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Efficacy and Safety of 8 Atropine Concentrations for Myopia Control in Children

A Network Meta-Analysis

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

Clinical Relevance: Atropine is known to be an effective intervention to delay myopia progression. Nonetheless, no well-supported evidence exists yet to rank the clinical outcomes of various concentrations of atropine.

Methods: We searched PubMed, EMBASE, Cochrane Central Register of Controlled Trials, the World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov on April 14, 2021. We selected studies involving atropine treatment of at least 1 year's duration for myopia control in children. We performed a network meta-analysis (NMA) of randomized controlled trials (RCTs) and compared 8 atropine concentrations (1% to 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 extracted data on the proportion of eyes showing myopia progression and safety outcomes (photopic and mesopic pupil diameter, accommodation amplitude, and distance and near best-corrected visual acuity [BCVA]).

Results: Thirty pairwise comparisons from 16 RCTs (3272 participants) were obtained. Our NMA ranked the 1%, 0.5%, and 0.05% atropine concentrations as the 3 most beneficial for myopia control, as assessed for both primary outcomes: 1% atropine (mean differences compared with control: refraction, 0.81 [95% confidence interval (CI), 0.58−1.04]; AXL, −0.35 [−0.46 to −0.25]); 0.5% atropine (mean differences compared with control: refraction, 0.70 [95% CI, 0.40−1.00]; AXL, −0.23 [−0.38 to −0.07]); 0.05% atropine (mean differences compared with control: refraction, 0.62 [95% CI, 0.17−1.07]; AXL, −0.25 [−0.44 to −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 concentration (RR, 0.39 [95% CI, 0.27−0.57]). The risk for adverse effects tended to rise as the atropine concentration was increased, although this tendency was not evident for distance BCVA. No valid network was formed for near BCVA.

Discussion: The ranking probability for efficacy was not proportional to dose (i.e., 0.05% atropine was comparable with that of high-dose atropine [1% and 0.5%]), although those for pupil size and accommodation amplitude were dose related. *Ophthalmology 2022;129:322-333 © 2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Myopia is the most common eye disease in children and adolescents and is most predominant in East Asia compared with other areas. It has been of increasing worldwide health concern over the past few decades, and has already reached a pandemic level.[1,2] Myopia is predicted to affect 4.8 billion people in the world by 2050, which means that in 30 years, 50% of the world's 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

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to retard or even stop myopia progression effectively in children is coveted by researchers, clinicians, and medical practitioners.

Several approaches have been used to slow down progression of myopia, such as increased outdoor activity, reduced near work, peripheral defocusing lenses, and orthokeratology contact lenses.[6] Atropine, a nonselective 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, much uncertainty remains, as do dosing and safety concerns, regarding the clinical use of atropine.

Previous methodologies, such as limited comparisons 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 to enable clinicians and parents to choose the optimal 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 compared directly with adequate precision, or at all.[12,13] Network meta-analysis concerns both direct and indirect treatment effects identifiable within an entire pool of evidence. This makes it possible to build up treatment hierarchies on the basis of valid statistical inference methods.[14] Therefore, we conducted the present study to draw more decisive conclusions regarding the ranking of various atropine concentrations for treatment efficacy and safety using NMA to enable integration of multiple direct and indirect comparisons uniquely.

Methods

The protocol of this systematic review was registered prospectively at The International Prospective Register of Systematic Reviews (PROSPERO) (Identifier, CRD42021248957). All research adhered to the tenets of the Declaration of Helsinki. Individual patient-level consent was not required. The reporting of this NMA is based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses 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 in The Cochrane Library, PubMed, and EMBASE from inception through April 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 (A.H. and Y.K.K.) independently assessed the titles and abstracts for potential eligibility, and the full-text articles were retrieved for those that seemed relevant. These articles were then assessed independently by the 2 investigators for final eligibility. Non−English-language reports were assessed by a single individual (A.H. and S.R.S.) 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 (J.H.J.). 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 (A.H. and Y.K.K.) independently extracted data and entered them in electronic format into Microsoft Access 2016 (Microsoft Corporation). An algorithm checked for conflicting data entries. Differences were discussed, and a third reviewer (J.H.J.) was contacted if consensus was not reached. Trial characteristics of interest included: (1) study identification (name of first author, year of publication), (2) country of study, (3) number of participants, (4) race or 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 or rapid myopic progression, and (11) adverse outcomes (i.e., photopic and mesopic pupil diameters, change in accommodation amplitude, and distance and near best-corrected visual acuity [BCVA]). For studies reporting more than 2 atropine concentrations that could be subjected independently 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 showed a similar effect to a placebo on myopia progression.[7] Likewise, single-vision spectacle lenses or multifocal progressive lenses were prespecified as a control along with a placebo.[16]

We extracted means and standard deviations for continuous outcomes. If standard deviations were not provided, we calculated them from standard errors, confidence intervals (CIs), or other measures.[30–32] In the studies where the results were represented only graphically, the numerical values from graphs were extracted using Adobe Acrobat's XI inbuilt measuring tool (Adobe Systems Incorporated).[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 5 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, or high risk of bias. Two investigators (A.H. and J.H.J.) independently assessed the risk of bias, and discrepancies were resolved through discussion.

Outcomes

We used mean annual change in refraction (in diopters/year) and mean annual change in AXL (in millimeters/year) as the 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 (in millimeters), change in accommodation (in amplitude/year), and distance and near BCVA (in logarithm of the minimum angle of resolution). We also extracted data on side effects such as frequencies of photophobia 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 the atropine group by that in the control group. The effects of different atropine concentrations were compared according to the RR with 95% CIs.

Network meta-analysis 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 (R Foundation for Statistical Computing, Vienna, Austria), 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 multiarm study.[38] We chose to apply random-effects models rather than fixed-effects models because the studies we included were heterogeneous and relatively few.[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 methodologic experience to identify the 5 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 (A.H., and J.H.J.) visually assessed the potential effect modifiers' distributions over the individual atropine concentrations and determined, by consensus, whether considerable dissimilarity existed that threatened 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 that were not the result of 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 (i.e., 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 semiautomated software to assess the confidence in NMA estimates based on the Confidence in Network Meta-analysis (Institute of Social and Preventive Medicine) web application, by which confidence is graded as high, moderate, low, or very low.[50,51] In Confidence in Network Meta-analysis, 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 2 levels. Some other concerns about a dimension resulted in confidence downgrading by 1 level. Some concerns about both imprecision and heterogeneity were downgraded by 1 level to avoid diminishing the overall level of confidence more than once for related concerns.[52]

To date, no concrete methodology exists yet 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 to test the effect of rerunning the NMA after removal of studies with 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 analog of the surface under the cumulative ranking curve. *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 1861 articles, including 1032 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, constituting a total of 3272 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%−0.25%) was investigated in 4 studies,[18,21,24,29] and high-dose atropine (0.5% or 1%) was investigated in 8 studies,[9,16–18,20,23,29,59] together resulting in 21 experimental groups. Thirteen studies reported both refraction and AXL outcomes,[9,16–18,20,21–27,58] 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 is 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 treatment. Figure 2A shows the network of eligible comparisons (16 trials, 9 arms, and 30 pairwise comparisons). As represented in Figure 3A, 5 atropine concentrations showed a higher MD relative to the control treatment when combined in the NMA: 1% (MD, 0.81; 95% CI, 0.58−1.04), 0.5% (MD, 0.70; 95% CI, 0.40−1.00), 0.1% (MD, 0.50; 95% CI, 0.14−0.87), 0.05% (MD, 0.62; 95% CI, 0.17−1.07), and 0.01% (MD, 0.39; 95% CI, 0.21−0.57). 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; Fig 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 showed a higher MD relative to the control treatment when combined in the NMA (Fig 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, 0.09−0.35; Fig 4).

For the primary outcomes, we examined the certainty of evidence in the network of all the comparisons and found it to be distributed widely 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 ($P = 0.0065$, Egger test), which resulted in downrating of the confidence for all comparisons.

Relative Risk of Myopia Progression

Ten studies reported the proportion of eyes showing myopic progression (Fig S1A, available at www.aaojournal.org). Eight of them defined "no myopia progression" as a less than 0.25-diopter (D) decrease in spherical equivalent,[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 showed a lower RR of myopic progression relative to the control treatment. Specifically, 0.05% atropine showed the lowest RR for overall myopia progression (RR, 0.39; 95% CI, 0.27−0.57), followed by 1% (RR, 0.43; 95% CI, 0.33−0.56; Fig S2A, available at www.aaojournal.org). The net league table of the head-to-head RR comparison for overall myopia progression is shown in Figure S3A (available at www.aaojournal.org).

The proportion of eyes demonstrating rapid myopic progression was assessed in 9 studies (Fig S1B). All of the studies defined rapid progression as spherical equivalent, change of 1.0 D or more,[17,18,21,22,24,27,29,59] with the exception of 1 study by Shih et al[16] (≥0.75 D). We found network inconsistency by both the global ($P = 0.007$; Table S1, available at www.aaojournal.org) 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 Table S2 (available at www.aaojournal.org). The photopic and mesopic pupil diameters were assessed in 5 and 4 studies with 6 and 5 different concentrations of atropine, respectively (Fig S1C, D). Atropines showed a higher MD of photopic pupil diameter relative to the control treatment, ranging from MD of 0.59 mm (95% CI, 0.16−1.01 mm for 0.01% atropine) to 2.96 mm (95% CI, 2.00−3.91 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, 2.20−2.88 mm for 0.5% atropine; Fig S2B, C).

The degree of accommodation change was assessed in 4 trials with 6 different concentrations of atropine (Fig S1E). 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 treatment (Fig S2D).

Distance and near BCVA data were reported in 3 and 2 studies, respectively, both with 5 different concentrations of atropine (Fig S1F, G). Differences between the various doses of atropine and the control treatment in terms of distance BCVA were not evident, except for 0.1% atropine (MD, 0.02; 95% CI,

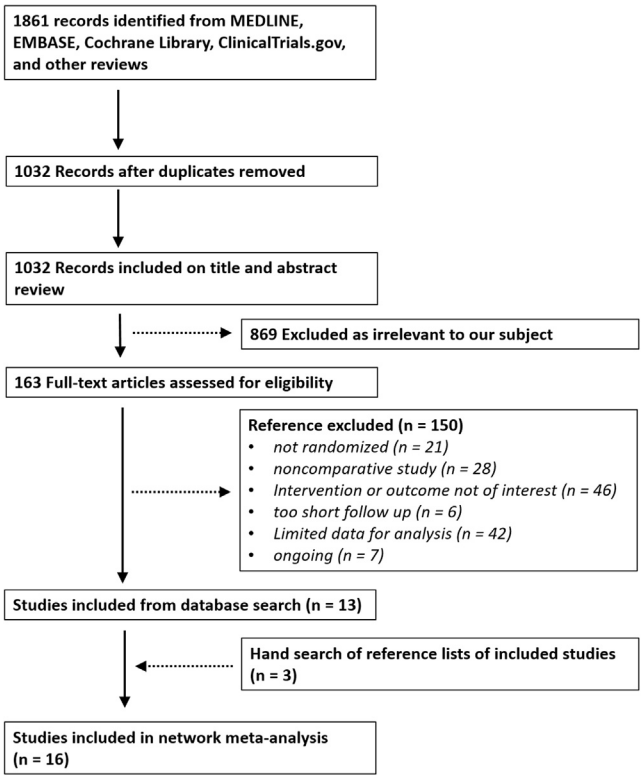

Figure 1. Flow diagram showing selection process for inclusion of studies in network meta-analysis.

0.00−0.05; Fig S2E). The network consistency for near BCVA was not satisfied (Appendix 7; Table S1); thus, no NMA estimates were generated. Figure S3B−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), we conducted sensitivity analyses on MD in refraction change, excluding studies (1) published before 2000, (2) with baseline mean refraction of less than −4 D, (3) with 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 modifiers. The detailed results are shown in Appendix 8 (available at www.aaojournal.org). The overall heterogeneity analysis results are summarized in Table S1.

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). Regarding photopic and mesopic pupil diameter and accommodation amplitude, the higher the atropine dose was, the lower the ranking probabilities were. This tendency was not evident in the *P* scores for distance BCVA.

Discussion

This NMA from 16 RCTs demonstrated significantly less myopia progression in the atropine treatment group than in the control group. Also, the 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 atropine (0.02%−0.25%), 0.05% showed efficacy comparable with 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 and mesopic pupil diameter, accommodation amplitude) compared with low-dose atropine.

Several meta-analyses have investigated various concentrations of atropine treatment in myopia control. In the 2011 meta-analysis by Song et al,[60] high-dose atropines (0.5% and 1.0%) showed better efficacy than moderate-dose atropines (0.1% and 0.25%), but that analysis included only the 6 studies (1 of which was a nonrandomized clinical trial) that were available at that time. 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 nonpharmacologic and pharmacologic interventions for control of myopia, atropine was the most effective in retarding myopia progression.[7] However, this NMA included a total of only 7 RCTs for atropine treatment and did not include 0.025% or 0.05% atropine. Gong et al,[11] in their 2017 meta-analysis of 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. The combination of different study types in their meta-analyses could be a major source of heterogeneity[61]; moreover, they did not evaluate either axial elongation or RR for myopia progression.

The hallmark of NMA is its usefulness for building up hierarchies of competing interventions indicative of treatments that are more or less likely to produce the most significant benefits.[36] The 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

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

Study	Country	Age (yrs)	Follow-up Duration (mos)	Arm	Sample Size	Baseline Refraction (D)	Baseline Axial Length (mm)	Mean Change in Refraction (D/yr)	Mean Change in Axial Length (mm/yr)	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 and Pinozo –Durán,[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 and Hao,[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 = diopter; NA = not available.

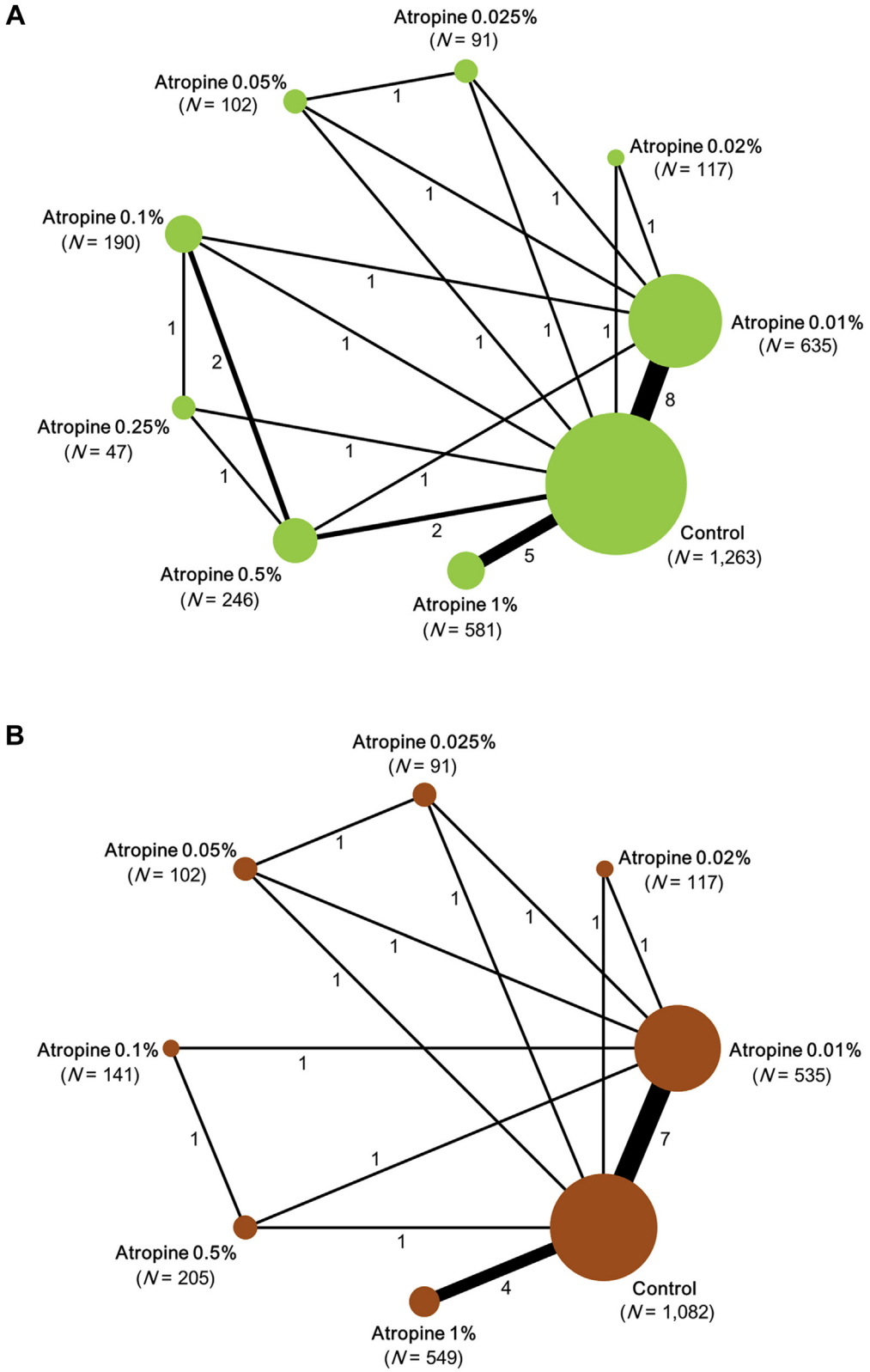

Figure 2. Network plots for efficacy: (**A**) mean annual refraction change and (**B**) mean annual axial length change. Each node represents 1 atropine concentration. The node size corresponds to the number of participants assigned to each treatment. Treatments with direct comparisons are linked with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

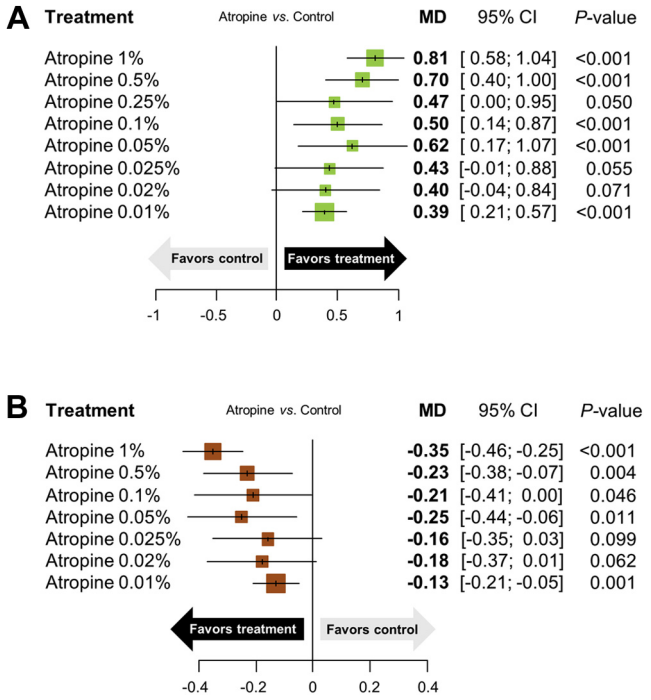

Figure 3. Forest plots of network meta-analysis comparing different doses of atropine for myopia interventions: (**A**) mean annual refraction change and (**B**) mean annual axial length change. Each atropine concentration was compared with the control treatment, which was the reference group. CI = confidence interval; MD = mean difference.

effects of various atropine concentrations for myopia control might not always follow a dose-dependent order.

Several previous studies demonstrated associations of higher concentrations of atropine with more adverse effects such as photophobia and near-vision problems.[5,11] The present 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, because accommodation and pupil size are components of near visual acuity.[62]

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 with high-dose atropine (1% and 0.5%). However, in terms of atropine-related adverse effects, 0.05% atropine showed better safety profiles relative to high-dose atropine. Well-supported evidence on ranking probabilities for near BCVA, acceptability, or both would be helpful to further assess the risk-to-benefit ratios of different atropine concentrations.

This study has several limitations that should be taken into account when interpreting its results. First, although strict inclusion and exclusion criteria were applied in the NMA, heterogeneity remained. Some of the RCTs included fewer than 100 patients. Thus, the so-called small-study effect may have been incurred in our analysis, in which smaller trials show different, often larger, treatment effects than larger trials.[63] Also, subject age varied widely (range, 4−18 years), but because the studies reported only the age range or mean, no definitive data were available on how treatment varied 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 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 White 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.[64] Further subgroup investigation is required to determine the relationship between ethnicity and optimal atropine dose. Third, our study considered information on efficacy and safety during the trial period, but not on myopic rebound, because of 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.[65] 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 Atropine in the Treatment of Myopia (ATOM) 2 study reported that children receiving higher doses of atropine showed lower prevalence of rapid (i.e., ≥−1.5 D) 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, may help to explain heterogeneity in atropine responses. Further studies examining other confounding factors along with doses are required 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 synthesis (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 the absence of such trials, meanwhile, the present NMA provides a valuable approach to the issue. The probable dose-response relationship between atropine and its efficacy and safety should be validated further by dose-response meta-analysis.[66] Additionally, the possible

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

Figure 4. Net league table of head-to-head comparisons for different doses of atropine in myopia intervention: (Lower left) mean difference in refraction change and (Upper Right) 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. Values of more than 0 mean differences favor the column-indicated treatment. CI = confidence interval; D = diopter.

acceptability differences among the various atropine doses have not yet been addressed fully. 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

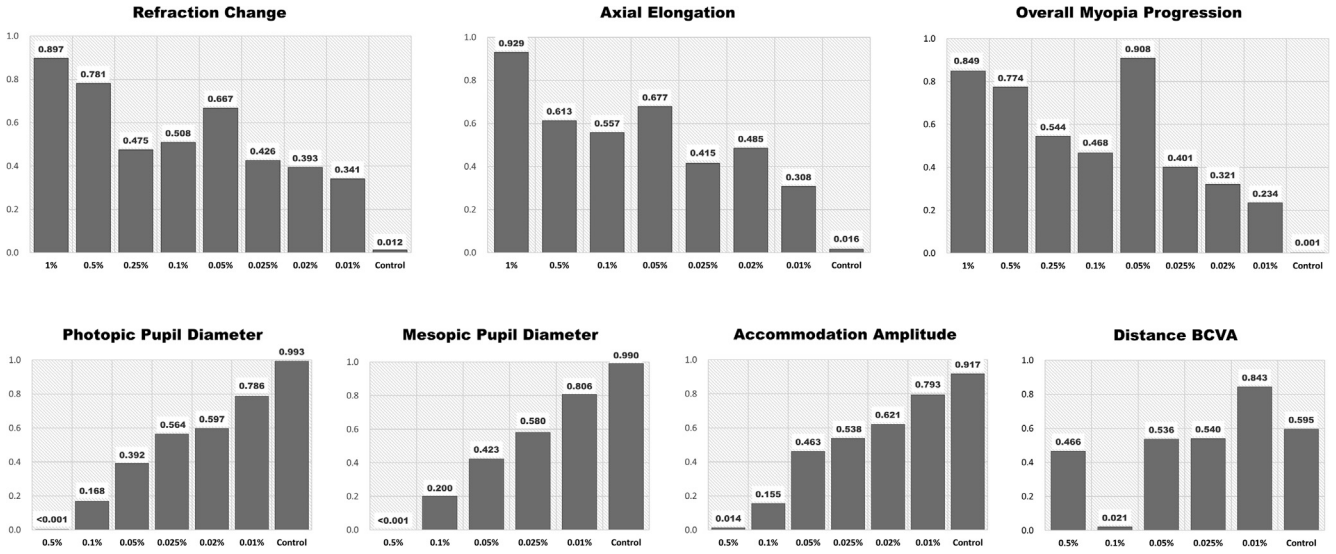

Figure 5. Bar graphs showing summaries of *P* scores of different doses of atropine for prevention of myopia progression: (Top row) efficacy outcomes and (Bottom row) safety outcomes. Higher and closer-to-1 *P* scores indicate a greater likelihood of a top-rank concentration.

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 and mesopic pupil size and accommodation amplitude, followed a dose-related order.

Footnotes and Disclosures

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The author(s) have no proprietary or commercial interest in any materials discussed in this article.

HUMAN SUBJECTS: No human subjects were included in this study. All research adhered to the tenets of the Declaration of Helsinki. Individual patient-level consent was not required. The protocol of this systematic review was registered prospectively at The International Prospective Register of Systematic Reviews (PROSPERO) (Identifier, CRD42021248957). The reporting of this NMA is based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2015 NMA Checklist.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Ha, S.J.Kim, Shim, Y.K.Kim, Jung

Analysis and interpretation: Ha, Shim, Y.K.Kim, Jung

Data collection: Ha, S.J.Kim, Y.K.Kim, Jung

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Overall responsibility: Ha, S.J.Kim, Shim, Y.K.Kim, Jung

Abbreviations and Acronyms:
AXL = axial length; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **D** = diopter; **MD** = mean difference; **NMA** = network meta-analysis; **RCT** = randomized controlled trial; **RR** = relative risk.

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Atropine, Myopia, Network meta-analysis.

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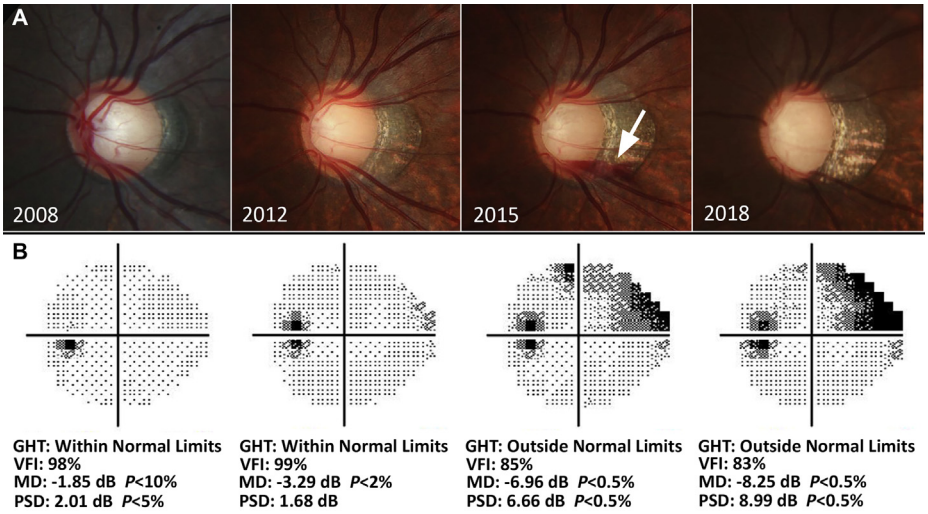
Pictures & Perspectives



Development of Glaucoma after Myopic Optic Disc Change in a Teenage Patient

An 11-year-old patient showed progressive change of the optic disc shape during adolescence (Fig **A**) with development of disc hemorrhage at the age of 17 (arrow). Myopia progressed with refractive error and axial length changing from −4.0 to −8.0 diopters, and from 25.7 to 28.5 mm, respectively. Progressive visual field change was also observed (Fig **B**). The patient did not have any systemic diseases or a family history of glaucoma. The intraocular pressure (IOP) ranged from 14 to 15 mmHg before starting topical pressure-lowering medication. The IOP was maintained at <12 mmHg after starting the medication in 2015. This case shows the development of glaucoma-like changes associated with progressive myopia and optic disc shape change (Magnified version of Fig **A**-**B** is available online at www.aaojournal.org).

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Footnotes and Disclosures

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