.77	0.71	56	0.54 [0.27 , 0.81]
Katz 2003	-1.33	0.84	97	-1.28	0.78	188	-0.05 [-0.25 , 0.15]
5.1.3 At 3 years							
CLAMP Study 2004	-1.56	0.95	59	-2.19	0.89	57	0.63 [0.30 , 0.96]



Footnotes
(1) Control group wore soft contact lenses.
(2) Control group wore single vision spectacles.

Analysis 5.2. Comparison 5: Rigid gas permeable contact lenses vs control, Outcome 2: Change in axial length from baseline

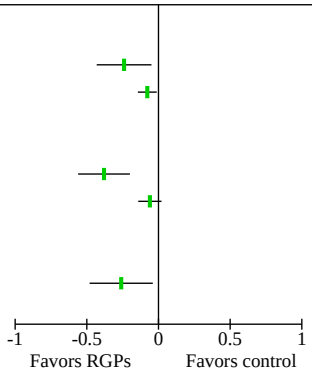
Study or Subgroup	RGPs Mean [mm]	RGPs SD [mm]	RGPs Total	Control Mean [mm]	Control SD [mm]	Control Total	Weight	Mean Difference IV, Fixed, 95% CI [mm]
5.2.1 At 1 year								
CLAMP Study 2004 (1)	0.38	0.33	58	0.35	0.3	56	39.7%	0.03 [-0.09 , 0.15]
Katz 2003 (2)	0.35	0.41	118	0.33	0.4	183	60.3%	0.02 [-0.07 , 0.11]
Subtotal (95% CI)			**176**			**239**	**100.0%**	**0.02 [-0.05 , 0.10]**
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%								
Test for overall effect: Z = 0.64 (P = 0.52)								
5.2.2 At 2 years								
CLAMP Study 2004	0.6	0.39	57	0.59	0.36	56	40.4%	0.01 [-0.13 , 0.15]
Katz 2003	0.84	0.47	97	0.79	0.45	184	59.6%	0.05 [-0.06 , 0.16]
Subtotal (95% CI)			**154**			**240**	**100.0%**	**0.03 [-0.05 , 0.12]**
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%								
Test for overall effect: Z = 0.75 (P = 0.45)								
5.2.3 At 3 years								
CLAMP Study 2004	0.81	0.51	59	0.76	0.44	57	100.0%	0.05 [-0.12 , 0.22]
Subtotal (95% CI)			**59**			**57**	**100.0%**	**0.05 [-0.12 , 0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.57 (P = 0.57)								
Test for subgroup differences: Chi² = 0.08, df = 2 (P = 0.96), I² = 0%								



Footnotes
(1) Control group wore soft contact lenses.
(2) Control group wore single vision spectacles.

Analysis 5.3. Comparison 5: Rigid gas permeable contact lenses vs control, Outcome 3: Change in corneal radius of curvature from baseline

Study or Subgroup	RGPs Mean [D]	RGPs SD [D]	RGPs Total	Control Mean [D]	Control SD [D]	Control Total	Mean Difference IV, Fixed, 95% CI [D]
5.3.1 At 1 year							
CLAMP Study 2004 (1)	0.39	0.53	58	0.63	0.51	56	-0.24 [-0.43 , -0.05]
Katz 2003 (2)	-0.08	0.33	120	-0.002	0.2	183	-0.08 [-0.14 , -0.01]
5.3.2 At 2 years							
CLAMP Study 2004	0.5	0.5	57	0.88	0.48	56	-0.38 [-0.56 , -0.20]
Katz 2003	-0.13	0.33	97	-0.07	0.33	185	-0.06 [-0.14 , 0.02]
5.3.3 At 3 years							
CLAMP Study 2004	0.62	0.64	59	0.88	0.57	57	-0.26 [-0.48 , -0.04]



Footnotes
(1) Control group wore soft contact lenses.
(2) Control group wore single vision spectacles.

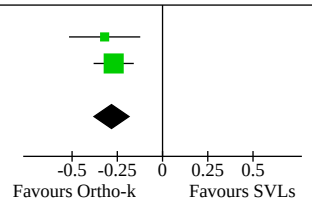
Comparison 6. Orthokeratology contact lenses vs single vision lenses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Change in axial length from baseline (2 years)	2	106	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.38, -0.19]

Analysis 6.1. Comparison 6: Orthokeratology contact lenses vs single vision lenses, Outcome 1: Change in axial length from baseline (2 years)

Study or Subgroup	Ortho-k Mean	Ortho-k SD	Ortho-k Total	SVLs Mean	SVLs SD	SVLs Total	Weight	Mean Difference IV, Fixed, 95% CI
Charm 2013	0.19	0.21	12	0.51	0.32	16	24.1%	-0.32 [-0.52 , -0.12]
ROMIO Study 2012	0.36	0.24	37	0.63	0.26	41	75.9%	-0.27 [-0.38 , -0.16]
Total (95% CI)			**49**			**57**	**100.0%**	**-0.28 [-0.38 , -0.19]**

Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 5.72 (P < 0.00001)
Test for subgroup differences: Not applicable



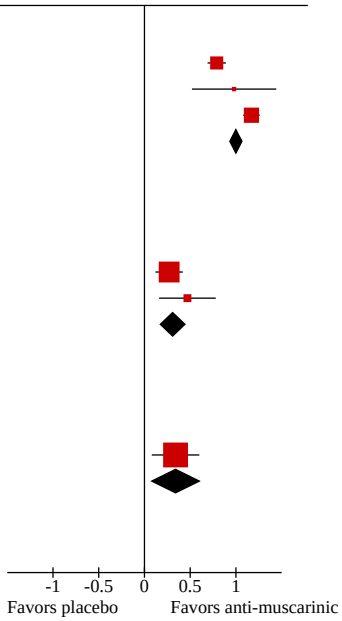
Comparison 7. Antimuscarinic agents vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Change in refractive error from baseline (1 year)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1.1 Atropine eye drops	3	629	Mean Difference (IV, Fixed, 95% CI)	1.00 [0.93, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1.2 Pirenzepine 2% gel	2	326	Mean Difference (IV, Fixed, 95% CI)	0.31 [0.17, 0.44]
7.1.3 Cyclopentolate eye drops	1	64	Mean Difference (IV, Fixed, 95% CI)	0.34 [0.08, 0.60]
7.2 Change in refractive error from baseline (2 years)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.2.1 Atropine eye drops	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.2.2 Pirenzepine 2% gel	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.3 Change in axial length from baseline (1 year)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.3.1 Atropine eye drops	2	502	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.38, -0.31]
7.3.2 Pirenzepine 2% gel	2	326	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.14, -0.12]
7.4 Change in axial length from baseline (2 years)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.5 Incidence of adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.5.1 Accomodation abnormality symptoms	2	387	Risk Ratio (M-H, Fixed, 95% CI)	9.05 [4.09, 20.01]
7.5.2 Papillae/follicles	2	387	Risk Ratio (M-H, Fixed, 95% CI)	3.22 [2.11, 4.90]
7.5.3 Medication residue on the eyelids/eyelashes	2	387	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.73, 1.12]

Analysis 7.1. Comparison 7: Antimuscarinic agents vs placebo, Outcome 1: Change in refractive error from baseline (1 year)

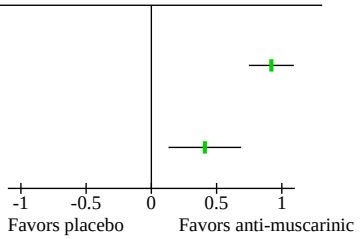
Study or Subgroup	MD	SE	Anti-muscarinic (topical) Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
7.1.1 Atropine eye drops						
ATOM Study 2006	0.79	0.051	182	188	43.8%	0.79 [0.69 , 0.89]
MIT Study 2001 (1)	0.98	0.235	66	61	2.1%	0.98 [0.52 , 1.44]
Yi 2015	1.17	0.0459	68	64	54.1%	1.17 [1.08 , 1.26]
Subtotal (95% CI)			**316**	**313**	**100.0%**	**1.00 [0.93 , 1.07]**
Heterogeneity: Chi² = 30.68, df = 2 (P < 0.00001); I² = 93%						
Test for overall effect: Z = 29.60 (P < 0.00001)						
7.1.2 Pirenzepine 2% gel						
PIR-205 Study 2004	0.27	0.0765	92	54	81.0%	0.27 [0.12 , 0.42]
Tan 2005 (1)	0.47	0.158	118	62	19.0%	0.47 [0.16 , 0.78]
Subtotal (95% CI)			**210**	**116**	**100.0%**	**0.31 [0.17 , 0.44]**
Heterogeneity: Chi² = 1.30, df = 1 (P = 0.25); I² = 23%						
Test for overall effect: Z = 4.47 (P < 0.00001)						
7.1.3 Cyclopentolate eye drops						
Yen 1989	0.34	0.1327	32	32	100.0%	0.34 [0.08 , 0.60]
Subtotal (95% CI)			**32**	**32**	**100.0%**	**0.34 [0.08 , 0.60]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.56 (P = 0.01)						
Test for subgroup differences: Chi² = 96.23, df = 2 (P < 0.00001), I² = 97.9%						



Footnotes
(1) Mean differences based on final measurements.

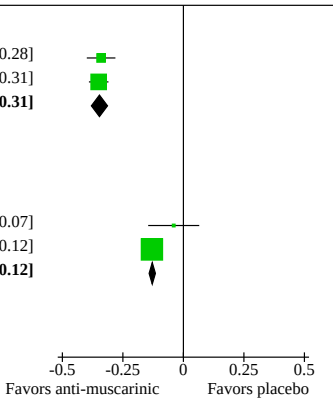
Analysis 7.2. Comparison 7: Antimuscarinic agents vs placebo, Outcome 2: Change in refractive error from baseline (2 years)

Study or Subgroup	Anti-muscarinic (topical) Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
7.2.1 Atropine eye drops							
ATOM Study 2006	-0.28	0.92	166	-1.2	0.69	180	0.92 [0.75 , 1.09]
7.2.2 Pirenzepine 2% gel							
PIR-205 Study 2004	-0.58	0.53	53	-0.99	0.68	31	0.41 [0.13 , 0.69]



Analysis 7.3. Comparison 7: Antimuscarinic agents vs placebo, Outcome 3: Change in axial length from baseline (1 year)

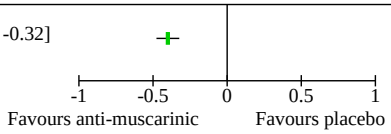
Study or Subgroup	Anti-muscarinic (topical) Mean [mm]	SD [mm]	Total	Placebo Mean [mm]	SD [mm]	Total	Weight	Mean Difference IV, Fixed, 95% CI [mm]
7.3.1 Atropine eye drops								
ATOM Study 2006	-0.14	0.28	182	0.2	0.3	188	31.8%	-0.34 [-0.40 , -0.28]
Yi 2015	-0.03	0.07	68	0.32	0.15	64	68.2%	-0.35 [-0.39 , -0.31]
Subtotal (95% CI)			**250**			**252**	**100.0%**	**-0.35 [-0.38 , -0.31]**
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%								
Test for overall effect: Z = 20.40 (P < 0.00001)								
7.3.2 Pirenzepine 2% gel								
PIR-205 Study 2004	0.19	0.24	92	0.23	0.35	54	1.5%	-0.04 [-0.15 , 0.07]
Tan 2005 (1)	0.2	0.0286	118	0.33	0.0485	62	98.5%	-0.13 [-0.14 , -0.12]
Subtotal (95% CI)			**210**			**116**	**100.0%**	**-0.13 [-0.14 , -0.12]**
Heterogeneity: Chi² = 2.76, df = 1 (P = 0.10); I² = 64%								
Test for overall effect: Z = 19.35 (P < 0.00001)								
Test for subgroup differences: Chi² = 142.89, df = 1 (P < 0.00001), I² = 99.3%								



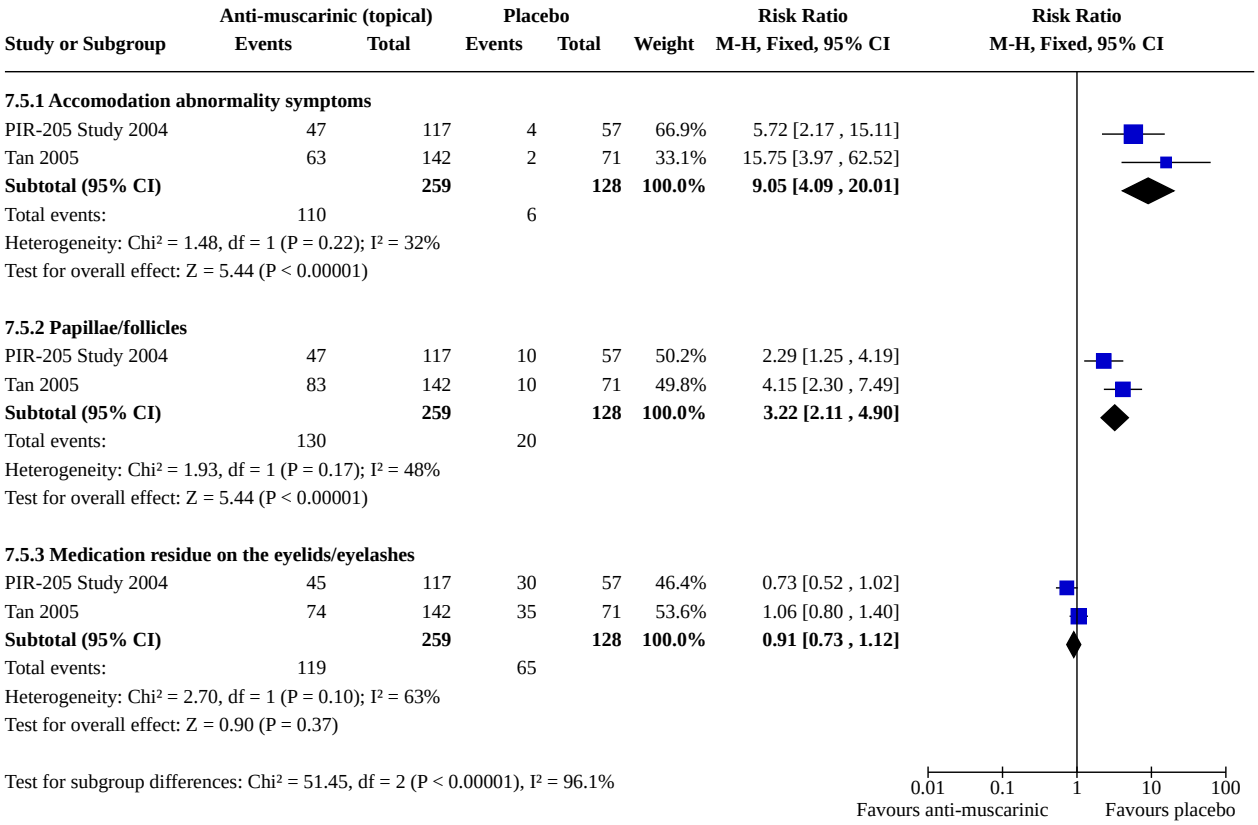
Footnotes
(1) Standard deviations estimated from graph.

Analysis 7.4. Comparison 7: Antimuscarinic agents vs placebo, Outcome 4: Change in axial length from baseline (2 years)

Study or Subgroup	Anti-muscarinic (topical) Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
ATOM Study 2006	-0.02	0.35	166	0.38	0.38	180	-0.40 [-0.48 , -0.32]



Analysis 7.5. Comparison 7: Antimuscarinic agents vs placebo, Outcome 5: Incidence of adverse events

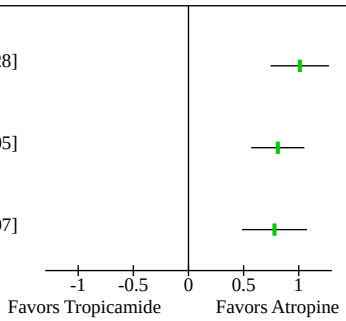


Comparison 8. Atropine vs tropicamide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Change in refractive error from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1.1 Atropine 0.5%	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1.2 Atropine 0.25%	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1.3 Atropine 0.1%	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.2 Change in refractive error from baseline (2 years)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.2.1 Atropine 0.5%	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.2.2 Atropine 0.25%	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.2.3 Atropine 0.1%	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8: Atropine vs tropicamide, Outcome 1: Change in refractive error from baseline (1 year)

Study or Subgroup	Atropine Mean [D]	Atropine SD [D]	Atropine Total	Tropicamide Mean [D]	Tropicamide SD [D]	Tropicamide Total	Mean Difference IV, Fixed, 95% CI [D]
8.1.1 Atropine 0.5%							
Shih 1999 (1)	-0.02	0.68	47	-1.03	0.65	50	1.01 [0.74 , 1.28]
8.1.2 Atropine 0.25%							
Shih 1999 (2)	-0.22	0.57	49	-1.03	0.65	50	0.81 [0.57 , 1.05]
8.1.3 Atropine 0.1%							
Shih 1999 (3)	-0.25	0.84	50	-1.03	0.65	50	0.78 [0.49 , 1.07]



Footnotes

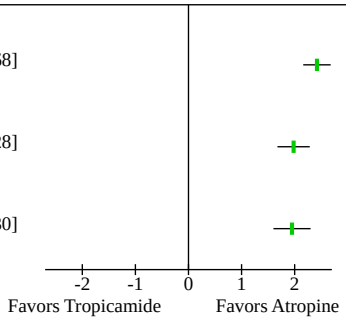
(1) Atropine 0.5% instilled daily, advised to wear bifocals; tropicamide 0.5% instilled daily

(2) Atropine 0.25% instilled daily, advised to wear slightly undercorrected lenses; tropicamide 0.5% instilled daily

(3) Atropine 0.1% instilled daily, advised to wear fully corrected lenses; tropicamide 0.5% instilled daily

Analysis 8.2. Comparison 8: Atropine vs tropicamide, Outcome 2: Change in refractive error from baseline (2 years)

Study or Subgroup	Atropine Mean [D]	Atropine SD [D]	Atropine Total	Tropicamide Mean [D]	Tropicamide SD [D]	Tropicamide Total	Mean Difference IV, Fixed, 95% CI [D]
8.2.1 Atropine 0.5%							
Shih 1999 (1)	-0.09	0.56	41	-2.51	0.69	49	2.42 [2.16 , 2.68]
8.2.2 Atropine 0.25%							
Shih 1999 (2)	-0.53	0.82	47	-2.51	0.69	49	1.98 [1.68 , 2.28]
8.2.3 Atropine 0.1%							
Shih 1999 (3)	-0.56	1.04	49	-2.51	0.69	49	1.95 [1.60 , 2.30]



Footnotes

(1) Atropine 0.5% instilled daily, advised to wear bifocals; tropicamide 0.5% instilled daily

(2) Atropine 0.25% instilled daily, advised to wear slightly undercorrected lenses; tropicamide 0.5% instilled daily

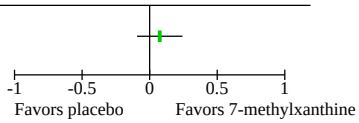
(3) Atropine 0.1% instilled daily, advised to wear fully corrected lenses; tropicamide 0.5% instilled daily

Comparison 9. Systemic 7-methylxanthine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Change in refractive error from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.2 Change in axial length from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.3 Change in corneal radius of curvature from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

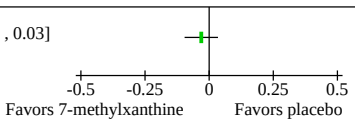
Analysis 9.1. Comparison 9: Systemic 7-methylxanthine vs placebo, Outcome 1: Change in refractive error from baseline (1 year)

Study or Subgroup	7-methylxanthine Mean [D]	SD [D]	Total	Placebo Mean [D]	SD [D]	Total	Mean Difference IV, Fixed, 95% CI [D]	Mean Difference IV, Fixed, 95% CI [D]
Trier 2008	-0.5233	0.3135	35	-0.5978	0.4358	42	0.07 [-0.09 , 0.24]	



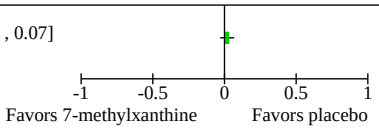
Analysis 9.2. Comparison 9: Systemic 7-methylxanthine vs placebo, Outcome 2: Change in axial length from baseline (1 year)

Study or Subgroup	7-methylxanthine Mean [mm]	SD [mm]	Total	Placebo Mean [mm]	SD [mm]	Total	Mean Difference IV, Fixed, 95% CI [mm]	Mean Difference IV, Fixed, 95% CI [mm]
Trier 2008	0.2638	0.1462	35	0.2945	0.1435	42	-0.03 [-0.10 , 0.03]	



Analysis 9.3. Comparison 9: Systemic 7-methylxanthine vs placebo, Outcome 3: Change in corneal radius of curvature from baseline (1 year)

Study or Subgroup	7-methylxanthine Mean [D]	SD [D]	Total	Placebo Mean [D]	SD [D]	Total	Mean Difference IV, Fixed, 95% CI [D]	Mean Difference IV, Fixed, 95% CI [D]
Trier 2008	-0.0243	0.1202	35	-0.0429	0.0965	42	0.02 [-0.03 , 0.07]	

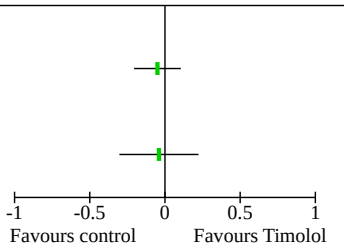


Comparison 10. Timolol eye drops vs no eye drops

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Change in refractive error from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1.1 At 1 year	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1.2 At 2 years	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 10.1. Comparison 10: Timolol eye drops vs no eye drops, Outcome 1: Change in refractive error from baseline

Study or Subgroup	Timolol Mean	Timolol SD	Timolol Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
10.1.1 At 1 year							
Jensen 1991 (1)	-0.7	0.3	46	-0.65	0.46	49	-0.05 [-0.21 , 0.11]
10.1.2 At 2 years							
Jensen 1991	-1.18	0.59	45	-1.14	0.71	49	-0.04 [-0.30 , 0.22]



Footnotes

(1) Timolol 0.25% twice daily; all children wore SVLs.

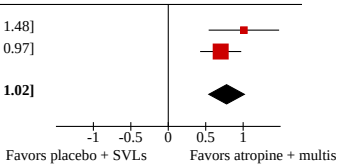
Comparison 11. Atropine + multifocal lenses vs placebo + single vision lenses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Change in refractive error from baseline (1 year)	2	191	Mean Difference (IV, Fixed, 95% CI)	0.78 [0.54, 1.02]
11.2 Change in axial length from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 11.1. Comparison 11: Atropine + multifocal lenses vs placebo + single vision lenses, Outcome 1: Change in refractive error from baseline (1 year)

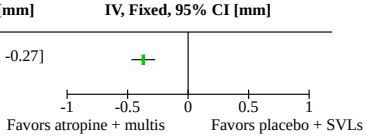
Study or Subgroup	MD	SE	Atropine eye drops + Multifocal lenses Total	Placebo eye drops + SVLs Total	Weight	Mean Difference IV, Fixed, 95% CI
MIT Study 2001	1.01	0.24	66	61	25.4%	1.01 [0.54 , 1.48]
Yen 1989	0.7	0.14	32	32	74.6%	0.70 [0.43 , 0.97]
Total (95% CI)			**98**	**93**	**100.0%**	**0.78 [0.54 , 1.02]**

Heterogeneity: Chi² = 1.24, df = 1 (P = 0.26); I² = 20%
Test for overall effect: Z = 6.44 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 11.2. Comparison 11: Atropine + multifocal lenses vs placebo + single vision lenses, Outcome 2: Change in axial length from baseline (1 year)

Study or Subgroup	Atropine eye drops + Multifocal lenses Mean [mm]	SD [mm]	Total	Placebo eye drops + SVLs Mean [mm]	SD [mm]	Total	Mean Difference IV, Fixed, 95% CI [mm]
MIT Study 2001	0.22	0.244	66	0.59	0.312	61	-0.37 [-0.47 , -0.27]

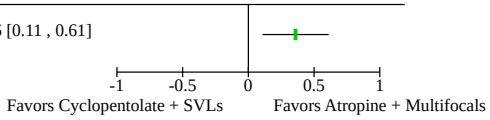


Comparison 12. Atropine + multifocal lenses vs cyclopentolate + single vision lenses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Change in refractive error from baseline (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 12.1. Comparison 12: Atropine + multifocal lenses vs cyclopentolate + single vision lenses, Outcome 1: Change in refractive error from baseline (1 year)

Study or Subgroup	Atropine + Multifocals Mean [D]	SD [D]	Total	Cyclopentolate + SVLs Mean [D]	SD [D]	Total	Mean Difference IV, Fixed, 95% CI [D]
Yen 1989 (1)	-0.219	0.538	32	-0.578	0.49	32	0.36 [0.11 , 0.61]



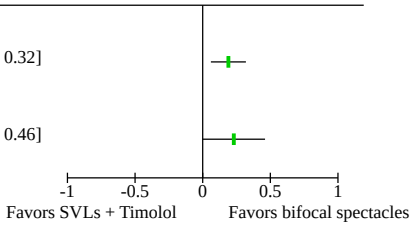
Footnotes
(1) 1% Atropine every other day + Bifocal spectacles; 1% Cyclopentolate every day + SVLs

Comparison 13. Bifocal spectacles vs single vision lenses + timolol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Change in refractive error from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1.1 At 1 year	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1.2 At 2 years	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 13.1. Comparison 13: Bifocal spectacles vs single vision lenses + timolol, Outcome 1: Change in refractive error from baseline

Study or Subgroup	Bifocals Mean [D]	SD [D]	Total	SVLs + Timolol Mean [D]	SD [D]	Total	Mean Difference IV, Fixed, 95% CI [D]
13.1.1 At 1 year							
Jensen 1991	-0.51	0.35	51	-0.7	0.3	46	0.19 [0.06 , 0.32]
13.1.2 At 2 years							
Jensen 1991	-0.95	0.56	51	-1.18	0.59	45	0.23 [-0.00 , 0.46]



ADDITIONAL TABLES

Table 1. Interventions of included studies

Study	Spectacles				Contact lenses					Pharmaceutical agents		Combination of interventions
	Under-corrected SVLs	Multifocal lenses			Fully corrected SVLs	Soft bifocal lenses	RGP	Ortho-k	SA-SCL	SVSCL	Test group	Reference group	
		Bifocal lenses	PALs	Peripheral plus lenses									
Adler 2006; 2 study arms	X				X								
Chung 2002; 2 study arms	X				X								
Koomson 2016; 2 study arms	X				X								
Cheng 2010; 3 study arms		+1.50 and +1.50 prism			X								
Fulk 1996; 2 study arms		+1.25			X								
Fulk 2002; 2 study arms		+1.50			X								
Houston Study 1987; 3 study arms		+1.00 and +2.00			X								
Jensen 1991; 3 study arms		+2.00			X								Timolol + SVLs
Pärssinen 1989; 3 study arms		+1.75			Continous use and distance only								
COMET Study 2003; 2 study arms			+2.00		X								

Table 1. Interventions of included studies *(Continued)*

COMET2 Study 2011; 2 study arms	+2.00		X							
Edwards 2002; 2 study arms	+1.50		X							
Hasebe 2008; 2 study arms[a]	+1.50		X							
MIT Study 2001; 3 study arms	Plus placebo drops		Plus placebo drops							Atropine + PALs
STAMP Study 2012; 2 study arms	+2.00		X							
Wang 2005; 2 study arms	Add NR		X							
Yang 2009; 2 study arms	+1.50		X							
Lu 2015; 2 study arms		+2.50	X							
Hasebe 2014; 3 study arms		+1.00 and +1.50	X							
Sankaridurg 2010; 4 study arms		+1.00, +1.90, and +2.00	X							
Anstice 2011; 2 study arms[a]				+2.00			X			
CONTROL Study 2016; 2 study arms				Add NR			X			
DISC Study 2011; 2 study arms				+2.50			X			
Fujikado 2014; 2 study arms[a]				+0.50			X			
CLAMP Study 2004; 2 study arms					X		X			
Katz 2003; 2 study arms			X		X					

Table 1. Interventions of included studies *(Continued)*

Charm 2013; 2 study arms	X			X				
ROMIO Study 2012; 2 study arms	X			X				
Swarbrick 2015; 2 study arms[a]			X	X				
Cambridge Anti-Myopia Study 2013; 4 study arms					With and without vision training	With and without vision training		
Cheng 2016; 2 study arms					X	X		
ATOM Study 2006; 2 study arms							1% atropine	Placebo drops
Yi 2015; 2 study arms							1% atropine	Placebo drops
Yen 1989; 3 study arms							1% atropine + bifocals	Saline + SVLs	Cyclopentolate + SVLs
Shih 1999; 4 study arms							0.1%, 0.25%, and 0.5% atropine	0.5% tropicamide
PIR-205 Study 2004; 2 study arms							2% pirenzepine gel	Placebo gel
Tan 2005; 3 study arms							2% pirenzepine gel once	Placebo gel

Table 1. Interventions of included studies *(Continued)*

			and twice daily		
Trier 2008; 2 study arms			Systemic 7-methylxanthine	Placebo tablet	
Schwartz 1981; 2 study arms	X				Tropicamide + bifocals

NR: not reported.
Ortho-k: orthokeratology lenses.
PALs: progressive addition lenses.
RGP: rigid gas permeable contact lenses.
SA-SCL: spherical aberration soft contact lenses.
SVLs: single vision lenses.
SVSCL: single vision soft contact lenses.
[a]Cross-over trial.

Table 2. Outcomes reported by studies of spectacle interventions[a]

Outcomes	Interventions studied		
	Undercorrected lenses: 3studies	**Multifocal lenses: 14studies**	Peripheral plus spectacles**: 3studies**
Primary outcome: change in refractive error	Analysis 1.1	Analysis 2.1; Analysis 2.2; Analysis 2.3	Analysis 3.1; Analysis 3.2
Secondary outcome: change in axial length	Analysis 1.2	Analysis 2.4; Analysis 2.5; Analysis 2.6	Analysis 3.3; Analysis 3.4
Secondary outcome: change in corneal radius of curvature	Not reported by 2 studies and reported only as nonsignificant by Chung 2002	Analysis 2.7	Not reported
Adverse effects	Two participants who were undercorrected complained of blurred vision (Adler 2006)	Three participants using PALs in 1 study had conjunctivitis, distance blur, or dizziness (COMET2 Study 2011)	Participants reported blurred side vision, visual distortion, dizziness, headaches, and falls (Sankaridurg 2010)

[a]Compared with fully corrected single vision lenses.

Table 3. Outcomes reported by studies of contact lens interventions[a]

Outcomes	Interventions studied			
	Soft bifocal contact lenses: 4studies	**Rigid gas permeable contact lenses: 2 studies**	**Orthokeratology: 3 studies**	**Spherical aberration soft contact lenses: 2 studies**
Primary outcome: change in refractive error	Analysis 4.1	Analysis 5.1	No data for analysis	Data reported by both studies, but not meta-analyzable
Secondary outcome: change in axial length	Analysis 4.2	Analysis 5.2	Analysis 6.1	Data reported by both studies, but not meta-analyzable
Secondary outcome: change in corneal radius of curvature	Analysis 4.3	Analysis 5.3	No data for analysis	Not reported
Adverse effects	Six children in 1 study withdrew from the study, 3 from each group (CONTROL Study 2016)	Not reported	Adverse effects reported from all 3 studies	One study reported 1 child with allergic conjunctivitis and 1 with contact dermatitis

[a]Compared with fully corrected single vision lenses or contact lenses.

Table 4. Outcomes reported by studies of pharmaceutical interventions[a]

Outcomes	Interventions studied				
	Antimuscarinic agents: 6**studies**	**Atropine vs** tropicamide**:** 1**study**	Systemic adenosine antagonists**:** 1**study**	**Timolol: 1 study**	**Tropicamide (plus bifocals): 1 study**
Primary outcome: change in refractive error	Analysis 7.1; Analysis 7.2	Analysis 8.1; Analysis 8.2	Analysis 9.1	Analysis 10.1	Control twins showed more progression in myopia than their co-twins who received tropicamide and bifocals, but this difference was not statistically significant (Schwartz 1981)
Secondary outcome: change in axial length	Analysis 7.3; Analysis 7.4	Not reported	Analysis 9.2	Not reported	Not reported
Secondary outcome: change in corneal radius of curvature	Not reported	Not reported	Analysis 9.3	Not reported	Not reported

[a]Compared with placebo or no drops.

Table 5. Unit of analysis for included studies

Unit of analysis	Studies reporting each type of unit of analysis
Average of both eyes	15 studies: Adler 2006; Chung 2002; COMET Study 2003 [a]; COMET2 Study 2011; CONTROL Study 2016; Fujikado 2014; Fulk 1996; Fulk 2002; Hasebe 2008 [a]; PIR-205 Study 2004; Sankaridurg 2010; Schwartz 1981; Shih 1999; Tan 2005; Trier 2008
Right eye only	15 studies: Cambridge Anti-Myopia Study 2013; Charm 2013; Cheng 2010; Cheng 2016; CLAMP Study 2004; DISC Study 2011; Edwards 2002; Houston Study 1987; Katz 2003; Koomson 2016; MIT Study 2001; ROMIO Study 2012; STAMP Study 2012; Yen 1989; Yi 2015
Right and left eyes reported as separate analyses	2 studies: Jensen 1991; Pärssinen 1989
One study eye randomized and treated per child	1 study: ATOM Study 2006
Child randomized and both eyes analyzed as independent units	2 studies: Hasebe 2014; Lu 2015
Paired-eye design	2 studies: Anstice 2011; Swarbrick 2015
Eye with more severe myopia	1 study: Wang 2017

Table 5. Unit of analysis for included studies *(Continued)*

Not reported	3 studies: Han 2018; Wang 2005; Yang 2009

[a]Average values of both eyes were used if the correlation coefficient was > 0.85 between eyes and the mean difference (MD) was not statistically significant; otherwise the eye with more myopic change was used for each child (COMET Study 2003). Mean of both eyes or of right eye only (Hasebe 2008).

Table 6. Adverse effects reported by studies of pharmaceutical interventions

Study	Interventions studied	Details
PIR-205 Study 2004	Pirenzepine gel vs placebo gel	Reported 6 ocular adverse events with P ≤ 0.15 • Accommodation abnormality symptoms: 40% vs 7% • Papillae and follicles: 40% vs 18% • Medication residue: 38% vs 53% • Visual acuity decreased: 15% vs 2% • Eye discomfort: 10% vs 4% • Mydriasis: 9% vs 2%
Tan 2005	Pirenzepine gel and placebo gel 1. PIR/PIR 2. PLC/PIR 3. PLC/PLC	Reported 4 ocular adverse events with P ≤ 0.15 (compared to PLC/PLC) • Papillae and follicles: 1 = 58.5%; 2 = 51.4%; 3 = 14.1% • Abnormality of accommodation: 1 = 44.4%; 2 = 22.1%; 3 = 2.8% • Eye itching: 2 = 10.0%; 3 = 18.3% • Visual acuity decreased: 1 = 16.9%; 2 = 14.3%; 3 = 1.4%
ATOM Study 2006	Atropine 1% vs placebo eye drops	No serious adverse events reported, but reasons for withdrawal among atropine users included allergic or hypersensitivity reactions or discomfort (4.5%), glare (1.5%), blurred near vision (1%), and logistical difficulties (3.5%)
Yen 1989	Atropine 1% + bifocals vs cyclopentolate + SVLs vs placebo + SVLs	All atropine users reported photophobia; most reported that they stopped gym classes and did not like going outdoors. No other systemic or ocular complications were observed
Shih 1999	Atropine 0.5%, 0.25%, 0.1%, and tropicamide 0.5%	Three events reported in the atropine 0.5% group: 2 patients complained of photophobia, 1 with allergic blepharitis

PIR: pirenzepine gel.
PLC: placebo gel.
SVLs: single vision lenses.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Myopia] explode all trees
#2 myop*
#3 (short near/3 sight*) or ("near" near/3 sight*)
#4 nearsighted*
#5 {or #1-#4}
#6 MeSH descriptor: [Eyeglasses] explode all trees
#7 spectacles or glasses or eyeglass*

#8 (progressive or single or vision or addition or bifocal or spectacle or corrective) near/2 lens*
#9 MeSH descriptor: [Contact Lenses] explode all trees
#10 (contact or "gas permeable") near/2 lens*
#11 {or #6-#10}
#12 MeSH descriptor: [Mydriatics] explode all trees
#13 mydriat* or cycloplegic*
#14 "7-methylxanthine" or "552-62-5"
#15 MeSH descriptor: [Cholinergic Antagonists] explode all trees
#16 Cholinergic* next/2 (antagonist* or block* or inhibitor*)
#17 cholinolytic*
#18 acetylcholine* next/2 (antagonist* or block* or inhibitor*)
#19 anticholinergic* or "anti cholinergic" or "anti cholinergics"
#20 muscarinic* next/2 (antagonist* or block* or inhibitor*)
#21 antimuscarinic* or "anti muscarinic" or "anti muscarinics"
#22 MeSH descriptor: [Parasympatholytics] explode all trees
#23 parasympathetic* next/2 (antagonist* or block* or inhibitor*)
#24 parasympathicolytic* or parasympaticolytic* or Parasympatholytic*
#25 pharmaceutical* or pharmacologic*
#26 MeSH descriptor: [Atropine] explode all trees
#27 Atropine or atrinal or "atro-polygyl" or atrop or atropen or atropin or atropina or "atropini sulfas" or atropinol or atropisol or atropt or atroptol or atrospan or "atrosulf-1" or "bar bropin" or "bellpino-artin" or "cendo tropine" or "dextro levo hyosciamine" or "ichtho bellol" or "isopto" or isoptoAtropine or "ocu-tropine" or "sal-tropine" or skiatropine or "tropine dextro levo tropate" or ximex or "51-55-8" or "55-48-1"
#28 berefrine or POPD or "105567-83-7"
#29 MeSH descriptor: [Cyclopentolate] explode all trees
#30 Cyclopentolate or "ak-pentolate" or akpentolate or "bell pentolate" or ciclolux or cyclogyl or cyclomydri or cyclopentol or cyclopentolat or cylate or cyplegin or diopentolate or midriodavi or mydrilate or "ocu-pentolate" or ocucyclo or "oftan-syklo" or pentolair or "refractyl ofeno" or skiacol or zyklolat or "512-15-2" or "5870-29-1"
#31 MeSH descriptor: [Epinephrine] explode all trees
#32 Epinephrine or Adrenaline or adrenalin or Epitrate or Lyophrin or Epifrin or adnephrin or adnephrine or adrenaclick or "adrenal hydrochloride" or adrenalina or adrenamine or adrenapax or adrenazin or adrenine or adrin or adrine or advaradin or balmadren or biorenine or bosmin or chelafrin or dylephrin or epiglaufrin or epimephrine or epinefrina or epinephran or epinephrin or epirenamine or epirenan or exadrin or glaucon or glaucosan or glaufrin or "glin epin" or glycirenan or haemostatin or hemisine or hemostasin or hemostatin or hypernephrin or "isopto epinal" or levoadrenalin or levoadrenaline or levoepinephrine or levorenin or levorenine or methylaminoethanolcatechol or methylarterenol or mucidrina or myosthenine or "n methylnoradrenalin" or nephridine or nieraline or paranephrin or posumin or renaglandin or renaglandulin or renaleptine or renalina or renaline or renoform or renostypticin or renostyptin or scurenaline or simplene or soladren or sphygmogenin or styptirenal or supracapsulin or supranephrane or supranephrin or supranol or suprarenaline or suprarenin or suprarenine or suprel or surenine or surrenine or "sus-phrine sulfite-free" or susphrine or "sympathin I" or takamina or tonogen or vasoconstrictine or vasodrine or vasotonin or weradren or "51-43-4" or "55-31-2" or "6912-68-1"
#33 MeSH descriptor: [Ethylmorphine] explode all trees
#34 Ethylmorphine or Ethomorphine or Trachyl or codethyline or diolan or dionine or "ethyl morphine" or ethylmorfine or ethylmorphin or "morphine ethyl ether" or "125-30-4" or "76-58-4"
#35 Eucatropine or euphthalmine or "100-91-4" or "536-93-6"
#36 Homatropine or homatro or homatrocil or homatropaire or homatropin or homatropina or isoptoHomatropine or "I Homatrine" or "mandelyl tropeine" or mandelyltropeine or "mydryn eye" or "omatropina lux" or "tropine mandelate" or "51-56-9" or "87-00-3"
#37 MeSH descriptor: [Hyoscyamine] explode all trees
#38 Hyoscyamine or anaspaz or cystospaz or cytospaz or daturine or donnamar or duboisine or egacen or hyoscamine or hyosciamine or hyoscyanin or hyosyne or "ib-stat" or levbid or levsin or "levsinex sr" or neosol or nulev or spasdel or "symax sl" or "symax sr" or "tropine l tropate" or "101-31-5" or "306-03-6"
#39 Ibopamine or "N-methyldopamine diisobutyrate" or "SB 7505" or "SB7505" or Escandine or Inopamil or "diisobutyric n methyldopamine ester" or scandine or "skf 100168" or "skf 100168 a" or "66195-31-1" or "75011-65-3"
#40 Methylatropine or "8-methylatropinium nitrate" or "31610-87-4"
#41 MeSH descriptor: [Naphazoline] explode all trees
#42 Naphazoline or "Afazol Grin" or "AK Con" or AKCon or Albalon or albasol or "All Clear" or allersol or antan or benil or cefasan or "Clear Eyes" or coldan or "Colirio Alfa" or "comfort eye drops" or dazolin or "degest 2" or derinox or Idril or imidin or minha or Miraclar or mirafrin or Nafazair or nafazoline or naftazolina or "naphacel ofteno" or naphasal or naphazolin or Naphcon or "naphozoline hydrochloride" or naphtears or naphthazoline or naphthizine or naphthyzin or nastizol or "nazil ofteno" or niazol or "ocu-zoline" or opcon or Optazine or Privin or privina or Privine or privine or Proculin or rhinantin or rhinazin or rhinoperd or rimidol or sanorin or sanotin or Siozwo or strictylon or "Tele Stulln" or TeleStulln or Vasoclear or Vasocon or "Vasoconstrictor Pensa" or VasoNit or vistalbalon or vistobalon or "5144-52-5" or "550-99-2" or "835-31-4"
#43 Oxedrine or Synephrine or Sympaethamin or Synephrin or aetaphen or pentedrine or vasoton or "94-07-5"
#44 MeSH descriptor: [Synephrine] explode all trees

#45 MeSH descriptor: [Oxyphenonium] explode all trees
#46 Oxyphenonium or Methacin or Oxyphenon or Atrenyl or Spastrex or antrenyl or "ba 5473" or ba5473 or "c 5473" or c5473 or helkamon or metacin or metacinum or oxyphenium or "oxyphenomium bromide" or spasmofen or spasmophen or "14214-84-7" or "50-10-2"
#47 MeSH descriptor: [Phenylephrine] explode all trees
#48 Phenylephrine or adrianol or "af-taf" or "ak-dilate" or "albalon relief" or alconefrin or almefrin or altafrin or biomidrin or biomydrin or derizene or "despec-sf" or "disneumon pernasal" or drosin or "efrin-10" or efrisel or fenylephrine or idrianol or isonefrine or isophrin or isophrine or "isopto frin" or isoptofrin or lexatol or "m synephrine" or mesaton or "meta sympathol" or "meta synephrine" or Metaoxedrin or metaoxedrine or Metasympatol or metasynephrine or Mezaton or "murucoll 2" or mydfrin or "n 105 to" or "nefrin-ofteno" or "Neo Synephrine" or neofrin or neooxedrine or neophryn or neosynephrin or Neosynephrine or "neosynephrin-pos" or neosynesin or neosynesine or "ocu-phrin" or "oftan-metaoksedrin" or optistin or phenoptic or phenylefrine or phenylephedrine or prefrin or "pupiletto forte" or rectasol or "rhinall 10" or "slv 325" or slv325 or sucraphen or vazculep or visadron or vistafrin or vistosan or "532-38-7" or "59-42-7" or "61-76-7"
#49 Pholedrine or "4 hydroxy n methylamphetamine" or "4 hydroxymethamphetamine" or adyston or "para hydroxymethamphetamine" or "p-hydroxymethamphetamine" or paredrinol or "Pholedrin liquidum" or "Pholedrin-longo-Isis" or pulsotyl or venosan or veritol or "370-14-9"
#50 MeSH descriptor: [p-Hydroxyamphetamine] explode all trees
#51 p-Hydroxyamphetamine or "1 para hydroxyphenyl 2 propylamine" or "alpha methyl para tyramine" or "alpha methyl tyramine" or "dl 1 p hydroxyphenyl 2 propylamine" or "dl 1 para hydroxyphenyl 2 propylamine" or "dl p hydroxy alpha methylphenethylamine" or "dl para hydroxy alpha methylphenethylamine" or "h 66 37" or "para hydroxy alpha methylphenethylamine" or Hydroxyamfetamine or Hydroxyamphetamin or Hydroxyamphetamine or Hydroxyphenylisopropylamine or Methyltyramine or Norpholedrin or norpholedrine or oxamphetamine or Oxyamphetamine or paradrine or parahydroxyamphetamine or Paredrine or paredrinea or paredrinex or pedrolone or pulsoton or "103-86-6" or "1518-86-1" or "306-21-8"
#52 MeSH descriptor: [Racepinephrine] explode all trees
#53 Racepinephrine or asthmanefrin or Micronefrin or micronefrine or Micronephrine or mikronephrin or racadrenalin or "Racepinefrine Hydrochloride" or racinephrine or Vaponefrin or vaponefrine or vaponephrin or "329-65-7"
#54 MeSH descriptor: [Scopolamine Hydrobromide] explode all trees
#55 Scopolamine or "Boro Scopol" or BoroScopol or Hyoscine or Kwells or "levo hyoscinehydrobromide" or Scoburen or Scopace or scopos or "Travacalm HO" or Vorigeno or "114-49-8" or atrochin or atroquin or atroscine or hyosceine or hysco or "kimite-patch" or "l epoxytropine tropate" or "n methylhyoscine" or oscine or scopalamine or "scopine tropate" or scopoderm or scopolamin or transcop or "transderm scop" or "transderm v" or "tropic acid ester with scopine" or "138-12-5" or "51-34-3" or "55-16-3"
#56 MeSH descriptor: [Tropicamide] explode all trees
#57 Tropicamide or "alcon-mydril" or bistropamide or "cendo mydriatyl" or "Colircusi Tropicamida" or midriaticum or mydiacyl or mydral or mydramide or mydriacyl or Mydriafair or Mydriaticum or "mydrin m" or "mydrin p" or Mydrum or "n ethyl 2 phenyl n pyrid 4 ylmethylhydracrylamide" or "n ethyl n 4 picolyltropamide" or "n ethyl n gamma picolyltropamide" or "n ethyl n pyrid 4 ylmethyltropamide" or "Ocu-Tropic" or OcuTropic or opticyl or sandol or sintropic or "tropamid forte" or "tropic acid n ethyl n gamma picolyl amide" or Tropicacyl or tropicamid or "tropico eye" or tropicol or tropikamid or tropimil or visumidriatic or "1508-75-4"
#58 MeSH descriptor: [Tyramine] explode all trees
#59 Tyramine or "4 hydroxyphenethylamine" or lyramine or mydrial or "para hydroxyphenethylamine" or paratyramine or systogene or tiramine or tocosine or tyramin or tyrosamine or uteramine or "51-67-2" or "60-19-5"
#60 Vibrocil or "8059-14-1"
#61 MeSH descriptor: [Yohimbine] explode all trees
#62 Yohimbine or actibine or aphrodine or aphrodyne or Corynanthine or "corynine hydrochloride" or "dayto-himbin" or "methyl yohimbine 16alpha carboxylate" or "methylyohimbane 16alpha carboxylate" or Pluriviron or quebrachin or "quebrachine hydrochloride" or Rauhimbine or Rauwolscine or urobine or yobin or yobinol or yocan or yocaral or Yocon or yocon or yohimbe or "yohimbic acid methyl ester" or yohimbin or Yohimex or yohimex or yohimibin or yovital or "146-48-5" or "65-19-0"
#63 MeSH descriptor: [Timolol] explode all trees
#64 timolol* or "apo timol" or "apo timop" or apotimol or apotimolol or apotimop or betimol or Blocadren or "chibro timoptol" or istalol or "l 714465" or l714465 or "MK 950" or MK950 or moducren or nyolol or ofal or ofan or optimol or timolo or Timoptic or Timoptol or Timacar or titol or "26839-75-8"
#65 MeSH descriptor: [Pirenzepine] explode all trees
#66 pirenzepin* or abrinac or azuzepin or bisvanil or "cl 2" or cl2 or gastricur or gastrocepin or gastrozepin or gastrozepina or gastrozepine or leblon or "ls 519" or "ls 519c12" or ls519 or ls519c12 or maghen or tabe or zinc00538196 or Pyrenzepine or "L S 519" or Ulgescum or "Piren basan" or Gastrotsepin or Ulcoprotect or "28797-61-7" or "29868-97-1"
#67 {or #12-#66}
#68 #11 or #67
#69 #5 and #68

Appendix 2. MEDLINE Ovid search strategy

1. Randomized Controlled Trial.pt.
2. Controlled Clinical Trial.pt.
3. (randomized or randomised).ab,ti.

4. placebo.ab,ti.
5. drug therapy.fs.
6. randomly.ab,ti.
7. trial.ab,ti.
8. groups.ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp myopia/
13. myop*.tw.
14. ((short or near) adj3 sight*).tw.
15. nearsighted*.tw.
16. or/12-15
17. exp Eyeglasses/
18. (spectacles or glasses or eyeglass*).tw.
19. ((progressive or single or vision or addition or bifocal or spectacle or corrective) adj2 lens*).tw.
20. exp contact lenses/
21. ((contact or "gas permeable") adj2 lens*).tw.
22. or/17-21
23. exp Mydriatics/
24. (mydriat* or cycloplegic*).tw.
25. ("7-methylxanthine" or "552-62-5").tw,rn.
26. exp cholinergic antagonists/
27. (cholinergic adj2 (antagonist* or block* or inhibitor*)).tw.
28. cholinolytic*.tw.
29. (acetylcholine* adj2 (antagonist* or block* or inhibitor*)).tw.
30. (anticholinergic* or "anti cholinergic" or "anti cholinergics").tw.
31. (muscarinic* adj2 (antagonist* or block* or inhibitor*)).tw.
32. (antimuscarinic* or "anti muscarinic" or "anti muscarinics").tw.
33. exp Parasympatholytics/
34. (parasympathetic* adj2 (antagonist* or block* or inhibitor*)).tw.
35. (parasympathicolytic* or parasympaticolytic* or Parasympatholytic*).tw.
36. (pharmaceutical* or pharmacologic*).tw.
37. exp Atropine/
38. (Atropine or atrinal or "atro-polygyl" or atrop or atropen or atropin or atropina or "atropini sulfas" or atropinol or atropisol or atropt or atroptol or atrospan or "atrosulf-1" or "bar bropin" or "bellpino-artin" or "cendo tropine" or "dextro levo hyosciamine" or "ichtho bellol" or "isopto" or isoptoAtropine or "ocu-tropine" or "sal-tropine" or skiatropine or "tropine dextro levo tropate" or ximex or "51-55-8" or "55-48-1").tw,rn.
39. (berefrine or POPD or "105567-83-7").tw,rn.
40. exp Cyclopentolate/
41. (Cyclopentolate or "ak-pentolate" or akpentolate or "bell pentolate" or ciclolux or cyclogyl or cyclomydri or cyclopentol or cyclopentolat or cylate or cyplegin or diopentolate or midriodavi or mydrilate or "ocu-pentolate" or ocucyclo or "oftan-syklo" or pentolair or "refractyl ofeno" or skiacol or zyklolat or "512-15-2" or "5870-29-1").tw,rn.
42. exp Epinephrine/
43. (Epinephrine or Adrenaline or adrenalin or Epitrate or Lyophrin or Epifrin or adnephrin or adnephrine or adrenaclick or "adrenal hydrochloride" or adrenalina or adrenamine or adrenapax or adrenazin or adrenine or adrin or adrine or advaradin or balmadren or biorenine or bosmin or chelafrin or dylephrin or epiglaufrin or epimephrine or epinefrina or epinephran or epinephrin or epirenamine or epirenan or exadrin or glaucon or glaucosan or glaufrin or "glin epin" or glycirenan or haemostatin or hemisine or hemostasin or hemostatin or hypernephrin or "isopto epinal" or levoadrenalin or levoadrenaline or levoepinephrine or levorenin or levorenine or methylaminoethanolcatechol or methylarterenol or mucidrina or myosthenine or "n methylnoradrenalin" or nephridine or nieraline or paranephrin or posumin or renaglandin or renaglandulin or renaleptine or renalina or renaline or renoform or renostypticin or renostyptin or scurenaline or simplene or soladren or sphygmogenin or styptirenal or supracapsulin or supranephrane or supranephrin or supranol or suprarenaline or suprarenin or suprarenine or suprel or surenine or surrenine or "sus-phrine sulfite-free" or susphrine or "sympathin I" or takamina or tonogen or vasoconstrictine or vasodrine or vasotonin or weradren or "51-43-4" or "55-31-2" or "6912-68-1").tw,rn.
44. exp Ethylmorphine/
45. (Ethylmorphine or Ethomorphine or Trachyl or codethyline or diolan or dionine or "ethyl morphine" or ethylmorfine or ethylmorphin or "morphine ethyl ether" or "125-30-4" or "76-58-4").tw,rn.
46. (Eucatropine or euphthalmine or "100-91-4" or "536-93-6").tw,rn.
47. (Homatropine or homatro or homatrocil or homatropaire or homatropin or homatropina or isoptoHomatropine or "I Homatrine" or "mandelyl tropeine" or mandelyltropeine or "mydryn eye" or "omatropina lux" or "tropine mandelate" or "51-56-9" or "87-00-3").tw,rn.
48. exp Hyoscyamine/

49. (Hyoscyamine or anaspaz or cystospaz or cytospaz or daturine or donnamar or duboisine or egacen or hyoscamine or hyosciamine or hyoscyanin or hyosyne or "ib-stat" or levbid or levsin or "levsinex sr" or neosol or nulev or spasdel or "symax sl" or "symax sr" or "tropine l tropate" or "101-31-5" or "306-03-6").tw,rn.
50. (Ibopamine or "N-methyldopamine diisobutyrate" or "SB 7505" or "SB7505" or Escandine or Inopamil or "diisobutyric n methyldopamine ester" or scandine or "skf 100168" or "skf 100168 a" or "66195-31-1" or "75011-65-3").tw,rn.
51. (Methylatropine or "8-methylatropinium nitrate" or "31610-87-4").tw,rn.
52. exp Naphazoline/
53. (Naphazoline or "Afazol Grin" or "AK Con" or AKCon or Albalon or albasol or "All Clear" or allersol or antan or benil or cefasan or "Clear Eyes" or coldan or "Colirio Alfa" or "comfort eye drops" or dazolin or "degest 2" or derinox or Idril or imidin or minha or Miraclar or mirafrin or Nafazair or nafazoline or naftazolina or "naphacel ofteno" or naphasal or naphazolin or Naphcon or "naphozoline hydrochloride" or naphtears or naphthazoline or naphthizine or naphthyzin or nastizol or "nazil ofteno" or niazol or "ocu-zoline" or opcon or Optazine or Privin or privina or Privine or privine or Proculin or rhinantin or rhinazin or rhinoperd or rimidol or sanorin or sanotin or Siozwo or strictylon or "Tele Stulln" or TeleStulln or Vasoclear or Vasocon or "Vasoconstrictor Pensa" or VasoNit or vistalbalon or vistobalon or "5144-52-5" or "550-99-2" or "835-31-4").tw,rn.
54. (Oxedrine or Synephrine or Sympaethamin or Synephrin or aetaphen or pentedrine or vasoton or "94-07-5").tw,rn.
55. exp Synephrine/
56. exp Oxyphenonium/
57. (Oxyphenonium or Methacin or Oxyphenon or Atrenyl or Spastrex or antrenyl or "ba 5473" or ba5473 or "c 5473" or c5473 or helkamon or metacin or metacinum or oxyphenium or "oxyphenomium bromide" or spasmofen or spasmophen or "14214-84-7" or "50-10-2").tw,rn.
58. exp Phenylephrine/
59. (Phenylephrine or adrianol or "af-taf" or "ak-dilate" or "albalon relief" or alconefrin or almefrin or altafrin or biomidrin or biomydrin or derizene or "despec-sf" or "disneumon pernasal" or drosin or "efrin-10" or efrisel or fenylephrine or idrianol or isonefrine or isophrin or isophrine or "isopto frin" or isoptofrin or lexatol or "m synephrine" or mesaton or "meta sympathol" or "meta synephrine" or Metaoxedrin or metaoxedrine or Metasympatol or metasynephrine or Mezaton or "murucoll 2" or mydfrin or "n 105 to" or "nefrin-ofteno" or "Neo Synephrine" or neofrin or neooxedrine or neophryn or neosynephrin or Neosynephrine or "neosynephrin-pos" or neosynesin or neosynesine or "ocu-phrin" or "oftan-metaoksedrin" or optistin or phenoptic or phenylefrine or phenylephedrine or prefrin or "pupiletto forte" or rectasol or "rhinall 10" or "slv 325" or slv325 or sucraphen or vazculep or visadron or vistafrin or vistosan or "532-38-7" or "59-42-7" or "61-76-7").tw,rn.
60. (Pholedrine or "4 hydroxy n methylamphetamine" or "4 hydroxymethamphetamine" or adyston or "para hydroxymethamphetamine" or "p-hydroxymethamphetamine" or paredrinol or "Pholedrin liquidum" or "Pholedrin-longo-Isis" or pulsotyl or venosan or veritol or "370-14-9").tw,rn.
61. exp p-Hydroxyamphetamine/
62. (p-Hydroxyamphetamine or "1 para hydroxyphenyl 2 propylamine" or "alpha methyl para tyramine" or "alpha methyl tyramine" or "dl 1 p hydroxyphenyl 2 propylamine" or "dl 1 para hydroxyphenyl 2 propylamine" or "dl p hydroxy alpha methylphenethylamine" or "dl para hydroxy alpha methylphenethylamine" or "h 66 37" or "para hydroxy alpha methylphenethylamine" or Hydroxyamfetamine or Hydroxyamphetamin or Hydroxyamphetamine or Hydroxyphenylisopropylamine or Methyltyramine or Norpholedrin or norpholedrine or oxamphetamine or Oxyamphetamine or paradrine or parahydroxyamphetamine or Paredrine or paredrinea or paredrinex or pedrolone or pulsoton or "103-86-6" or "1518-86-1" or "306-21-8").tw,rn.
63. exp Racepinephrine/
64. (Racepinephrine or asthmanefrin or Micronefrin or micronefrine or Micronephrine or mikronephrin or racadrenalin or "Racepinefrine Hydrochloride" or racinephrine or Vaponefrin or vaponefrine or vaponephrin or "329-65-7").tw,rn.
65. exp Scopolamine Hydrobromide/
66. (Scopolamine or "Boro Scopol" or BoroScopol or Hyoscine or Kwells or "levo hyoscinehydrobromide" or Scoburen or Scopace or scopos or "Travacalm HO" or Vorigeno or "114-49-8" or atrochin or atroquin or atroscine or hyosceine or hysco or "kimite-patch" or "l epoxytropine tropate" or "n methylhyoscine" or oscine or scopalamine or "scopine tropate" or scopoderm or scopolamin or transcop or "transderm scop" or "transderm v" or "tropic acid ester with scopine" or "138-12-5" or "51-34-3" or "55-16-3").tw,rn.
67. exp Tropicamide/
68. (Tropicamide or "alcon-mydril" or bistropamide or "cendo mydriatyl" or "Colircusi Tropicamida" or midriaticum or mydiacyl or mydral or mydramide or mydriacyl or Mydriafair or Mydriaticum or "mydrin m" or "mydrin p" or Mydrum or "n ethyl 2 phenyl n pyrid 4 ylmethylhydracrylamide" or "n ethyl n 4 picolyltropamide" or "n ethyl n gamma picolyltropamide" or "n ethyl n pyrid 4 ylmethyltropamide" or "Ocu-Tropic" or OcuTropic or opticyl or sandol or sintropic or "tropamid forte" or "tropic acid n ethyl n gamma picolyl amide" or Tropicacyl or tropicamid or "tropico eye" or tropicol or tropikamid or tropimil or visumidriatic or "1508-75-4").tw,rn.
69. exp Tyramine/
70. (Tyramine or "4 hydroxyphenethylamine" or lyramine or mydrial or "para hydroxyphenethylamine" or paratyramine or systogene or tiramine or tocosine or tyramin or tyrosamine or uteramine or "51-67-2" or "60-19-5").tw,rn.
71. (Vibrocil or "8059-14-1").tw,rn.
72. exp Yohimbine/
73. (Yohimbine or actibine or aphrodine or aphrodyne or Corynanthine or "corynine hydrochloride" or "dayto-himbin" or "methyl yohimbine 16alpha carboxylate" or "methylyohimbane 16alpha carboxylate" or Pluriviron or quebrachin or "quebrachine hydrochloride" or Rauhimbine or Rauwolscine or urobine or yobin or yobinol or yocan or yocaral or Yocon or yocon or yohimbe or "yohimbic acid methyl ester" or yohimbin or Yohimex or yohimex or yohimibin or yovital or "146-48-5" or "65-19-0").tw,rn.
74. exp Timolol/

75. (timolol* or "apo timol" or "apo timop" or apotimol or apotimolol or apotimop or betimol or Blocadren or "chibro timoptol" or istalol or "l 714465" or l714465 or "MK 950" or MK950 or moducren or nyolol or ofal or ofan or optimol or timolo or Timoptic or Timoptol or Timacar or titol or "26839-75-8").tw,rn.
76. exp Pirenzepine/
77. (pirenzepin* or abrinac or azuzepin or bisvanil or "cl 2" or cl2 or gastricur or gastrocepin or gastrozepin or gastrozepina or gastrozepine or leblon or "ls 519" or "ls 519c12" or ls519 or ls519c12 or maghen or tabe or zinc00538196 or Pyrenzepine or "L S 519" or Ulgescum or "Piren basan" or Gastrotsepin or Ulcoprotect or "28797-61-7" or "29868-97-1").tw,rn.
78. or/23-77
79. 22 or 78
80. 11 and 16 and 79

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

Appendix 3. Embase.com search strategy

#1 'randomized controlled trial'/exp
#2 'randomization'/exp
#3 'double blind procedure'/exp
#4 'single blind procedure'/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'animal'/exp OR 'animal experiment'/exp
#8 'human'/exp
#9 #7 AND #8
#10 #7 NOT #9
#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp
#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp
#26 'evaluation'/exp
#27 'prospective study'/exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31
#33 'myopia'/exp
#34 myop*:ab,ti
#35 ((short OR near) NEAR/3 sight*):ab,ti
#36 nearsighted*:ab,ti
#37 #33 OR #34 OR #35 OR #36
#38 'spectacles'/exp
#39 spectacles:ab,ti OR glasses:ab,ti OR eyeglass*:ab,ti
#40 ((progressive OR single OR vision OR addition OR bifocal OR spectacle OR corrective) NEAR/2 lens*):ab,ti
#41 'contact lens'/exp
#42 ((contact OR 'gas permeable') NEAR/2 lens*):ab,ti
#43 #38 OR #39 OR #40 OR #41 OR #42
#44 'mydriatic agent'/exp
#45 mydriat*:ab,ti OR cycloplegic*:ab,ti
#46 'cholinergic receptor blocking agent'/exp
#47 (cholinergic* NEXT/2 (antagonist* OR block* OR inhibitor*)):ab,ti

#48 cholinolytic*:ab,ti
#49 (acetylcholine* NEXT/2 (antagonist* OR block* OR inhibitor*)):ab,ti
#50 anticholinergic*:ab,ti OR 'anti cholinergic':ab,ti OR 'anti cholinergics':ab,ti
#51 (muscarinic* NEXT/2 (antagonist* OR block* OR inhibitor*)):ab,ti
#52 antimuscarinic*:ab,ti OR 'anti muscarinic':ab,ti OR 'anti muscarinics':ab,ti
#53 (parasympathetic* NEXT/2 (antagonist* OR block* OR inhibitor*)):ab,ti
#54 parasympathicolytic*:ab,ti OR parasympaticolytic*:ab,ti OR parasympatholytic*:ab,ti
#55 pharmaceutical*:ab,ti OR pharmacologic*:ab,ti
#56 atropine:tn,ab,ti OR atrinal:tn,ab,ti OR 'atro-polygyl':tn,ab,ti OR atrop:tn,ab,ti OR atropen:tn,ab,ti OR atropin:tn,ab,ti OR atropina:tn,ab,ti OR 'atropini sulfas':tn,ab,ti OR atropinol:tn,ab,ti OR atropisol:tn,ab,ti OR atropt:tn,ab,ti OR atroptol:tn,ab,ti OR atrospan:tn,ab,ti OR 'atrosulf-1':tn,ab,ti OR 'bar bropin':tn,ab,ti OR 'bellpino-artin':tn,ab,ti OR 'cendo tropine':tn,ab,ti OR 'dextro levo hyosciamine':tn,ab,ti OR 'ichtho bellol':tn,ab,ti OR 'isopto':tn,ab,ti OR isoptoatropine:tn,ab,ti OR 'ocu-tropine':tn,ab,ti OR 'sal-tropine':tn,ab,ti OR skiatropine:tn,ab,ti OR 'tropine dextro levo tropate':tn,ab,ti OR ximex:tn,ab,ti OR '51-55-8':tn,ab,ti OR '55-48-1':tn,ab,ti
#57 berefrine:tn,ab,ti OR popd:tn,ab,ti OR '105567-83-7':tn,ab,ti
#58 cyclopentolate:tn,ab,ti OR 'ak-pentolate':tn,ab,ti OR akpentolate:tn,ab,ti OR 'bell pentolate':tn,ab,ti OR ciclolux:tn,ab,ti OR cyclogyl:tn,ab,ti OR cyclomydri:tn,ab,ti OR cyclopentol:tn,ab,ti OR cyclopentolat:tn,ab,ti OR cylate:tn,ab,ti OR cyplegin:tn,ab,ti OR diopentolate:tn,ab,ti OR midriodavi:tn,ab,ti OR mydrilate:tn,ab,ti OR 'ocu-pentolate':tn,ab,ti OR ocucyclo:tn,ab,ti OR 'oftan-syklo':tn,ab,ti OR pentolair:tn,ab,ti OR 'refractyl ofeno':tn,ab,ti OR skiacol:tn,ab,ti OR zyklolat:tn,ab,ti OR '512-15-2':tn,ab,ti OR '5870-29-1':tn,ab,ti
#59 'adrenalin'/exp
#60 epinephrine:tn,ab,ti OR adrenaline:tn,ab,ti OR adrenalin:tn,ab,ti OR epitrate:tn,ab,ti OR lyophrin:tn,ab,ti OR epifrin:tn,ab,ti OR adnephrin:tn,ab,ti OR adnephrine:tn,ab,ti OR adrenaclick:tn,ab,ti OR 'adrenal hydrochloride':tn,ab,ti OR adrenalina:tn,ab,ti OR adrenamine:tn,ab,ti OR adrenapax:tn,ab,ti OR adrenazin:tn,ab,ti OR adrenine:tn,ab,ti OR adrin:tn,ab,ti OR adrine:tn,ab,ti OR advaradin:tn,ab,ti OR balmadren:tn,ab,ti OR biorenine:tn,ab,ti OR bosmin:tn,ab,ti OR chelafrin:tn,ab,ti OR dylephrin:tn,ab,ti OR epiglaufrin:tn,ab,ti OR epimephrine:tn,ab,ti OR epinefrina:tn,ab,ti OR epinephran:tn,ab,ti OR epinephrin:tn,ab,ti OR epirenamine:tn,ab,ti OR epirenan:tn,ab,ti OR exadrin:tn,ab,ti OR glaucon:tn,ab,ti OR glaucosan:tn,ab,ti OR glaufrin:tn,ab,ti OR 'glin epin':tn,ab,ti OR glycirenan:tn,ab,ti OR haemostatin:tn,ab,ti OR hemisine:tn,ab,ti OR hemostasin:tn,ab,ti OR hemostatin:tn,ab,ti OR hypernephrin:tn,ab,ti OR 'isopto epinal':tn,ab,ti OR levoadrenalin:tn,ab,ti OR levoadrenaline:tn,ab,ti OR levoepinephrine:tn,ab,ti OR levorenin:tn,ab,ti OR levorenine:tn,ab,ti OR methylaminoethanolcatechol:tn,ab,ti OR methylarterenol:tn,ab,ti OR mucidrina:tn,ab,ti OR myosthenine:tn,ab,ti OR 'n methylnoradrenalin':tn,ab,ti OR nephridine:tn,ab,ti OR nieraline:tn,ab,ti OR paranephrin:tn,ab,ti OR posumin:tn,ab,ti OR renaglandin:tn,ab,ti OR renaglandulin:tn,ab,ti OR renaleptine:tn,ab,ti OR renalina:tn,ab,ti OR renaline:tn,ab,ti OR renoform:tn,ab,ti OR renostypticin:tn,ab,ti OR renostyptin:tn,ab,ti OR scurenaline:tn,ab,ti OR simplene:tn,ab,ti OR soladren:tn,ab,ti OR sphygmogenin:tn,ab,ti OR styptirenal:tn,ab,ti OR supracapsulin:tn,ab,ti OR supranephrane:tn,ab,ti OR supranephrin:tn,ab,ti OR supranol:tn,ab,ti OR suprarenaline:tn,ab,ti OR suprarenin:tn,ab,ti OR suprarenine:tn,ab,ti OR suprel:tn,ab,ti OR surenine:tn,ab,ti OR surrenine:tn,ab,ti OR 'sus-phrine sulfite-free':tn,ab,ti OR susphrine:tn,ab,ti OR 'sympathin i':tn,ab,ti OR takamina:tn,ab,ti OR tonogen:tn,ab,ti OR vasoconstrictine:tn,ab,ti OR vasodrine:tn,ab,ti OR vasotonin:tn,ab,ti OR weradren:tn,ab,ti OR '51-43-4':tn,ab,ti OR '55-31-2':tn,ab,ti OR '6912-68-1':tn,ab,ti
#61 ethylmorphine:tn,ab,ti OR ethomorphine:tn,ab,ti OR trachyl:tn,ab,ti OR codethyline:tn,ab,ti OR diolan:tn,ab,ti OR dionine:tn,ab,ti OR 'ethyl morphine':tn,ab,ti OR ethylmorfine:tn,ab,ti OR ethylmorphin:tn,ab,ti OR 'morphine ethyl ether':tn,ab,ti OR '125-30-4':tn,ab,ti OR '76-58-4':tn,ab,ti
#62 eucatropine:tn,ab,ti OR euphthalmine:tn,ab,ti OR '100-91-4':tn,ab,ti OR '536-93-6':tn,ab,ti
#63 homatropine:tn,ab,ti OR homatro:tn,ab,ti OR homatrocil:tn,ab,ti OR homatropaire:tn,ab,ti OR homatropin:tn,ab,ti OR homatropina:tn,ab,ti OR isoptohomatropine:tn,ab,ti OR 'i homatrine':tn,ab,ti OR 'mandelyl tropeine':tn,ab,ti OR mandelyltropeine:tn,ab,ti OR 'mydryn eye':tn,ab,ti OR 'omatropina lux':tn,ab,ti OR 'tropine mandelate':tn,ab,ti OR '51-56-9':tn,ab,ti OR '87-00-3':tn,ab,ti
#64 'hyoscyamine'/exp
#65 hyoscyamine:tn,ab,ti OR anaspaz:tn,ab,ti OR cystospaz:tn,ab,ti OR cytospaz:tn,ab,ti OR daturine:tn,ab,ti OR donnamar:tn,ab,ti OR duboisine:tn,ab,ti OR egacen:tn,ab,ti OR hyoscamine:tn,ab,ti OR hyosciamine:tn,ab,ti OR hyoscyanin:tn,ab,ti OR hyosyne:tn,ab,ti OR 'ib-stat':tn,ab,ti OR levbid:tn,ab,ti OR levsin:tn,ab,ti OR 'levsinex sr':tn,ab,ti OR neosol:tn,ab,ti OR nulev:tn,ab,ti OR spasdel:tn,ab,ti OR 'symax sl':tn,ab,ti OR 'symax sr':tn,ab,ti OR 'tropine l tropate':tn,ab,ti OR '101-31-5':tn,ab,ti OR '306-03-6':tn,ab,ti
#66 'ibopamine'/exp
#67 ibopamine:tn,ab,ti OR 'n-methyldopamine diisobutyrate':tn,ab,ti OR 'sb 7505':tn,ab,ti OR 'sb7505':tn,ab,ti OR escandine:tn,ab,ti OR inopamil:tn,ab,ti OR 'diisobutyric n methyldopamine ester':tn,ab,ti OR scandine:tn,ab,ti OR 'skf 100168':tn,ab,ti OR 'skf 100168 a':tn,ab,ti OR '66195-31-1':tn,ab,ti OR '75011-65-3':tn,ab,ti
#68 methylatropine:tn,ab,ti OR '8-methylatropinium nitrate':tn,ab,ti OR '31610-87-4':tn,ab,ti
#69 naphazoline:tn,ab,ti OR 'afazol grin':tn,ab,ti OR 'ak con':tn,ab,ti OR akcon:tn,ab,ti OR albalon:tn,ab,ti OR albasol:tn,ab,ti OR 'all clear':tn,ab,ti OR allersol:tn,ab,ti OR antan:tn,ab,ti OR benil:tn,ab,ti OR cefasan:tn,ab,ti OR 'clear eyes':tn,ab,ti OR coldan:tn,ab,ti OR 'colirio alfa':tn,ab,ti OR 'comfort eye drops':tn,ab,ti OR dazolin:tn,ab,ti OR 'degest 2':tn,ab,ti OR derinox:tn,ab,ti OR idril:tn,ab,ti OR imidin:tn,ab,ti OR minha:tn,ab,ti OR miraclar:tn,ab,ti OR mirafrin:tn,ab,ti OR nafazair:tn,ab,ti OR nafazoline:tn,ab,ti OR naftazolina:tn,ab,ti OR 'naphacel ofteno':tn,ab,ti OR naphasal:tn,ab,ti OR naphazolin:tn,ab,ti OR naphcon:tn,ab,ti OR 'naphozoline hydrochloride':tn,ab,ti OR naphtears:tn,ab,ti OR naphthazoline:tn,ab,ti OR naphthizine:tn,ab,ti OR naphthyzin:tn,ab,ti OR nastizol:tn,ab,ti OR 'nazil ofteno':tn,ab,ti OR niazol:tn,ab,ti OR 'ocu-zoline':tn,ab,ti OR opcon:tn,ab,ti OR optazine:tn,ab,ti OR privin:tn,ab,ti OR privina:tn,ab,ti OR privine:tn,ab,ti OR proculin:tn,ab,ti OR rhinantin:tn,ab,ti OR rhinazin:tn,ab,ti OR rhinoperd:tn,ab,ti OR rimidol:tn,ab,ti OR sanorin:tn,ab,ti OR sanotin:tn,ab,ti OR siozwo:tn,ab,ti OR strictylon:tn,ab,ti OR 'tele stulln':tn,ab,ti OR telestulln:tn,ab,ti OR vasoclear:tn,ab,ti OR vasocon:tn,ab,ti

OR 'vasoconstrictor pensa':tn,ab,ti OR vasonit:tn,ab,ti OR vistalbalon:tn,ab,ti OR vistobalon:tn,ab,ti OR '5144-52-5':tn,ab,ti OR '550-99-2':tn,ab,ti OR '835-31-4':tn,ab,ti
#70 oxedrine:tn,ab,ti OR synephrine:tn,ab,ti OR sympaethamin:tn,ab,ti OR synephrin:tn,ab,ti OR aetaphen:tn,ab,ti OR pentedrine:tn,ab,ti OR vasoton:tn,ab,ti OR '94-07-5':tn,ab,ti
#71 'oxyphenonium bromide'/exp
#72 oxyphenonium:tn,ab,ti OR methacin:tn,ab,ti OR oxyphenon:tn,ab,ti OR atrenyl:tn,ab,ti OR spastrex:tn,ab,ti OR antrenyl:tn,ab,ti OR 'ba 5473':tn,ab,ti OR ba5473:tn,ab,ti OR 'c 5473':tn,ab,ti OR c5473:tn,ab,ti OR helkamon:tn,ab,ti OR metacin:tn,ab,ti OR metacinum:tn,ab,ti OR oxyphenium:tn,ab,ti OR 'oxyphenomium bromide':tn,ab,ti OR spasmofen:tn,ab,ti OR spasmophen:tn,ab,ti OR '14214-84-7':tn,ab,ti OR '50-10-2':tn,ab,ti
#73 phenylephrine:tn,ab,ti OR adrianol:tn,ab,ti OR 'af-taf':tn,ab,ti OR 'ak-dilate':tn,ab,ti OR 'albalon relief':tn,ab,ti OR alconefrin:tn,ab,ti OR almefrin:tn,ab,ti OR altafrin:tn,ab,ti OR biomidrin:tn,ab,ti OR biomydrin:tn,ab,ti OR derizene:tn,ab,ti OR 'despec-sf':tn,ab,ti OR 'disneumon pernasal':tn,ab,ti OR drosin:tn,ab,ti OR 'efrin-10':tn,ab,ti OR efrisel:tn,ab,ti OR fenylephrine:tn,ab,ti OR idrianol:tn,ab,ti OR isonefrine:tn,ab,ti OR isophrin:tn,ab,ti OR isophrine:tn,ab,ti OR 'isopto frin':tn,ab,ti OR isoptofrin:tn,ab,ti OR lexatol:tn,ab,ti OR 'm synephrine':tn,ab,ti OR mesaton:tn,ab,ti OR 'meta sympathol':tn,ab,ti OR 'meta synephrine':tn,ab,ti OR metaoxedrin:tn,ab,ti OR metaoxedrine:tn,ab,ti OR metasympatol:tn,ab,ti OR metasynephrine:tn,ab,ti OR mezaton:tn,ab,ti OR 'murucoll 2':tn,ab,ti OR mydfrin:tn,ab,ti OR 'n 105 to':tn,ab,ti OR 'nefrin-ofteno':tn,ab,ti OR 'neo synephrine':tn,ab,ti OR neofrin:tn,ab,ti OR neooxedrine:tn,ab,ti OR neophryn:tn,ab,ti OR neosynephrin:tn,ab,ti OR neosynephrine:tn,ab,ti OR 'neosynephrin-pos':tn,ab,ti OR neosynesin:tn,ab,ti OR neosynesine:tn,ab,ti OR 'ocu-phrin':tn,ab,ti OR 'oftan-metaoksedrin':tn,ab,ti OR optistin:tn,ab,ti OR phenoptic:tn,ab,ti OR phenylefrine:tn,ab,ti OR phenylephedrine:tn,ab,ti OR prefrin:tn,ab,ti OR 'pupiletto forte':tn,ab,ti OR rectasol:tn,ab,ti OR 'rhinall 10':tn,ab,ti OR 'slv 325':tn,ab,ti OR slv325:tn,ab,ti OR sucraphen:tn,ab,ti OR vazculep:tn,ab,ti OR visadron:tn,ab,ti OR vistafrin:tn,ab,ti OR vistosan:tn,ab,ti OR '532-38-7':tn,ab,ti OR '59-42-7':tn,ab,ti OR '61-76-7':tn,ab,ti
#74 pholedrine:tn,ab,ti OR '4 hydroxy n methylamphetamine':tn,ab,ti OR '4 hydroxymethamphetamine':tn,ab,ti OR adyston:tn,ab,ti OR 'para hydroxymethamphetamine':tn,ab,ti OR 'p-hydroxymethamphetamine':tn,ab,ti OR paredrinol:tn,ab,ti OR 'pholedrin liquidum':tn,ab,ti OR 'pholedrin-longo-isis':tn,ab,ti OR pulsotyl:tn,ab,ti OR venosan:tn,ab,ti OR veritol:tn,ab,ti OR '370-14-9':tn,ab,ti
#75 'hydroxyamphetamine'/exp
#76 'p hydroxyamphetamine':tn,ab,ti OR '1 para hydroxyphenyl 2 propylamine':tn,ab,ti OR 'alpha methyl para tyramine':tn,ab,ti OR 'alpha methyl tyramine':tn,ab,ti OR 'dl 1 p hydroxyphenyl 2 propylamine':tn,ab,ti OR 'dl 1 para hydroxyphenyl 2 propylamine':tn,ab,ti OR 'dl p hydroxy alpha methylphenethylamine':tn,ab,ti OR 'dl para hydroxy alpha methylphenethylamine':tn,ab,ti OR 'h 66 37':tn,ab,ti OR 'para hydroxy alpha methylphenethylamine':tn,ab,ti OR hydroxyamfetamine:tn,ab,ti OR hydroxyamphetamin:tn,ab,ti OR hydroxyamphetamine:tn,ab,ti OR hydroxyphenylisopropylamine:tn,ab,ti OR methyltyramine:tn,ab,ti OR norpholedrin:tn,ab,ti OR norpholedrine:tn,ab,ti OR oxamphetamine:tn,ab,ti OR oxyamphetamine:tn,ab,ti OR paradrine:tn,ab,ti OR parahydroxyamphetamine:tn,ab,ti OR paredrine:tn,ab,ti OR paredrinea:tn,ab,ti OR paredrinex:tn,ab,ti OR pedrolone:tn,ab,ti OR pulsoton:tn,ab,ti OR '103-86-6':tn,ab,ti OR '1518-86-1':tn,ab,ti OR '306-21-8':tn,ab,ti
#77 'racepinefrine'/exp
#78 racepinephrine:tn,ab,ti OR asthmanefrin:tn,ab,ti OR micronefrin:tn,ab,ti OR micronefrine:tn,ab,ti OR micronephrine:tn,ab,ti OR mikronephrin:tn,ab,ti OR racadrenalin:tn,ab,ti OR 'racepinefrine hydrochloride':tn,ab,ti OR racinephrine:tn,ab,ti OR vaponefrin:tn,ab,ti OR vaponefrine:tn,ab,ti OR vaponephrin:tn,ab,ti OR '329-65-7':tn,ab,ti
#79 'scopolamine bromide'/exp
#80 scopolamine:tn,ab,ti OR 'boro scopol':tn,ab,ti OR boroscopol:tn,ab,ti OR hyoscine:tn,ab,ti OR kwells:tn,ab,ti OR 'levo hyoscinehydrobromide':tn,ab,ti OR scoburen:tn,ab,ti OR scopace:tn,ab,ti OR scopos:tn,ab,ti OR 'travacalm ho':tn,ab,ti OR vorigeno:tn,ab,ti OR '114-49-8':tn,ab,ti OR atrochin:tn,ab,ti OR atroquin:tn,ab,ti OR atroscine:tn,ab,ti OR hyosceine:tn,ab,ti OR hysco:tn,ab,ti OR 'kimite-patch':tn,ab,ti OR 'l epoxytropine tropate':tn,ab,ti OR 'n methylhyoscine':tn,ab,ti OR oscine:tn,ab,ti OR scopalamine:tn,ab,ti OR 'scopine tropate':tn,ab,ti OR scopoderm:tn,ab,ti OR scopolamin:tn,ab,ti OR transcop:tn,ab,ti OR 'transderm scop':tn,ab,ti OR 'transderm v':tn,ab,ti OR 'tropic acid ester with scopine':tn,ab,ti OR '138-12-5':tn,ab,ti OR '51-34-3':tn,ab,ti OR '55-16-3':tn,ab,ti
#81 tropicamide:tn,ab,ti OR 'alcon-mydril':tn,ab,ti OR bistropamide:tn,ab,ti OR 'cendo mydriatyl':tn,ab,ti OR 'colircusi tropicamida':tn,ab,ti OR midriaticum:tn,ab,ti OR mydiacyl:tn,ab,ti OR mydral:tn,ab,ti OR mydramide:tn,ab,ti OR mydriacyl:tn,ab,ti OR mydriafair:tn,ab,ti OR mydriaticum:tn,ab,ti OR 'mydrin m':tn,ab,ti OR 'mydrin p':tn,ab,ti OR mydrum:tn,ab,ti OR 'n ethyl 2 phenyl n pyrid 4 ylmethylhydracrylamide':tn,ab,ti OR 'n ethyl n 4 picolyltropamide':tn,ab,ti OR 'n ethyl n gamma picolyltropamide':tn,ab,ti OR 'n ethyl n pyrid 4 ylmethyltropamide':tn,ab,ti OR 'ocu-tropic':tn,ab,ti OR ocutropic:tn,ab,ti OR opticyl:tn,ab,ti OR sandol:tn,ab,ti OR sintropic:tn,ab,ti OR 'tropamid forte':tn,ab,ti OR 'tropic acid n ethyl n gamma picolyl amide':tn,ab,ti OR tropicacyl:tn,ab,ti OR tropicamid:tn,ab,ti OR 'tropico eye':tn,ab,ti OR tropicol:tn,ab,ti OR tropikamid:tn,ab,ti OR tropimil:tn,ab,ti OR visumidriatic:tn,ab,ti OR '1508-75-4':tn,ab,ti
#82 tyramine:tn,ab,ti OR '4 hydroxyphenethylamine':tn,ab,ti OR lyramine:tn,ab,ti OR mydrial:tn,ab,ti OR 'para hydroxyphenethylamine':tn,ab,ti OR paratyramine:tn,ab,ti OR systogene:tn,ab,ti OR tiramine:tn,ab,ti OR tocosine:tn,ab,ti OR tyramin:tn,ab,ti OR tyrosamine:tn,ab,ti OR uteramine:tn,ab,ti OR '51-67-2':tn,ab,ti OR '60-19-5':tn,ab,ti
#83 vibrocil:tn,ab,ti OR '8059-14-1':tn,ab,ti
#84 'yohimbine'/exp
#85 yohimbine:tn,ab,ti OR actibine:tn,ab,ti OR aphrodine:tn,ab,ti OR aphrodyne:tn,ab,ti OR corynanthine:tn,ab,ti OR 'corynine hydrochloride':tn,ab,ti OR 'dayto-himbin':tn,ab,ti OR 'methyl yohimbine 16alpha carboxylate':tn,ab,ti OR 'methylyohimbane 16alpha carboxylate':tn,ab,ti OR pluriviron:tn,ab,ti OR quebrachin:tn,ab,ti OR 'quebrachine hydrochloride':tn,ab,ti OR rauhimbine:tn,ab,ti OR rauwolscine:tn,ab,ti OR urobine:tn,ab,ti OR yobin:tn,ab,ti OR yobinol:tn,ab,ti OR yocan:tn,ab,ti OR yocaral:tn,ab,ti OR yocon:tn,ab,ti OR yohimbe:tn,ab,ti OR 'yohimbic acid methyl ester':tn,ab,ti OR yohimbin:tn,ab,ti OR yohimex:tn,ab,ti OR yohimibin:tn,ab,ti OR yovital:tn,ab,ti OR '146-48-5':tn,ab,ti OR '65-19-0':tn,ab,ti

#86 'timolol'/exp
#87 timolol*:ab,ti,tn OR 'apo timol':ab,ti,tn OR 'apo timop':ab,ti,tn OR apotimol:ab,ti,tn OR apotimolol:ab,ti,tn OR apotimop:ab,ti,tn OR betimol:ab,ti,tn OR blocadren:ab,ti,tn OR 'chibro timoptol':ab,ti,tn OR istalol:ab,ti,tn OR 'l 714465':ab,ti,tn OR l714465:ab,ti,tn OR 'mk 950':ab,ti,tn OR mk950:ab,ti,tn OR moducren:ab,ti,tn OR nyolol:ab,ti,tn OR ofal:ab,ti,tn OR ofan:ab,ti,tn OR optimol:ab,ti,tn OR timolo:ab,ti,tn OR timoptic:ab,ti,tn OR timoptol:ab,ti,tn OR timacar:ab,ti,tn OR titol:ab,ti,tn OR '26839-75-8':ab,ti,tn
#88 pirenzepin*:ab,ti,tn OR abrinac:ab,ti,tn OR azuzepin:ab,ti,tn OR bisvanil:ab,ti,tn OR 'cl 2':ab,ti,tn OR cl2:ab,ti,tn OR gastricur:ab,ti,tn OR gastrocepin:ab,ti,tn OR gastrozepin:ab,ti,tn OR gastrozepina:ab,ti,tn OR gastrozepine:ab,ti,tn OR leblon:ab,ti,tn OR 'ls 519':ab,ti,tn OR 'ls 519c12':ab,ti,tn OR ls519:ab,ti,tn OR ls519c12:ab,ti,tn OR maghen:ab,ti,tn OR tabe:ab,ti,tn OR zinc00538196:ab,ti,tn OR pyrenzepine:ab,ti,tn OR 'l s 519':ab,ti,tn OR ulgescum:ab,ti,tn OR 'piren basan':ab,ti,tn OR gastrotsepin:ab,ti,tn OR ulcoprotect:ab,ti,tn OR '28797-61-7':ab,ti,tn OR '29868-97-1':ab,ti,tn
#89 '7 methylxanthine'/exp
#90 '7 methylxanthine':ti,ab,tn
#91 #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90
#92 #43 OR #91
#93 #37 AND #92
#94 #32 AND #93

Appendix 4. PubMed search strategy

1. ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])
2. myop*[tw] NOT Medline[sb]
3. (short sight*[tw] OR near sight*[tw]) NOT Medline[sb]
4. nearsighted*[tw] NOT Medline[sb]
5. #2 OR #3 OR #4
6. (Spectacles[tw] OR glasses[tw] OR eyeglass*[tw]) NOT Medline[sb]
7. ((progressive[tw] OR single[tw] OR vision[tw] OR addition[tw] OR bifocal[tw] OR spectacle[tw] OR corrective[tw] OR contact[tw] OR "gas permeable"[tw]) AND lens*[tw]) NOT Medline[sb]
8. (mydriatic*[tw] OR cycloplegic*[tw]) NOT Medline[sb]
9. ("7-methylxanthine"[tw] OR "552-62-5"[tw]) NOT Medline[sb]
10. ((Cholinergic*[tw] OR acetylcholine*[tw] OR muscarinic[tw] OR parasympathetic*[tw]) AND (antagonist*[tw] OR block*[tw] OR inhibitor*[tw])) NOT Medline[sb]
11. cholinolytic*[tw] NOT Medline[sb]
12. (anticholinergic*[tw] OR "anti cholinergic"[tw] OR "anti cholinergics"[tw]) NOT Medline[sb]
13. (antimuscarinic*[tw] OR "anti muscarinic"[tw] OR "anti muscarinics"[tw]) NOT Medline[sb]
14. (parasympathicolytic*[tw] OR parasympaticolytic*[tw] OR Parasympatholytic*[tw]) NOT Medline[sb]
15. (pharmaceutical*[tw] OR pharmacologic*[tw]) NOT Medline[sb]
16. (Atropine [tw] OR atrinal [tw] OR "atro-polygyl" [tw] OR atrop [tw] OR atropen [tw] OR atropin [tw] OR atropina [tw] OR "atropini sulfas" [tw] OR atropinol [tw] OR atropisol [tw] OR atropt [tw] OR atroptol [tw] OR atrospan [tw] OR "atrosulf-1" [tw] OR "bar bropin" [tw] OR "bellpino-artin" [tw] OR "cendo tropine" [tw] OR "dextro levo hyosciamine" [tw] OR "ichtho bellol" [tw] OR "isopto" [tw] OR isoptoAtropine [tw] OR "ocu-tropine" [tw] OR "sal-tropine" [tw] OR skiatropine [tw] OR "tropine dextro levo tropate" [tw] OR ximex [tw] OR "51-55-8" [tw] OR "55-48-1"[tw]) NOT Medline[sb]
17. (berefrine [tw] OR POPD [tw] OR "105567-83-7"[tw]) NOT Medline[sb]
18. (Cyclopentolate [tw] OR "ak-pentolate" [tw] OR akpentolate [tw] OR "bell pentolate" [tw] OR ciclolux [tw] OR cyclogyl [tw] OR cyclomydri [tw] OR cyclopentol [tw] OR cyclopentolat [tw] OR cylate [tw] OR cyplegin [tw] OR diopentolate [tw] OR midriodavi [tw] OR mydrilate [tw] OR "ocu-pentolate" [tw] OR ocucyclo [tw] OR "oftan-syklo" [tw] OR pentolair [tw] OR "refractyl ofeno" [tw] OR skiacol [tw] OR zyklolat [tw] OR "512-15-2" [tw] OR "5870-29-1"[tw]) NOT Medline[sb]
19. (Epinephrine [tw] OR Adrenaline [tw] OR adrenalin [tw] OR Epitrate [tw] OR Lyophrin [tw] OR Epifrin [tw] OR adnephrin [tw] OR adnephrine [tw] OR adrenaclick [tw] OR "adrenal hydrochloride" [tw] OR adrenalina [tw] OR adrenamine [tw] OR adrenapax [tw] OR adrenazin [tw] OR adrenine [tw] OR adrin [tw] OR adrine [tw] OR advaradin [tw] OR balmadren [tw] OR biorenine [tw] OR bosmin [tw] OR chelafrin [tw] OR dylephrin [tw] OR epiglaufrin [tw] OR epimephrine [tw] OR epinefrina [tw] OR epinephran [tw] OR epinephrin [tw] OR epirenamine [tw] OR epirenan [tw] OR exadrin [tw] OR glaucon [tw] OR glaucosan [tw] OR glaufrin [tw] OR "glin epin" [tw] OR glycirenan [tw] OR haemostatin [tw] OR hemisine [tw] OR hemostasin [tw] OR hemostatin [tw] OR hypernephrin [tw] OR "isopto epinal" [tw] OR levoadrenalin [tw] OR levoadrenaline [tw] OR levoepinephrine [tw] OR levorenin [tw] OR levorenine [tw] OR methylaminoethanolcatechol [tw] OR methylarterenol [tw] OR mucidrina [tw] OR myosthenine [tw] OR "n methylnoradrenalin" [tw] OR nephridine [tw] OR nieraline [tw] OR paranephrin [tw] OR posumin [tw] OR renaglandin [tw] OR renaglandulin [tw] OR renaleptine [tw] OR renalina [tw] OR renaline [tw] OR renoform [tw] OR renostypticin [tw] OR renostyptin [tw] OR scurenaline [tw] OR simplene [tw] OR soladren [tw] OR sphygmogenin [tw] OR styptirenal [tw] OR supracapsulin [tw] OR supranephrane [tw] OR supranephrin [tw] OR supranol [tw] OR suprarenaline [tw] OR suprarenin [tw] OR suprarenine [tw] OR suprel [tw] OR surenine [tw] OR surrenine [tw] OR "sus-phrine sulfite-free" [tw] OR susphrine [tw]

OR "sympathin I" [tw] OR takamina [tw] OR tonogen [tw] OR vasoconstrictine [tw] OR vasodrine [tw] OR vasotonin [tw] OR weradren [tw] OR "51-43-4" [tw] OR "55-31-2" [tw] OR "6912-68-1"[tw]) NOT Medline[sb]
20. (Ethylmorphine[tw] OR Ethomorphine[tw] OR Trachyl[tw] OR codethyline[tw] OR diolan[tw] OR dionine[tw] OR "ethyl morphine"[tw] OR ethylmorfine[tw] OR ethylmorphin[tw] OR "morphine ethyl ether"[tw] OR "125-30-4"[tw] OR "76-58-4"[tw]) NOT Medline[sb]
21. (Eucatropine[tw] OR euphthalmine[tw] OR "100-91-4"[tw] OR "536-93-6"[tw]) NOT Medline[sb]
22. (Homatropine[tw] OR homatro[tw] OR homatrocil[tw] OR homatropaire[tw] OR homatropin[tw] OR homatropina[tw] OR isoptoHomatropine[tw] OR "I Homatrine"[tw] OR "mandelyl tropeine"[tw] OR mandelyltropeine[tw] OR "mydryn eye"[tw] OR "omatropina lux"[tw] OR "tropine mandelate"[tw] OR "51-56-9"[tw] OR "87-00-3"[tw]) NOT Medline[sb]
23. (Hyoscyamine[tw] OR anaspaz[tw] OR cystospaz[tw] OR cytospaz[tw] OR daturine[tw] OR donnamar[tw] OR duboisine[tw] OR egacen[tw] OR hyoscamine[tw] OR hyosciamine[tw] OR hyoscyanin[tw] OR hyosyne[tw] OR "ib-stat"[tw] OR levbid[tw] OR levsin[tw] OR "levsinex sr"[tw] OR neosol[tw] OR nulev[tw] OR spasdel[tw] OR "symax sl"[tw] OR "symax sr"[tw] OR "tropine l tropate"[tw] OR "101-31-5"[tw] OR "306-03-6"[tw]) NOT Medline[sb]
24. (Ibopamine[tw] OR "N-methyldopamine diisobutyrate"[tw] OR "SB 7505"[tw] OR "SB7505"[tw] OR Escandine[tw] OR Inopamil[tw] OR "diisobutyric n methyldopamine ester"[tw] OR scandine[tw] OR "skf 100168"[tw] OR "skf 100168 a"[tw] OR "66195-31-1"[tw] OR "75011-65-3"[tw]) NOT Medline[sb]
25. (Methylatropine[tw] OR "8-methylatropinium nitrate"[tw] OR "31610-87-4"[tw]) NOT Medline[sb]
26. (Naphazoline[tw] OR "Afazol Grin"[tw] OR "AK Con"[tw] OR AKCon[tw] OR Albalon[tw] OR albasol[tw] OR "All Clear"[tw] OR allersol[tw] OR antan[tw] OR benil[tw] OR cefasan[tw] OR "Clear Eyes"[tw] OR coldan[tw] OR "Colirio Alfa"[tw] OR "comfort eye drops"[tw] OR dazolin[tw] OR "degest 2"[tw] OR derinox[tw] OR Idril[tw] OR imidin[tw] OR minha[tw] OR Miraclar[tw] OR mirafrin[tw] OR Nafazair[tw] OR nafazoline[tw] OR naftazolina[tw] OR "naphacel ofteno"[tw] OR naphasal[tw] OR naphazolin[tw] OR Naphcon[tw] OR "naphozoline hydrochloride"[tw] OR naphtears[tw] OR naphthazoline[tw] OR naphthizine[tw] OR naphthyzin[tw] OR nastizol[tw] OR "nazil ofteno"[tw] OR niazol[tw] OR "ocu-zoline"[tw] OR opcon[tw] OR Optazine[tw] OR Privin[tw] OR privina[tw] OR Privine[tw] OR privine[tw] OR Proculin[tw] OR rhinantin[tw] OR rhinazin[tw] OR rhinoperd[tw] OR rimidol[tw] OR sanorin[tw] OR sanotin[tw] OR Siozwo[tw] OR strictylon[tw] OR "Tele Stulln"[tw] OR TeleStulln[tw] OR Vasoclear[tw] OR Vasocon[tw] OR "Vasoconstrictor Pensa"[tw] OR VasoNit[tw] OR vistalbalon[tw] OR vistobalon[tw] OR "5144-52-5"[tw] OR "550-99-2"[tw] OR "835-31-4"[tw]) NOT Medline[sb]
27. (Oxedrine[tw] OR Synephrine[tw] OR Sympaethamin[tw] OR Synephrin[tw] OR aetaphen[tw] OR pentedrine[tw] OR vasoton[tw] OR "94-07-5"[tw]) NOT Medline[sb]
28. (Oxyphenonium[tw] OR Methacin[tw] OR Oxyphenon[tw] OR Atrenyl[tw] OR Spastrex[tw] OR antrenyl[tw] OR "ba 5473"[tw] OR ba5473[tw] OR "c 5473"[tw] OR c5473[tw] OR helkamon[tw] OR metacin[tw] OR metacinum[tw] OR oxyphenium[tw] OR "oxyphenomium bromide"[tw] OR spasmofen[tw] OR spasmophen[tw] OR "14214-84-7"[tw] OR "50-10-2"[tw]) NOT Medline[sb]
29. (Phenylephrine[tw] OR adrianol[tw] OR "af-taf"[tw] OR "ak-dilate"[tw] OR "albalon relief"[tw] OR alconefrin[tw] OR almefrin[tw] OR altafrin[tw] OR biomidrin[tw] OR biomydrin[tw] OR derizene[tw] OR "despec-sf"[tw] OR "disneumon pernasal"[tw] OR drosin[tw] OR "efrin-10"[tw] OR efrisel[tw] OR fenylephrine[tw] OR idrianol[tw] OR isonefrine[tw] OR isophrin[tw] OR isophrine[tw] OR "isopto frin"[tw] OR isoptofrin[tw] OR lexatol[tw] OR "m synephrine"[tw] OR mesaton[tw] OR "meta sympathol"[tw] OR "meta synephrine"[tw] OR Metaoxedrin[tw] OR metaoxedrine[tw] OR Metasympatol[tw] OR metasynephrine[tw] OR Mezaton[tw] OR "murucoll 2"[tw] OR mydfrin[tw] OR "n 105 to"[tw] OR "nefrin-ofteno"[tw] OR "Neo Synephrine"[tw] OR neofrin[tw] OR neooxedrine[tw] OR neophryn[tw] OR neosynephrin[tw] OR Neosynephrine[tw] OR "neosynephrin-pos"[tw] OR neosynesin[tw] OR neosynesine[tw] OR "ocu-phrin"[tw] OR "oftan-metaoksedrin"[tw] OR optistin[tw] OR phenoptic[tw] OR phenylefrine[tw] OR phenylephedrine[tw] OR prefrin[tw] OR "pupiletto forte"[tw] OR rectasol[tw] OR "rhinall 10"[tw] OR "slv 325"[tw] OR slv325[tw] OR sucraphen[tw] OR vazculep[tw] OR visadron[tw] OR vistafrin[tw] OR vistosan[tw] OR "532-38-7"[tw] OR "59-42-7"[tw] OR "61-76-7"[tw]) NOT Medline[sb]
30. (Pholedrine[tw] OR "4 hydroxy n methylamphetamine"[tw] OR "4 hydroxymethamphetamine"[tw] OR adyston[tw] OR "para hydroxymethamphetamine"[tw] OR "p-hydroxymethamphetamine"[tw] OR paredrinol[tw] OR "Pholedrin liquidum"[tw] OR "Pholedrin-longo-Isis"[tw] OR pulsotyl[tw] OR venosan[tw] OR veritol[tw] OR "370-14-9"[tw]) NOT Medline[sb]
31. (p-Hydroxyamphetamine [tw] OR "1 para hydroxyphenyl 2 propylamine" [tw] OR "alpha methyl para tyramine" [tw] OR "alpha methyl tyramine" [tw] OR "dl 1 p hydroxyphenyl 2 propylamine" [tw] OR "dl 1 para hydroxyphenyl 2 propylamine" [tw] OR "dl p hydroxy alpha methylphenethylamine" [tw] OR "dl para hydroxy alpha methylphenethylamine" [tw] OR "h 66 37" [tw] OR "para hydroxy alpha methylphenethylamine" [tw] OR Hydroxyamfetamine [tw] OR Hydroxyamphetamin [tw] OR Hydroxyamphetamine [tw] OR Hydroxyphenylisopropylamine [tw] OR Methyltyramine [tw] OR Norpholedrin [tw] OR norpholedrine [tw] OR oxamphetamine [tw] OR Oxyamphetamine [tw] OR paradrine [tw] OR parahydroxyamphetamine [tw] OR Paredrine [tw] OR paredrinea [tw] OR paredrinex [tw] OR pedrolone [tw] OR pulsoton [tw] OR "103-86-6" [tw] OR "1518-86-1" [tw] OR "306-21-8"[tw]) NOT Medline[sb]
32. (Racepinephrine[tw] OR asthmanefrin [tw] OR Micronefrin[tw] OR micronefrine[tw] OR Micronephrine[tw] OR mikronephrin[tw] OR racadrenalin[tw] OR "Racepinefrine Hydrochloride"[tw] OR racinephrine[tw] OR Vaponefrin[tw] OR vaponefrine[tw] OR vaponephrin[tw] OR "329-65-7"[tw]) NOT Medline[sb]
33. (Scopolamine[tw] OR "Boro Scopol"[tw] OR BoroScopol[tw] OR Hyoscine[tw] OR Kwells[tw] OR "levo hyoscinehydrobromide"[tw] OR Scoburen[tw] OR Scopace[tw] OR scopos[tw] OR "Travacalm HO"[tw] OR Vorigeno[tw] OR "114-49-8"[tw] OR atrochin[tw] OR atroquin[tw] OR atroscine[tw] OR hyosceine[tw] OR hysco[tw] OR "kimite-patch"[tw] OR "l epoxytropine tropate"[tw] OR "n methylhyoscine"[tw] OR oscine[tw] OR scopalamine[tw] OR "scopine tropate"[tw] OR scopoderm[tw] OR scopolamin[tw] OR transcop[tw] OR "transderm scop"[tw] OR "transderm v"[tw] OR "tropic acid ester with scopine"[tw] OR "138-12-5"[tw] OR "51-34-3"[tw] OR "55-16-3"[tw]) NOT Medline[sb]
34. (Tropicamide[tw] OR "alcon-mydril"[tw] OR bistropamide[tw] OR "cendo mydriatyl"[tw] OR "Colircusi Tropicamida"[tw] OR midriaticum[tw] OR mydiacyl[tw] OR mydral[tw] OR mydramide[tw] OR mydriacyl[tw] OR Mydriafair[tw] OR Mydriaticum[tw] OR "mydrin m"[tw] OR "mydrin p"[tw] OR Mydrum[tw] OR "n ethyl 2 phenyl n pyrid 4 ylmethylhydracrylamide"[tw] OR "n ethyl n 4 picolyltropamide"[tw] OR "n ethyl n gamma picolyltropamide"[tw] OR "n ethyl n pyrid 4 ylmethyltropamide"[tw] OR "Ocu-Tropic"[tw] OR

OcuTropic[tw] OR opticyl[tw] OR sandol[tw] OR sintropic[tw] OR "tropamid forte"[tw] OR "tropic acid n ethyl n gamma picolyl amide" [tw] OR Tropicacyl[tw] OR tropicamid[tw] OR "tropico eye"[tw] OR tropicol[tw] OR tropikamid[tw] OR tropimil[tw] OR visumidriatic[tw] OR "1508-75-4"[tw]) NOT Medline[sb]
35. (Tyramine[tw] OR "4 hydroxyphenethylamine"[tw] OR lyramine[tw] OR mydrial[tw] OR "para hydroxyphenethylamine"[tw] OR paratyramine[tw] OR systogene[tw] OR tiramine[tw] OR tocosine[tw] OR tyramin[tw] OR tyrosamine[tw] OR uteramine[tw] OR "51-67-2"[tw] OR "60-19-5"[tw]) NOT Medline[sb]
36. (Vibrocil[tw] OR "8059-14-1"[tw]) NOT Medline[sb]
37. (Yohimbine[tw] OR actibine[tw] OR aphrodine[tw] OR aphrodyne[tw] OR Corynanthine[tw] OR "corynine hydrochloride"[tw] OR "dayto-himbin"[tw] OR "methyl yohimbine 16alpha carboxylate"[tw] OR "methylyohimbane 16alpha carboxylate"[tw] OR Pluriviron[tw] OR quebrachin[tw] OR "quebrachine hydrochloride"[tw] OR Rauhimbine[tw] OR Rauwolscine[tw] OR urobine[tw] OR yobin[tw] OR yobinol[tw] OR yocan[tw] OR yocaral[tw] OR Yocon[tw] OR yocon[tw] OR yohimbe[tw] OR "yohimbic acid methyl ester"[tw] OR yohimbin[tw] OR Yohimex[tw] OR yohimex[tw] OR yohimibin[tw] OR yovital[tw] OR "146-48-5"[tw] OR "65-19-0"[tw]) NOT Medline[sb]
38. (Timolol*[tw] OR "apo timol"[tw] OR "apo timop"[tw] OR apotimol[tw] OR apotimolol[tw] OR apotimop[tw] OR betimol[tw] OR Blocadren[tw] OR "chibro timoptol"[tw] OR istalol[tw] OR "l 714465"[tw] OR l714465[tw] OR "MK 950"[tw] OR MK950[tw] OR moducren[tw] OR nyolol[tw] OR ofal[tw] OR ofan[tw] OR optimol[tw] OR timolo[tw] OR Timoptic[tw] OR Timoptol[tw] OR Timacar[tw] OR titol[tw] OR "26839-75-8"[tw]) NOT Medline[sb]
39. (Pirenzepin*[tw] OR abrinac[tw] OR azuzepin[tw] OR bisvanil[tw] OR "cl 2"[tw] OR cl2[tw] OR gastricur[tw] OR gastrocepin[tw] OR gastrozepin[tw] OR gastrozepina[tw] OR gastrozepine[tw] OR leblon[tw] OR "ls 519"[tw] OR "ls 519c12"[tw] OR ls519[tw] OR ls519c12[tw] OR maghen[tw] OR tabe[tw] OR zinc00538196[tw] OR Pyrenzepine[tw] OR "L S 519"[tw] OR Ulgescum[tw] OR "Piren basan"[tw] OR Gastrotsepin[tw] OR Ulcoprotect[tw] OR "28797-61-7"[tw] OR "29868-97-1"[tw]) NOT Medline[sb]
40. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39
41. #5 AND #40
42. #1 AND #41

Appendix 5. LILACS search terms

(Myopi$ OR Miopi$ OR MH:C11.744.636$ OR (near sight$) OR (short sight$) OR nearsighted$) AND (MH:E07.632.500.300$ OR MH:VS2.006.001.009.002$ OR spectacles OR glasses OR eyeglass$ OR Anteojos OR Óculos OR MH:E07.632.500.276$ OR MH:VS2.006.001.009.001$ OR ((progressive OR single OR vision OR addition OR bifocal OR spectacle OR corrective OR contact OR "gas permeable") AND lens$) OR MH:D27.505.519.625.120.200$ OR MH:D27.505.696.577.120.200$ OR ((Cholinergic$ OR acetylcholine$ OR muscarinic$ OR parasympathetic$) AND (antagonist$ OR block$ OR inhibitor$)) OR cholinolytic$ OR anticholinergic$ OR "anti cholinergic" OR "anti cholinergics" OR antimuscarinic$ OR "anti muscarinic" OR "anti muscarinics" OR Parasympathicolytic$ OR parasympaticolytic $ OR Parasympatholytic$ OR pharmaceutical$ OR pharmacologic$ OR MH:D27.505.696.663.050.650$ OR Parasympatholytic$ OR Parasimpatolítico$ OR Parassimpatolítico$ OR mydriatic$ OR Midriáticos OR cycloplegic$ OR "7-methylxanthine" OR Atropin$ OR MH:D02.145.074.722.229.199$ OR MH:D03.132.760.180.572.199$ OR MH:D03.132.889.180.648.199$ OR MH:D03.605.869.229.199$ OR MH:D04.075.080.875.099.722.229.199 OR berefrine OR Cyclopentolate OR Ciclopentolato OR MH:D02.241.223.601.200$ OR Epinephrine OR Epinefrina OR MH:D02.033.100.291.310$ OR MH:D02.092.063.291.310$ OR MH:D02.092.211.215.311.461$ OR MH:D02.092.311.461$ OR Ethylmorphine OR Etilmorfina OR MH:D03.132.577.249.562.430$ OR MH:D03.549.686.607.460$ OR MH:D03.605.497.607.460$ OR MH:D04.615.723.795.576.430$ OR Eucatropine OR Homatropine OR Hyoscyamine OR Hiosciamina OR MH:D02.145.074.722.229.199.500$ OR MH:D03.132.760.180.572.199.500$ OR MH:D03.132.889.180.648.199.500$ OR MH:D03.605.869.229.199.500$ OR MH:D04.075.080.875.099.722.229.199.500$ OR Ibopamine OR Methylatropine OR Naphazoline OR Nafazolina OR MH:D03.383.129.308.585$ OR Oxedrine OR Synephrine OR Sinefrina OR MH:D02.033.100.291.870$ OR MH:D02.092.063.291.870$ OR MH:D02.092.211.215.811.875$ OR Oxyphenonium OR Oxifenonio OR MH:D02.092.877.648$ OR MH:D02.675.276.648$ OR Phenylephrine OR Fenilefrina OR MH:D02.033.100.291.617$ OR MH:D02.092.063.291.617$ OR Pholedrine OR "p-Hydroxyamphetamine" OR "p-Hidroxianfetamina" OR MH:D02.092.471.683.152.500$ OR Racepinephrine OR Racepinefrina OR MH:D02.033.100.291.310.500$ OR MH:D02.092.063.291.310.500$ OR MH:D02.092.211.215.311.461.700$ OR MH:D02.092.311.461.825$ OR Scopolamine OR Escopolamina OR MH:D02.145.074.722.822.775$ OR MH:D03.132.760.180.848$ OR MH:D03.132.889.601.775$ OR MH:D03.605.869.822.775$ OR MH:D04.075.080.875.099.722.822.775$ OR Tropicamide OR Tropicamida OR MH:D03.383.725.942$ OR Tyramine OR Tiramina OR MH:D02.092.211.215.811$ OR Vibrocil OR Yohimbine OR Yohimbina OR Ioimbina OR MH:D03.132.436.681.933$ OR MH:D03.438.473.402.681.933$ OR Timolol$ OR MH:D02.033.100.624.915$ OR MH:D02.033.755.624.915$ OR MH:D02.092.063.624.915$ OR MH:D02.886.675.867.768$ OR MH:D03.383.129.708.867.768$ OR MH:D03.383.533.640.775$ OR Pirenzepin$ OR MH:D03.438.079.080.070.750$)

Appendix 6. ISRCTN search strategy

myopia

Appendix 7. ClinicalTrials.gov search strategy

myopia OR myopic

Appendix 8. WHO ICTRP search strategy

myopia OR myopic

WHAT'S NEW

Date	Event	Description
3 September 2021	Amended	Editorial note added

HISTORY

Protocol first published: Issue 1, 2008
Review first published: Issue 12, 2011

Date	Event	Description
12 December 2019	New search has been performed	Issue 1, 2020: searches updated
12 December 2019	New citation required and conclusions have changed	Issue 1, 2020: 16 new studies added (Anstice 2011; Cambridge Anti-Myopia Study 2013; Charm 2013; Cheng 2016; COMET2 Study 2011; DISC Study 2011; Fujikado 2014; Hasebe 2014; Koomson 2016; Lu 2015; ROMIO Study 2012; STAMP Study 2012; Swarbrick 2015; Trier 2008; Wang 2005; Yi 2015); data added for 1 included study from previous version (CONTROL Study 2016); 6 ongoing trials identified (BLINK Study 2017a; Li 2013; JPRN-UMIN000005054; PACT Study 2017; ACTRN12611000499987; 11000582954)
30 January 2013	New search has been performed	Search updated; new studies added
25 June 2008	Amended	Scope of the review changed to assess all interventions for slowing myopia progression in children
25 June 2008	Amended	Review converted to new review format

CONTRIBUTIONS OF AUTHORS

Contributions of authors to previous versions of this review have been published (Walline 2011).

For this version of the review:
JJW contributed to screening search results, appraising studies, extracting data, analyzing and interpreting results, and writing the manuscript; KL contributed to screening search results, appraising studies, extracting data, analyzing and interpreting results, and writing the manuscript; SAC, DOM, and JDT contributed to interpreting results and providing substantial comments and edits to the manuscript. All authors provided final approval of the manuscript.

DECLARATIONS OF INTEREST

Jeffrey Walline was the Principal Investigator (PI) of the Contact Lens and Myopia Progression (CLAMP) Study, which was a randomized controlled trial conducted to examine the effects of rigid gas permeable contact lenses (RGPCLs) on myopia progression in children. Susan Cotter, OD, MS, was a clinical site PI and served on the writing committee for the PIR-205 study—a trial evaluating pirenzepine ophthalmic gel for slowing myopia progression in children. Dr. Cotter was also a clinical site PI and served on the steering committee and the writing committee for the Correction of Myopia Evaluation Trial-2 (COMET-2) study evaluating progressive addition lenses versus single vision lenses for slowing progression of myopia in children with high accommodative lag and near esophoria. Both studies were included in this review.

Jeffrey Walline received research funding, consulted for companies, received honoraria from companies, and has pending grants with companies, all related to myopia and/or myopia progression. Susan Cotter's institution received grant funding for participation in the NIH/NEI-funded multicenter study COMET-2 and the industry-sponsored PIR-205 study. Susan Cotter and J. Daniel Twelker are clinical site PIs for an industry-sponsored multicenter trial—the Childhood Atropine for Myopia Progression (CHAMP) Study, which evaluates low-dose atropine for myopia progression in children. Donald O. Mutti received research funding, consulted for companies, and has received honoraria from companies with interests in myopia and/or myopia progression.

Kristina Lindsley and Swaroop Vedula were methodologists employed by CEV@US; CEV@US has been funded by various grants/contracts over years from the National Eye Institute, National Institutes of Health.

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- National Institute for Health Research (NIHR), UK

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o This review updated was supported by the NIHR, via Cochrane Infrastructure funding to the CEV UK editorial base.

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We modified the interventions under review compared with the published protocol. Single vision soft contact lenses (SVSCLs) are considered a control intervention, and we did not study them as an active treatment intervention for the purposes of this review. Thus, we did not include in this review studies that compared SVSCLs with single vision lenses (SVLs) (spectacles).

We added methods for the Summary of findings table and the GRADE assessment, both of which we incorporated in this review update.

INDEX TERMS

Medical Subject Headings (MeSH)

Atropine [therapeutic use]; Contact Lenses; Cyclopentolate [therapeutic use]; Muscarinic Antagonists [therapeutic use]; Myopia, Degenerative [*therapy]; Ophthalmic Solutions [*therapeutic use]; Pirenzepine [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans