Discontinuation Approach and Follow-Up of Low-Concentration Atropine for Myopia Progression Eight-Year Results of the LAMP Randomized Clinical Trial

1. Yuzhou Zhang, PhD1; Xiu Juan Zhang, PhD1,6; Ebenezer Zaabaar, PhD1

2. et al

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JAMA Ophthalmol
Published Online: March 26, 2026
doi: 10.1001/jamaophthalmol.2026.0436

Key Points

Question Does tapering vs stopping 0.05% atropine for treatment of myopia result in less progression over 3 years?

Findings In the Low-Concentration Atropine for Myopia Progression (LAMP) randomized clinical trial, children in the taper group had less myopia progression than those in the stop group over 3 years. Older age and less myopia were associated with less myopia progression, while younger children with more myopia benefited more from the taper approach.

Meaning These findings support tapering atropine concentration before treatment discontinuation, particularly for children at a younger age and with more severe myopia.

Abstract

Importance Some but not all clinical trials have found 0.05% atropine effective for myopia control; however, discontinuation management remains unclear.

Objective To evaluate a taper vs stop treatment discontinuation approach.

Design, Setting, and Participants This randomized clinical trial involved children aged 4 to 12 years originally from the Low-Concentration Atropine for Myopia Progression (LAMP) study who were followed up for 8 years. All children who completed year 5 follow-up and were receiving atropine treatment were randomized into taper and stop groups at a 1:1 ratio.

Interventions During the prediscontinuation period (year 6), participants in the taper group received 0.05% atropine for 6 months and then 0.025% atropine for another 6 months, while the stop group received 0.05% atropine eye drops for a full year. During the discontinuation period (years 7 and 8), all participants stopped the treatment and were monitored for 2 years.

Main Outcomes and Measures Myopia progression in the taper and stop groups over 3 years; proportion of good response to treatment discontinuation, defined as spherical equivalent (SEP) progression −0.5 diopter (D) or more in both eyes during the discontinuation period; and associated factors with myopia progression over 3 years.

Results Among 246 children who completed the year 5 follow-up, 180 children (73.2%) went on to complete 8 years of follow-up. The mean (SD) age was 13.47 (1.63) years; there were 139 male children (56.5%) and 107 female (43.5%). Over 3 years, SEP and axial length (AL) elongation were faster in the stop group than in the taper group: –0.78 D vs –0.54 D, respectively (difference, −0.24 D; 95% CI, −0.46 to −0.03 D; *P* = .02) and 0.44 mm vs 0.33 mm, respectively (difference, 0.11; 95% CI, 0.03 to 0.19 D; *P* = .01). The proportion of good response to treatment discontinuation in the taper group was greater than in the stop group (65.1% vs 42.6%, respectively; *P* = .003). Younger age and more myopic spherical equivalent/longer AL at prediscontinuation were associated with faster SEP and AL elongation over 3 years. Notably, the younger the age and the more myopic the spherical equivalent, the greater the estimated mean differences of SEP/AL elongation between the taper and stop groups.

Conclusions and Relevance This study found that over 3 years, the participants in the taper group had less myopia progression than the stop group, particularly in children who were younger and had more myopia. However, to our knowledge, the clinical relevance of this approximately 0.25-D difference between treatment groups is not well understood from the current medical literature.

Introduction

Myopia has become a global health threat.[1] Its prevalence has been increasing rapidly over the past decades.[2-4] High myopia is associated with sight-threatening complications because of the excessive elongation of the eyeball.[5] Low-concentration atropine is an effective intervention for slowing myopia progression.[6-10] Studies have shown that its continuous use over 5 years is well tolerated and demonstrates sustained efficacy.[11,12]

Strategy for discontinuation treatment is not clear and is based mainly on expert opinions without robust evidence for long-term therapeutic decisions.[13,14] The World Health Organization recommended tapering the frequency before stopping atropine treatment.[15] One key factor that needs to be considered for the discontinuation strategy is the rebound after stopping treatment.[6] The ATOM2 study demonstrated that rebound was concentration dependent.[16] The 3-year report of the (Low-Concentration Atropine for Myopia Progression) LAMP study found that atropine concentration and age were associated with rebound.[17] However, there is a lack of evidence on whether tapered discontinuation is better than abrupt discontinuation.

To address this question, we aimed to evaluate the following: (1) which is a better treatment discontinuation strategy for low-concentration atropine 0.05%, the taper approach (tapering

atropine concentration before stopping) or stop approach (stopping treatment without tapering), (2) the proportion of good response to treatment discontinuation for each approach, and (3) the factors associated with the outcomes of treatment discontinuation. In addition, factors were explored that were associated with myopia progression over 8 years in children who used low-concentration atropine for 5 to 6 years.

Methods

Study Design

The study design for the initial 5-year follow-up of the LAMP study was described previously (see the trial protocol in Supplement 1 and eFigure 3 in Supplement 2).[9,11,17,18] All study participants using atropine eye drops at the end of year 5 were recruited into the year 6 through 8 follow-up. Block randomization was performed using computer-generated random numbers, with block sizes of 2, 4, or 6 to balance randomization confidentially. Recruited participants were randomized into 2 groups at a 1:1 ratio, the taper group and stop group, stratified by age, sex, and spherical equivalent. The taper group received 0.05% atropine daily in the first 6 months followed by 0.025% atropine daily for the following 6 months, and the stop group received 0.05% atropine daily for a full year. Both groups received no treatment for the next 2 years (Figure 1).

Figure 1. Flowchart of the Discontinuation and Follow-Up Phase of the Low-Concentration Atropine for Myopia Progression (LAMP) Study

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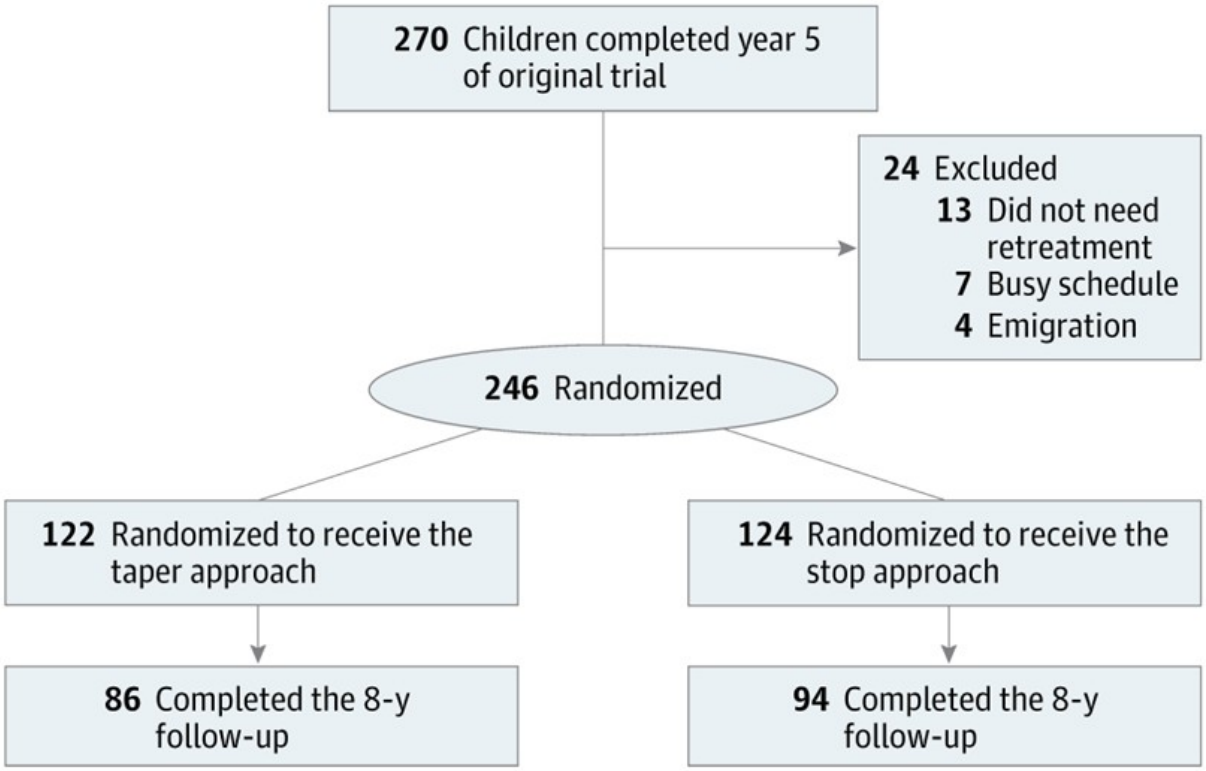

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The taper group continued to take 0.05% atropine for the first 6 months of year 6, tapering to 0.025% for 6 months after that. They stopped treatment at the beginning of year 7. The stop group continued to take 0.05% atropine for all 12 months of year 6 and stopped treatment at the beginning of year 7.

Parents or guardians, participants, and study investigators were kept masked to the group allocations. Trial medication was prepackaged as monodose eye drops with atropine sulfate concentrations of 0.05% and 0.025% (0.5 mL unit-concentration, preservative-free, pH 4.6) by Aseptic Innovative Medicine Co Ltd (Taipei, Taiwan). The expiry duration for each batch of eye drops was 2 years. The manufacturer provided certificates of analysis for both concentrations, while the Hong Kong Special Administrative Region Department of Health granted drug trial certificates.

All parents or guardians gave written informed consent, with verbal assent from the study participants. None of the participants in this study received any stipend or other incentive. The study was registered with the Chinese Clinical Trial Registry (identifier: ChiCTR-TRC-13004032). The trial protocol was approved by the Central Institutional Review Board of Hospital Authority. All procedures were conducted according to the tenets of the Declaration of Helsinki. This randomized clinical trial adhered to the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[19]

Ocular Measures and Questionnaire

The ophthalmic examinations conducted during years 6 through 8 were the same as in the previous 5 years.[9,11,17,18] Ophthalmic parameters collected at each visit included distance best-corrected visual acuity measured using a logMAR chart, as well as near visual acuity under best-corrected distance spectacle correction at 40 cm, and the near point of accommodation. Accommodation amplitude was calculated as the inverse of the near point of accommodation. Photopic and mesopic pupil sizes were measured using an OPD-Scan III unit (Nidek). Cycloplegic autorefraction was performed using an autorefractor (Nidek ARK-510A) after a cycloplegic regimen, which consisted of at least 2 cycles of eye drops. In the first cycle, 2 separate eye drops, cyclopentolate, 1% (Cyclogyl; Alcon-Couvreur) and tropicamide, 1% (Santen), were administered to both eyes 5 minutes apart. A second cycle of the same cycloplegic drops was administered 10 minutes after the first cycle. Further cycles of cycloplegic eye drops were administered if necessary to ensure the pupils were well dilated. Axial length (AL) was measured using a Zeiss IOL Master 700 (Carl Zeiss Meditec). Autorefraction and AL were measured at least 30 minutes after the last cycle of cycloplegic drops.

The Chinese version of the National Eye Institute Visual Function Questionnaire, along with validated questionnaires on outdoor time and near work, were administered to the parents or guardians at the end of years 6, 7, and 8.[20] During each visit, the children and their parents were invited to report freely any adverse effects, medical illness, or hospitalizations since the previous visit. Adverse events were documented regardless of whether they appeared related to atropine use, including symptoms related to allergies, glare, and blurred near vision.

Outcomes

Primary outcomes were as follows: (1) myopia progression in terms of spherical equivalent progression (SEP) and AL elongation over 3 years (years 6-8); (2) the proportion of good response to treatment discontinuation, defined as SEP −0.5 diopter (D) or more in both eyes after treatment discontinuation over 2 years (years 7-8); and (3) the factors associated with myopia progression over 3 years (years 6-8). Secondary outcomes included adverse effects and safety parameters. Exploratory outcome included factors associated with myopia progression over 8 years.

Sample Size Calculation

To calculate the required number of study participants, SEP was estimated to be –0.35 D and –0.28 D in the prediscontinuation period[17] and –0.50 D and –0.98 D in the discontinuation period for the taper group and stop group, respectively. Therefore, the cumulative SEP over 3 years was estimated to be –0.85 D and –1.26 D for taper and stop groups, respectively. The within-group SD was assumed to be 0.80 D for both groups.[17] To detect significant differences in SEP over 3 years, a sample size of 162 participants (81 participants per group) was required to achieve 80% power at a significance level of .05.

Statistical Analysis

All data were analyzed based on the intention-to-treat principle. Participants' demographics and clinical characteristics, adverse events, and patient-reported visual function questionnaire results were summarized using descriptive statistics. Continuous variables were reported in terms of means (SD), and categorical variables were reported in frequencies and percentages. Changes in ocular parameters were calculated as the difference between 2 visits. Data analysis was based on complete case data, excluding participants who had dropped out of the study before completing 8 years.[21] Generalized estimating equations (GEEs) with robust standard errors for longitudinal data analysis were used to adjust the intereye correlations and incorporate all valuable data.[22,23] Logistic regression was used to compare the proportion of good response to discontinuation between 2 groups. Group differences in categorical data were tested by the χ^2 test and Fisher exact test. For analyses of exploratory outcomes, which were eye-based, GEEs were used to explore the effect of variables, including atropine concentration, baseline age, sex, and baseline spherical equivalent and AL, on the 8-year SEP/AL elongation. The software SPSS (version 24.0; IBM Corp) was used for data analyses. All *P* values were 2-sided, and a *P* value <.05 for the primary outcome was considered statistically significant; other *P* values were not adjusted for multiplicity.

Results

Study Participants

A total of 246 children who completed the LAMP 5-year follow-up and were receiving atropine treatment were enrolled in this study. The mean (SD) age was 13.47 (1.63) years; there were 139 male children (56.5%) and 107 female (43.5%). Of these, 122 children were randomized receive the taper approach, and 124 children were randomized to receive the stop approach. One-hundred eighty children (73.2%) completed the 8-year follow-up (Figure 1). The characteristics in the taper and stop groups were similar (Table 1 and eFigure 1 in Supplement 2). The characteristics of participants who completed 8 years of follow-up were similar to those who did not (eTable 1 in Supplement 2). Overall dropout rates were similar between the taper and stop groups over 3 years (36 [29.5%] vs 30 [24.2%]; *P* = .35), and dropout was not related to treatment discontinuation approach (eTable 2 in Supplement 2).

Table 1. Demographics and Clinical Characteristics at Year 5 for Participants in the Taper and Stop Groups

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Table 1. Demographics and Clinical Characteristics at Year 5 for Participants in the Taper and Stop Groups

Characteristic	Mean (SD)	
	Taper group (n = 122)	Stop group (n = 124)
Age, y	13.59 (1.69)	13.35 (1.57)
Sex, No. (%)		
Male	68 (55.7)	71 (57.3)
Female	54 (45.3)	53 (42.7)
Body mass index[a]	19.41 (2.85)	19.00 (3.44)
Spherical equivalent, D	−6.29 (2.73)	−6.26 (3.09)
Axial length, mm	25.90 (1.12)	25.99 (1.29)
Central corneal thickness, um	548.29 (37.03)	554.08 (27.85)
IOP, mm Hg	16.52 (2.61)	16.38 (1.99)
Photopic pupil size, mm	4.94 (1.08)	4.87 (1.03)
Mesopic pupil size, mm	7.28 (0.79)	7.21 (0.80)
Accommodation amplitude, D	8.87 (2.60)	9.27 (2.94)
Distance VA, logMAR[b]	−0.03 (0.08)	−0.03 (0.07)
Snellen equivalent	20/20	20/20
Near VA, logMAR[b]	0.02 (0.08)	0.01 (0.07)
Snellen equivalent	20/20	20/20
Initial treatment used at baseline, No. (%)[b]		
0.05% Atropine	31 (25.4)	30 (24.2)
0.025% Atropine	28 (23.0)	25 (20.2)
0.01% Atropine	33 (27.0)	36 (29.0)
Placebo	30 (24.6)	33 (26.6)

Abbreviations: D, diopter; IOP, intraocular pressure; logMAR, logarithm of the minimum angle of resolution; VA, visual acuity.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Baseline refers to the time point at which participants receive the first randomization (year 0) in the LAMP study.

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Taper vs Stop: Myopia Progression Over 3 Years (Years 6, 7, and 8)

Over 3 years, changes in spherical equivalent were −0.54 D in the taper group and −0.78 D in the stop group (difference, 0.24 D; 95% CI, 0.03 to 0.46 D; *P* = .02), and changes in AL were 0.33 mm in the taper group and 0.44 mm in the stop group (difference, −0.11 mm; 95% CI, −0.19 to −0.03 mm; *P* = .01). In the prediscontinuation period, there were no differences between the 2 groups in SEP and AL elongation (Table 2 and Figure 2). In the discontinuation period, change in spherical equivalent were −0.31 D and −0.57 D in the taper and stop groups, respectively (difference, 0.28 D; 95% CI, 0.14 to 0.42 D; *P* < .001), and change in AL was 0.21 mm and 0.32 mm in the taper and stop groups, respectively (difference, −0.10 mm; 95% CI, −0.15 to −0.04 mm; *P* < .001) (Table 3). Results of sensitivity analysis showed similar trends (eTable 3 in Supplement 2).

Table 2. Change in Ophthalmic Parameters Over 3 Years (Years 6, 7, and 8) in the Taper and Stop Groups

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Table 2. Change in Ophthalmic Parameters Over 3 Years (Years 6, 7, and 8) in the Taper and Stop Groups

Parameter	Change from year 5		
	Year 6	Year 7	Year 8
Spherical equivalent progression, D			
Taper group	−0.22 (0.37)	−0.44 (0.53)	−0.54 (0.68)
Stop group	−0.21 (0.38)	−0.59 (0.57)	−0.78 (0.78)
Difference (95% CI)	−0.01 (−0.10 to 0.08)	0.15 (0.02 to 0.28)	0.24 (0.03 to 0.46)
P value[a]	.82	.03	.02
Adjusted difference (95% CI)	−0.02 (−0.11 to 0.06)	0.14 (0.02 to 0.27)	0.26 (0.08 to 0.45)
Adjusted *P* value[b]	.62	.03	.006
Axial length elongation, mm			
Taper group	0.12 (0.11)	0.24 (0.17)	0.33 (0.24)
Stop group	0.12 (0.13)	0.30 (0.22)	0.44 (0.32)
Difference (95% CI)	−0.005 (−0.04 to 0.03)	−0.06 (−0.12 to −0.01)	−0.11(−0.19 to −0.03)
P value[a]	.77	.03	.01
Adjusted difference (95% CI)	0.003 (−0.02 to 0.03)	−0.05 (−0.10 to −0.01)	−0.09 (−0.16 to −0.02)
Adjusted *P* value[c]	.84	.04	.01

Abbreviation: D, diopter.

[a] *P* values were calculated by generalized estimated equation without adjustment.

[b] *P* values were generated by generalized estimating equation models with age at year 5, sex, and spherical equivalent at year-5 adjustment for spherical equivalent comparisons.

[c] *P* values were generated by generalized estimating equation models with age at year 5, sex, and axial length at year-5 adjustment for axial length comparisons.

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Parameter	**Change from year 5**		
	Year 6	**Year 7**	**Year 8**
Spherical equivalent progression, D			
Taper group	−0.22 (0.37)	−0.44 (0.53)	−0.54 (0.68)
Stop group	−0.21 (0.38)	−0.59 (0.57)	−0.78 (0.78)
Difference (95% CI)	−0.01 (−0.10 to 0.08)	0.15 (0.02 to 0.28)	0.24 (0.03 to 0.46)
P value[a]	.82	.03	.02
Adjusted difference (95% CI)	−0.02 (−0.11 to 0.06)	0.14 (0.02 to 0.27)	0.26 (0.08 to 0.45)
Adjusted P value[b]	.62	.03	.006

Parameter	Change from year 5		
	Year 6	Year 7	Year 8
Axial length elongation, mm			
Taper group	0.12 (0.11)	0.24 (0.17)	0.33 (0.24)
Stop group	0.12 (0.13)	0.30 (0.22)	0.44 (0.32)
Difference (95% CI)	−0.005 (−0.04 to 0.03)	−0.06 (−0.12 to −0.01)	−0.11(−0.19 to −0.03)
P value[a]	.77	.03	.01
Adjusted difference (95% CI)	0.003 (−0.02 to 0.03)	−0.05 (−0.10 to −0.01)	−0.09 (−0.16 to −0.02)
Adjusted P value[c]	.84	.04	.01

Figure 2. Spherical Equivalent Progression and Axial Length (AL) Elongation Over 3 Years (Years 6, 7, and 8)

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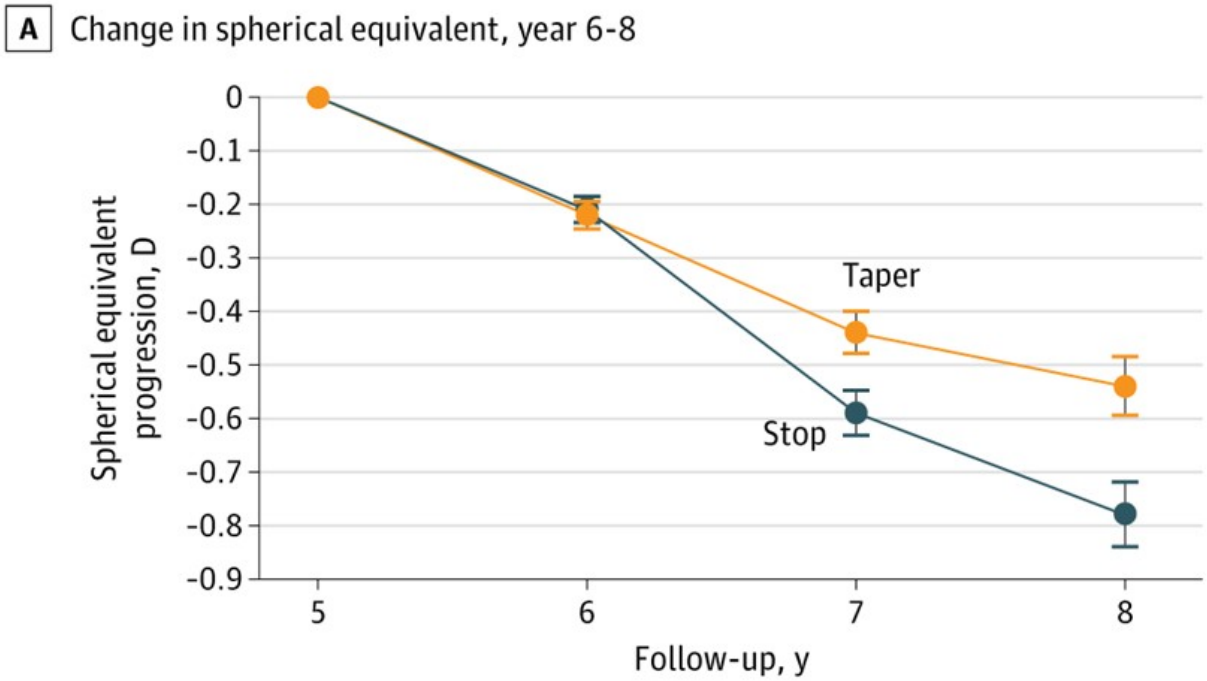
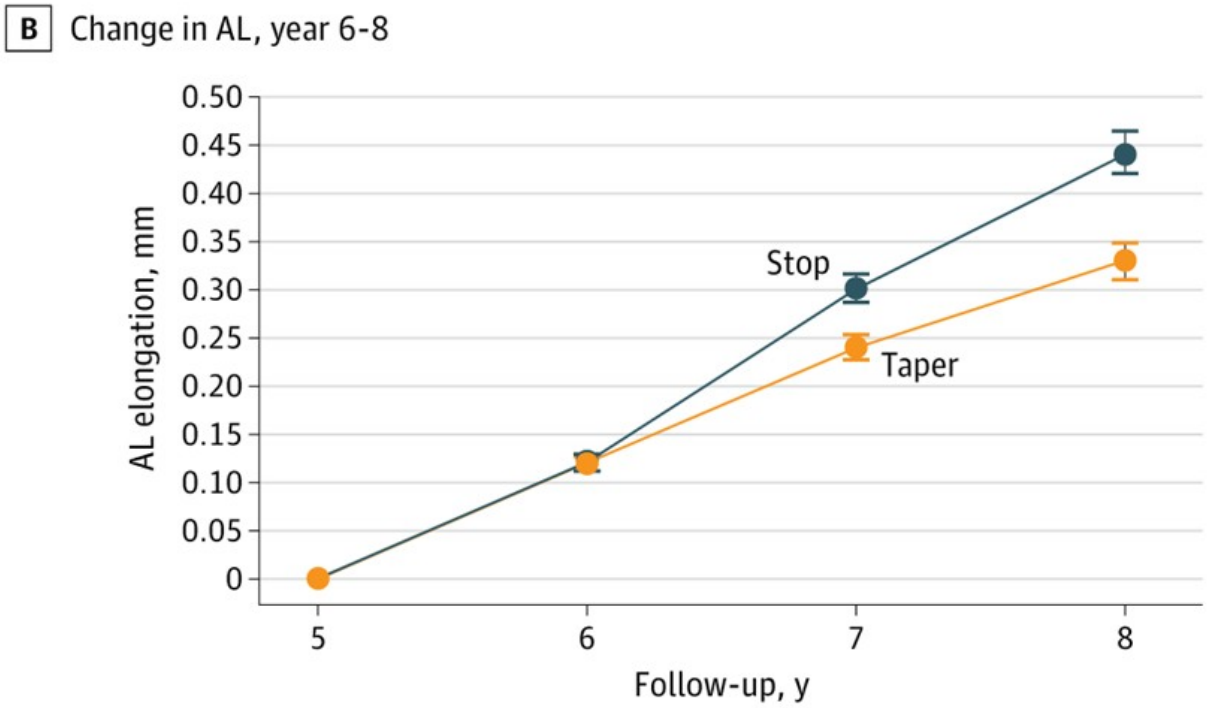


No. of participants				
Stop	124	113	106	94
Taper	122	109	97	86



No. of participants				
Stop	124	112	104	94
Taper	122	109	96	86

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Table 3. Proportion of Good Response to Treatment Discontinuation in Taper Group and Stop Group

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Table 3. Proportion of Good Response to Treatment Discontinuation in Taper Group and Stop Group

Variable	Taper	Stop	Adjusted difference (95% CI)	*P* value
No. with good response/total No. of patients	56/86	40/94	NA	NA
Proportion of good response to treatment discontinuation (%)[a]	65.1	42.6	22.9 (7.2 to 38.5)	.003[b]
Spherical equivalent progression, D				
From year 6 to year 7	−0.22 (0.36)	−0.36 (0.40)	0.13 (0.04 to 0.23)	.006[c]
From year 7 to year 8	−0.31 (0.50)	−0.57 (0.58)	0.28 (0.14 to 0.42)	<.001[c]
AL elongation, mm				
From year 6 to year 7	0.13 (0.10)	0.17 (0.14)	−0.04 (−0.07 to −0.01)	.007[d]
From year 7 to year 8	0.21 (0.17)	0.32 (0.24)	−0.10 (−0.15 to −0.04)	<.001[d]

Abbreviations: AL, axial length; D, diopter; NA, not applicable.

[a] Good response to treatment discontinuation was defined as spherical equivalent progression −0.5 D or more in both eyes after treatment discontinuation over 2 years.

[b] *P* value was generated by logistic regression with age at year 6, sex, and spherical equivalent at year-6 adjustment.

[c] *P* values were generated by generalized estimating equation models with age at year 6, sex, and spherical equivalent at year-6 adjustment.

[d] *P* values were generated by generalized estimating equation models with age at 72-month, sex, and AL at year-6 adjustment.

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Variable	Taper	Stop	Adjusted difference (95% CI)	P value
No. with good response/total No. of patients	56/86	40/94	NA	NA
Proportion of good response to treatment discontinuation (%)[a]	65.1	42.6	22.9 (7.2 to 38.5)	.003[b]
Spherical equivalent progression, D				
From year 6 to year 7	−0.22 (0.36)	−0.36 (0.40)	0.13 (0.04 to 0.23)	.006[c]
From year 7 to year 8	−0.31 (0.50)	−0.57 (0.58)	0.28 (0.14 to 0.42)	<.001[c]
AL elongation, mm				
From year 6 to year 7	0.13 (0.10)	0.17 (0.14)	−0.04 (−0.07 to −0.01)	.007[d]
From year 7 to year 8	0.21 (0.17)	0.32 (0.24)	−0.10 (−0.15 to −0.04)	<.001[d]

Taper vs Stop: Proportion of Good Response to Treatment Discontinuation (Years 7 and 8)

During discontinuation period, the proportion of good response to treatment discontinuation was 56 of 86 participants (65.1%) and 40 of 94 (42.6%) in the taper and stop groups, respectively (*P* = .003). Results of sensitivity analysis showed similar trends (eTable 4 in Supplement 2). The taper group had less myopia progression than the stop group at 1 year and at 2 years after discontinuation (Table 3).

Factors Associated With Myopia Progression Over 3 Years (Years 6, 7, and 8)

The taper group (vs stop group) was associated with reduced SEP and less axial elongation (eTable 5 in Supplement 2). One additional year older and 1 D less myopic at prediscontinuation were associated with less SEP (β = 0.15; 95% CI, 0.08 to 0.22; *P* < .001' and β = 0.08; 95% CI, 0.04 to 0.12; *P* < .001, respectively), and less AL elongation (β = −0.07; 95% CI, −0.10 to −0.05; *P* < .001; and β = 0.06; 95% CI, 0.02 to 0.10; *P* = .002, respectively) (eTable 5 in Supplement 2).

Age- and Spherical Equivalent–Stratified Myopia Progression Over 3 Years (Years 6, 7, and 8) in the Taper and Stop Groups

eTables 6 and 7 in Supplement 2 present the age- and spherical equivalent–stratified estimated means for SEP and AL elongation across the 2 discontinuation approaches over 3 years. The younger the age, the greater the estimated mean differences of SEP between the taper and stop groups. Similar trends were observed in the estimated mean difference of AL elongation (eTable 6 and eFigure 2 in Supplement 2). The greater the myopia, the greater the estimated mean differences of SE progression between the taper and stop groups. Similar trends were also observed in the estimated mean difference of AL elongation (eTable 7 and eFigure 2 in Supplement 2). No interaction effect was found between treatment discontinuation approach with age, spherical equivalent, or AL (Table 3).

Pupil Size, Accommodation, Visual Acuity, Adverse Effects, and Patient-Reported Vision-Related Quality of Life

The mean values of pupil size, accommodation, and visual acuity are reported (eTable 8 in Supplement 2). In year 8, no photophobia was reported in either group. A total of 3 severe adverse events requiring hospitalization were reported, but none were related to atropine treatment (eTable 9 in Supplement 2). No significant differences among groups were observed in patient-reported vision-related quality of life in year 8 (eTable 10 in Supplement 2).

Factors Associated With Myopia Progression Over 8 Years

In the exploratory analysis, treatment duration of 0.05% atropine, baseline age, and sex were associated with 8-year SEP and AL elongation (eTable 11 in Supplement 2). A longer treatment duration with 0.05% atropine was protective for myopia progression, with each additional year of treatment associated with 0.22 D less SEP (95% CI, 0.04-0.41, *P* = .02) and 0.07 mm less AL elongation (95% CI, −0.13 to −0.02, *P* = .01) over 8 years.

Discussion

Our study has some notable findings. First, tapering atropine concentration before treatment discontinuation yielded less myopia progression over 3 years than stopping without taper. However, short-term changes in myopic progression are relatively poor predictors of longer-term changes, meaning that children who have less myopia progression over 3 years may not be successful over longer periods of time. Furthermore, older age and less myopic spherical

equivalent at prediscontinuation resulted in less myopia progression over 3 years. Notably, children with younger age and more myopia benefited more from the taper approach.

In terms of discontinuation strategy, the taper group had better efficacy. However, to our knowledge, the clinical relevance of this approximately 0.25-D difference between treatment groups is not well understood from the current medical literature. We hypothesize that the transition to a lower concentration would lead to less rebound. We have previously shown that stopping atropine treatment at a lower concentration results in a smaller rebound.[17] Chronic atropine use has been reported to induce compensatory upregulation of muscarinic receptors,[24,25] likely making the eyes more sensitive and primed to receive any available growth signal. Abrupt withdrawal unmasks this hypersensitivity, potentially leading to a rebound overstimulation of pathways that drive axial elongation. On the other hand, a gradual tapering of concentration may allow for a controlled downregulation of these receptors, permitting the signaling pathways that control eye growth to find a new stable balance without a rapid rebound progression.[26] While the present study demonstrated a better efficacy of using the taper approach, a recent study found that gradual tapering showed no significant difference compared with prompt discontinuation of 0.01% atropine.[27] Another study conducted by Loughman et al[28] showed that in the third year of the MOSAIC trial, the rebound difference between the ceasing 0.01% atropine group and tapering 0.01% atropine group was not significant. There are some potential explanations: first, the taper approach may need to apply on a higher concentration rather than lower concentration because of the dose-dependent rebound effect; in other words, the taper approach may have minimal or even no effect when using 0.01% atropine, which may be due to the limited efficacy of 0.01% atropine in slowing myopia progression found by the Pediatric Eye Disease Investigator Group. Second, the retrospective design of the study by Erdinest et al,[27] as well as the secondary analysis of the MOSAIC, which was not primarily designed to evaluate the tapering approach, may introduce bias due to the lack of adjustment for potential confounding factors. Furthermore, because of the limited sample size, the results of both studies should be interpreted with caution, as the statistical power may be insufficient to test the hypothesis of the tapering approach.

There is an age-dependent effect on the treatment discontinuation response. First, older age at treatment discontinuation was associated with a larger discontinuation success. Second, at younger age, the response to the taper approach was more prominent than the stop approach when compared with older age. Discontinuation at a younger age coincided with a period of more malleable sclera[29,30] and inherent rapid axial elongation.[31] During this critical phase, the discontinuation of atropine’s muscarinic antagonism may not only unmask this natural growth course but also potentially incite a rebound effect. This rebound could be exacerbated by the heightened influence of extrinsic factors, such as prolonged nearvwork and limited time outdoors, on a still-malleable sclera. On the other hand, in older children, where physiological eye growth may have stabilized or slowed down, therapeutic gains achieved with atropine are more likely to be preserved after discontinuation.

Less myopic spherical equivalent at discontinuation resulted in less rebound and greater discontinuation success. In addition, the response to the taper approach was more prominent than the stop approach in children with more severe myopia. High compared with low degrees of myopia progressed faster, even in late childhood and adulthood.[32-35] Previous studies have demonstrated the association of high myopic spherical equivalent at baseline with poor response to atropine treatment.[36-39] Higher myopic eyes have a stronger intrinsic biological drive for axial elongation,[40] making them more sensitive to and dependent on the inhibitory

effects of atropine. Tapering the concentration allows for a gradual normalization of adaptation,[24] thereby mitigating the more pronounced rebound experiences resulting from discontinuation strategies.

Another finding is about exploratory outcomes. Treatment duration of 0.05% atropine was associated with 8-year outcomes, where no significant association was found for 0.025% or 0.01%. The ATLAS study demonstrated no difference of efficacy after 3 to 4 years of treatment with 1% to 0.01% and then stopped for 20 years. In our study, with continued treatment of at least 5 years, the efficacy was demonstrated at 8 years of follow-up. Our result may provide evidence that longer treatment duration for 0.05% atropine can result in reduction of spherical equivalent and AL after treatment discontinuation. However, whether this result can be translated to a longer period, such as 10 to 20 years, or whether treatment should last for a longer period, remains to be investigated.

Limitations

The study has some limitations. First, there was no placebo group to compare with the taper and stop groups. This complicates the attribution of the observed changes to the treatment intervention. Notwithstanding, the study provides evidence of which treatment discontinuation approach is more effective. Second, the observed treatment effect (0.24 D) was smaller than the estimate (0.40 D) used for the sample size calculation. It may have limited our power to detect significant effects in secondary outcomes and subgroup analyses. Furthermore, this discrepancy highlights that the calculated sample size was based on the potentially optimistic data, which may have influenced the effect magnitude. Third, the previous treatment concentration and duration in different children were not same, which may lead to the potential bias. However, after stratified randomization, the parameters between the taper and stop groups were found to be similar. Fourth, the difference of myopia progression after treatment discontinuation between the taper and stop groups was clinically small; however, the difference became larger in children with younger age and more myopia, which highlights the importance of age and spherical equivalent on treatment discontinuation. Fifth, we included only Chinese participants, restricting the generalizability of its findings to other ethnic groups.

Conclusions

This study found that tapering atropine concentration before treatment discontinuation is better than stopping without taper, resulting in less AL elongation and SEP, particularly in children of younger age and with more severe myopia. However, to our knowledge, the clinical relevance of this approximately 0.25-D difference between treatment groups is not well understood from the current medical literature.

Article Information

Accepted for Publication: February 2, 2026.

Published Online: March 26, 2026. doi:10.1001/jamaophthalmol.2026.0436

Corresponding Author: Jason C. Yam, MD, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong Eye Hospital, 147K Argyle St, Kowloon, Hong Kong (yamcheuksing@cuhk.edu.hk).

Author Contributions: Dr Yam had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Y. Zhang and X. Zhang contributed equally as co–first authors.

Concept and design: Y. Zhang, X. Zhang, Ng, Pang, Yam.

Acquisition, analysis, or interpretation of data: Y. Zhang, X. Zhang, Zaabaar, Yim, Yip, Kam, Young, Tham, Chen.

Drafting of the manuscript: Y. Zhang, Zaabaar.

Critical review of the manuscript for important intellectual content: X. Zhang, Zaabaar, Yim, Yip, Kam, Ng, Young, Tham, Chen, Pang, Yam.

Statistical analysis: Y. Zhang, Young.

Obtained funding: X. Zhang, Yam.

Administrative, technical, or material support: Y. Zhang, Ng, Chen, Pang.

Supervision: X. Zhang, Yim, Yip, Kam, Tham, Pang, Yam.

Conflict of Interest Disclosures: Dr Yam reported being a director of the start-up company OCUS Innovation (HK) Limited. No other disclosures were reported.

Funding/Support: This study was supported in part by the National Natural Science Foundation of China (82425017 and 82171089 [Dr Yam]); General Research Fund, Research Grants Council, Hong Kong (14102422 [Dr Yam]); Health and Medical Research Fund, Hong Kong (10210246 [Dr Y. Zhang], 09202466 [Dr Chen], and 11220206 [Dr Yam]); Strategic Impact Enhancement Fund, The Chinese University of Hong Kong (WW/SC/rc/SIEF2324/0366/24vw and TL/JF/rc/SIEF2223/0759/23vw [Dr Yam]); and Chinese University of Hong KongJockey Club Myopia Prevention Programme.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

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