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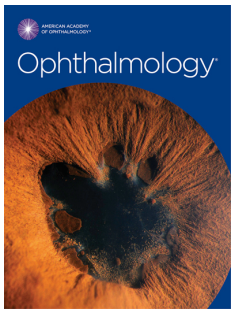

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Efficacy and Safety of 8 Atropine Concentrations for Myopia Control in Children: A Network Meta-Analysis

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This article contains additional online-only material. The following should appear online-only: Appendices 1-8, eTables 1-2, and eFigures 1-3.

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Abbreviations and Acronyms

NMA = network meta-analysis; RCTs = randomized controlled trials; AXL = axial length; BCVA = best-corrected visual acuity; RR = relative risk; SDs = standard deviations; CIs = confidence intervals; MD = mean difference; logMAR = logarithm of the minimum angle of resolution; CINeMA = Confidence in Network Meta-analysis

Abstract

Topic: Comparative efficacy and safety of different concentrations of atropine for myopia control in children.

Clinical relevance: Atropine is known to be an effective intervention to delay childhood myopia progression. Nonetheless, there is as yet no well-supported evidence ranking the clinical outcomes of various concentrations of atropine.

Methods: We searched PubMed, EMBASE, Cochrane Central Register of Controlled Trials, WHO International Clinical Trials Registry Platform and ClinicalTrials.gov on Apr 14, 2021. We selected studies involving atropine treatment of at least 1-year duration for control of myopia in children. We performed a network meta-analysis (NMA) of placebo-controlled and head-to-head randomized controlled trials (RCTs) and compared 8 atropine concentrations (1, 0.5, 0.25, 0.1, 0.05, 0.025, 0.02, and 0.01%). We ranked the atropine concentrations for the corresponding outcomes by P-score (estimate of probability of being best treatment). Our primary outcomes were mean annual changes in refraction (diopters/year) and axial length ([AXL] millimeters/year). We also extracted data on the proportion of eyes showing myopia progression and safety outcomes (photopic/mesopic pupil diameter, accommodation amplitude, distance/near best-corrected visual acuity [BCVA]).

Results: Thirty (30) pairwise comparisons from 16 RCTs (3,272 participants) were obtained. Our NMA ranked the 1, 0.5 and 0.05% atropine concentrations as the 3 most beneficial for myopia control based on P-scores, as assessed for both primary outcomes: 1% atropine (mean difference and 95% CI in refraction compared to control: 0.81 [0.58;1.04]; AXL: -0.35 [-0.46;-0.25]), 0.5% atropine (refraction: 0.70 [0.40;1.00]; AXL: -0.23 [-0.38;-0.07]), 0.05% atropine (refraction: 0.62 [0.17;1.07]; AXL: -0.25 [-0.44;-0.06]). In terms of myopia control as assessed by relative risk (RR) for overall myopia progression, 0.05% was ranked as the most beneficial atropine concentration (RR:0.39 [95% CI: 0.27;0.57]) followed by 1% (0.43 [0.33;0.56]). The ranking probability for adverse effects (photopic/mesopic pupil diameter and accommodation

amplitude) tended to decline as the atropine concentration was increased, though this tendency was not evident for distance BCVA. No valid network was formed for near BCVA.

Conclusion: The ranking probability for efficacy was not proportional to dose (i.e., 0.05% atropine was comparable to that of high-dose [1 and 0.5%]), though those for pupil size and accommodation amplitude were dose-related.

Myopia is the most common eye disease in children and adolescents, predominantly in East Asia. It has been of increasing worldwide health concern over the past few decades, and indeed, has already reached a pandemic level.[1, 2] Myopia has been predicted to affect 4.8 billion people in the world by the year 2050, which means that in 30 years, 50% of the world population will be myopic.[3] In any case, myopia is now the leading cause of preventable blindness in children and adolescents, which makes it an urgent public health issue.

Myopia is a multifactorial disease that has both environmental and genetic causes. Progressive high myopia has been confirmed as a particularly significant risk of open-angle glaucoma, cataract, myopic macular degeneration, rhegmatogenous retinal detachment, and myopic choroidal neovascularization.[4] These complications can lead to irreversible visual impairment later in life. Myopia also impacts children's overall quality of life, specifically in terms of academic performance, physical activity, social interaction, and future job choices.[5] Therefore, a treatment to effectively retard or even stop myopia progression in children is coveted by researchers, clinicians and medical practitioners.

There have been several approaches employed to slow down progression of myopia, such as increased outdoor activity, reduced near work, peripheral defocusing lenses, and orthokeratology contact lenses.[6] Atropine, a non-selective muscarinic antagonist, has been studied widely in recent years as an option for myopia control.[7] Reports have indicated that 1.0% atropine can halt myopia progression, but this treatment was associated with vision-related adverse effects as well.[8, 9] In one recent study, 0.01% atropine was determined to be effective and to have fewer adverse vision-related effects.[10] To date, there is still much uncertainty, not to mention dosing and safety concerns, about the clinical use of atropine.

Previous methodologies, such as limited comparisons and/or conventional meta-analysis using pairwise comparisons, were not able to demonstrate hierarchies among various

atropine concentrations.[5, 11] Direct and indirect comparison of different doses is essential in order to enable clinicians and parents to choose the safest and most effective treatment for myopia control. Network meta-analysis (NMA), an extension of traditional meta-analysis, provides an inclusive estimate of the efficacy or safety of multiple experimental trials not previously directly compared with adequate precision or at all.[12, 13] NMA concerns both direct and indirect treatment effects identifiable within an entire pool of evidence. This makes possible the building up of treatment hierarchies on the basis of valid statistical inference methods.[14]

Therefore, we conducted the present study to draw more decisive conclusions on the ranking of various atropine concentrations for treatment efficacy and safety, using NMA to uniquely enable integration of multiple direct and indirect comparisons.

Methods

The protocol of this systematic review was prospectively registered at PROSPERO (CRD42021248957). The reporting of this NMA is based on the PRISMA 2015 NMA Checklist.[15]

Eligibility Criteria for Consideration of Studies for This Review

We included randomized controlled trials (RCTs) of atropine to halt or slow myopic progression. The studies were selected according to the following criteria: (1) participants were younger than 18 years and had myopia, (2) atropine of any concentration was used in at least 1 treatment arm, (3) treatment duration was at least 12 months, and (4) reporting of at least 1 outcome of interest including annual rate of myopia progression.

Search Methods for Identification of Studies

We systematically searched the Cochrane Register of Controlled Trials (CENTRAL) in The Cochrane Library, PubMed, and EMBASE from inception until Apr 14, 2021. Our search strategies were developed with assistance from an academic librarian with expertise in systematic review and based on established terminology using the extensive MESH and EMBASE search terms when available. The keywords included were *myopia, refractive errors*, and *atropine*. We also screened the World Health Organization International Clinical Trials Registry Platform and *clinicaltrials.gov*. We hand-searched the reference lists[9, 11, 16-28] of published articles to identify additional relevant studies. We did not impose any language restriction in the electronic searches. The full search strategies are described in Appendix 1 (available at www.aaojournal.org).

Study Selection

To identify relevant reports, retrieved articles were exported to Endnote (version X9; Thomson Reuters), wherein duplicates were found and removed. Two investigators (AH/YKK) independently assessed the titles and abstracts for potential eligibility, and the full-text articles

were retrieved for those that appeared relevant. These articles were then independently assessed by the 2 investigators for final eligibility. Non-English-language reports were assessed by a single individual who was a native or fluent speaker of the language. We resolved discrepancies in the eligibility classification of the full-text articles through discussion and consensus or, if needed, adjudication by a third investigator (JHJ). When more than 1 report used data from the same study, we included only the latest report to avoid duplicate counting of the data.

Data Collection and Risk of Bias Assessment

For each included trial, 2 individuals (AH/YKK) independently extracted data and entered them in electronic format into Microsoft Access 2016 (Microsoft Corporation, Redmond, WA, USA). An algorithm checked for conflicting data entries. Differences were discussed, and a third reviewer (JHJ) was contacted if consensus was not reached. Trial characteristics of interest included: (1) study ID (name of first author, year of publication), (2) country of study, (3) number of subjects, (4) race/ethnicity of study population, (5) ages and sexes of participants, (6) intervention and control, (7) length of follow-up, (8) baseline and annual mean change in refraction, (9) baseline and annual mean change in axial length (AXL), (10) proportion of eyes showing overall/rapid myopic progression, and (11) adverse outcomes (i.e., photopic/mesopic pupil diameters, change in accommodation amplitude, and distance/near best-corrected visual acuity [BCVA]). For studies reporting more than 2 atropine concentrations that could be independently subjected to the present NMA, data were extracted from all of the atropine-treated arms. In the cases of studies involving interventions other than atropine, we included only the data from the atropine-treated arms.

We specified tropicamide as a control at the outset, because a previous study by Shih et al.[29] found that 0.5% tropicamide had a similar effect to a placebo on myopia progression.[7] Likewise, single-vision spectacle lenses or multi-focal progressive lenses were prespecified as a control along with a placebo.[16]

We extracted means and standard deviations (SDs) for continuous outcomes. If SDs were not provided, we calculated them from standard errors, confidence intervals (CIs), or other measures.[30-32] In the studies where the results were only graphically represented, the numerical values from graphs were extracted using Adobe Acrobat's XI inbuilt measuring tool (Adobe Systems Incorporated, San Jose, CA, USA).[33, 34]

We assessed the risk of bias by the revised tool used for assessment of risk of bias in randomized trials (RoB 2).[35] This tool evaluated five bias domains, including randomization processes, adherence to assigned interventions, missing outcome data, bias of measurement, and bias of reported results. Each domain was graded as follows: low risk-of-bias; some concerns; high risk-of-bias. Two investigators (AH/JHJ) independently assessed the risk of bias, and discrepancies were resolved through discussion.

Outcomes

We used mean annual change in refraction (diopters/year) and mean annual change in AXL (millimeters/year) as our primary outcomes. For all of the comparisons, the stated values represent the differences in primary outcomes between the first and second interventions. In terms of refractive error, a positive mean difference (MD) therefore indicates that the first intervention was better (less myopia progression). In terms of AXL, a negative MD indicates that the first intervention was better (less axial elongation).

Secondary outcomes were proportion of eyes showing overall myopia progression, proportion of eyes showing rapid myopia progression, photopic and mesopic pupil diameter (mm), change in accommodation (amplitude/year), and distance and near BCVA (logarithm of the minimum angle of resolution [logMAR]). We also extracted data on side effects such as frequencies of photophopia or allergic conjunctivitis.

Data Synthesis and Analysis

We compared the effects of competing interventions on the primary outcomes (i.e., refractive error and AXL) and adverse effects according to the MD with 95% CIs. In terms of the

proportion of eyes showing myopia progression, relative risk (RR) was calculated, specifically by dividing the progression proportion in atropine group by that in the control group. The effects of different atropine concentrations were compared according to the RR with 95% CIs.

NMA is a technique for simultaneous comparison of 3 or more interventions in a single analysis by combining direct with indirect evidence across an entire network of studies.[36] Indirect comparisons, which are those that are not made directly within studies, can be estimated by mathematical combinations of the available direct intervention effect estimates.[36] To combine direct and indirect evidence in the present study, an NMA was performed using the R package "*netmeta*" (the R Foundation), which implements a frequentist method based on a graph-theoretical approach according to the electrical network theory.[37] The "*netmeta*" function accounts for within-study correlation by reweighting (based on back-calculation of variances using the Laplacian matrix and its pseudoinverse) all of the comparisons of each multi-arm study.[38] We chose to apply random-effects models rather than fixed-effects models, because the studies we included were heterogeneous and relatively small in number.[39]

Assumption of Transitivity

Transitivity is the key assumption underlying NMA's valid estimation of effects for indirect comparisons.[40] Transitivity assumes that distributions of effect modifiers (covariates that are associated with intervention effects) are balanced across comparisons in the network.[41] Given the lack of any evidence for robust effect modifiers in trials on atropine's effects on childhood myopia progression, we used both clinical and methodological experience to identify the five potential effect modifiers that follow: *(1) publication year, (2) mean age, (3) baseline mean refraction, (4) sample size,* and *(5) follow-up duration*. The transitivity-assumption plausibility was evaluated by comparison of these potential effect modifiers' distributions across studies grouped by comparison.[42] Two independent investigators (AH/JHJ) visually assessed the potential effect modifiers' distributions over the individual atropine concentrations and determined, by consensus, whether there was considerable dissimilarity threatening the

transitivity assumption (Appendix 2, available at www.aaojournal.org). Then, we explored the influence of potential effect modifiers showing dissimilarity by network meta-regression and sensitivity analyses.

Assessment of Network Heterogeneity and Consistency

Heterogeneity, which influences the extent to which generalizable conclusions can be drawn, manifests as variability among study designs, analytical methods, participants, outcomes, or interventions.[36] We presented the estimates of this parameter (τ^2 network) from the NMA models along with the estimated proportions of variability not due to sampling error (I^2 network).[43] Additionally, we estimated Q statistics for total network heterogeneity (Q_{total}), heterogeneity within designs (Q_{within}), and heterogeneity between designs (Q_{between}), "designs" representing the individual elements in the set of trial designs.[44] To facilitate the clinical interpretation of heterogeneity, prediction intervals for estimation of the true treatment effects to be expected in future settings were calculated.[45]

Consistency, a property of closed loops of evidence, reflects agreement of direct with indirect treatment effects.[40] We evaluated consistency across our entire network using the Q statistics (above), the decomposed Q_{within} and Q_{between}, an alternative estimation for Q_{between} using the 'design-by-treatment' interaction model,[46, 47] and an approach known as Separating Indirect from Direct Evidence (SIDE; aka node-splitting).[48] We formed judgements on notable inconsistencies using all of the measures of global and local consistency: global, meaning, within the entire evidence network, and local, meaning, of a specific treatment comparison. Only in cases where network consistency was satisfied for a specific outcome did we generate NMA estimates.[49]

Certainty of Evidence in Network Estimates

We used semi-automated software to assess the confidence in NMA estimates based on the Confidence in Network Meta-analysis (CINeMA; Institute of Social and Preventive Medicine) web application, by which confidence is graded as high, moderate, low, or very low.[50, 51] In

CINeMA, the quality of a body of evidence is characterized based on (1) within-study bias, (2) reporting bias, (3) indirectness, (4) imprecision, (5) heterogeneity, and (6) inconsistency. Presence of reporting bias or major concern on any dimension resulted in downgrading by two levels. Some other concerns about a dimension resulted in confidence downgrading by one level. Some concerns about both "imprecision" and "heterogeneity" were downgraded by one level to avoid diminishing the overall level of confidence more than once for related concerns.[52]

To date, there is still no concrete methodology for assessment of cross-study bias (publication bias) in NMA. Therefore, a comparison-adjusted funnel plot was drawn, and an accompanying Egger test for asymmetry was conducted.[53]

Network Meta-regression and Sensitivity Analysis

We performed random-effects network meta-regression within the Bayesian hierarchical framework using the "*gemtc*" package in R (Appendix 3, available at www.aaojournal.org).[54] Network meta-regression, an extension of NMA, determines if effect size (i.e., treatment outcome) differs according to a given covariate (i.e., a potential effect modifier).[55] In addition, a sensitivity analysis was applied in order to test the effect of rerunning the NMA after removal of studies having potential effect modifiers that had been identified in the network meta-regression analysis. We considered effect modifiers to be important if their interpretation resulted in any difference relative to the primary analysis.

Ranking Probability

Finally, we ranked 8 atropine concentrations and the control for each outcome using P-scores, the most frequent analogue of the surface under the cumulative ranking curve (SUCRA). P-score, having a value between 0 and 1, is a probability of a given treatment being among the best treatments.[56, 57] P-scores represent a treatment ranking that mostly follows that of point estimates but additionally takes precision into account.[57]

Results

Search Results and Study Characteristics

Figure 1 shows a flowchart of the study analysis. Our systematic search identified 1,861 articles, including 1,032 unique reports, and 163 full-text articles were retrieved after exclusion of reports on the basis of their titles and abstracts. On fully evaluating the remaining 163 citations, we found 16 RCTs that met the inclusion criteria in the NMA, comprising a total of 3,272 individuals.

Among the 16 trials contributing to the analysis, 8 different concentrations of atropine were involved: 1, 0.5, 0.25, 0.1, 0.05, 0.025, 0.02, and 0.01%. Low-dose atropine (0.01%) was investigated in 9 studies,[18, 19, 21, 22, 24-27, 58] moderate-dose atropine (0.02 to 0.25%) in 4 studies,[18, 21, 24, 29] and high-dose atropine (0.5 or 1%) in 8 studies,[9, 16-18, 20, 23, 29, 59] together resulting in 21 experimental groups. Thirteen studies reported both refraction and AXL outcomes.[9, 16-18, 20, 22-27, 58, 60] and 3 studies reported only refraction.[19, 29, 59] The individual characteristics of the 16 studies included in the NMAs are provided in Table 1. The risk of bias for individual trials are indicated in Appendix 4 (available at www.aaojournal.org). Overall, most of the trials that we included in this analysis seemed to have a low-to-moderate risk of bias.

Mean Difference in Refraction Change

The NMA compared the efficacy in mean annual refraction change among the different atropine concentrations (1, 0.5, 0.25, 0.1, 0.05, 0.025, 0.02, and 0.01%) and the control. Figure 2A shows the network of eligible comparisons (16 trials, 9 arms, and 30 pairwise comparisons). As represented in Figure 3A, 5 atropine concentrations had a higher MD relative to the control when combined in the NMA: 1% (MD = 0.81, 95% CI = 0.58 to 1.04), 0.5% (MD = 0.70, 95% CI, 0.40 to 1.00), 0.1% (MD = 0.50, 95% CI = 0.14 to 0.87), 0.05% (MD = 0.62, 95% CI = 0.17 to 1.07), and 0.01% (MD = 0.39, 95% CI = 0.21 to 0.57). According to the head-to-head comparisons, no statistical difference was found among the atropine concentrations, with the exception of 0.01 versus 1% (MD = -0.42, 95% CI = -0.71 to -0.13, Figure 4).

Mean Difference in Axial Elongation

Figure 2B shows the network of eligible comparisons in mean annual AXL change (13 trials, 8 arms, and 22 pairwise comparisons). Four atropine concentrations had a higher MD relative to the control when combined in the NMA (Figure 3B): 1% (MD = -0.35, 95% CI = -0.46 to -0.25), 0.5% (MD = -0.23, 95% CI = -0.38 to -0.07), 0.05% (MD = -0.25, 95% CI = -0.44 to -0.06), and 0.01% (MD = -0.13, 95% CI = -0.21 to -0.05). In the head-to-head comparisons, no statistical difference was found among the different atropine concentrations, with the exception of 0.01 versus 1% (MD = 0.22, 95% CI = 0.09 to 0.35, Figure 4).

For the primary outcomes, we examined the certainty of evidence in the network of all of the comparisons, and found it to be widely distributed from very low to high (Appendices 5-7, available at www.aaojournal.org). Specifically, the low and very-low confidence levels of evidence for refraction change were caused mainly by suspected reporting bias (Egger test, P = 0.0065), which resulted in down-rating of the confidence for all comparisons.

Relative Risk of Myopia Progression

Ten studies reported the proportion of eyes showing myopic progression (eFigure 1A). Eight of them defined "no myopia progression" as less than 0.25 D decrease in SE,[17-19, 21, 22, 24, 27, 59] and the other 2 as less than 0.50 D.[16, 29] We found that all of the different concentrations of atropine had a lower RR of myopic progression relative to the control. Specifically, 0.05% atropine showed the lowest RR for overall myopia progression (RR = 0.39, 95% CI = 0.27 to 0.57), followed by 1% (RR = 0.43, 95% CI = 0.33 to 0.56, eFigure 2A). The net league table of the head-to-head RR comparison for overall myopia progression is shown in eFigure 3A.

The proportion of eyes presenting rapid myopic progression was assessed in 9 studies (eFigure 1B). All of the studies defined rapid progression as SE change of 1.0 D or greater,[17, 18, 21, 22, 24, 27, 29, 59] with the exception of 1 study (Shih et al.,[16] 0.75 D or greater). We found network inconsistency by both the global (P = 0.007; eTable 1) and local (atropine 0.5% versus control, P = 0.04; Appendix 7) approaches; thus, no NMA estimates were generated.

Safety

The detailed data on safety for the 16 studies included in the NMAs are given in eTable 2. The Photopic and mesopic pupil diameters were assessed in 5 and 4 studies with 6 and 5 different concentrations of atropine, respectively (eFigure 1C, D). Atropines had a higher MD of photoic pupil diameter relative to the control, ranging from MD 0.59 mm (95% CI = 0.16 to 1.01 mm for 0.01% atropine) to 2.96 mm (95% CI = 2.00 to 3.91 mm for 0.5% atropine). In terms of mesopic pupil diameter, atropines were likely to increase MDs, ranging from 0.13 mm (95% CI = -0.02 to 0.28 mm for 0.01% atropine) to 2.54 mm (95% CI = 2.20 to 2.88 mm for 0.5% atropine) (eFigure 2B, C).

The degree of accommodation change was assessed in 4 trials with 6 different concentrations of atropine (eFigure 1E). Among them, 0.5% (MD = -7.65, 95% CI = -10.44 to -4.85) and 0.1% (MD = -5.95, 95% CI = -8.73 to -3.16) atropine showed a lower MD for accommodation amplitude relative to the control (eFigure 2D).

Distance and near BCVA data were reported in 3 and 2 studies, respectively, both with 5 different concentrations of atropine (eFigure 1F, G). Differences between the various doses of atropine and the control in terms of distance BCVA were not evident, except for 0.1% (MD = 0.02, 95% CI = 0.00 to 0.05 eFigure 2E). The network consistency for near BCVA was not satisfied (Appendix 7 and eTable 1); thus, no NMA estimates were generated. eFigure 3B-D shows the net league table of head-to-head comparisons for each adverse effect.

Sensitivity Analysis

Referring to the results of the network meta-regression analyses (Appendix 3; available at www.aaojournal.org), we conducted sensitivity analyses on MD in refraction change, excluding studies (1) published before 2000, (2) with baseline mean refraction less than -4 diopters, (3) fewer than 50 participants or (4) with a high risk of bias. We noted that the conclusions on the primary outcome did not change substantially after accounting for potential

effect moderators. The detailed results are shown in Appendix 8 (available at www.aaojournal.org). The overall heterogeneity analysis results are summarized in eTable 1.

Rank Probability

Figure 5 provides graphical summaries of the P-scores for each outcome. The highest ranked atropine concentration for control of myopia as assessed by refraction change was 1% (P-score = 0.897), followed by 0.5% (P-score = 0.781) and 0.05% (P-score = 0.667). The P-scores ranked 1% (P-score = 0.929), 0.05% (P-score = 0.677), and 0.5% (P-score = 0.613) as the 3 most beneficial atropine concentrations for control of myopia as evaluated by axial elongation. As for the RR of overall myopia progression, the highest ranked dose was 0.05% (P-score = 0.908), followed by 1% (P-score = 0.849) and 0.5% (P-score = 0.774). As regards photopic/mesopic pupil diameter and accommodation amplitude, the higher the atropine dose was, the lower were the ranking probabilities. This tendency was not evident in the P-scores for distance BCVA.

Discussion

Our NMA from 16 RCTs demonstrated that there was significantly less myopia progression in the atropine treatment group than in the control group. Also, our NMA could build up hierarchies of atropine treatment in terms of efficacy and safety among the 8 concentrations. Higher-dose atropine ranked as a better intervention in slowing down refraction changes and axial elongation than did lower-dose atropine. Among moderate-dose (0.02 to 0.25%) atropine, 0.05% showed comparable efficacy to that of high-dose atropine, and was ranked third in terms of retarding refraction changes and second in slowing down axial elongation. In terms of myopia control assessed by RR for overall myopia progression, 0.05% was ranked as the most beneficial atropine concentration. This NMA also demonstrated that the adverse effects of atropine treatment might be dose-related. High-dose atropine showed lower-ranking probabilities for 3 safety outcomes (i.e., photopic/mesopic pupil diameter, accommodation amplitude) compared with low-dose atropine.

There have been several meta-analyses investigating various concentrations of atropine treatment in myopia control. In the 2011 meta-analysis by Song et al., high-dose (0.5 and 1.0%) showed better efficacy than did moderate-dose (0.1 and 0.25%) atropines, but that analysis included only the 6 studies (one of which was a non-randomized clinical trial) that were available at that time.[61] The next meta-analysis, published in 2014, included 11 studies, and reported a positive effect for atropine in both RCTs and cohort studies; however, the low dose (0.01%) was not included, and no stratification by dose was performed. In a 2016 NMA comparing various nonpharmacological and pharmacologic interventions for control of myopia, atropine was the most effective in retarding myopia progression.[7] However, this NMA included only a total of 7 RCTs for atropine treatment, and did not include 0.025 or 0.05% atropine. Gong et al., in their 2017 meta-analysis on 19 studies (both RCT and cohort studies), found

that all doses were equally beneficial, on which basis they suggested that the efficacy of atropine is dose independent.[11] The combination of different study types in their meta-analysis can be a major source of heterogeneity;[62] moreover, they did not evaluate either axial elongation or RR for myopia progression.

The hallmark of NMA is its utility for building up hierarchies of competing interventions indicative of treatments that are more or less likely to produce the most significant benefits.[36] Our present NMA ascribed hierarchies among various atropine doses based on rank probabilities, finding that 1, 0.5 and 0.05% atropine were the 3 most beneficial atropine concentrations for myopia control as evaluated by either refraction changes or axial elongation. Interestingly, 0.05% atropine had the best rank probability in terms of prevention of myopia progression as assessed by RR for overall progression. Our rank probability trends in efficacy outcomes signified that the effects of various atropine concentrations for myopia control might not always follow a dose-dependent order.

Several previous studies have demonstrated associations of higher concentrations of atropine with more adverse effects such as photophobia and near-vision problems.[5, 11] Our NMA showed similar results: the lower the atropine concentration was, the higher the ranking probabilities for safety profiles in pupil size and accommodation were. Although we were not able to obtain a reliable network for analysis of near BCVA, we can speculate that lower atropine concentration is correlated with lower possibility of decreased near BCVA, since accommodation and pupil size are components of near visual acuity.[63]

The optimal atropine concentration should be the one with the best balance between efficacy and safety. Of note, comprehensively considering the analysis results for 3 efficacy outcomes (i.e., refraction change, axial elongation, and RR for myopia progression), 0.05% was comparable to high-dose (1 and 0.5%) atropine. In terms of atropine-related adverse effects,

on the other hand, 0.05% showed better safety profiles relative to the high-dose atropine. Well-supported evidence on ranking probabilities for near BCVA and/or acceptability would be helpful to further assessment of the risk/benefit ratios of different atropine concentrations.

There are several limitations to this study that should be taken into account when interpreting its results. First, although strict inclusion and exclusion criteria were applied in the NMA, heterogeneity still existed. Some of the RCTs had had less than 100 patients. Thus, the so-called small-study effect may have been incurred in our analysis, smaller trials showing different, often larger, treatment effects than larger trials.[64] Also, there was a wide variation in subject age (range: 4-18 years), but because the studies reported only the age range or mean, there was no definitive data on how treatment varies with age. Although sensitivity analyses showed that the results of our NMA were both stable and consistent after consideration of potential effect modifiers, further trials with larger sample sizes are required in order to provide better-quality data. Second, most of the RCTs included in this NMA were based on Asian populations. It has been suggested that there may be differences between Asian and Caucasian children in their responses to interventions for myopia progression.[7] Iris color, for example, may be related to different responses to treatment administered to slow myopia progression.[65] Further subgroup investigation is required in order to determine the relation between ethnicity and optimal atropine dose. Third, our study considered information on efficacy and safety during the trial period but not on myopic rebound, due to insufficient data within the included articles. A previous study reported that discontinuation of atropine can lead to myopic rebound and even faster progression, and that the higher the dose, the higher the risk of progression.[66] Given the possible effects of atropine concentration on the rebound phenomenon, future studies should focus on assessing optimal atropine dosage, not only during the trial period but also after administration stoppage. Fourth, we were unable to investigate factors associated with

variegation among responses to atropine. The ATOM 2 study reported that children on higher doses of atropine showed lower prevalence of rapid (i.e., ≥ -1.5 diopters) myopia progression (4.3, 6.4, and 9.3% relative to 0.5, 0.1, and 0.01% doses, respectively);[18] however, many factors other than concentration, such as genetics, environmental exposure, and severity of disease, might help to explain heterogeneity in atropine responses. Further studies examining other confounding factors along with doses are required in order to determine the optimal atropine doses, which is to say, those that are both effective and easily tolerable. Fifth and finally, the fundamental challenge in this analysis was the lack of sufficient data on some concentrations, resulting in wide and overlapping CIs overall. Although assessment of NMA transitivity and subsequent incorporation into data synthesization (by network meta-regression and sensitivity analyses) were performed to enhance NMA robustness, the results nonetheless should be interpreted with caution.

Notwithstanding these limitations, it is less likely that the number of large head-to-head trials necessary to address all these clinical questions will be conducted; at least 45 trials would be needed for comparison of all atropine doses in myopia control. In their absence of such trials, meanwhile, our NMA provides a valuable approach to the issue. The probable dose-response relationship between atropine and its efficacy/safety should be validated further by dose-response meta-analysis.[67] Additionally, the possible acceptability differences among the various atropine doses have not yet been fully addressed. These certainly are worthy questions for future studies seeking to discover the keys to myopia-control treatments that are both efficacious and safe.

In conclusion, our NMA uncovered strong evidence that atropine treatment in children with myopia has efficacy in retarding refraction changes and axial elongation relative to a control group. The ranking probabilities for the efficacy of the 8 atropine concentrations were

not proportional to the doses. We found that 1, 0.5 and 0.05% atropine were the 3 most efficacious atropine concentrations in the NMA ranking probabilities, and notably, that 0.05% was the most beneficial atropine concentration as assessed for overall myopia progression. The ranking probabilities for most of the safety outcomes, such as photopic/mesopic pupil size and accommodation amplitude, followed a dose-related order.

Figure legends

Figure 1. Flow diagram showing selection process for inclusion of studies in network meta-analysis (NMA).

Figure 2. Network plot for efficacy. A, mean annual refraction change. B, mean annual axial length change. Each node represents 1 atropine concentration. The node size corresponds to the number of participants assigned to each treatment. Treatments with direct comparisons are linked with a line; the line thickness corresponds to the number of trials evaluating the comparison.

Figure 3. Forest plot of NMA comparing different doses of atropine for myopia interventions. A, mean annual refraction change. B, mean annual axial length change. Each atropine concentration was compared with the control, which was the reference group. MD = mean difference; CI = confidence interval.

Figure 4. Net league table of head-to-head comparisons for different doses of atropine in myopia intervention. Lower-left corner: mean difference in refraction change. Upper-right corner: mean difference in axial length change. The treatment comparisons should be read from left to right; the estimate is shown in the shared cell between the "treatment" column and row. Greater-than-0 mean differences favor the column-indicated treatment.

Figure 5. Graphical summary of P-scores of different doses of atropine for prevention of myopia progression. Upper row: P-scores of efficacy outcomes. Bottom row: P-scores of safety outcomes. Higher and closer-to-1 P-scores indicate a greater likelihood of a top-rank concentration.

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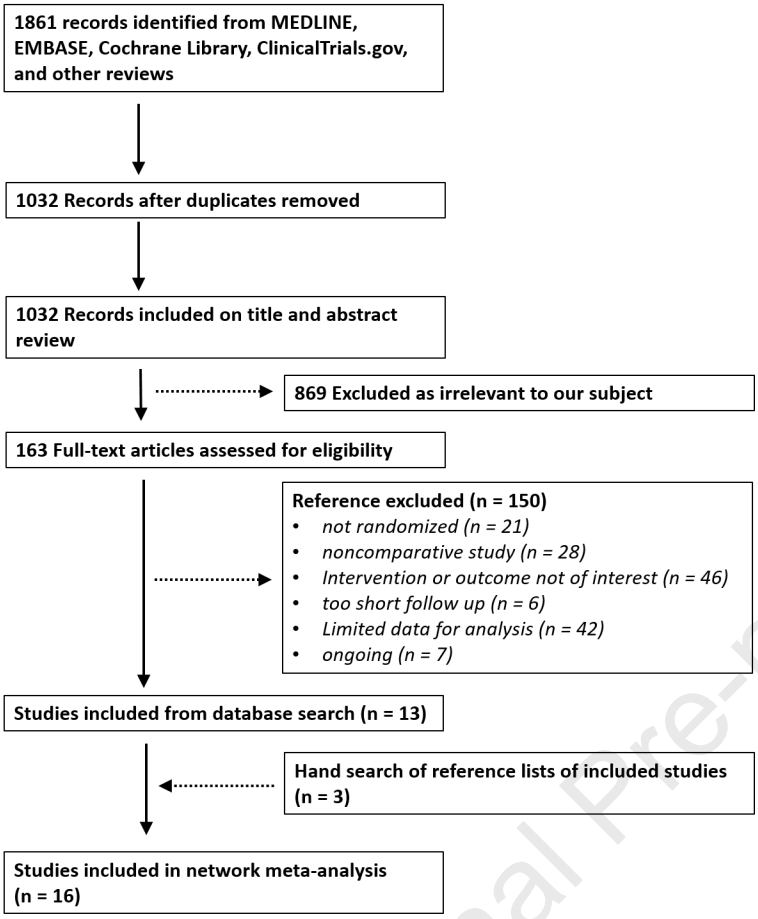
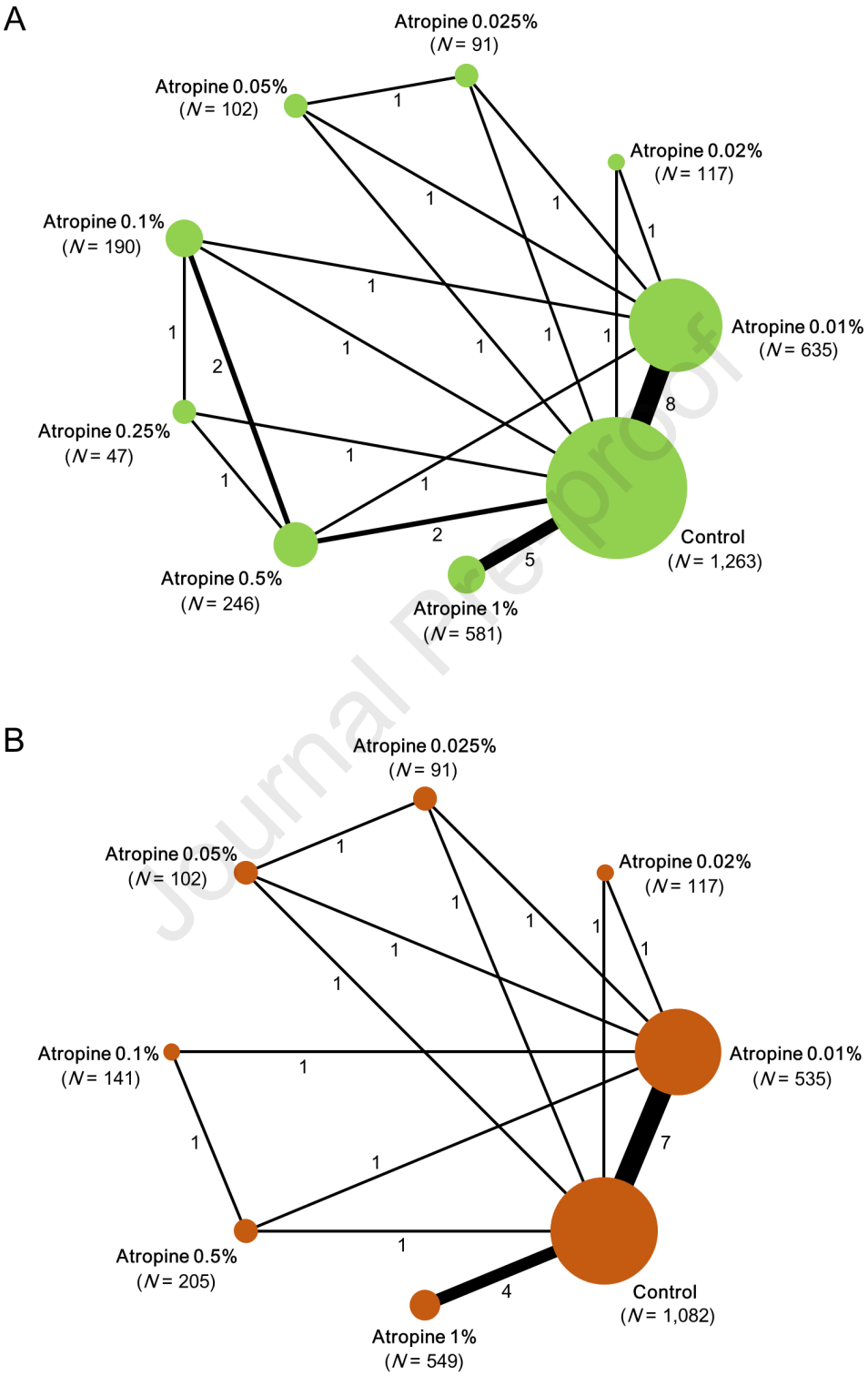
Table 1. Characteristics of Studies Included in the Meta-analysis

Study	Country	Age (year)	Follow-up duration (month)	Arm	Sample size	Baseline refraction (D)	Basline AXL (mm)	Mean change in refraction (D/year)	Mean change in AXL (mm/year)	Proportion of myopic progression (%)	Proportion of rapid myopic progression (%)
Yen et al.,[59] 1989	Taiwan	6-14	12	1%	32	-1.52 (0.96)	NA	-0.22 (0.54)	NA	43.8	3.1
				Control	32	-1.59 (0.92)		-0.91 (0.58)		93.8	31.3
Shih et al.,[29] 1999	Taiwan	6-13	21	0.5%	41	-4.89 (2.06)	NA	-0.04 (0.63)	NA	39.0	4.0
			20	0.25%	47	-4.24 (1.74)		-0.45 (0.55)		51.0	17.0
			20	0.1%	49	-4.41 (1.47)		-0.47 (0.91)		58.0	33.0
			23	Control	49	-4.50 (1.86)		-1.06 (0.61)		92.0	44.0
Shih et al.,[16] 2001	Taiwan	6-13	18	0.5%	66	-3.28 (0.13)	24.62 (0.10)	-0.28 (0.05)	0.15 (0.02)	42.4	10.6
				Control	61	-3.20 (0.14)	24.75 (0.10)	-0.93 (0.06)	0.39 (0.03)	95.1	72.1
Chua et al.,[17] 2006	Singapore	6-12	24	1%	166	-3.36 (1.38)	24.80 (0.83)	-0.14 (0.46)	-0.01 (0.18)	34.3	13.9
				Control	190	-3.58 (1.17)	24.80 (0.84)	-0.60 (0.35)	0.19 (0.19)	83.9	63.9
Chia et al.,[18] 2012	Singapore	6-12	24	0.5%	139	-4.30 (1.80)	25.10 (0.90)	-0.15 (0.30)	0.14 (0.13)	37.0	15.8
				0.1%	141	-4.50 (1.40)	25.10 (0.80)	-0.19 (0.30)	0.14 (0.14)	42.0	16.7
				0.01%	75	-4.50 (1.50)	25.20 (1.00)	-0.25 (0.32)	0.21 (0.16)	50.0	16.7
Yi et al.,[9] 2015	China	7-12	12	1%	68	-1.23 (0.32)	23.75 (0.12)	0.32 (0.22)	-0.03 (0.07)	NA	NA
				Control	64	-1.15 (0.30)	23.72 (0.12)	-0.85 (0.31)	0.32 (0.15)		
Diaz-Llopis et al.,[19] 2018	Spain	9-12	60	0.01%	100	-1.10 (0.50)	NA	-0.14 (0.35)	NA	2.0	NA
				Control	100	-1.20 (0.40)		-0.65 (0.54)		21.0	
Han et al.,[20] 2019	China	6-12	24	1%	53	-1.74 (1.40)	24.30 (0.99)	-0.25 (0.37)	0.16 (0.15)	NA	NA
				Control	25	-1.81 (1.01)	24.04 (0.65)	-1.31 (0.51)	0.76 (0.12)		
Yam et al.,[21] 2019	Hong Kong	4-12	12	0.05%	102	-3.98 (1.69)	24.85 (0.90)	-0.27 (0.61)	0.20 (0.25)	30.4	15.2
				0.025%	91	-3.71 (1.85)	24.86 (0.95)	-0.46 (0.45)	0.29 (0.20)	48.4	12.6
				0.01%	97	-3.77 (1.85)	24.70 (0.99)	-0.59 (0.61)	0.36 (0.29)	56.2	27.8
				Control	93	-3.85 (1.95)	24.82 (0.97)	-0.81 (0.53)	0.41 (0.22)	75.8	37.1
Wei et al.,[22] 2020	China	6-12	12	0.01%	76	-2.52 (1.33)	24.50 (0.76)	-0.49 (0.42)	0.32 (0.19)	51.3	13.2
				Control	83	-2.64 (1.46)	24.69 (0.97)	-0.76 (0.50)	0.41 (0.19)	69.9	34.9

Zhu et al.,[23] 2020	China	6-12	24	1%	262	-3.82 (0.44)	24.93 (0.21)	-0.21 (0.22)	0.12 (0.10)	NA	NA
				Control	308	-3.74 (0.51)	24.91 (0.18)	-0.89 (0.23)	0.39 (0.19)		
Alam et al.,[58] 2020	Bangladesh	6-18	12	0.01%	24	-3.00 (1.60)	24.30 (1.00)	0.50 (2.40)	0.10 (0.10)	NA	NA
				Control	12	-3.50 (1.60)	24.60 (1.10)	-0.40 (0.40)	0.20 (0.20)		
Fu et al.,[24] 2020	China	6-14	12	0.02%	117	-2.76 (1.47)	24.60 (0.72)	-0.38 (0.35)	0.30 (0.21)	49.8	16.7
				0.01%	119	-2.70 (1.64)	24.58 (0.74)	-0.47 (0.45)	0.37 (0.22)	54.9	20.3
				Control	100	-2.68 (1.42)	24.55 (0.71)	-0.70 (0.60)	0.46 (0.35)	71.9	35.6
Hieda et al.,[25] 2020	Japan	6-12	24	0.01%	77	-2.91 (1.30)	24.43 (0.74)	-0.63 (0.20)	0.32 (0.09)	NA	NA
				Control	81	-2.98 (1.59)	24.51 (0.78)	-0.74 (0.21)	0.39 (0.09)		
Zhao et al.,[26] 2021	China	5-14	12	0.01%	20	-1.98 (0.45)	24.17 (0.68)	-0.34 (0.16)	0.24 (0.12)	NA	NA
				Control	20	-1.93 (0.74)	24.28 (0.83)	-1.30 (0.44)	0.72 (0.21)		
Saxena et al.,[27] 2021	India	6-14	12	0.01%	47	-3.38 (1.32)	24.60 (1.02)	-0.16 (0.38)	0.22 (0.20)	13.0	0.0
				Control	45	-3.71 (1.37)	24.70 (0.80)	-0.35 (0.40)	0.28 (0.28)	38.0	8.9

D = diopters; AXL = axial length; NA = not available.





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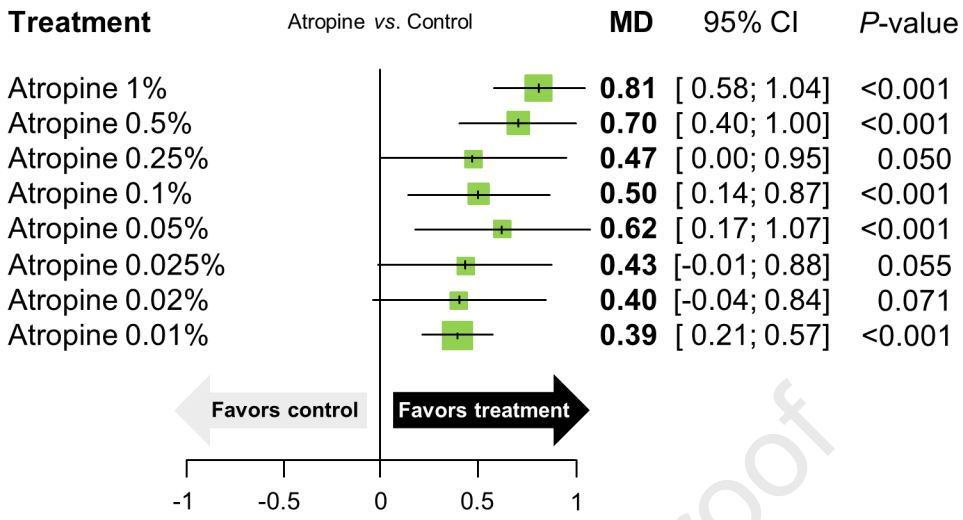

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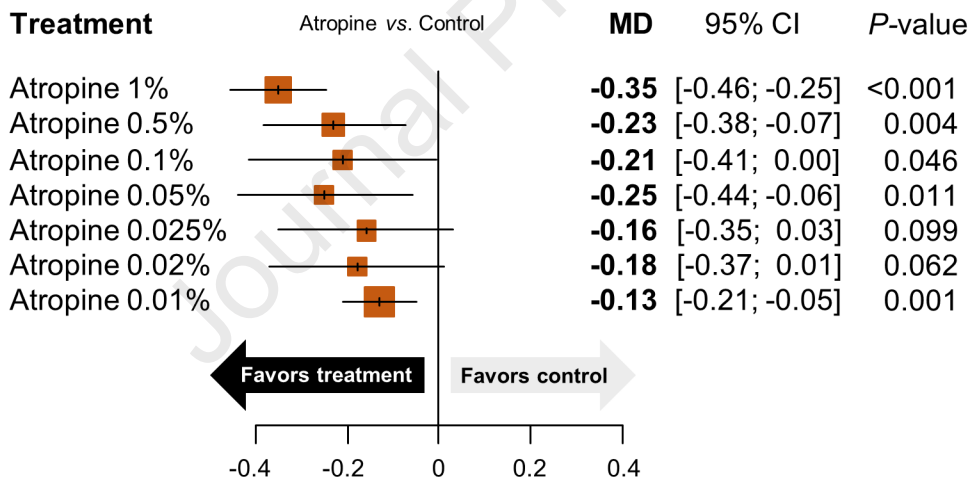
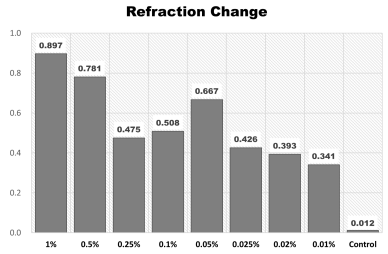
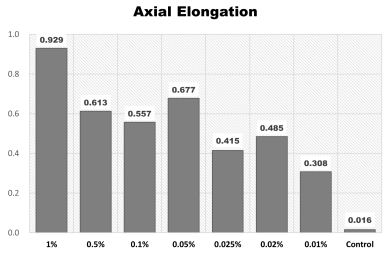


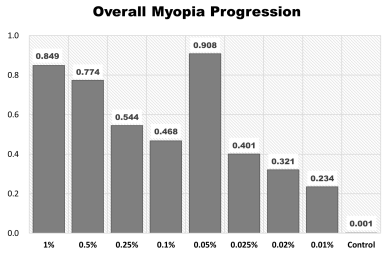
Mean difference (95% CI) in **axial length change**, mm/yr

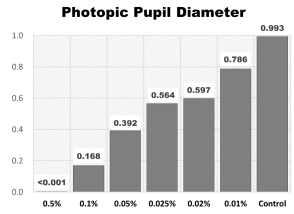
Atropine 0.01%	0.05 (−0.14; 0.24)	0.03 (−0.16; 0.22)	0.12 (−0.08; 0.31)	0.08 (−0.12; 0.27)	.	0.09 (−0.06; 0.25)	0.22 (0.09; 0.35)	−0.13 (−0.21; −0.05)
−0.01 (−0.46; 0.44)	*Atropine 0.02%*	−0.02 (−0.29; 0.24)	0.07 (−0.20; 0.33)	0.03 (−0.24; 0.30)	.	0.04 (−0.20; 0.28)	0.17 (−0.05; 0.39)	−0.18 (−0.37; 0.01)
−0.04 (−0.50; 0.42)	−0.03 (−0.66; 0.60)	*Atropine 0.025%*	0.09 (−0.13; 0.31)	0.05 (−0.22; 0.32)	.	0.06 (−0.17; 0.30)	0.19 (−0.03; 0.41)	−0.16 (−0.35; 0.03)
−0.23 (−0.70; 0.23)	−0.22 (−0.86; 0.41)	−0.19 (−0.71; 0.33)	*Atropine 0.05%*	−0.04 (−0.31; 0.23)	.	−0.03 (−0.26; 0.21)	0.10 (−0.12; 0.32)	−0.25 (−0.44; −0.06)
−0.11 (−0.49; 0.27)	−0.10 (−0.68; 0.47)	−0.07 (−0.65; 0.51)	0.12 (−0.46; 0.70)	*Atropine 0.1%*	.	0.02 (−0.18; 0.21)	0.14 (−0.09; 0.37)	−0.21 (−0.41; 0.00)
−0.08 (−0.59; 0.42)	−0.07 (−0.73; 0.59)	−0.04 (−0.70; 0.62)	0.15 (−0.52; 0.82)	0.03 (−0.48; 0.54)	*Atropine 0.25%*	.	.	.
−0.31 (−0.62; 0.01)	−0.30 (−0.81; 0.22)	−0.26 (−0.79; 0.26)	−0.07 (−0.60; 0.46)	−0.19 (−0.55; 0.16)	−0.22 (−0.70; 0.25)	*Atropine 0.5%*	0.13 (−0.06; 0.31)	−0.23 (−0.38; −0.07)
−0.42 (−0.71; −0.13)	−0.41 (−0.90; 0.09)	−0.38 (−0.87; 0.12)	−0.19 (−0.69; 0.32)	−0.31 (−0.74; 0.12)	−0.34 (−0.86; 0.19)	−0.11 (−0.49; 0.26)	*Atropine 1%*	−0.35 (−0.46; −0.25)
0.39 (0.21; 0.57)	0.40 (−0.04; 0.84)	0.43 (−0.01; 0.88)	0.62 (0.17; 1.07)	0.50 (0.14; 0.87)	0.47 (0.00; 0.95)	0.70 (0.40; 1.00)	0.81 (0.58; 1.04)	*Control*

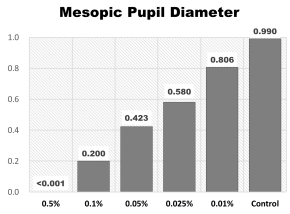
Mean difference (95% CI) in **refraction change**, D/yr

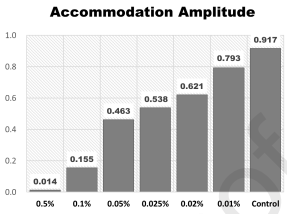


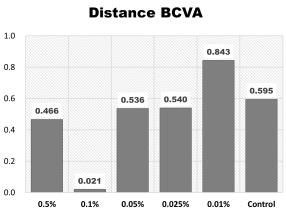








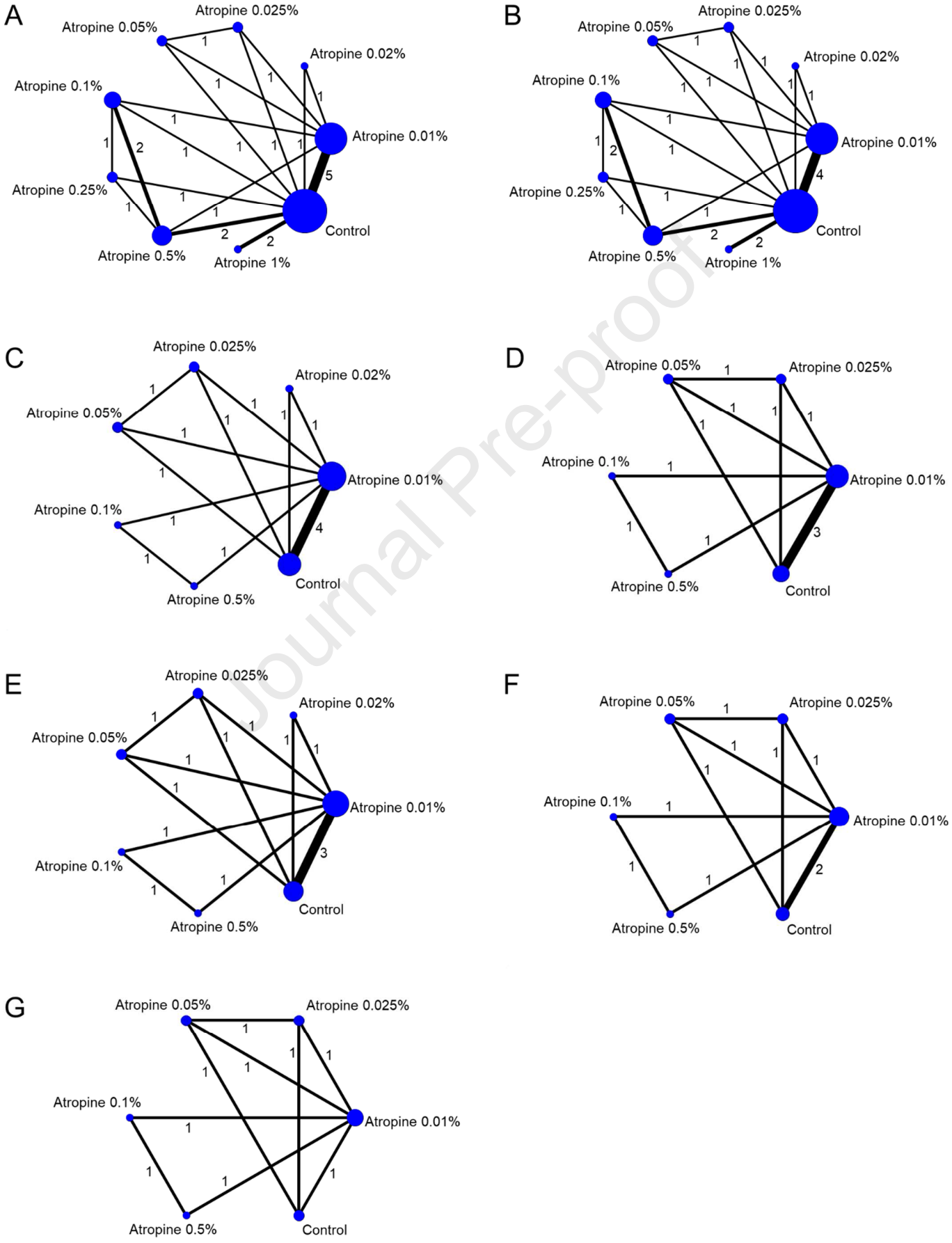




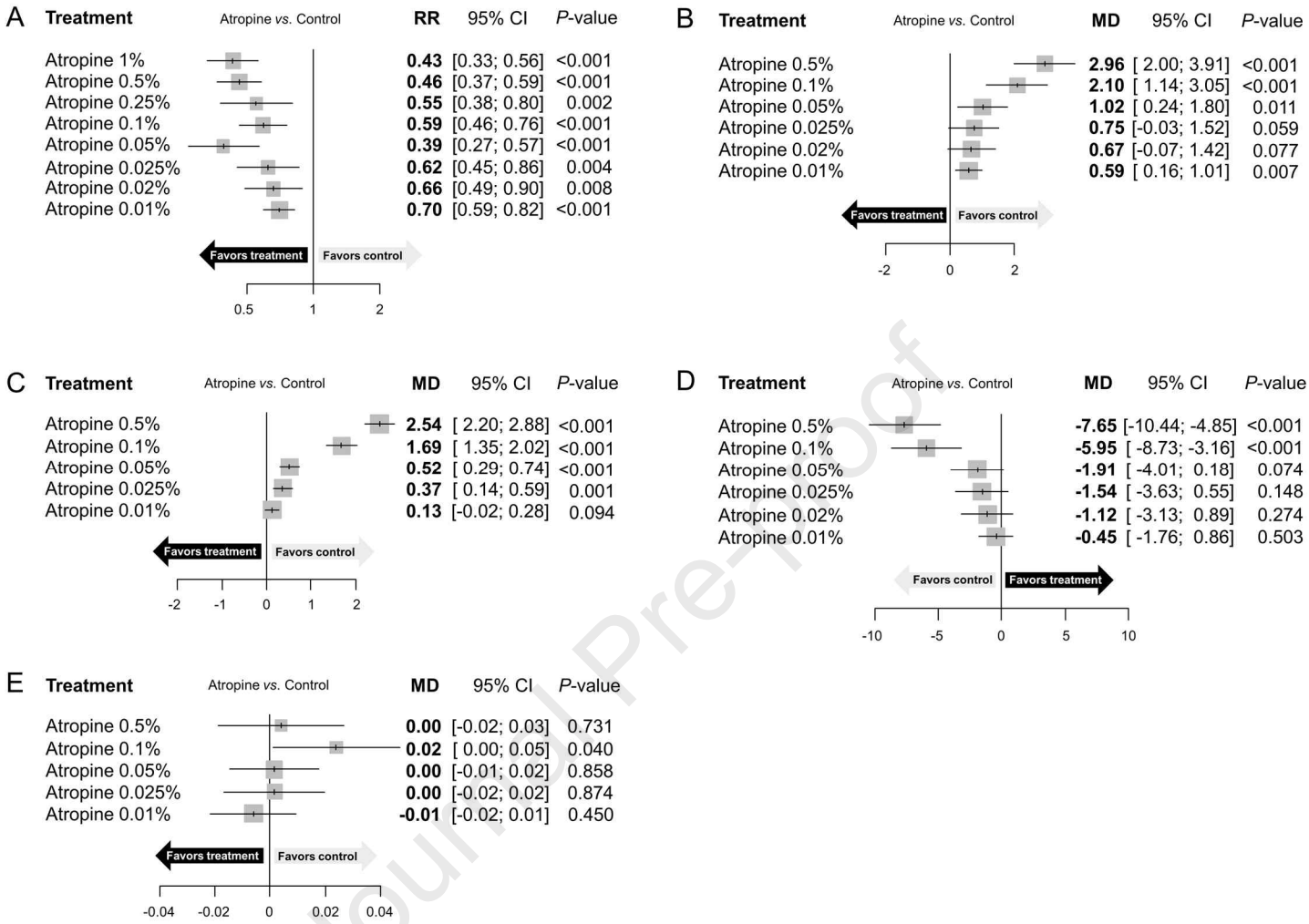
Précis

Eight atropine concentrations (0.1 – 1%) to delay childhood myopia progression were analyzed in a network meta-analysis. The ranking probabilities for efficacy outcomes were not proportional to dose, but those for adverse effects were dose-related.

eFigure 1. Network plots for secondary outcomes. **A**, proportion of eyes showing overall myopia progression. **B**, proportion of eyes showing rapid myopia progression. **C**, photopic pupil diameter. **D**, mesopic pupil diameter. **E**, accommodation amplitude. **F**, distance best-corrected visual acuity. **G**, near best-corrected visual acuity. The node size corresponds to the number of participants assigned to each treatment. Treatments with direct comparisons are linked with a line; line thickness corresponds to the number of trials evaluating the comparison.



eFigure 2. Forest plots of network meta-analysis for secondary outcomes. A, proportion of eyes showing overall myopia progression. **B**, photopic pupil diameter. **C**, mesopic pupil diameter. **D**, accommodation amplitude. **E**, distance best-corrected visual acuity. RR = relative risk; MD = mean difference; CI = confidence interval.



eFigure 3. Net league table of head-to-head comparisons for secondary outcomes. A, relative risk for overall myopia progression. **B,** Lower-left corner: mean difference in photopic pupil diameter. Upper-right corner: mean difference in mesopic pupil diameter. In the left lower half, mean differences lower than 0 favor the column-defining treatment. In the upper right half, mean differences lower than 0 favor the row-defining treatment. **C**, mean difference in accommodation amplitude. **D,** mean difference in distance best-corrected visual acuity. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment.

A

Atropine 0.01%								
1.05 (0.77; 1.43)	*Atropine 0.02%*							
1.12 (0.81; 1.55)	1.07 (0.69; 1.64)	*Atropine 0.025%*						
1.78 (1.21; 2.62)	1.70 (1.06; 2.73)	1.59 (1.03; 2.45)	*Atropine 0.05%*					
1.18 (0.90; 1.55)	1.13 (0.77; 1.65)	1.06 (0.71; 1.57)	0.66 (0.42; 1.04)	*Atropine 0.1%*				
1.25 (0.85; 1.86)	1.20 (0.75; 1.92)	1.12 (0.69; 1.82)	0.70 (0.42; 1.19)	1.06 (0.71; 1.59)	*Atropine 0.25%*			
1.50 (1.16; 1.93)	1.43 (0.98; 2.07)	1.34 (0.91; 1.97)	0.84 (0.54; 1.30)	1.26 (0.96; 1.67)	1.19 (0.79; 1.79)	*Atropine 0.5%*		
1.63 (1.19; 2.23)	1.55 (1.04; 2.32)	1.45 (0.96; 2.20)	0.91 (0.57; 1.45)	1.37 (0.95; 1.99)	1.30 (0.82; 2.04)	1.09 (0.76; 1.55)	*Atropine 1%*	
0.70 (0.59; 0.82)	0.66 (0.49; 0.90)	0.62 (0.45; 0.86)	0.39 (0.27; 0.57)	0.59 (0.46; 0.76)	0.55 (0.38; 0.80)	0.46 (0.37; 0.59)	0.43 (0.33; 0.56)	*Control*

Relative risk (95% CI) for **overall progression**

B

Mean difference (95% CI) in **mesopic pupil diameter**

Atropine 0.01%	.	−0.24 (−0.46; −0.02)	−0.39 (−0.61; −0.17)	−1.56 (−1.86; −1.26)	−2.41 (−2.71; −2.11)	0.13 (−0.02; 0.28)
−0.09 (−0.83; 0.66)	*Atropine 0.02%*	.	.	.	.	.
−0.16 (−0.93; 0.61)	−0.07 (−1.11; 0.96)	*Atropine 0.025%*	−0.15 (−0.40; 0.10)	−1.32 (−1.69; −0.95)	−2.17 (−2.55; −1.80)	0.37 (0.14; 0.59)
−0.43 (−1.21; 0.35)	−0.34 (−1.38; 0.69)	−0.27 (−1.13; 0.59)	*Atropine 0.05%*	−1.17 (−1.54; −0.80)	−2.02 (−2.39; −1.65)	0.52 (0.29; 0.74)
−1.51 (−2.36; −0.66)	−1.42 (−2.56; −0.29)	−1.35 (−2.50; −0.20)	−1.08 (−2.23; 0.07)	*Atropine 0.1%*	−0.85 (−1.17; −0.53)	1.69 (1.35; 2.02)
−2.37 (−3.23; −1.51)	−2.28 (−3.42; −1.15)	−2.21 (−3.36; −1.06)	−1.94 (−3.09; −0.78)	−0.86 (−1.72; 0.00)	*Atropine 0.5%*	2.54 (2.20; 2.88)
0.59 (0.16; 1.01)	0.67 (−0.07; 1.42)	0.75 (−0.03; 1.52)	1.02 (0.24; 1.80)	2.10 (1.14; 3.05)	2.96 (2.00; 3.91)	*Control*

Mean difference (95% CI) in **photopic pupil diameter**

C

Atropine 0.01%						
0.67 (−1.35; 2.69)	*Atropine 0.02%*					
1.10 (−1.00; 3.19)	0.42 (−2.33; 3.17)	*Atropine 0.025%*				
1.47 (−0.63; 3.56)	0.79 (−1.96; 3.55)	0.37 (−1.92; 2.66)	*Atropine 0.05%*			
5.50 (3.04; 7.96)	4.83 (1.65; 8.01)	4.40 (1.17; 7.63)	4.03 (0.80; 7.27)	*Atropine 0.1%*		
7.20 (4.73; 9.67)	6.53 (3.34; 9.71)	6.10 (2.87; 9.34)	5.73 (2.50; 8.97)	1.70 (−0.68; 4.08)	*Atropine 0.5%*	
−0.45 (−1.76; 0.86)	−1.12 (−3.13; 0.89)	−1.54 (−3.63; 0.55)	−1.91 (−4.01; 0.18)	−5.95 (−8.73; −3.16)	−7.65 (−10.44; −4.85)	*Control*

Mean difference (95% CI) in **accommodation amplitude**

D

Atropine 0.01%					
−0.01 (−0.03; 0.01)	*Atropine 0.025%*				
−0.01 (−0.03; 0.01)	−0.00 (−0.02; 0.02)	*Atropine 0.05%*			
−0.03 (−0.05; −0.01)	−0.02 (−0.05; 0.00)	−0.02 (−0.05; 0.00)	*Atropine 0.1%*		
−0.01 (−0.03; 0.01)	−0.00 (−0.03; 0.02)	−0.00 (−0.03; 0.02)	0.02 (0.01; 0.03)	*Atropine 0.5%*	
−0.01 (−0.02; 0.01)	0.00 (−0.02; 0.02)	0.00 (−0.01; 0.02)	0.02 (0.00; 0.05)	0.00 (−0.02; 0.03)	*Control*

Mean difference (95% CI) in **distance BCVA**

eTable 1. Network Heterogeneity and Coherence

		Network Heterogeneity					Coherence
		τ^2 network	I^2 network (%, 95% conficence intervals)	Total network heterogeneity (Q_{total})	Heterogeneity within designs (Q_{within})	Heterogeneity between designs ($Q_{between}$)	$Q_{between}$ using the 'design-by-treatment' interaction model
Efficacy	MD in refraction change	0.06	94.8 (92.9; 96.3)	271.33 (P < 0.001)	223.6 (P < 0.001)	47.73 (P < 0.001)	2.51 (P = 0.775)
	MD in axial length change	0.01	95.0 (92.8; 96.6)	200.85 (P < 0.001)	186.9 (P < 0.001)	13.95 (P = 0.003)	0.71 (P = 0.870)
	RR for myopic progression	0.01	37.4 (0.0; 71.2)	12.77 (P = 0.120)	10.49 (P = 0.015)	2.29 (P = 0.808)	1.88 (P = 0.865)
	RR for rapid myopic progression	0.17	59.1 (10.8; 81.3)	17.13 (P = 0.017)	1.26 (P = 0.533)	15.87 (P = 0.007)	15.87 (P = 0.007)
Satety	MD in photopic pupil diameter change	0.17	54.2 (88.2; 97.1)	51.40 (P < 0.001)	42.89 (P < 0.001)	8.51 (P = 0.014)	0.12 (P = 0.944)
	MD in mesopic pupil diameter change	0.01	44.2 (0.0; 83.4)	3.59 (P = 0.166)	1.76 (P = 0.185)	1.83 (P = 0.176)	0.81 (P = 0.367)
	MD in accommodation change	1.21	91.1 (76.8; 96.6)	22.42 (P < 0.001)	-	22.42 (P < 0.001)	22.42 (P < 0.001)
	MD in distance BCVA change	-	-	0.38 (P = 0.536)	-	0.38 (P = 0.536)	0.38 (P = 0.536)
	MD in near BCVA change	-	-	-	-	-	-

eTable 2. Adverse Effects and Dropout Rates of Studies Included the Meta-analysis

Study	Arm	Dropout, n (%)	Change in Photopic Pupil Size (mm)	Change in Mesopic Pupil Size (mm)	Distance VA Decrease (logMAR)	Near VA Decrease (logMAR)	Change in Accommodation (Amplitude/y)	Photophobia (%)	Allergic Conjunctivitis (%)	Other
Yen et al.,[59] 1989	1%	NA	NA	NA	NA	NA	NA	NA	NA	All patients in the atropine group had photophobia. No systemic or ocular complications were observed during this study.
	Control									
Shih et al.,[29] 1999	0.5%	18.0	NA	NA	NA	NA	NA	NA	NA	All (100%) of the children in the 0.1% atropine group and 93% of the children in the 0.25% atropine group had no complaints of photophobia or near work problems after 4 weeks.
	0.25%	6.0								
	0.1%	2.0								
	Control	2.0								
Shih et al.,[16] 2001	0.5%	13.2	NA	NA	NA	NA	NA	NA	NA	NA
	Control	19.7								
Chua et al.,[17] 2006	1%	17.0	NA	NA	NA	NA	NA	NA	NA	No serious adverse events related to atropine were reported. There was no deterioration in best-corrected visual acuity. Allergic or hypersensitivity reactions or discomfort (4.5%), glare (1.5%), blurred near vision (1%).
	Control	5.0								
Chia et al.,[18] 2012	0.5%	13.7	3.11 (1.10)	3.56 (1.14)	-0.01 (0.06)	0.25 (0.19)	-11.80 (4.40)	NA	4.3	NA
	0.1%	9.0	2.25 (1.01)	2.71 (1.12)	0.01 (0.06)	0.06 (0.13)	-10.10 (4.30)		3.9	
	0.01%	10.7	0.74 (0.75)	1.15 (0.71)	-0.02 (0.06)	-0.02 (0.08)	-4.60 (4.20)		0.0	
Yi et al.,[9] 2015	1%	8.6	NA	NA	NA	NA	NA	NA	NA	No patients complained of itching and distention of eyes, ocular redness, or foreign body sensation, and so forth. During this trial, there was no deterioration in best corrected visual acuity in either group.
	Control	2.9								
Diaz-Llopis et al.,[19] 2018	0.01%	2.0	NA	NA	NA	NA	NA	NA	NA	Up to 5% of subjects referred slight photophobia, diffuculties in very near reading and excessive midriasis that did not require the withdrawal of the treatment.
	Control	NA								
Han et al.,[20] 2019	1%	11.7	NA	NA	NA	NA	NA	NA	NA	No systemic adverse reactions were found. In the atropine group, 13.2% experienced conjunctival injection. Five withdrew due to inability to tolerate photophobia and blurred near vision.
	Control	16.7								
Yam et al.,[21] 2019	0.05%	6.4	1.03 (1.02)	0.58 (0.63)	-0.02 (0.06)	-0.01 (0.13)	-1.98 (2.82)	7.8	2.8	Symptoms of photophobia from subjects were different from baseline among groups at the 2-week visit but were reduced over time in 1 year. There was no difference in the vision-related quality of life among all groups. Occurrence of allergic conjunctivitis was similar among all groups.
	0.025%	15.7	0.76 (0.90)	0.43 (0.61)	-0.02 (0.07)	0.00 (0.13)	-1.61 (2.61)	6.6	6.5	
	0.01%	11.8	0.49 (0.80)	0.23 (0.46)	-0.03 (0.08)	-0.03 (0.13)	-0.26 (3.04)	2.1	6.4	
	Control	16.2	0.13 (1.07)	0.02 (0.55)	-0.02 (0.06)	-0.02 (0.11)	-0.32 (2.91)	4.3	6.3	
Wei et al.,[22] 2020	0.01%	30.9	NA	NA	NA	NA	NA	4.5	2.7	None of the children in either group reported near-blurred vision.
	Control	24.5						0.9	0.9	
Zhu et al.,[23] 2020	1%	20.6	NA	NA	NA	NA	NA	62.1	0.9	Blurred near vision 19.7%, headache 11.8%, eye irritation 18.5%, and infections 5.5% of atropine group / NA in control group.
	Control	6.7						NA	NA	

Alam et al.,[58] 2020	0.01% Control	NA	NA	NA	NA	NA	NA	NA	NA	No report on adverse effects.
Fu et al.,[24] 2020	0.02%	15.2	0.79 (0.44)	NA	NA	NA	-1.90 (1.65)	23.2	0	Photophobia evaluated in bright sunlight. 5.1% and 4.9% of atropine groups had mild near-vision blur for 2 to 4 weeks. In the control group, one child experienced mild near-vision blur during the first week after changing to new glasses.
	0.01%	16.2	0.70 (0.61)				-1.80 (2.23)	23.2	0.7	
	Control	16.7	0.12 (0.20)				-0.24 (0.77)	2.5	0	
Hieda et al.,[25] 2020	0.01%	9.4	0.26 (0.83)	0.09 (0.71)	NA	NA	NA	1.2	0	Between both groups, no significant differences in the changes of corrected distance VA before and after instillation. The decrease in corrected near VA before and after instillation was greater in the atropine group.
	Control	5.8	0.13 (0.85)	0.14 (0.72)				0	0	
Zhao et al.,[26] 2021	0.01% Control	NA	NA	NA	NA	NA	NA	NA	NA	No statistically significant differences in Schirmer's test and tear film break-up time test between the two groups.
Saxena et al.,[27] 2021	0.01%	6.0	1.20 (0.47)	0.05 (0.43)	0.002 (0.08)	NA	-0.98 (1.86)	NA	NA	None of the patients reported any blurring of vision or photophobia, or required discontinuation of therapy.
	Control	10.0	-0.06 (0.58)	-0.12 (0.64)	0.002 (0.03)		-1.25 (2.01)			