

Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1%, and 0.01% Doses (Atropine for the Treatment of Myopia 2)

Audrey Chia, FRANZCO,^{1,2} Wei-Han Chua, FRCSEd(Ophth), FAMS,^{1,2} Yin-Bun Cheung, PhD,^{3,4} Wan-Ling Wong, Mbiostat,² Anushia Lingham, SRN,⁴ Allan Fong FRCSEd(Ophth),^{1,2} Donald Tan, FRCS, FRCOphth^{1,2,5}

Purpose: Our previous study, Atropine for the Treatment of Myopia 1 (ATOM1), showed that atropine 1% eyedrops were effective in controlling myopic progression but with visual side effects resulting from cycloplegia and mydriasis. The aim of this study was to compare efficacy and visual side effects of 3 lower doses of atropine: 0.5%, 0.1%, and 0.01%.

Design: Single-center, double-masked, randomized study.

Participants: A total of 400 children aged 6–12 years with myopia of at least -2.0 diopters (D) and astigmatism of -1.50 D or less.

Intervention: Children were randomly assigned in a 2:2:1 ratio to 0.5%, 0.1%, and 0.01% atropine to be administered once nightly to both eyes for 2 years. Cycloplegic refraction, axial length, accommodation amplitude, pupil diameter, and visual acuity were noted at baseline, 2 weeks, and then every 4 months for 2 years.

Main Outcome Measures: Myopia progression at 2 years. Changes were noted and differences between groups were compared using the Huber–White robust standard error to allow for data clustering of 2 eyes per person.

Results: The mean myopia progression at 2 years was -0.30 ± 0.60 , -0.38 ± 0.60 , and -0.49 ± 0.63 D in the atropine 0.5%, 0.1%, and 0.01% groups, respectively ($P=0.02$ between the 0.01% and 0.5% groups; between other concentrations $P > 0.05$). In comparison, myopia progression in ATOM1 was -1.20 ± 0.69 D in the placebo group and -0.28 ± 0.92 D in the atropine 1% group. The mean increase in axial length was 0.27 ± 0.25 , 0.28 ± 0.28 , and 0.41 ± 0.32 mm in the 0.5%, 0.1%, and 0.01% groups, respectively ($P < 0.01$ between the 0.01% and 0.1% groups and between the 0.01% and 0.5% groups). However, differences in myopia progression (0.19 D) and axial length change (0.14 mm) between groups were small and clinically insignificant. Atropine 0.01% had a negligible effect on accommodation and pupil size, and no effect on near visual acuity. Allergic conjunctivitis and dermatitis were the most common adverse effect noted, with 16 cases in the 0.1% and 0.5% atropine groups, and no cases in the 0.01% group.

Conclusions: Atropine 0.01% has minimal side effects compared with atropine at 0.1% and 0.5%, and retains comparable efficacy in controlling myopia progression.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology* 2011;xx:xxx © 2011 by the American Academy of Ophthalmology.

Atropine eyedrops were first proposed as a treatment of myopia in the 1920s.¹ Since then, there have been numerous studies on this subject.^{2–12} However, evidence from randomized control trials has become available only over the last 2 decades.^{13–18} These trials confirm that atropine eyedrops are effective in the control of myopia in a dose-related manner.^{13–18} Our previous randomized trial, Atropine for the Treatment of Myopia 1 (ATOM1), involving 400 children aged 6 to 12 years found that, over 2 years, atropine 1% slowed myopia progression (mean \pm standard deviation) to -0.28 ± 0.92 diopters (D) in children, compared with -1.20 ± 0.69 D in the placebo group ($P < 0.001$).¹⁶ Shih et

al¹⁴ showed that the myopic progression in Taiwanese children was -0.04 ± 0.63 , -0.47 ± 0.91 , and -0.47 ± 0.91 D/year in the 0.5%, 0.25%, and 0.1% atropine groups, respectively, compared with -1.06 ± 0.61 D/year in their tropicamide (control) group. Liang et al,¹⁷ in a smaller study of 65 children, demonstrated myopic progression of -0.15 ± 0.15 , -0.38 ± 0.32 , and -0.21 ± 0.23 D/year in the 0.5%, 0.25%, and 0.25% atropine plus auricular pressure groups, respectively.

In the second study, Atropine for the Treatment of Myopia 2 (ATOM2), we examined the effect of lower doses of atropine to determine whether these concentrations could result in efficacy in preventing myopia progression, with

less visual side effects (i.e., pupil dilation, loss of accommodation, and near vision blur). The ATOM2 study comprises 2 phases: a treatment phase lasting 24 months, followed by a washout period of 12 months, and then a second phase in which children showing myopic progression will recommence taking atropine at a dosage found optimal in the first phase. This article presents results in the first 24 months (first phase) of the ATOM2 study.

Materials and Methods

Children aged 6 to 12 years with myopic refraction of at least 2.0 D in both eyes, astigmatism of less than 1.5 D, and documented myopic progression of at least 0.5 D in the past year were enrolled in a double-masked, single-center clinical trial. Excluded were those with ocular pathology (e.g., amblyopia, strabismus), previous use of atropine or pirenzepine, an allergy to atropine, or systemic ill health (e.g., cardiac or respiratory illness). Written informed consent was obtained from parents or guardians, and verbal assent was obtained from children. The study was conducted according to the tenets of the Declaration of Helsinki, with ethics approval from the Singapore Eye Research Institute Review Board. This study was registered with the ClinicalTrials.gov website (registration no: NCT00371124).

Participants were randomized to receive 0.5%, 0.1%, or 0.01% atropine once nightly in both eyes at an allocation ratio of 2:2:1 in 6 strata defined by gender and age groups of 6 to 7, 8 to 10, and 11 to 12 years, respectively, to ensure gender and age balance across the 3 treatment arms. Trial medications were prepackaged so that bottles were pre-labeled with subject number and of similar appearance. Trial medication consisted of the appropriate dose of atropine sulfate with 0.02% of 50% benzalkonium chloride as a preservative (Ashwood Laboratories Ltd., Macau, China).

After assessment at the time of recruitment (baseline), children were reassessed 2 weeks after starting atropine (baseline 2) and then at 4, 8, 12, 16, 20, and 24 months. At each visit, distance best-corrected visual acuity (BCVA) logarithm of the minimum angle of resolution (logMAR) was assessed by an optometrist using the Early Treatment Diabetic Retinopathy study chart. Near visual acuity was assessed using best-corrected distance spectacle correction with a reduced logMAR reading chart placed at 40 cm under well-lit conditions. The near point of accommodation was measured using a Royal Air Force near point rule using best-corrected distance spectacle correction. Children were instructed to move the target inward until the N5 print became slightly blurred and then outward until it just became clear. Accommodation amplitude was calculated as the inverse of near point of accommodation. Mesopic pupil size was measured with the Procyon 3000 pupillometer (Lion House, Red Lion Street, London, UK), using the Meso-Hi (4 lux) setting. Photopic pupil size was measured using the Neuroptics pupillometer (Neuroptics Inc., Irvine, CA), while children were viewing a target placed at 3 m, after at least 10 seconds of exposure to lamps providing 300 lux of luminance. In both cases, at least 5 pupil size readings (with range <0.5 mm) were recorded and averaged.

Cycloplegic autorefractometry was determined 30 minutes after 3 drops of cyclopentolate 1% (Cyclogyl, Alcon-Convreur, Rijksweg, Belgium) were administered at 5 minutes apart using a Canon RK-F1 autorefractor (Canon Inc. Ltd., Tochigiken, Japan). Five readings, all of which had to be less than 0.25 D apart, were obtained and averaged. Spherical equivalent was calculated as sphere plus half cylinder power. The Zeiss IOLMaster (Carl Zeiss Meditec Inc., Dublin, CA), a non-contact partial coherence interferometry, was used to measure the ocular axial length. Five

readings, with a maximum-minimum deviation of 0.05 mm or less, were taken and averaged.

Parents or guardians, children, and study investigators were kept masked to the assigned dosage of trial medications. Each child kept a diary of use of the trial medication. Compliance level of each subject was classified according to the mean number of frequency of using atropine per week as reported by participants over the first 24 months. Subjects with 75% compliance rate (≥ 5.25 days/week) were considered compliant.

Children were also offered photochromatic glasses (which darken on exposure to ultraviolet or sunlight) if they experienced glare or their parents were worried of excessive light exposure, or progressive glasses (reading add) if children experienced difficulty with near vision.

The primary end point was myopia progression over 2 years. Because a hyperopic shift may occur after commencing atropine, myopia progression was calculated from the second baseline, when children had been taking trial medication for 2 weeks. Level of myopia progression in each eye was further categorized as mild (<0.5 D), moderate (0.5–0.99 D), or severe (≥ 1.0 D).

Secondary end points included myopia progression at 1 year, change in axial length at 1 and 2 years, and side effect parameters, such as changes in accommodation amplitude, mesopic and photopic pupil size, and distance and near BCVA. Myopia and axial changes were noted from second baseline, whereas accommodation, pupil size, and visual acuity were monitored from the first baseline.

During each visit, children and parents were given an open-ended opportunity to report any medical illness or side effects. They were also specifically asked about symptoms related to allergy, blurred near vision, glare, or visual loss, and if children had been ill or hospitalized since the last visit. Any adverse events, regardless of whether they appeared relevant to atropine use, were documented.

Statistic Analysis

On the basis of findings from the various studies, it was estimated that the myopia progression rate for 0.5%, 0.1%, and 0.01% atropine would be -0.04 , -0.47 , and -0.76 D, respectively.^{13–18} To achieve 90% power using a 2:2:1 randomization for 0.5%:0.1%:0.01%, a sample size of 325 subjects (130:130:65) is needed. By factoring in an attrition rate of 20%, a sample size of 400 subjects (i.e., 160:160:80) is needed.

All analyses were based on intention-to-treat principle and performed with Stata statistical software (version 10.1, StataCorp., College Station, TX). For demographic and other person-level data, such as compliance and ever experiencing adverse events, the Fisher exact test was used to test for the difference in the proportion of subjects between treatment groups, and analysis of variance was used for the difference in means between treatment groups. End points from both eyes were pooled in a combined analysis using the Huber–White robust standard errors to allow for the correlation between eyes within person.¹⁹ The results on left and right eyes were similar. For example, the mean difference (95% confidence interval [CI]) in 2-year myopia progression between left and right eyes was -0.01 (-0.06 to 0.03). For brevity and better precision, this report shows analyses pooling both eyes with robust standard errors for clustered data. The global null hypothesis of no difference among 3 treatment groups was tested first, followed by pairwise comparisons. A nominal level of statistical significance (P value) was reported, i.e., no adjustment for multiple comparison. Interpretation will begin with considering the global null hypothesis among 3 groups to prevent inflated type I

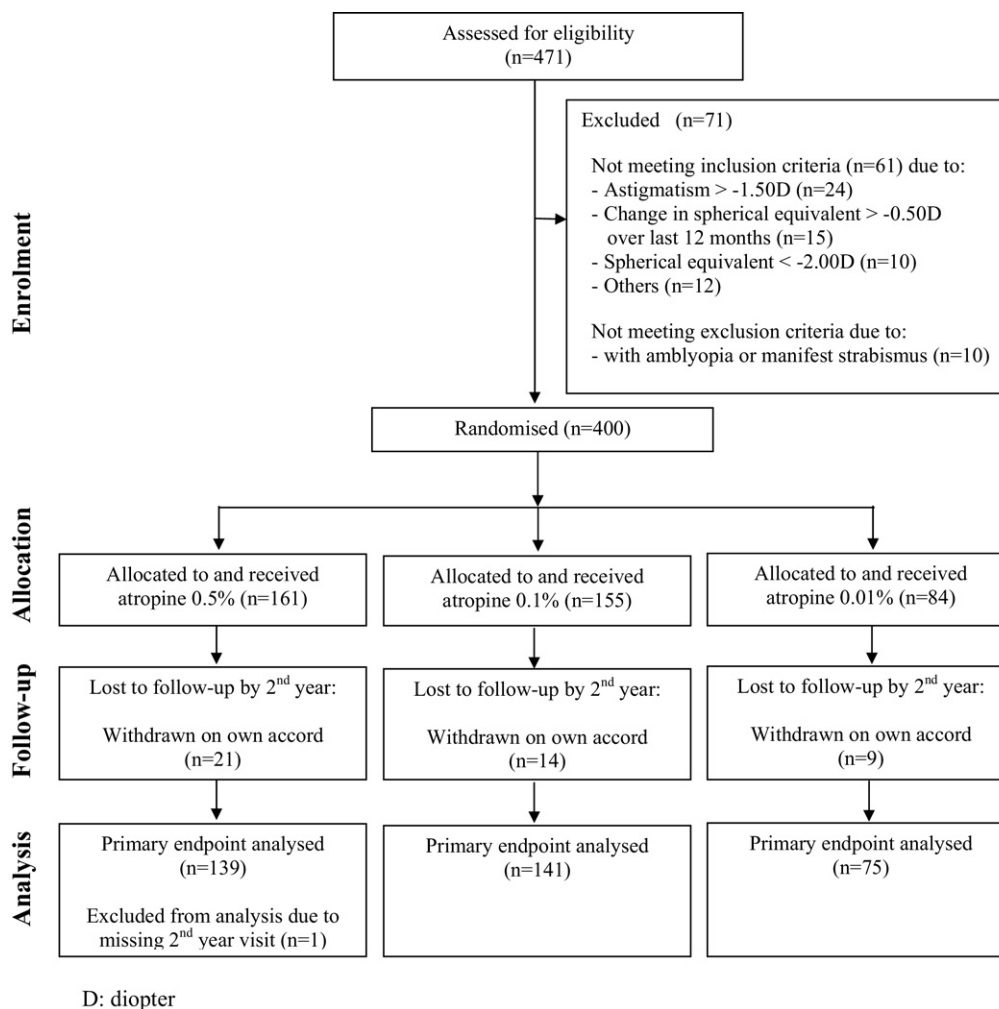


Figure 1. ATOM2 subject flow chart. ATOM = Atropine for the Treatment of Myopia.

error rate. Placebo and atropine-treated eyes in ATOM1 were used for reference in the secondary analyses.

Results

A total of 400 children were recruited into the study, with 161, 155, and 84 children in the 0.5%, 0.1%, and 0.01% atropine treatment arms, respectively (Fig 1). There were almost equal numbers of male and female children, and 91% of children were of ethnic Chinese origin (Table 1). No differences were noted in demographics, baseline refractive error, accommodation, pupil diameter, or BCVA among groups (Table 1). The correlation between change in spherical equivalent and axial length over 2 years was high (correlation coefficient = 0.82, $P < 0.001$), suggesting good measurement validity.

Two-year primary end point data were available for 355 of 400 subjects (88.8%). Forty-four subjects withdrew participation on their own accord: 9 (10.7%), 14 (9.0%), and 21 (13.0%) from the 0.01%, 0.1%, and 0.5% treatment groups, respectively ($P=0.43$); 1 participant did not attend the second year assessment. Compliance, defined as $>75\%$ expected use, was 98.7%, 96.8%, and 98.8% in the 0.5%, 0.1%, and 0.01% arms, respectively ($P=0.53$), in the 2-year period.

Change in Myopic Progression and Axial Length

A dose-related response on myopia was noted among the 3 treatment arms, but differences between treatment arms were clinically small (Fig 2). An initial hyperopia shift of 0.3 to 0.4 D was noted in the 0.1% and 0.5% groups but not in the 0.01% group (Table 1). At the end of 1 year, there was a significant difference in myopia progression between the 0.5% atropine group and the 0.01% ($P < 0.001$) and 0.1% ($P=0.01$) groups, but there was no statistical significant difference between the 0.01% and 0.1% groups. The final myopia progression over 2 years was -0.49 ± 0.60 , -0.38 ± 0.60 , and -0.30 ± 0.63 D in the atropine 0.01%, 0.1%, and 0.5% groups, respectively ($P=0.07$), with a significant difference only between the 0.01% and 0.5% groups (Table 2). There was no significant difference in spherical equivalent levels between groups ($P=0.20$). Fifty percent of the 0.01% group had progressed by less than 0.5 D, compared with 58% and 63% in the 0.1% and 0.5% groups, respectively, with approximately 18% progressing by ≥ 1.0 D in all 3 groups (Fig 3).

With regard to axial length, change at 1 year was larger in the 0.01% group (0.24 ± 0.19 mm) than in the 0.1% (0.13 ± 0.18 mm) and 0.5% (0.11 ± 0.17 mm) groups ($P < 0.001$) (Fig 4). Pairwise comparison showed a statistically significant difference between

Table 1. Characteristics at Baseline and Second Baseline (i.e., 2 Weeks after Starting Trial Medication)

| Variables | Atropine(A) Dose | | | P Value* |
|------------------------------|------------------|------------------|------------------|----------|
| | A 0.01% (n = 84) | A 0.1% (n = 155) | A 0.5% (n = 161) | |
| Age (yr), mean (SD) | 9.5 (1.5) | 9.7 (1.6) | 9.7 (1.5) | 0.95 |
| Female, % | 48.8 | 46.5 | 47.2 | 0.95 |
| Chinese % | 90.5 | 92.3 | 90.0 | 0.99 |
| Spherical equivalent (D) | | | | |
| -baseline | -4.5 (1.5) | -4.8 (1.5) | -4.7 (1.8) | 0.40 |
| -second baseline | -4.5 (1.5) | -4.5 (1.4) | -4.3 (1.8) | 0.67 |
| Axial length (mm) | | | | |
| -baseline | 25.1 (1.0) | 25.2 (0.8) | 25.2 (0.9) | 0.94 |
| -second baseline | 25.2 (1.0) | 25.1 (0.8) | 25.1 (0.9) | 0.93 |
| Accommodation (D) | | | | |
| -baseline | 16.2 (3.4) | 16.7 (3.0) | 15.8 (3.4) | 0.01 |
| -second baseline | 11.3 (4.3) | 3.8 (2.5) | 2.2 (1.2) | <0.001 |
| Mesopic pupil diameter (mm) | | | | |
| -baseline | 3.9 (0.6) | 3.9 (0.6) | 4.0 (0.7) | 0.21 |
| -second baseline | 5.2 (0.8) | 7.2 (0.7) | 7.8 (0.5) | <0.001 |
| Photopic pupil diameter (mm) | | | | |
| -baseline | 4.7 (0.7) | 4.6 (0.7) | 4.6 (0.7) | 0.63 |
| -second baseline | 5.8 (0.8) | 7.4 (0.7) | 7.9 (0.6) | <0.001 |
| Distant BCVA (logMAR) | | | | |
| -baseline | 0.01 (0.05) | 0.02 (0.06) | 0.02 (0.06) | 0.56 |
| -second baseline | 0.01 (0.05) | 0.03 (0.05) | 0.01 (0.06) | 0.86 |
| Near vision (logMAR) | | | | |
| -baseline | 0.04 (0.09) | 0.04 (0.08) | 0.04 (0.07) | 0.38 |
| -second baseline | 0.06 (0.08) | 0.29 (0.18) | 0.48 (0.16) | <0.001 |

SD = standard deviation.

*Fisher exact test for binary demographic variables; analysis of variance for age; Huber-White robust standard error for clustered data (both eyes pooled) on ocular parameters.

the 0.01% group and the other 2 groups ($P < 0.001$). This difference persisted to the end of the 24-month period (Table 2).

Changes in Accommodation, Pupil Diameter, and Visual Acuity

There was no difference in accommodation, mesopic, and photopic pupil diameter among groups at baseline (Table 1). How-

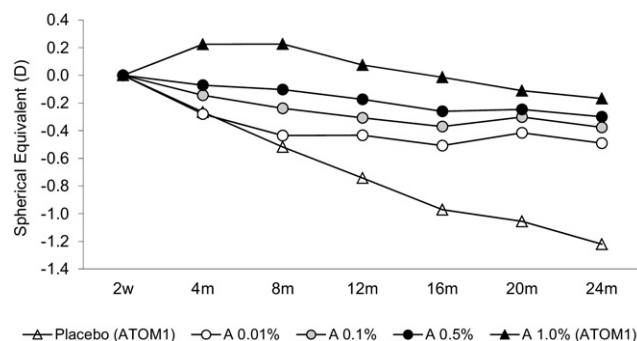


Figure 2. Mean change in spherical equivalent for groups from baseline, 2 weeks, and 4 to 24 months with atropine 0.01%, 0.1%, and 0.5% from the ATOM2 study, and placebo and atropine 1.0% from the ATOM1 study. A = atropine; ATOM = Atropine for the Treatment of Myopia; D = diopter; m = month; w = week.

ever, significant dose-related differences quickly became evident by the second baseline visit (Table 1). Changes within the 0.01% group were significantly less than in the 2 other groups. Accommodation amplitude in the 0.01% group was reduced to only 11.3 D compared with 3.8 D and 2.2 D in the 0.1% and 0.5% groups, respectively (Table 1). In functional terms, this meant that near visual acuity was not significantly impaired in the 0.01% group, whereas deficiencies were noted in the 2 other groups. Mean best-corrected distant visual acuity was not affected by atropine use (Table 2), although 10% of children did encounter mild distance blur (Table 3).

Pupil size, under both photopic and mesopic conditions, in the 0.01% group increased by only 1 mm, whereas pupils in the 0.1% and 0.5% groups were ~3 mm larger (Table 2). Although the atropine effect on pupil diameter remained unchanged over time, the accommodation appeared to improve in the 0.1% and 0.5% groups over time (Table 2). The mean accommodation amplitude in the 0.5% group, for example, decreased from 15.8 D at baseline to 2.2 D at the second baseline visit but increased to 3.6 D and 4.1 D by the end of the first and second years, respectively. Changes in the 0.01% group were less, varying from 16.2 to 11.3, 11.7, and 11.8 D over the same time period.

Children receiving lower concentrations of atropine were less likely to require progressive lens power in their glasses. For example, in the 234 children aged 8 to 10 years at the start of study, 70%, 61%, and 6% of the children receiving atropine 0.5%, 0.1%, and 0.01%, respectively, requested combined photochromatic progressive glasses, whereas the remainder opted for single-vision photochromatic glasses.

Table 2. Ophthalmology Parameters at Second Annual Visit

| | Atropine (A) Dose, Mean (SD) | | | P Value |
|--------------------------|------------------------------|----------------|----------------|-------------------------|
| | A 0.01% | A 0.1% | A 0.5% | |
| Spherical equivalent (D) | | | | |
| -at 1 yr | -4.9 (1.5) | -4.8 (1.4) | -4.6 (1.9) | 0.26 |
| -at 2 yrs | -5.1 (1.5) | -4.9 (1.3) | -4.7 (1.7) | 0.20 |
| -mean change over 1 yr | -0.43 (0.52) | -0.31 (0.50) | -0.17 (0.47) | <0.001 ^{*,‡} |
| -mean change over 2 yrs | -0.49 (0.63) | -0.38 (0.60) | -0.30 (0.60) | 0.07* |
| Axial length (mm) | | | | |
| -at 1 yr | 25.4 (1.0) | 25.3 (0.8) | 25.3 (0.9) | 0.36 |
| -at 2 yrs | 25.7 (1.0) | 25.4 (0.8) | 25.4 (1.0) | 0.08 [†] |
| -mean change over 1 yr | 0.24 (0.19) | 0.13 (0.18) | 0.11 (0.17) | <0.001 ^{*,†} |
| -mean change over 2 yrs | 0.41 (0.32) | 0.28 (0.27) | 0.27 (0.25) | 0.002 ^{*,†} |
| Accommodation (D) | | | | |
| -at 1 yr | 11.7 (4.3) | 6.0 (3.4) | 3.6 (3.2) | <0.001 ^{*,†,‡} |
| -at 2 yrs | 11.8 (3.2) | 6.8 (3.4) | 4.0 (2.6) | <0.001 ^{*,†,‡} |
| -mean change over 1 yr | -4.4 (4.9) | -10.9 (4.0) | -12.4 (3.3) | <0.001 ^{*,†,‡} |
| -mean change over 2 yrs | -4.6 (4.2) | -10.1 (4.3) | -11.8 (4.4) | <0.001 ^{*,†,‡} |
| Mesopic pupil size (mm) | | | | |
| -at 1 yr | 5.1 (0.9) | 6.7 (1.0) | 7.5 (1.1) | <0.001 ^{*,†,‡} |
| -at 2 yrs | 5.1 (0.9) | 6.7 (1.1) | 7.5 (1.2) | <0.001 ^{*,†,‡} |
| -mean change over 1 yr | 1.15 (0.78) | 2.77 (1.03) | 3.50 (1.05) | <0.001 ^{*,†,‡} |
| -mean change over 2 yrs | 1.15 (0.71) | 2.71 (1.12) | 3.56 (1.14) | <0.001 ^{*,†,‡} |
| Photopic pupil size (mm) | | | | |
| -at 1 yr | 5.6 (0.8) | 7.0 (1.0) | 7.7 (1.0) | <0.001 ^{*,†,‡} |
| -at 2 yrs | 5.5 (0.8) | 6.9 (1.0) | 7.8 (1.1) | <0.001 ^{*,†,‡} |
| -mean change over 1 yr | 0.91 (0.78) | 2.42 (0.91) | 3.11 (1.08) | <0.001 ^{*,†,‡} |
| -mean change over 2 yrs | 0.74 (0.75) | 2.25 (1.01) | 3.11 (1.10) | <0.001 ^{*,†,‡} |
| Distant BCVA (logMAR) | | | | |
| -at 1 yr | -0.005 (0.042) | -0.003 (0.054) | -0.003 (0.054) | 0.99 |
| -at 2 yrs | -0.001 (0.057) | 0.005 (0.054) | 0.011 (0.057) | 0.25 |
| -mean change over 1 yr | -0.02 (0.05) | -0.02 (0.06) | -0.03 (0.05) | 0.21 |
| -mean change over 2 yrs | -0.02 (0.06) | 0.01 (0.06) | -0.01 (0.06) | 0.44 |
| Near vision (logMAR) | | | | |
| -at 1 yr | 0.03 (-0.06) | 0.15 (0.15) | 0.35 (0.18) | <0.001 ^{*,†,‡} |
| -at 2 yrs | 0.01 (0.07) | 0.10 (0.13) | 0.29 (0.18) | <0.001 ^{*,†,‡} |
| -mean change over 1 yr | -0.01 (0.10) | 0.10 (0.16) | 0.32 (0.19) | <0.001 ^{*,†,‡} |
| -mean change over 2 yrs | -0.02 (0.08) | 0.06 (0.13) | 0.25 (0.19) | <0.001 ^{*,†,‡} |

SD = standard deviation.

Myopia progression and axial length: change from second baseline; other parameters: change from initial baseline. P values for test of global null hypotheses of all groups being the same are shown. Pairwise comparison P values are represented by*significant ($P < 0.05$) difference between atropine 0.01% and 0.5%;[†]significant difference between atropine 0.01% and 0.1%; and[‡]significant difference between atropine 0.1% and 0.5%.

Adverse Events

The majority of the adverse events were deemed to be unrelated to study treatment (e.g., flu-like illness) (Table 3). Adverse reactions directly attributable to atropine included allergic conjunctivitis, which occurred in 13 children (4.1%) in the atropine 0.1% and 0.5% groups. In 3 subjects (1.2%), symptoms were severe enough to warrant ceasing trial medication. Four children in the 0.1% and 0.5% groups (1.3%) had allergy-related dermatitis of the eyelids. Six children had other eye symptoms, 5 of which could be attributed to atropine, including 1 case of irritation and 1 case of blur in the atropine 0.01% group, and 2 cases of ocular irritation and 1 case of intolerable glare in the atropine 0.5% group.

Seven children had a severe adverse event requiring hospitalization. In the 0.01% group, 1 child had acute gastric pain. In the 0.1% group, there was 1 case each of appendicitis, respiratory infection, and Ewing's sarcoma. In the 0.5% group, there was 1 case each of tachycardia, dengue fever, and gastroenteritis. None of these events are thought to be associated with atropine.

Discussion

Childhood myopia is a major public health problem in Singapore. In a recent Strabismus, Amblyopia and Refractive Error in Singaporean Children study (2005–2009) involving preschool Chinese children, myopia (spherical equivalence, ≤ -0.5 D) was already present in 7% of 4- to 5-year-old children.²⁰ The prevalence of myopia in the Singapore Cohort Study of Risk Factors for Myopia study (1999–2003) was noted to be 28%, 32%, and 43% in 7-, 8-, and 9-year-old children, respectively, with a subsequent 3-year cumulative myopia progression of -2.4 D (95% CI, -2.6 to -2.2), -2.0 D (95% CI, -2.1 to -1.8), and -1.7 D (95% CI, -2.0 to -1.4) in each group, respectively.²¹ By the time children were aged 12 years, 61% were myopic and 10% were highly myopic (< -6 D) (Saw SM, personal communication, 2011). Army-based studies (1996–1997)

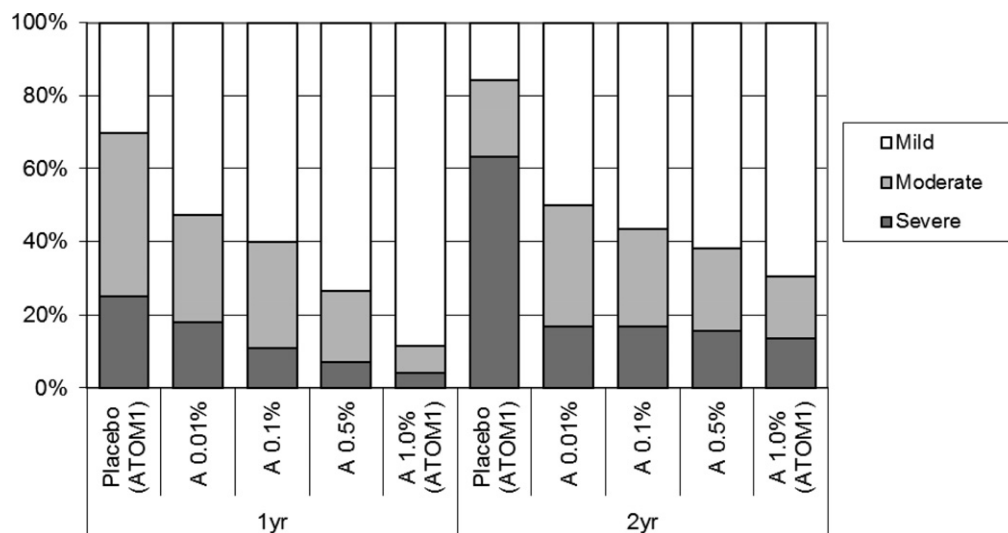


Figure 3. Progression of myopia according to severity (pooled eyes) with atropine 0.01%, 0.1%, and 0.5% from the ATOM2 study, and placebo and atropine 1.0% from the ATOM1 study, at 1 and 2 years. Myopia progression from baseline 2 if >1 D (severe), 0.5–0.99 D (moderate), and <0.5 D (mild). A = atropine; ATOM = Atropine for the Treatment of Myopia; D = diopter.

place the prevalence of myopia in young male conscripts at 79%, with 13% being highly myopic.²²

Atropine is a nonspecific muscarinic antagonist.^{1,23} It is uncertain how atropine acts to inhibit myopia progression.^{1,24–28} Initially, inhibition of accommodation was thought to be important, but subsequent studies have shown that atropine also inhibits myopia in animals (e.g., in chickens) that have no accommodative facility.²⁴ One theory is that atropine and other muscarinic antagonists may have biochemical effects on the retina or sclera, which in turn affect remodeling of the sclera.^{25,26} Another theory suggests that increased ultraviolet exposure (secondary to pupil dilation) may increase collagen cross-linking within the sclera, thereby limiting scleral growth.²⁸

Atropine at 1.0% and 0.5% has been demonstrated through randomized trials to be effective in slowing myopia progression.^{13–18} However, the safety profile of atropine (i.e., its effect on pupil size and accommodation) often has been a source of concern and deterred many from using this medication. Every unit increase in pupil size results in an

exponential increase in the amount of light entering the eye, and this can cause glare and potential phototoxicity. Atropine also decreases accommodation amplitude and near vision so that children may require bifocal or progressive glasses to read. The ideal atropine dose would be one with the best balance between efficacy and safety.

In the ATOM1 study, 400 children aged 6–12 years with spherical equivalents of -1.00 and -6.00 D were randomly assigned to atropine 1% and placebo medication in 1 eye.¹⁶ These children were slightly younger (9.2 vs. 9.6 years) and had lower spherical equivalents (-3.4 vs. -4.7 D) and smaller axial lengths (24.8 vs. 25.2 mm) than those in the ATOM2 group. Axial lengths were also measured differently between studies, with the A-scan ultrasonography used in ATOM1 and the IOLMaster used in ATOM2. At the end of 2 years, the mean myopia and axial length progression in the ATOM1 study were -0.28 ± 0.92 D and -0.02 ± 0.35 mm, respectively, in the atropine 1% eyes compared with -1.20 ± 0.69 D and 0.38 ± 0.38 mm, respectively, in the placebo eyes. The progression of myopia in the ATOM2 subjects lies in a dose-related manner between these 2 extremes (Fig 2). Such a dose-related effect on myopia progression was also noted in other studies.^{14,15,17}

In ATOM2, the progression of myopia on atropine 0.5% was -0.17 ± 0.47 D over 1 year and -0.30 ± 0.60 D over 2 years. This was similar to the progression noted in children receiving atropine 1% in the ATOM1 study (Fig 2), and within the ranges noted in studies using atropine 0.5%. Shih et al¹⁴ noted a 0.04 ± 0.63 per year progression in 41 children aged 6–13 years. In a later study, Shih et al¹⁵ noted progression of 0.41 ± 0.07 D over an 18-month period in 66 children aged 6–13 years, whereas Liang et al¹⁷ obtained 0.15 ± 0.15 per year in 22 school-aged children.

Changes in myopia and axial lengths outcome in the atropine 0.1% group were similar to those in the 0.5% group. The myopia progression was initially larger in the

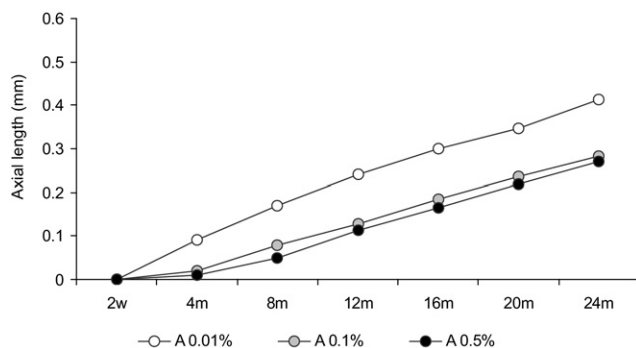


Figure 4. Mean change in axial lengths for groups from baseline, 2 weeks, and 4 to 24 months. A = atropine; ATOM = Atropine for the Treatment of Myopia; m = month; w = week.

Table 3. Adverse Event and Serious Adverse Events

| | Atropine (A) Dose | | | Exact Test P Value* |
|----------------------------------|---|------------------|------------------|------------------------|
| | No. of Episode/No. of Children (% Children) | | | |
| | A 0.01% (n = 84) | A 0.1% (n = 155) | A 0.5% (n = 161) | |
| Adverse events | | | | |
| Allergic conjunctivitis | 0/0 (0) | 7/6 (4) | 7/7 (4) | 0.16 |
| Dermatitis involving eyelids | 0/0 (0) | 2/1 (1) | 4/3 (2) | 0.54 |
| Stye/chalazion | 2/2 (2) | 16/12 (8) | 16/12 (7) | 0.22 |
| Loss of distant BCVA >1 line | 11/11 (13) | 20/20 (13) | 13/13 (8) | 0.38 |
| Others, eye related | 2/1 (1) | 2/2 (2) | 3/3 (2) | 1.00 |
| Others, non-eye related | 306/69 (82) | 470/122 (78) | 477/132 (82) | 0.73 |
| Severe adverse events | | | | |
| Events requiring hospitalization | 1/1 (1) | 3/3 (2) | 3/3 (2) | 1.00 |

*Fisher exact test for proportion of children with adverse events.

atropine 0.1% group at 1 year (-0.31 vs. -0.17 D, $P=0.01$), but this gap had closed by 2 years (-0.38 vs. -0.30 D, $P=0.25$). This level of progression was less than the -0.47 D per year noted in children treated with 0.1% drops in Taiwan.¹⁴ In terms of effect on other ocular parameters, accommodation (-10.9 vs. -2.4 D), mesopic pupil diameter (2.7 vs. 3.5 mm), and photopic pupil diameter (2.2 vs. 3.1 D) were also significantly less in the 0.1% group compared with the 0.5% group, making the overall efficacy side effect profile of atropine 0.1% better than atropine 0.5%.

In designing this study, atropine 0.01% was initially assumed to have minimal effect and act as a potential control, thus, the lower allocation of subjects to this group. However, contrary to expectations, atropine 0.01% also had significant clinical effects as evident by its effect on myopia progression, accommodation, and pupil size. The myopia progression rate in this group (-0.49 ± 0.63 D/2 years) was less than the -1.20 ± 0.69 D/2 years in the ATOM1 placebo groups.¹⁶ It was also less than the cumulative progression over 2 years of -1.3 D (95% CI, -1.24 to -1.37), -1.07 D (95% CI, -1.01 to -1.13), and -0.78 D (95% CI, -0.72 to -0.85) in 8-, 9-, and 10-year-old myopic children, respectively, from the Singapore Cohort Study of Risk Factors for Myopia study (Saw SM, personal communication, 2011). Compared with the 2 higher doses, the difference in myopia progression at 2 years in the 0.01% group was statistically significant compared with the 0.5% group. Likewise, the difference in axial length increase was statistically larger than in both the 0.1% and 0.5% groups. However, absolute differences between groups were clinically small with differences in myopic progression and axial length increase of only 0.19 D and 0.13 mm, respectively, over 2 years (Table 2, Figs 2 and 4). In addition, the ocular side effect profile was significantly better with accommodation remaining at 11.8 D, a mean pupil size of 5 mm, and a mean near logMAR vision of 0.01.

There are no published data on atropine 0.01% for direct comparison. However, in a nonrandomized study, Lee et al¹¹ found that myopia in 21 children aged 6–12 years receiving atropine 0.05% progressed at a rate of 0.28 ± 0.26 D per year, compared with 0.75 ± 0.35 D per year in 57

consecutive untreated clinic patients. In a retrospective review of 50 pre-myopia children, 24 of whom were started on atropine 0.025%, Fang et al²⁹ noted that subsequent myopia shift was less (-0.14 ± 0.24 D) in the atropine 0.025% groups compared with controls (-0.58 ± 0.34 D).

Overall, atropine-related adverse effects were uncommon at the 0.01% dose. Allergic reactions were most frequent, with 3.2% experiencing allergic conjunctivitis and 0.8% experiencing an allergy-associated dermatitis, all of which were in the 0.1% or 0.5% groups. A number of children (11%) also noted at least 1 line loss in distance BCVA (Table 3). These effects are reversible on stopping medication.¹⁸ There are no long-term studies on the effect of atropine on the eye, and continued vigilance is necessary. However, atropine has been clinically available since the early 1900s, and so far there are no known long-term adverse effects associated with its use.²³

The strength of this study was its randomized double-blind design and low dropout rate, whereas an acknowledged weakness of the study was the lack of a placebo control group, necessitating use of external (historical and population) controls. The non-inclusion of a placebo group was a decision based on findings from the ATOM1 study, which clearly showed the efficacy of atropine treatment compared with placebo, rendering a placebo arm unethical. The more important aspect of this trial remained the comparison of low dose versus high dose in terms of not only the efficacy but also the visual side effects of atropine. ATOM2 was otherwise designed to have largely similar study parameters so that direct comparison with ATOM1 was deemed appropriate.

In conclusion, our results suggest that 0.5%, 0.1%, and 0.01% atropine remain effective in reducing myopia progression, compared with placebo treatment, and that the clinical differences in myopia progression among these 3 groups are small. The lowest concentration of 0.01% atropine thus seems to retain efficacy and is a viable concentration for reducing myopia progression in children, while attaining a clinically significant improved safety profile in terms of accommodation, pupil size, and near visual acuity, and subsequently reduced adverse impact on visual function. Moreover, the 0.01% formulation exhibited fewer ad-

verse events. Atropine 0.01% is currently not commercially available. However, these findings collectively suggest that a nightly dose of atropine at 0.01% seems to be a safe and effective regimen for slowing myopia progression in children, with minimal impact on visual function in children.

References

- Gimbel HV. The control of myopia with atropine. *Can J Ophthalmol* 1973;8:527–32.
- Kelly TS, Chatfield C, Tustin G. Clinical assessment of the arrest of myopia. *Br J Ophthalmol* 1975;59:529–38.
- Bedrossian RH. The effects of atropine on myopia. *Ophthalmology* 1979;86:713–7.
- Brodstein RS, Brodstein DE, Olson RJ, et al. The treatment of myopia with atropine and bifocals: a long-term prospective study. *Ophthalmology* 1984;91:1373–9.
- Brenner RL. Further observations on use of atropine in the treatment of myopia. *Ann Ophthalmol* 1985;17:137–40.
- Chou AC, Shih YF, Ho TC, Lin LL. The effectiveness of 0.5% atropine in controlling high myopia in children. *J Ocul Pharmacol Ther* 1997;13:61–7.
- Romano PE, Donovan JP. Management of progressive school myopia with topical atropine eyedrops and photochromic bifocal spectacles. *Binocul Vis Strabismus Q* 2000;15:257–60.
- Kennedy RH, Dyer JA, Kennedy MA, et al. Reducing the progression of myopia with atropine: a long term cohort study of Olmsted County students. *Binocul Vis Strabismus Q* 2000;15(Suppl):281–304.
- Chiang MF, Kouzis A, Pointer RW, Repka MX. Treatment of childhood myopia with atropine eyedrops and bifocal spectacles. *Binocul Vis Strabismus Q* 2001;16:209–15.
- Syniuta LA, Isenberg SJ. Atropine and bifocals can slow the progression of myopia in children. *Binocul Vis Strabismus Q* 2001;16:203–8.
- Lee JJ, Fang PC, Yang IH, et al. Prevention of myopia progression with 0.05% atropine solution. *J Ocul Pharmacol Ther* 2006;22:41–6.
- Fan DS, Lam DS, Chan CK, et al. Topical atropine in retarding myopic progression and axial length growth in children with moderate to severe myopia: a pilot study. *Jpn J Ophthalmol* 2007;51:27–33.
- Yen MY, Liu JH, Kao SC, Shiao CH. Comparison of the effect of atropine and cyclopentolate on myopia. *Ann Ophthalmol* 1989;21:180–2, 187.
- Shih YF, Chen CH, Chou AC, et al. Effects of different concentrations of atropine on controlling myopia in myopic children. *J Ocul Pharmacol Ther* 1999;15:85–90.
- Shih YF, Hsiao CK, Chen CJ, et al. An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression. *Acta Ophthalmol Scand* 2001;79:233–6.
- Chua WH, Balakrishnan V, Chan YH, et al. Atropine for the treatment of childhood myopia. *Ophthalmology* 2006;113:2285–91.
- Liang CK, Ho TY, Li TC, et al. A combined therapy using stimulating auricular acupoints enhances lower-level atropine eyedrops when used for myopia control in school-aged children evaluated by a pilot randomized controlled clinical trial. *Complement Ther Med* 2008;16:305–10.
- Tong L, Huang XL, Koh AL, et al. Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. *Ophthalmology* 2009;116:572–9.
- Williams RL. A note on robust variance estimation for cluster-correlated data. *Biometrics* 2000;56:645–6.
- Dirani M, Chan YH, Gazzard G, et al. Prevalence of refractive error in Singaporean Chinese children: the Strabismus, Amblyopia and Refractive Error in young Singaporean Children (STARS) Study. *Invest Ophthalmol Vis Sci* 2010;51:1348–55.
- Saw SM, Tong L, Chua WH, et al. Incidence and progression of myopia in Singaporean school children. *Invest Ophthalmol Vis Sci* 2005;45:51–7.
- Wu HM, Seet B, Yap EP, et al. Does education explain ethnic difference in myopia prevalence? A population-based study of young adult males in Singapore. *Optom Vis Sci* 2001;78:234–9.
- North RV, Kelly ME. A review of the uses and adverse effects of topical administration of atropine. *Ophthalmic Physiol Opt* 1987;7:109–14.
- Saw SM, Gazzard G, Au Eong KG, Tan DT. Myopia: attempts to arrest progression. *Br J Ophthalmol* 2002;86:1306–11.
- Saw SM, Shih-Yen EC, Koh A, Tan D. Interventions to retard myopia progression in children: an evidence-based update. *Ophthalmology* 2002;109:415–21.
- Duncan G, Collison DJ. Role of the non-neuronal cholinergic system in the eye: a review. *Life Sci* 2003;72:2013–9.
- Morgan I, Megaw P. Using natural STOP growth signals to prevent excessive axial elongation and the development of myopia. *Ann Acad Med Singapore* 2004;33:16–20.
- Prepas SB. Light, literacy and the absence of ultraviolet radiation in the development of myopia. *Med Hypotheses* 2008;70:635–7.
- Fang PC, Chung MY, Yu HJ, Wu PC. Prevention of myopia onset with 0.025% atropine in premyopic children. *J Ocul Pharmacol Ther* 2010;26:341–5.

Footnotes and Financial Disclosures

Originally received: April 5, 2011.

Final revision: July 20, 2011.

Accepted: July 20, 2011.

Available online: ●●●.

Manuscript no. 2011-538.

¹ Singapore National Eye Center.

² Singapore Eye Research Institute.

³ Duke-NUS Graduate Medical School, Singapore.

⁴ Singapore Clinical Research Institute.

⁵ Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore.

Financial Disclosure(s):

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

Supported by grants from the National Medical Research Council (MH 95:03/1-23) and SingHealth (SHF/FG039/2004 and TEST 08-03).

Correspondence:

Donald Tan, FRCS, FRCOphth, Singapore National Eye Center, 11 Third Hospital Avenue, Singapore 168751. E-mail: snecdt@pacific.net.sg.