

Efficacy, Systemic Safety, and Laboratory Outcomes of Low-Dose Atropine for the Prevention of Myopia Progression in Children: A Systematic Review and Meta-Analysis of Randomized Controlled Trials and Primary Studies

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ABSTRACT

Introduction: Myopia is the most prevalent refractive disorder of childhood, projected to approach 50% of the population by 2050. Low-dose atropine (0.01–0.05%) is the most investigated pharmacological intervention to slow myopia progression. **Methods:** A systematic review and meta-analysis was conducted per PRISMA 2020, including RCTs, cohort, case-control, and cross-sectional studies. Risk of bias assessed with RoB 2 and NOS. DerSimonian-Laird random-effects models were used; heterogeneity quantified by I^2 ; certainty by GRADE. **Results:** Twenty-eight reports from 22 independent populations comprising $\geq 5,251$ children were included. Atropine reduced spherical equivalent refraction (SER) progression at 12 months (MD 0.232 D; 95% CI 0.160–0.304; $p < 0.001$; $I^2 = 0\%$) and axial elongation (AL) (MD -0.106 mm; 95% CI -0.141 to -0.071 ; $p < 0.001$; $I^2 = 36.1\%$). Effects persisted at 24–36 months: SER MD 0.200 D ($p = 0.019$; $I^2 = 72.1\%$) and AL MD -0.101 mm ($p = 0.005$; $I^2 = 61.9\%$). Fast progression proportion decreased (RR 0.710; $p = 0.003$). Concentration-response gradient: 0.220 D, 0.350 D, and 0.540 D for 0.01%, 0.025%, and 0.05%. Laboratory outcomes: photopic mydriasis 0.431 mm and mesopic 0.268 mm ($p < 0.001$). Systemic safety was favourable: photophobia not increased at 0.01% (RR 1.151; $p = 0.693$). No serious adverse events occurred. Long-term heterogeneity originated from one US trial; its removal yielded SER MD 0.276 D ($I^2 = 0\%$) and AL MD -0.134 mm ($I^2 = 0\%$). **Conclusion:** Low-dose atropine 0.01–0.05% slows myopia progression with favourable systemic safety. Concentrations of 0.025–0.05% provide greater efficacy without prohibitive adverse effects. Atropine should be considered first-line therapy for progressive childhood myopia.

Keywords: Atropine, Low-Dose Atropine, Myopia Control, Axial Length, Spherical Equivalent, Children

1. INTRODUCTION

Myopia has become the most common ocular disorder of the paediatric age group and one of the fastest-growing chronic conditions in global public health. Contemporary projections indicate that the global prevalence of myopia will approach fifty % of the world population by the year 2050, with a disproportionate concentration of disease burden in East and Southeast Asia, where school-based surveys repeatedly document prevalence exceeding eighty % among adolescents completing secondary education. The clinical significance of this epidemic derives not from the refractive error itself, which is readily corrected by spectacles or contact lenses, but from the structural remodelling of the globe that underlies it. Myopia is fundamentally a disorder of excessive axial elongation, and each additional millimetre of axial length is associated with a substantial and permanent increase in the lifetime risk of myopic maculopathy, rhegmatogenous retinal detachment, open-angle glaucoma, and premature nuclear cataract.

The Low-Concentration Atropine for Myopia Progression programme conducted in Hong Kong subsequently established a monotonic concentration–response relationship across 0.05%, 0.025%, and 0.01% atropine over one and two years, identifying 0.05% as the optimal concentration among those studied, with preservation of visual acuity and of vision-related quality of life at all

concentrations. Parallel single-concentration trials in mainland China confirmed a statistically significant effect of 0.01% atropine on both refraction and axial length. The evidence base has since expanded substantially beyond East Asia. A phase 3 multicentre trial conducted across North America and five European countries evaluated a novel preservative-free formulation at 0.01% and 0.02%, a large multicentre trial in the United Kingdom evaluated preserved 0.01% atropine over two years, an Irish trial evaluated tapering and switching regimens, and a United States trial reported a null result for 0.01% atropine over twenty-four months.

Notwithstanding the substantial volume of primary research and the existence of several previous quantitative syntheses, four material gaps persist in the literature. The first concerns temporal stratification. Most previous meta-analyses have pooled trials of heterogeneous duration into a single annualised estimate, thereby obscuring the fact that the treatment effect and the between-study heterogeneity behave very differently over one year than over two to three years; the present review addresses this by analysing the two horizons separately. The second concerns geographical generalisability.

The general objective of this systematic review and meta-analysis was to determine, on the basis of the totality of available randomized and observational evidence, the efficacy, systemic safety, and laboratory outcome profile of low-dose atropine for the prevention of myopia progression in children and adolescents. The novelty of the present work resides in five features. First, it incorporates the most recent large randomized evidence, including the United Kingdom multicentre placebo-controlled trial and the three-year Irish regimen trial, alongside the established East Asian programmes, producing a geographically balanced evidence base that has not previously been assembled. Second, it deliberately separates short-term and long-term analyses and demonstrates that the apparent heterogeneity of the long-term literature is attributable to a single identifiable trial rather than to genuine inconsistency of the underlying biological effect.

2. LITERATURE REVIEW

2.1 *Low-Dose Atropine and the Concentration–Response Evidence*

The pharmacological control of myopia progression has a longer history than is often appreciated. Topical atropine, a non-selective muscarinic acetylcholine receptor antagonist, has been employed for this indication for several decades, and the early Atropine for the Treatment of Myopia trials established unequivocally that concentrations of 0.5% and 1% produce a marked slowing of refractive progression. These high concentrations, however, proved clinically unsustainable. They produce profound and sustained cycloplegia requiring progressive addition spectacles for near work, marked mydriasis with disabling photophobia necessitating photochromic correction, and, critically, a pronounced rebound acceleration of myopia when treatment is withdrawn. The five-year Atropine for the Treatment of Myopia 2 trial demonstrated that this rebound phenomenon is inversely dose-related, such that children treated with 0.01% atropine, despite a smaller effect during the active treatment phase, exhibited the lowest cumulative five-year progression of all concentrations studied, with minimal pupillary dilation and minimal loss of accommodation.

The Low-Concentration Atropine for Myopia Progression programme conducted in Hong Kong subsequently established a monotonic concentration–response relationship

across 0.05%, 0.025%, and 0.01% atropine over one and two years, identifying 0.05% as the optimal concentration among those studied, with preservation of visual acuity and of vision-related quality of life at all concentrations. Parallel single-concentration trials in mainland China confirmed a statistically significant effect of 0.01% atropine on both refraction and axial length. The evidence base has since expanded substantially beyond East Asia.

2.2 *Laboratory Outcomes and Mechanistic Rationale*

Alongside the refractive and biometric endpoints, a second and increasingly important dimension of the evidence concerns what may be termed the laboratory outcomes of atropine therapy: the instrument-measured ocular physiological and biometric parameters that both define the safety profile of the drug and illuminate its mechanism of action. These include photopic and mesopic pupillary diameter measured by infrared pupillometry, accommodative amplitude measured by push-up or objective methods, subfoveal choroidal thickness and choroidal vascularity index measured by enhanced-depth optical coherence tomography, anterior chamber depth, lens thickness and vitreous chamber depth measured by optical biometry, intraocular pressure, tear-film break-up time and lipid layer thickness, corneal endothelial cell density, and best-corrected distance and near visual acuity. Contemporary mechanistic work has demonstrated that choroidal thickening is not merely an epiphenomenon of atropine exposure but a quantifiable mediator of its antimyopic effect, and that pupillary dilation is independently associated with slower axial elongation. These parameters therefore occupy a dual role as safety endpoints and as mechanistic biomarkers, and their systematic synthesis constitutes an essential component of any comprehensive appraisal of low-dose atropine [1], [15], [17], [18], [19], [20], [30].

The mechanism by which a topical antimuscarinic agent slows axial elongation is not the classical accommodative mechanism that motivated its original use. The observation that 0.01% atropine produces measurable antimyopic effect while causing little or no accommodative loss, as demonstrated by the essentially null accommodative mean difference in the Hong Kong trial, effectively excludes accommodation as the principal pathway. Contemporary evidence instead implicates a non-accommodative, receptor-mediated action upon the retina, the retinal pigment epithelium, the choroid, and ultimately the sclera.

2.3 *Safety, Cessation, and Combination Therapy*

The systemic safety of low-dose atropine is, on the present evidence, excellent. Across the entire randomized evidence base comprising more than four thousand five hundred treated children, no trial reported a serious systemic adverse event attributable to the study medication. The multinational phase 3 trial, which is the largest and most rigorously monitored safety dataset in the field, reported no serious ocular adverse events and few serious non-ocular events, none of which was judged to be associated with atropine. The United Kingdom trial reported no difference in the frequency of adverse events or in any tolerability measure between atropine and placebo, and no serious adverse event related to the trial drugs.

The question of when and how to stop treatment is among the most clinically pressing and the least satisfactorily answered in this field. The three-year randomized

comparison of continuation against washout provides the most direct evidence: during the third year, progression was faster in every washout subgroup than in the corresponding continuation subgroup across all three concentrations, and over the full three years cumulative progression was lower in the continuation subgroups. The differences in rebound magnitude across concentrations were clinically small, and older age at cessation and lower concentration were both associated with smaller rebound.

A substantial proportion of the included evidence addressed the combination of low-dose atropine with optical modalities, and this literature is coherent. The two-year randomized combination trial demonstrated that adding 0.01% atropine to orthokeratology halved axial elongation relative to orthokeratology alone, from 0.34 to 0.17 millimetres, and that this benefit was accompanied by, and statistically associated with, greater pupillary dilation and greater choroidal thickening.

3. METHODS

3.1 Protocol, Eligibility, and Outcomes

This systematic review and meta-analysis was designed, conducted, and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review protocol, including the eligibility criteria, the outcome hierarchy, the analytical model, and the prespecified sensitivity and subgroup analyses, was established before the commencement of data extraction and was not modified thereafter except for the addition of a post hoc leave-one-out analysis of the long-term outcomes, which is explicitly identified as post hoc wherever it is reported. Because the review analysed only aggregate data extracted from previously published studies and did not involve the recruitment of human participants, the collection of identifiable personal data, or any intervention upon patients, institutional ethical approval and individual informed consent were not required.

Eligibility was defined a priori using the Population, Intervention, Comparator, Outcomes, and Study design framework, which is presented in full in Table 1. The population of interest comprised children and adolescents, conventionally defined as individuals below eighteen years of age, with either established myopia or premyopia, without restriction on ethnicity, sex, baseline refractive error severity, or geographical setting. The intervention of interest was topical atropine sulphate ophthalmic solution administered at a concentration of 0.05% or lower, instilled once nightly into both eyes, whether as monotherapy or in combination with an optical modality such as orthokeratology or defocus-incorporated multiple segment spectacles, provided that the atropine contribution to the comparison could be isolated. Eligible comparators included placebo or vehicle eye drops, no pharmacological treatment, single-vision spectacle correction, optical monotherapy, and alternative atropine concentrations.

Table 1. PICOS eligibility framework

Domain	Inclusion criteria	Key exclusions
Population (P)	Children and adolescents aged <18 years with myopia (cycloplegic spherical equivalent ≤ -0.50 D) or premyopia (SER between +1.00 D and -0.50 D); any ethnicity, sex, or country; any baseline severity including high myopia.	Adults ≥ 18 years; pathological or syndromic myopia; myopia secondary to ocular surgery, keratoconus, or systemic syndrome; amblyopia or strabismus requiring occlusion therapy (except isolated intermittent exotropia).

Domain	Inclusion criteria	Key exclusions
Intervention (I)	Topical atropine sulphate $\leq 0.05\%$ (0.01%, 0.02%, 0.025%, 0.04%, 0.05%), once nightly, as monotherapy or as an isolable component of combination therapy with an optical modality.	Atropine $> 0.05\%$ as the sole treatment arm; other antimuscarinic agents (pirenzepine, cyclopentolate, tropicamide) without an atropine arm; systemic or non-ophthalmic atropine administration.
Comparator (C)	Placebo or vehicle drops; no pharmacological treatment; single-vision spectacles; optical monotherapy (orthokeratology, DIMS, dual-focus contact lens); an alternative atropine concentration.	Studies without any comparator group; single-arm case series with no internal or modelled control.
Outcomes (O)	At least one of: cycloplegic SER progression; axial elongation; proportion with fast progression; incident myopia; pupillary diameter; accommodative amplitude; choroidal thickness; ocular biometrics; IOP; tear-film parameters; BCVA; adverse events; quality of life.	Studies reporting only surrogate or non-ocular outcomes; studies reporting no extractable numerical outcome data in any form.
Study design (S)	Randomized controlled trials (prioritised); prospective cohort; retrospective cohort; case-control; cross-sectional; other observational designs (prospective or retrospective).	Previously published systematic reviews and meta-analyses (excluded from the principal characteristics table; retained for the outcome comparison table and discussion); narrative reviews; editorials; commentaries; case reports; conference abstracts without full text; animal and in-vitro studies; trial protocols without results.
Timing and setting	Minimum follow-up of one month for laboratory and mechanistic outcomes; minimum follow-up of six months for refractive and biometric efficacy outcomes; hospital, university, community, or primary-care settings.	Single-instillation pharmacodynamic studies for efficacy endpoints (retained for mechanistic discussion only).

Source: Eligibility Criteria Specified in the Original Manuscript.

Twelve outcome domains were prespecified. The primary efficacy outcomes were the change in cycloplegic spherical equivalent refraction from baseline, expressed in dioptres, and the change in axial length from baseline, expressed in millimetres, each analysed separately at the short-term horizon of six to twelve months and at the long-term horizon of twenty-four to thirty-six months. For the spherical equivalent outcome a positive mean difference denotes less myopic progression in the atropine group and therefore favours atropine; for the axial length outcome a negative mean difference denotes less elongation and therefore favours atropine. Secondary efficacy outcomes comprised the proportion of participants meeting a study-defined threshold for fast progression and the cumulative incidence of incident myopia in premyopic cohorts. Laboratory outcomes comprised photopic pupillary diameter, mesopic pupillary diameter, accommodative amplitude, subfoveal choroidal thickness, and the anterior segment biometric components.

3.2 Search Strategy and Study Selection

The Boolean MeSH keywords inputted on databases for this research are: ("Children with myopia" OR "Paediatric myopia" OR "Premyopic children") AND ("Low-dose atropine" OR "Atropine 0.01% / 0.05%" OR "Topical atropine") AND ("Placebo" OR "No treatment" OR "Optical monotherapy") AND ("Spherical equivalent progression" OR "Axial length elongation" OR "Myopia control efficacy").

All records retrieved by the electronic search were exported and de-duplicated. Two reviewers independently screened the titles and abstracts of the de-duplicated records against the eligibility criteria specified in Table 1. Records judged potentially eligible by either reviewer were advanced to full-text assessment, at which stage both reviewers independently applied the complete eligibility criteria and recorded the reason for any exclusion. Disagreement at either stage was resolved by discussion, with recourse to a third adjudicator in the event of persistent disagreement.

Table 2. Database search results and PRISMA study-selection counts

Database	Hits
Pubmed	2
Google Scholar	372
Semantic Scholar	252
Science-direct	35
Cochrane	8
Records identified (all databases)	670
Records screened after duplicate/automation removal	606
Reports sought for retrieval	503
Reports assessed for eligibility	355
Reports excluded: wrong study design	327
Reports included in systematic review	28

Source: Article Search Strategy and PRISMA Flow Reported in The Original Manuscript.

3.3 Data Extraction, Risk of Bias, and Statistical Analysis

Data were extracted independently and in duplicate onto a standardised electronic form piloted on three studies before deployment. The extracted fields comprised the first author, year of publication, country and study setting, study design, unit of randomization or observation, sample size at randomization and at final analysis, participant age range and mean age, sex distribution, baseline cycloplegic spherical equivalent and baseline axial length, atropine concentration and dosing schedule, nature of the comparator, duration of the treatment phase and of any washout phase, method of refraction and of biometry, method of pupillometry and of accommodative measurement, all reported efficacy outcomes with their measures of dispersion, all reported laboratory and biometric outcomes, all reported adverse events, the proportion of participants completing follow-up, and the funding source. Where an outcome was reported as a mean with a standard deviation, those values were extracted directly; where an outcome was reported as an adjusted mean difference with a 95% confidence interval, the standard error was recovered by dividing the width of the interval by 3.92; where an outcome was reported only as a percentage, the numerator was reconstructed from the denominator and the reported proportion.

Methodological quality was appraised independently and in duplicate. Randomized evidence was appraised with the Cochrane Risk of Bias 2 tool across its five domains, namely bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported

result, with an overall judgement of low risk, some concerns, or high risk derived according to the algorithm specified in the tool. Non-randomized evidence was appraised with the Newcastle–Ottawa Scale, which allocates a maximum of four stars for selection, two for comparability, and three for outcome or exposure ascertainment, with a total of seven to nine stars denoting high quality, five to six moderate quality, and four or fewer low quality. Domain-level judgements were assessed using the prespecified RoB 2 and Newcastle–Ottawa Scale criteria.

All quantitative synthesis was performed on the aggregate data extracted from the published reports. Continuous outcomes were expressed as mean differences with 95% confidence intervals, the mean difference being the preferred metric because all studies reported outcomes on the same natural scale, namely dioptres for refraction, millimetres for axial length and pupillary diameter, and micrometres for choroidal thickness. Dichotomous outcomes were expressed as risk ratios with 95% confidence intervals, computed from reconstructed two-by-two tables. Pooling was performed under the DerSimonian–Laird random-effects model, which was selected a priori on the grounds that the included studies differed materially in concentration, population ancestry, formulation, and duration and therefore could not reasonably be assumed to estimate a single common effect. For every outcome the fixed-effect estimate was additionally computed and is reported alongside the random-effects estimate as a sensitivity analysis.

Where a single trial contributed more than one active arm sharing a common control group, as occurred in the low-concentration atropine incidence trial and in the concentration–response analysis, the shared control group was divided proportionately among the contributing comparisons in order to avoid the unit-of-analysis error that arises from repeated inclusion of the same control participants. Where multiple sequential reports described the same randomized cohort, as occurred across the four phases of the Hong Kong programme and across the two reports of the Shanghai choroidal cohort, only one estimate per outcome per population was admitted to any single pooled analysis, the estimate selected being that corresponding most closely to the prespecified time horizon. Prespecified sensitivity analyses comprised re-estimation under the fixed-effect model, iterative leave-one-out omission, and restriction of the analysis to randomized evidence with exclusion of observational contributions. Subgroup analysis by atropine concentration was performed within the single randomized comparison in which three concentrations were contemporaneously compared against a common placebo.

The certainty of the pooled evidence for each of the principal outcomes was rated using the Grading of Recommendations, Assessment, Development and Evaluations framework. Evidence derived from randomized trials commenced at high certainty and was downgraded for serious or very serious limitations in study limitations, inconsistency, indirectness, imprecision, and suspected publication bias; evidence derived from observational designs commenced at low certainty and could be upgraded for a large magnitude of effect, for a demonstrable dose–response gradient, or where all plausible residual confounding would act to reduce the observed effect. [1], [7], [8], [10]

4. RESULTS AND DISCUSSION

4.1 *Study Characteristics and Methodological Quality*

The characteristics of the twenty-eight included reports are set out in Table 3. Geographically, the evidence base is dominated by East Asian research, with fourteen reports originating from mainland China, Hong Kong, or Singapore, but now includes substantial contributions from the United Kingdom, Ireland, Spain, Italy, Denmark, Australia, and a multinational North American and European consortium. Participant ages ranged from three to seventeen years, and baseline cycloplegic spherical equivalent ranged from approximately +0.50 dioptres in the premyopic prevention trials to –6.00 dioptres in the treatment trials, with one trial admitting myopia as severe as –10.00 dioptres. Atropine concentration ranged from 0.01% to 0.05% in the eligible arms, with 0.01% by far the most frequently studied.

Every randomized trial contributing to the efficacy analyses measured refraction under cycloplegia, which eliminates the accommodative artefact that renders non-cycloplegic refraction unreliable in children, and every such trial measured axial length by optical biometry, which is the most reproducible available index of myopic structural progression. Masked outcome assessment was documented in the majority of randomized trials. The principal methodological weakness of the literature is attrition, which exceeded twenty-five % in four of the randomized populations and was accompanied by a between-arm imbalance in one. [1], [6], [7], [10], [14].

Table 3. Characteristics of the included primary-study reports

Study	Country	Design	Intervention/comparator	Duration
Yam JC (LAMP 1) (2019)	Hong Kong	RCT, placebo-controlled	Atropine 0.05% / 0.025% / 0.01% nightly vs Placebo drops	12 mo
Yam JC (LAMP 2) (2019)	Hong Kong	RCT extension of LAMP 1	Atropine 0.05% / 0.025% / 0.01% vs Former placebo switched to 0.05%	24 mo
Yam JC (LAMP 3) (2021)	Hong Kong	RCT, re-randomized continuation vs washout	Continued 0.05% / 0.025% / 0.01% vs Washout subgroups	36 mo
Zhang X (LAMP 4) (2024)	Hong Kong	RCT, extended follow-up with PRN re-treatment	Continued vs PRN 0.05% atropine vs Between-concentration comparison	60 mo
Yam JC (LAMP2) (2023)	Hong Kong	RCT, placebo-controlled	Atropine 0.05% or 0.01% nightly vs Placebo drops	24 mo
Wei S (2020)	China (Beijing)	RCT, placebo-controlled	Atropine 0.01% nightly vs Placebo drops	12 mo
Repka MX (2023)	United States	RCT, placebo-controlled (2:1)	Atropine 0.01% nightly vs Placebo drops	24 mo + 6 mo off
Zadnik K (CHAMP) (2023)	North America and Europe	RCT, phase 3, placebo-controlled, parallel group	NVK002 preservative-free 0.01% / 0.02% vs Placebo drops	36 mo
Chia A (ATOM2) (2016)	Singapore	RCT, dose-comparative	Atropine 0.01% (vs 0.1%, 0.5%) vs Higher atropine concentrations	60 mo
Azuara-Blanco A (CHAMP-UK) (2026)	United Kingdom	RCT, multicentre, placebo-controlled (2:1)	Preserved atropine 0.01% daily vs Placebo drops	24 mo
Loughman J (MOSAIC2) (2025)	Ireland	RCT, regimen comparison	0.05% atropine; 0.01% taper regimens vs Placebo / tapering placebo	36 mo
Wang Z (2024)	China	RCT, placebo-controlled (2:1)	Atropine 0.01% nightly vs Placebo drops	12 mo
Wang WQ (2023)	China	RCT, placebo-controlled crossover	Atropine 0.01% nightly vs Placebo drops	13 mo (2 × 6 mo)
Xu H (2025)	China (Shanghai)	RCT, three-arm, multicentre	Atropine 0.04% or 0.01% daily vs Overnight orthokeratology	24 mo
Tan Q (AOK) (2022)	China	RCT, two-arm, parallel	0.01% atropine plus orthokeratology vs Orthokeratology alone	24 mo

Study	Country	Design	Intervention/comparator	Duration
Zhao W (ACO) (2020)	China	RCT, four-arm, prospective	0.01% atropine ± orthokeratology vs Placebo and single-vision spectacles	1 mo
Ye L (2020)	China (Shanghai)	RCT, two-arm, dose-comparative	Atropine 0.01% daily vs Atropine 1% weekly	6 mo
Ye L (2023)	China (Shanghai)	RCT with embedded mediation analysis	Atropine 0.01% daily vs Atropine 1% then 0.01%	12 mo
Hvid-Hansen A (2023)	Denmark	RCT, placebo-controlled, multicentre	0.1% loading then 0.01% atropine vs Placebo drops	24 mo + 12 mo washout
Lee SS (2024)	Australia	RCT, placebo-controlled (2:1)	Atropine 0.01% daily vs Placebo drops	24 mo + 12 mo washout
Zhang J (2023)	China	Retrospective cohort	Atropine 0.01% vs Orthokeratology; single-vision spectacles	12 mo
Chen Z (2019)	China	Retrospective self-controlled cohort	0.01% atropine added to orthokeratology vs Orthokeratology alone (phase 1)	24 mo
Guo Y (2024)	China	Prospective observational study	Low-concentration atropine ± orthokeratology vs Spectacles alone; orthokeratology alone	12 mo
Cao X (2024)	China	Retrospective cohort	0.01% atropine plus SV, DIMS, or ortho-k vs Between-modality comparison	12 mo
Wen L (2024)	China	Retrospective cohort	0.05% atropine added to orthokeratology vs Orthokeratology alone	12 mo
Nucci P (2023)	Italy	Non-randomized prospective controlled, examiner-masked	0.01% atropine ± DIMS spectacles vs Single-vision spectacles	12 mo
Alvarez-Peregrina C (2026)	Spain	Retrospective longitudinal cohort	Atropine 0.01% / 0.025% / 0.05% vs Modelled age- and ancestry-adjusted expected growth	12 mo
Song D (2025)	China (Nanjing)	Non-randomized controlled clinical study	DIMS spectacles plus atropine vs Orthokeratology	12 mo

Source: Included-study characteristics in the original manuscript [1]–[28].

4.2 Efficacy at Short- and Long-Term Follow-up

Four independent randomized populations contributed data to the short-term refractive analysis, comprising a total of five hundred and eighteen children analysed at the twelve-month endpoint or, in the crossover trial, at the six-month period endpoint. All four estimates favoured atropine, and the individual confidence intervals excluded the null in every case. The pooled random-effects mean difference was 0.232 dioptres in favour of atropine, with a 95% confidence interval of 0.160 to 0.304 dioptres and a two-sided p value below 0.001. Statistical heterogeneity was entirely absent, with a Cochran Q statistic of 0.60 on three degrees of freedom, a between-study

variance of zero, and an I^2 statistic of 0.0%, such that the random-effects and fixed-effect estimates were numerically identical.

Five independent populations contributed to the short-term biometric analysis, four randomized and one a retrospective cohort. Every estimate favoured atropine, and all but one excluded the null individually. The pooled random-effects mean difference was -0.106 millimetres, with a 95% confidence interval of -0.141 to -0.071 millimetres and a two-sided p value below 0.001. Heterogeneity was low to moderate, with a Cochran Q statistic of 6.26 on four degrees of freedom and an I^2 statistic of 36.1%, and the fixed-effect estimate of -0.105 millimetres was almost identical to the random-effects estimate.

Three large placebo-controlled randomized trials, together enrolling one thousand and fifty-two children across the United States, the United Kingdom, North America, and continental Europe, contributed to the long-term refractive analysis. The pooled random-effects mean difference was 0.200 dioptres in favour of atropine, with a 95% confidence interval of 0.034 to 0.367 dioptres and a two-sided p value of 0.019. Heterogeneity was substantial, with a Cochran Q statistic of 7.16 on two degrees of freedom and an I^2 statistic of 72.1%, and the fixed-effect estimate of 0.209 dioptres carried a considerably narrower interval of 0.122 to 0.296 dioptres. The source of the heterogeneity is transparent from inspection of the individual estimates: the United States trial reported an effect indistinguishable from zero, whereas the United Kingdom and multinational trials reported effects of 0.330 and 0.240 dioptres respectively, both with intervals excluding the null. Leave-one-out analysis confirmed that omission of the United States trial abolished heterogeneity entirely and raised the pooled estimate to 0.276 dioptres. [7], [8], [10].

The same three trials contributed to the long-term biometric analysis. The pooled random-effects mean difference was -0.101 millimetres, with a 95% confidence interval of -0.172 to -0.030 millimetres and a two-sided p value of 0.005. Heterogeneity was again substantial at an I^2 statistic of 61.9%, and again originated exclusively in the null result of the United States trial; omission of that trial produced a pooled estimate of -0.134 millimetres with a confidence interval of -0.180 to -0.089 millimetres and an I^2 statistic of 0.0%.

Three populations reported the proportion of participants meeting a predefined threshold for rapid progression, defined variously as refractive progression of at least 0.50 dioptres over the study year, a fast myopic shift of at least 0.50 dioptres, or axial elongation exceeding 0.30 millimetres over the study year. The pooled random-effects risk ratio was 0.710, with a 95% confidence interval of 0.565 to 0.892 and a two-sided p value of 0.003, corresponding to a relative risk reduction of twenty-nine %. Heterogeneity was moderate at an I^2 statistic of 48.5%, reflecting the differing thresholds employed, and the fixed-effect estimate of 0.722 was closely comparable.

Table 4. Consolidated meta-analytic outcomes

Outcome	Pooled effect (95% CI)	p	I^2	Interpretation
SER progression, 6–12 mo	MD 0.232 D (0.160 to 0.304)	<0.001	0.0%	Favours atropine
Axial elongation, 6–12 mo	MD -0.106 mm (-0.141 to -0.071)	<0.001	36.1%	Favours atropine
SER progression, 24–36 mo	MD 0.200 D (0.034 to 0.367)	0.019	72.1%	Persistent effect; heterogeneous
Axial elongation, 24–36 mo	MD -0.101 mm (-0.172 to -0.030)	0.005	61.9%	Persistent effect; heterogeneous
Fast myopic progression	RR 0.710 (0.565 to 0.892)	0.003	48.5%	29% relative risk reduction
Incident myopia, premyopia	RR 0.690 (0.432 to 1.102)	0.120	72.9%	Interpret by concentration
Photopic pupil diameter	MD $+0.431$ mm (0.303 to 0.559)	<0.001	12.7%	Small mydriasis

Outcome	Pooled effect (95% CI)	p	I ²	Interpretation
Mesopic pupil diameter	MD +0.268 mm (0.103 to 0.433)	0.001	35.5%	Small mydriasis
Accommodative amplitude	MD -1.563 D (-4.738 to 1.612)	0.335	97.1%	Pooled estimate not interpretable
Subfoveal choroidal thickness	MD +20.487 μ m (-0.368 to 41.341)	0.054	93.6%	Directionally positive; heterogeneous
Photophobia, 0.01%	RR 1.151 (0.572 to 2.315)	0.693	44.6%	No significant excess
Exploratory pooled AUC	0.607 (0.562 to 0.652)	<0.001	31.6%	Above chance; poor-to-fair discrimination

Source: Authors' pooled analyses reported in the original manuscript.

4.3 Concentration–Response, Laboratory Outcomes, and Safety

A formal concentration–response analysis was possible within the single randomized comparison in which three low concentrations were contemporaneously compared against a common placebo group over twelve months, with the placebo group divided proportionately between the three comparisons. A strictly monotonic gradient was observed for both the refractive and the biometric endpoint. For spherical equivalent progression the mean difference rose from 0.220 dioptres at 0.01%, through 0.350 dioptres at 0.025%, to 0.540 dioptres at 0.05%; for axial elongation it rose in absolute magnitude from -0.050 millimetres, through -0.120 millimetres, to -0.210 millimetres across the same concentrations. Only the two higher concentrations achieved statistical significance for the axial endpoint within this partitioned analysis.

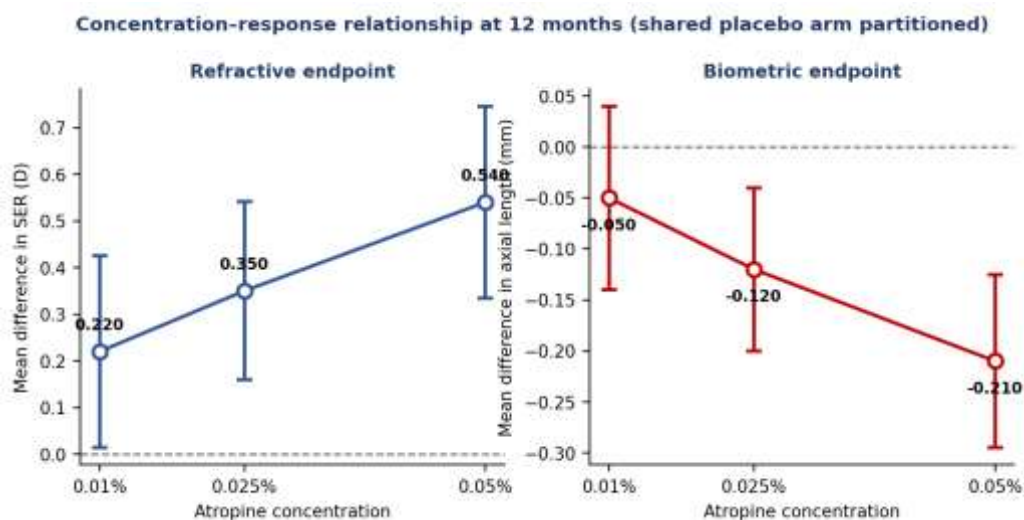


Figure 1. Concentration–response relationship at 12 months (shared placebo arm partitioned)
Source: Original Manuscript, Based on the Yam 2019 Randomized Comparison [1].

Three populations reported the change in pupillary diameter measured under photopic conditions. All three demonstrated a statistically significant increase in the atropine group, and the pooled random-effects mean difference was 0.431 millimetres, with a 95% confidence interval of 0.303 to 0.559 millimetres and a two-sided p value below 0.001. Heterogeneity was low at an I² statistic of 12.7%.

Two populations reported the change in pupillary diameter under mesopic conditions, which is the more relevant measure for night-time visual function and for driving in older adolescents. The pooled random-effects mean difference was 0.268 millimetres, with a 95%

confidence interval of 0.103 to 0.433 millimetres and a two-sided *p* value of 0.001. Heterogeneity was low to moderate at an *I*² statistic of 35.5%.

Two populations reported the change in accommodative amplitude with a placebo comparator, and the two results were profoundly discordant. The Hong Kong trial reported that 0.01% atropine produced essentially no measurable accommodative loss relative to placebo, with a mean difference of 0.060 dioptres and a wide confidence interval spanning the null, whereas the Chinese trial conducted in children with concomitant intermittent exotropia reported a substantial accommodative loss of 3.180 dioptres. The pooled random-effects estimate of -1.563 dioptres was not statistically significant, with a confidence interval of -4.738 to 1.612 dioptres and a *p* value of 0.335, and the *I*² statistic of 97.1% indicates that the two estimates cannot legitimately be regarded as estimating a common quantity.

Two randomized populations provided a directly comparable estimate of the effect of low-dose atropine on subfoveal choroidal thickness. The short-term four-week study reported a mean difference of 10.300 micrometres in favour of atropine over control, and the two-year combination study reported a mean difference of 31.600 micrometres in favour of combined atropine and orthokeratology over orthokeratology alone. The pooled random-effects estimate of 20.487 micrometres approached but did not attain conventional statistical significance, with a confidence interval of -0.368 to 41.341 micrometres and a *p* value of 0.054, whereas the fixed-effect estimate of 13.765 micrometres was significant with a confidence interval of 9.852 to 17.678 micrometres.

Two randomized populations provided placebo-controlled estimates of the incidence of photophobia with 0.01% atropine. The pooled random-effects risk ratio was 1.151, with a 95% confidence interval of 0.572 to 2.315 and a two-sided *p* value of 0.693, indicating no statistically detectable excess risk relative to placebo. Heterogeneity was moderate at an *I*² statistic of 44.6%, one trial reporting a risk ratio marginally below unity and the other marginally above. This null finding is consistent with the wider safety literature, in which the United Kingdom trial reported no difference in the frequency of adverse events or in tolerability measures between atropine and placebo, and the multinational phase 3 trial reported no serious ocular adverse events and no serious non-ocular event judged to be associated with atropine.

Blurred near vision was formally quantified against placebo in a single randomized population, in which it occurred in 6.0% of children receiving 0.01% atropine and 7.0% of children receiving placebo, corresponding to a risk ratio of 0.857 with a 95% confidence interval of 0.348 to 2.110 and therefore no detectable excess. A concentration-dependent gradient is nonetheless evident across the literature, blurred near vision being reported by 15% of participants during a year of 0.05% atropine as against 3% during a year of tapering 0.01% atropine within the same trial. Across the entire randomized evidence base no trial reported a serious systemic adverse event attributable to low-dose atropine. Tachycardia, dry mouth, flushing, urinary retention, central nervous system disturbance, and other manifestations of systemic antimuscarinic toxicity were not reported at any concentration at or below 0.05%.

4.4 Sensitivity Analyses and Certainty of Evidence

Three families of sensitivity analysis were prespecified and one further leave-one-out analysis of the long-term outcomes was performed post hoc. Re-estimation under the fixed-effect model altered no conclusion for any efficacy outcome and is reported alongside each principal estimate. Leave-one-out iteration of the short-term refractive analysis produced pooled estimates ranging narrowly from 0.219 to 0.244 dioptres, every one of which retained a *p* value below 0.001 and an *I*² statistic of zero, demonstrating that no single trial drives the short-term result. Leave-one-out iteration of the two long-term analyses produced a wholly different pattern: omission of the United States trial abolished heterogeneity and increased the pooled estimates, whereas omission of either of the two positive trials rendered the pooled estimate non-significant and left substantial residual heterogeneity.

The certainty of the evidence for each principal outcome was rated using the GRADE framework, and the resulting summary of findings is presented in Table 5. Certainty was rated high for the short-term refractive and biometric outcomes, which derive exclusively from registered randomized trials, display no heterogeneity, and yield precise estimates. Certainty was rated moderate for the long-term outcomes, downgraded once for inconsistency on account of the substantial and unexplained I^2 values. Certainty was rated moderate for the dichotomous fast-progression outcome, downgraded once for the heterogeneity of threshold definitions, and low for accommodative amplitude and choroidal thickness, downgraded for very serious inconsistency and for imprecision respectively.

Table 5. GRADE Summary of Principal Outcomes

Outcome	Evidence	Pooled effect	Certainty
SER progression ≤ 12 mo	4 RCT; n=518+	MD 0.232 D (0.160 to 0.304)	●●●● High
Axial elongation ≤ 12 mo	4 RCT + 1 cohort; n=700+	MD -0.106 mm (-0.141 to -0.071)	●●●● High
SER progression ≥ 24 mo	3 RCT; n=1,052	MD 0.200 D (0.034 to 0.367)	●●●○ Moderate
Axial elongation ≥ 24 mo	3 RCT; n=1,052	MD -0.101 mm (-0.172 to -0.030)	●●●○ Moderate
Fast myopic progression	2 RCT + 1 cohort; n=638	RR 0.710 (0.565 to 0.892)	●●●○ Moderate
Incident myopia in premyopia	1 RCT (2 arms); n=474	RR 0.690 (0.432 to 1.102)	●●○○ Low
Photopic pupil diameter	3 studies; n=680+	MD 0.431 mm (0.303 to 0.559)	●●●● High

Source: GRADE Assessment in the Original Manuscript.

4.5 Interpretation, Clinical Implications, and Research Priorities

This systematic review and meta-analysis, assembling twenty-eight reports of twenty-two independent study populations and at least five thousand two hundred and fifty-one children and adolescents, establishes four principal findings. First, low-dose atropine produces a statistically robust and clinically meaningful attenuation of myopic progression over twelve months, reducing spherical equivalent progression by a pooled mean difference of 0.232 dioptres and axial elongation by a pooled mean difference of 0.106 millimetres, with an I^2 statistic of zero for the refractive endpoint and complete stability under leave-one-out iteration. Second, the treatment effect persists over twenty-four to thirty-six months, with pooled mean differences of 0.200 dioptres and -0.101 millimetres, although the long-term evidence displays substantial heterogeneity that is localisable to a single trial. Third, the effect is concentration-dependent, rising monotonically across 0.01, 0.025, and 0.05% for both the refractive and the biometric endpoint.

Several explanations for this discordance merit consideration. The first is pharmaceutical. Low-dose atropine is not a standardised product: the trials employed compounded preparations, preserved commercial preparations, and a novel preservative-free formulation, and these differ in pH, in buffering, in tonicity, in the presence and identity of preservative, and in chemical stability of the atropine molecule over the shelf-life of the bottle. Atropine undergoes hydrolysis to tropic acid and tropine at neutral and alkaline pH, and a preparation that has degraded during storage will deliver a lower effective dose than its nominal label indicates.

This gradient must, however, be reconciled with the historical observation from the five-year Singaporean trial that 0.01% atropine ultimately outperformed 0.1 and 0.5% when the entire five-year trajectory including washout and re-treatment was considered, because the rebound during washout was inversely dose-related. The apparent paradox dissolves once it is recognised that the rebound gradient and the efficacy gradient operate over different ranges. Between 1% and 0.01% the rebound penalty is large enough to overwhelm the efficacy advantage; between 0.05% and 0.01% it is not. The three-year randomized comparison of continuation against washout demonstrated that the differences in rebound across 0.05, 0.025, and 0.01% were clinically small and

did not differ significantly, and that over the full three years the cumulative progression remained lowest in the 0.05% group in both the continued and the washout subgroups.

The collective implication is that low-dose atropine should be conceptualised as a suppressive rather than a curative therapy, analogous in this respect to topical therapy for glaucoma or inhaled therapy for asthma. Treatment should be continued through the period of active ocular growth and withdrawn, when withdrawal is attempted at all, at an older age and from a lower concentration, with structured biometric surveillance and a predefined threshold for re-treatment. The finding that restarted 0.05% atropine achieves efficacy equivalent to uninterrupted therapy is clinically reassuring, since it indicates that a trial of cessation does not forfeit the option of subsequent effective treatment. [3], [4].

The clinical corollary is that atropine and optical defocus therapies appear to act through at least partially independent pathways and are therefore additive. For the child who continues to progress rapidly despite optical monotherapy, the addition of low-dose atropine is supported by randomized evidence; for the child who continues to progress despite atropine monotherapy, the addition of an optical modality is supported by the same body of evidence read in the opposite direction. Escalation of atropine concentration and addition of an optical modality are both defensible responses to inadequate control, and the choice between them should be governed by the child's tolerance of pupillary and accommodative side effects, by the practicality of contact lens wear, and by cost. [15], [24], [26], [30].

The present review nonetheless differs from its predecessors in three material respects. It incorporates the most recent large European randomized evidence, which was unavailable to the earlier syntheses and which materially alters the geographical balance of the evidence base. It separates the short-term and long-term horizons rather than annualising across heterogeneous durations, and in doing so demonstrates that the apparent inconsistency of the literature is confined to the long-term analyses and is localisable to a single trial.

Several practical recommendations follow from this synthesis. Children with documented progressive myopia, defined conventionally as progression of at least 0.50 dioptres or axial elongation of at least 0.20 millimetres per year, should be offered pharmacological therapy, and low-dose atropine is the pharmacological agent with the strongest evidence base. Initiation at 0.05%, or at 0.025% where photophobia is anticipated to be poorly tolerated, is supported by the concentration–response data in preference to routine initiation at 0.01%, particularly in younger children and in rapid progressors. Baseline and serial cycloplegic autorefraction and optical biometry should be performed at intervals of six months, with axial length regarded as the primary index of response because of its superior reproducibility. Families should be counselled that photophobia and near-vision blur are dose-related, generally mild, and reversible, and that photochromic lenses and, in a minority, progressive addition lenses may be required.

For the Indonesian and wider Southeast Asian context these recommendations require local adaptation. No included trial was conducted in Indonesia, Malaysia, Thailand, the Philippines, or Vietnam, and the applicability of East Asian dose–response data to Southeast Asian populations, which differ in ancestry, iris pigmentation, and environmental exposure, has not been formally established. Access is a further constraint: commercially manufactured low-dose atropine preparations are not universally available, and compounded preparations vary in concentration accuracy, sterility assurance, and shelf-life stability, which is precisely the variable most likely to explain the discordant trial results discussed above. Primary-care physicians working in puskesmas and comparable community settings are well positioned to identify progressive myopia early through school-based vision screening and to refer for biometric confirmation, and the development of a structured national referral pathway would represent a high-yield, low-cost intervention independent of drug availability. [7], [10], [26], [27].

Four research priorities emerge. The first is a head-to-head randomized comparison of 0.05, 0.025, and 0.01% atropine conducted outside East Asia with objective electronic adherence monitoring and with formulation chemistry, including pH, preservative content, and assayed

atropine concentration at the point of instillation, reported as prespecified covariates. The second is the systematic stratification of treatment response by iris pigmentation and by genetic ancestry, which would directly test the hypothesis that population differences in dose–response account for the discordant trial results. The third is the conduct of adequately powered trials in Southeast Asian populations, including Indonesian children, both to establish local efficacy and to inform national policy in a region experiencing rapid growth in myopia prevalence.

CONCLUSION

This systematic review and meta-analysis of twenty-eight reports describing twenty-two independent study populations and at least five thousand two hundred and fifty-one children and adolescents demonstrates that low-dose atropine, administered as a nightly topical instillation at concentrations between 0.01 and 0.05%, significantly attenuates the progression of childhood myopia. The systemic safety profile is favourable across the entire low-dose range: no included randomized trial reported a serious adverse event attributable to the study medication, photophobia and blurred near vision were not significantly increased at 0.01%, and best-corrected visual acuity, intraocular pressure, tear-film parameters, corneal endothelial cell density, and vision-related quality of life were uniformly preserved. The discordance between the positive United Kingdom and multinational trials and the null United States trial constitutes the principal unresolved question in this field. The weight of the available evidence nonetheless supports the efficacy of low-dose atropine, and the hypotheses specified at the outset of this review were confirmed for the primary efficacy endpoints, for the concentration–response relationship, for the persistence of effect over two to three years, and for systemic safety. [7], [8], [10]

Low-dose atropine should be regarded as a first-line pharmacological option for children with documented progressive myopia, defined as refractive progression of at least 0.50 dioptres or axial elongation of at least 0.20 millimetres per year. The initial concentration should be individualised rather than defaulted to 0.01%. Concentrations of 0.025 to 0.05% are supported by the concentration–response data, particularly in younger children and in rapid progressors, and should be preferred where photophobia is likely to be tolerated. Response should be monitored by cycloplegic autorefractometry and optical biometry at six-monthly intervals, with axial length regarded as the primary index of response on account of its superior reproducibility and its direct relationship to long-term structural risk. Treatment should be continued through the period of active ocular growth rather than withdrawn empirically. Where cessation is attempted, it should occur at an older age, from a lower concentration, and under structured biometric surveillance with a predefined threshold for re-treatment. Families should receive anticipatory counselling regarding dose-related photophobia and near-vision blur, and photochromic spectacle correction should be offered where symptoms arise; progressive addition lenses are required only in a minority. Where control remains inadequate on atropine monotherapy, escalation of concentration or the addition of an optical modality such as orthokeratology or defocus-incorporated multiple segment spectacles is supported by randomized evidence, the two approaches appearing to act additively. Health systems, and particularly those in Indonesia and the wider Southeast Asian region, should establish school-based vision screening pathways with structured referral for biometric confirmation, and should regulate the concentration accuracy, sterility, and shelf-life stability of compounded low-dose atropine preparations. Future trials should be conducted in under-represented populations, including Indonesian and other Southeast Asian children, should incorporate objective electronic adherence monitoring, should report formulation chemistry as a prespecified covariate, and should stratify treatment response by iris pigmentation and genetic ancestry.

DECLARATIONS

Author Contributions, Funding, and Conflicts of Interest

Both authors contributed to the conception and design of the review. dr. Nita Nopiani (UPTD Puskesmas Lelea) developed the search strategy, performed study screening and data extraction, conducted the statistical analysis, and drafted the manuscript. dr. Hilmi Aziz (UPTD Puskesmas Cidempet) performed independent duplicate screening, data extraction and risk-of-bias appraisal, verified the extracted numerical data against the source records, and critically revised the manuscript for important intellectual content. Both authors approved the final version and accept accountability for all aspects of the work. This review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors declare no financial or non-financial conflicts of interest. No patient-identifiable data were used and no institutional ethical approval was required. All data supporting the findings of this review are contained within the tables of this manuscript and within the cited primary publications, each of which is accessible through the verified link supplied in the reference list

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