# Atropine for the Treatment of Childhood Myopia: Changes after Stopping Atropine 0.01%, 0.1% and 0.5%

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• PURPOSE: To study the change in spherical equivalent and other ocular parameters 1 year after stopping the administration of atropine.

• DESIGN: Prospective randomized double-masked clinical trial.

• METHODS: We assigned 400 myopic children, 6 to 12 years of age, to receive atropine 0.5%, 0.1% or 0.01% for 24 months, after which medication was stopped. Parents and children gave informed consent to participate in the research. Children were reviewed at 26, 32 and 36 months, and changes in cycloplegic spherical equivalent (SE), axial length (AL), visual acuity, pupil size, and accommodation were assessed.

• RESULTS: Of the children, 356 (89%) entered into the washout phase. At entry, there was no significant difference in age, gender, SE, or AL among the children in the various atropine groups. Over the following 12 months, myopic progression was greater in the 0.5% eyes (−0.87 ± 0.52 D), compared to the 0.1% (−0.68 ± 0.45 D) and 0.01% eyes (−0.28 ± 0.33 D, $P < 0.001$). AL growth was also greater in the 0.5% (0.35 ± 0.20 mm) and 0.1% (0.33 ± 0.18 mm) eyes, compared to the 0.01% eyes (0.19 ± 0.13 mm, $P < 0.001$). Pupil size and near visual acuity returned to pre-atropine levels in all groups, but accommodation at 36 months was less in the 0.5% eyes (13.24 ± 2.72 D) compared to the 0.1% (14.45 ± 2.61 D) and 0.01% eyes (14.04 ± 2.90 D, $P < 0.001$). The overall increase in SE over the entire 36 months in the 0.5%, 0.1% and 0.01% groups was −1.15 ± 0.81 D, −1.04 ± 0.83 D and −0.72 ± 0.72 D, respectively ($P < 0.001$).

• CONCLUSION: There was a myopic rebound after atropine was stopped, and it was greater in eyes that had received 0.5% and 0.1% atropine. The 0.01% atropine effect, however, was more modulated and sustained. (Am J Ophthalmol 2014;157:451–457. © 2014 by Elsevier Inc. All rights reserved.)

ATROPINE HAS BEEN SHOWN IN SEVERAL STUDIES TO slow myopia progression in children.[1–19] In the Atropine Treatment of Myopia trials (ATOM1 and ATOM2), atropine 1.0%, 0.5%, 0.1%, and 0.01% slowed myopia progression by 80%, 75%, 70%, and 60%, respectively, over the first 24 months compared to placebo-treated eyes.[16,19] The mean changes in spherical equivalents were −0.28 ± −0.69; −0.30 ± 0.60; −0.38 ± 0.60; and −0.49 ± 0.63 diopters (D), respectively, compared to −1.20 ± 0.69 D in placebo-treated eyes. However, in the ATOM1 study, when atropine 1.0% was stopped, there was a rebound in myopia of −1.14 ± 0.80 D in those eyes, so that the overall change in spherical equivalent (SE) in atropine-treated eyes was −1.37 ± 0.78 D compared to −1.56 ± 0.89 D in placebo-treated eyes at 36 months.[18]

We report here the phase 2 results of our ATOM2 study. The aim of phase 2 was to assess changes in SE, axial length (AL), pupil size, accommodation, and visual acuity in eyes treated with atropine 0.01%, 0.1% and 0.5% after cessation of medication immediately following phase 1 of our ATOM2 study.

## METHODS

THE RESULTS DESCRIBED ARE BASED ON A 12-MONTH washout period after the phase 1 stage of the ATOM2 study, a randomized double-masked control study. In phase 1 of this study, 400 children (aged 6 to 12 years) with myopia ≥2.0 D, astigmatism of <1.50 D and documented myopic progression of ≥0.50 D over the past year were randomized to daily 0.01%, 0.1% or 0.5% atropine in a 1:2:2 ratio in 6 gender and age strata to ensure an equal gender-age balance among the groups. Study investigators, parents and children were all masked to the dosage of atropine assigned throughout the entire 5-year study period. The study was conducted according to the tenets of the Declaration of Helsinki. Ethics approval was obtained from the Singapore Eye Research Institute Review Board, and the study was registered with the ClinicalTrial.gov website (registration no: NTC00371124). Parents and children gave informed consent to participate in the research.

Methods used in this first phase are described in detail elsewhere.[19] Briefly, children were reviewed at 4, 8, 12, 16, 20, and 24 months. In phase 2, the washout phase, children were reviewed at 26, 32 and 36 months. At each visit, best-corrected visual acuity for distance and near, accommodation, pupil size under mesopic and photopic conditions, cycloplegic autorefraction, and ALs were measured.

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Distance vision was assessed using the Early Treatment Diabetic Retinopathy study chart and recorded as a logarithm of the minimum angle of resolution (logMAR). Near vision was tested using a reduced logMAR chart at 40 cm. Accommodation was measured using a Royal Air Force near-point rule with accommodation amplitude calculated as the inverse of the near point of accommodation. Mesopic and photopic pupil sizes were measured using the Procyon 3000 pupillometer (Lion House, London, UK) and the neuroptic pupillometer (Neuroptics, Irvine, CA, USA) under 4 and 300 lux illumination, respectively.

Cycloplegia was achieved with 3 drops of cyclopentolate 1% (Cyclogyl; Alcon-Convreur, Rijkswerg, Belgium) administered at 5-minute intervals. Cycloplegic autorefraction was then determined, 30 minutes after the last drop, using the Canon RK-F1 autorefractor (Canon, Tochigiken, Japan). Five readings, all of which were ≤0.50 D apart, were averaged, and SE was calculated as sphere plus half cylinder power. AL was measured using the Zeiss IOLMaster (Carl Zeiss Meditec, Dublin, CA, USA). Five AL readings, all of which were <0.05 mm apart, were averaged.

• **STATISTICAL ANALYSIS:** All analyses were based on the intention-to-treat principle and were performed using the statistical software Stata (v 10.1; Stata, College Station, TX, USA). The demographic information, such as age and gender, was reported at the beginning of the washout period (ie, the second annual visit). The mean and the standard deviation (SD) were summarized according to the atropine-dosage group for continuous variables, and analysis of variance (ANOVA) was used to test the mean difference among atropine groups. For the categorical variables, the number and the proportion were summarized by atropine group, and the Fisher exact test was used to test for the difference in proportion among atropine groups.

For the measured ocular parameters, the intraclass correlation between 2 eyes was examined for the screening visit (pre-atropine) or the baseline visit (after having taken atropine for 2 weeks), the second annual visit, the 26-month visit, the 32-month visit, and the 36-month visit. With the measurements of both eyes pooled together, the mean and the SD of the ocular parameters were reported at these visits for each atropine-dosage group. When comparing the effect across atropine groups, the measurements from both eyes were pooled in a combined analysis using the Huber-White robust standard errors, in order to allow for the correlation between eyes within each person.[20] The corresponding *P* value was reported for the global null hypothesis of no difference among atropine groups. For spherical equivalent and AL, the changes from the baseline visit or the second annual visit to the 36-month visit were studied similarly. In addition, for each atropine group, the change in spherical equivalent and the change in axial length were plotted over visits until the 36-month visit.

# RESULTS

WE STUDIED 356 CHILDREN (89%) WHO ENTERED INTO THE phase 2 washout phase of the ATOM2 study, with 75, 141 and 140 children in the 0.01%, 0.1% and 0.5% atropine groups, respectively (Fig. 1). At the 24-month visit, there was no significant difference in age, gender, SE, or AL in the children in each group (Table 1).

Analysis showed that 44 children (11%) were lost to follow-up by the 24-month visit. These children were found to have similar ages (9.7 ± 1.5 vs 9.7 ± 1.9 years, $P = 0.99$); similar ALs (25.01 ± 0.97 vs 25.18 ± 1.59 mm, $P = 0.264$); and similar spherical equivalents at baseline (−3.89 ± 1.82 vs −4.48 ± 1.59 D, $P = 0.052$) to those still in the study. By 36 months, 52 children (13%) had been lost to follow-up (15.5%, 10.3% and 14.3% in the 0.01%, 0.1% and 0.5% groups, respectively). These children had similar ages and ALs at baseline but had lower levels of myopia (−3.89 ± 1.76 vs −4.49 ± 1.59D, $P = 0.037$) at baseline.

• **CHANGE IN SPHERICAL EQUIVALENT AND AXIAL LENGTH:** On cessation of atropine, a myopic rebound was noted in all 3 groups that was statistically greater in 0.5% eyes (−0.87 ± 0.52 D) than in 0.1% (−0.68 ± 0.45 D) and 0.01% (−0.28 ± 0.33D) eyes ($P < 0.001$) (Table 1; Fig. 2). The increase was greater in the first 8 months and slowed over the next 4 months. This resulted in overall progression over the 36-month period being significantly less in the 0.01% eyes (−0.72 ± 0.72 D) than in the 0.1% (−1.04 ± 0.83 D) and 0.5% eyes (−1.15 ± 0.81 D) (Table 1, Fig. 2). A larger proportion of children in the higher dose atropine groups also had greater increases in myopia between 24 and 36 months compared to the 0.01% group (Fig. 3).

With regard to AL, during the phase 2 period, there was a significantly greater increase in AL in the 0.5% (0.35 mm) and 0.1% eyes (0.33 mm) compared to the 0.01% (0.19 mm) eyes ($P < 0.0001$) (Table 1). However, the overall change from baseline to 36 months was similar in all groups ($P = 0.787$) (Fig. 4).

• **CHANGE IN PUPIL SIZE, ACCOMMODATION AND DISTANCE/NEAR VISION:** Photopic and mesopic pupil sizes were much larger in the 0.1% and 0.5% groups compared to the 0.01% group at 24 months (end of phase 1). In phase 2, upon cessation of atropine, there was a reduction in pupil size in all groups, with recovery being quicker in the 0.01% eyes. There was no difference in pupil size among groups at 36 months, but the pupil sizes were slightly smaller (photopic, 0.37 mm; mesopic, 0.22 mm) than those noted at the first screening visit ($P < 0.001$, for both photopic and mesopic) in all 3 groups.

Recovery of accommodation also occurred in all groups but was again quicker in the 0.01% eyes (26 months) than in the 0.1% and 0.5% eyes (32 months). At 36 months, however, accommodation in the 0.5% eyes was still significantly less than that in the 0.1% and 0.01% eyes

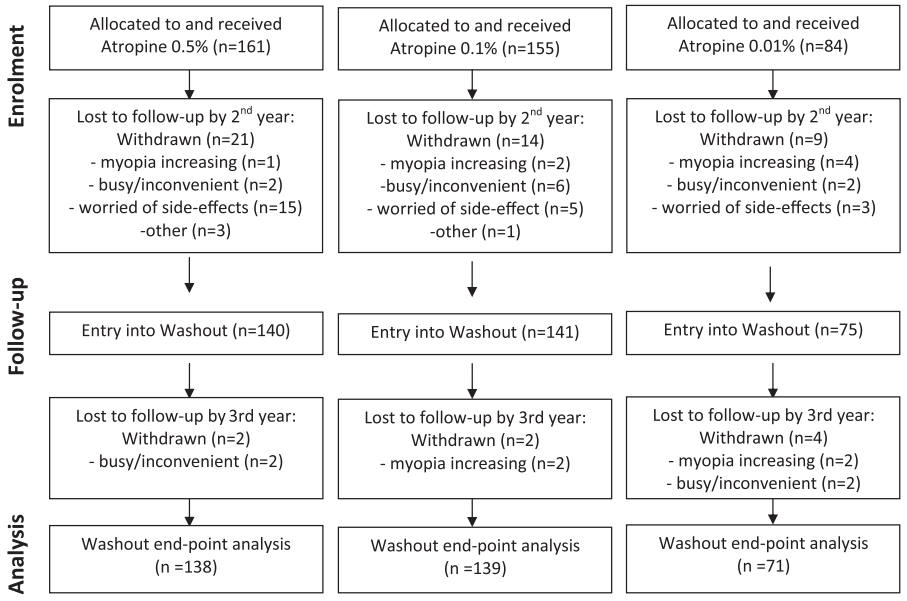


**FIGURE 1. Atropine for the Treatment of Childhood Myopia study 2 (ATOM2) subject flowchart for washout phase.**

**TABLE 1.** Demographic and Biometric Parameters of Spherical Equivalent and Axial Length Over Time in the Atropine 0.01%, 0.1% and 0.5% groups

| | ICC | Atropine 0.01% | Atropine 0.1% | Atropine 0.5% | *P* value |
|---|---|---|---|---|---|
| Age at 24 months (yr), mean (SD) | - | 11.65 (1.44) | 11.68 (1.52) | 11.73 (1.53) | 0.9368 |
| Female, n (%) | - | 36 (48.00) | 67 (47.52) | 67 (47.86) | 1.000[a] |
| Spherical equivalent (SE) (D) | | Mean (SD) | Mean (SD) | Mean (SD) | |
| Baseline | 0.93 | −4.47 (1.50) | −4.49 (1.45) | −4.33 (1.83) | 0.6704 |
| 24 months | 0.90 | −5.10 (1.51) | −4.85 (1.29) | −4.70 (1.70) | 0.2027 |
| 26 months | 0.91 | −5.14 (1.50) | −5.00 (1.29) | −4.97 (1.69) | 0.7214 |
| 32 months | 0.91 | −5.31 (1.57) | −5.36 (1.32) | −5.42 (1.74) | 0.8852 |
| 36 months | 0.91 | −5.32 (1.55) | −5.53 (1.34) | −5.57 (1.74) | 0.5088 |
| Change of SE (D) | | | | | |
| 24 to 36 months | 0.82 | −0.28 (0.33) | −0.68 (0.45) | −0.87 (0.52) | <0.0001 |
| Baseline to 36 months | 0.87 | −0.72 (0.72) | −1.04 (0.83) | −1.15 (0.81) | 0.0002 |
| Axial length (AL) (mm) | | | | | |
| Baseline | 0.96 | 25.17 (0.98) | 25.13 (0.83) | 25.14 (0.92) | 0.9352 |
| 24 months | 0.95 | 25.68 (1.01) | 25.39 (0.82) | 25.43 (0.97) | 0.0821 |
| 26 months | 0.95 | 25.71 (1.01) | 25.46 (0.82) | 25.50 (0.98) | 0.1602 |
| 32 months | 0.95 | 25.81 (1.05) | 25.62 (0.84) | 25.67 (0.99) | 0.4054 |
| 36 months | 0.95 | 25.84 (1.05) | 25.71 (0.85) | 25.77 (1.00) | 0.6498 |
| Change in AL ( mm) | | | | | |
| 24 to 36 months | 0.86 | 0.19 (0.13) | 0.33 (0.18) | 0.35 (0.20) | <0.0001 |
| Baseline to 36 months | 0.89 | 0.58 (0.38) | 0.60 (0.38) | 0.61 (0.35) | 0.7871 |

Note: Baseline: measurements taken 2 weeks after onset of atropine.
[a]The P value is based on the Fisher exact test.

($P < 0.001$). Accommodation in all groups at 36 months was also −2.56 D less than that recorded at screening visit 3 years earlier ($P < 0.001$).

Distance logMAR visual acuity remained good throughout the first phase and continued to remain unchanged through the washout period in all 3 groups (Table 2). Near logMAR visual acuity was reduced in the 0.1% and 0.5% eyes at 24 months but had recovered quickly and completely by 26 months in all 3 groups.

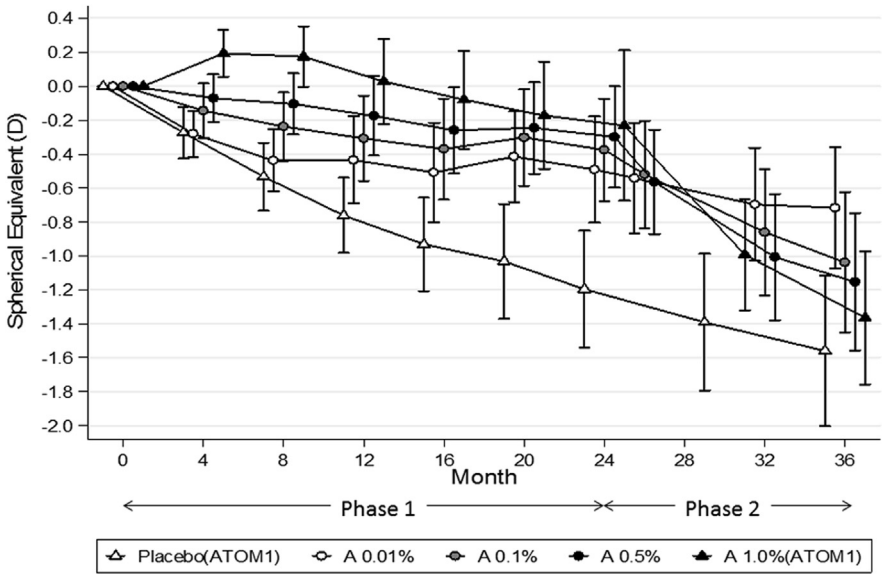


**FIGURE 2. Change in spherical equivalent in the Atropine for the Treatment of Childhood Myopia study 1 (ATOM1) eyes that received 1.0% atropine and placebo, and Atropine for the Treatment of Childhood Myopia study 2 (ATOM2) eyes that received 0.5%, 0.1% and 0.01% atropine. Error bars indicate standard deviation (SD).**

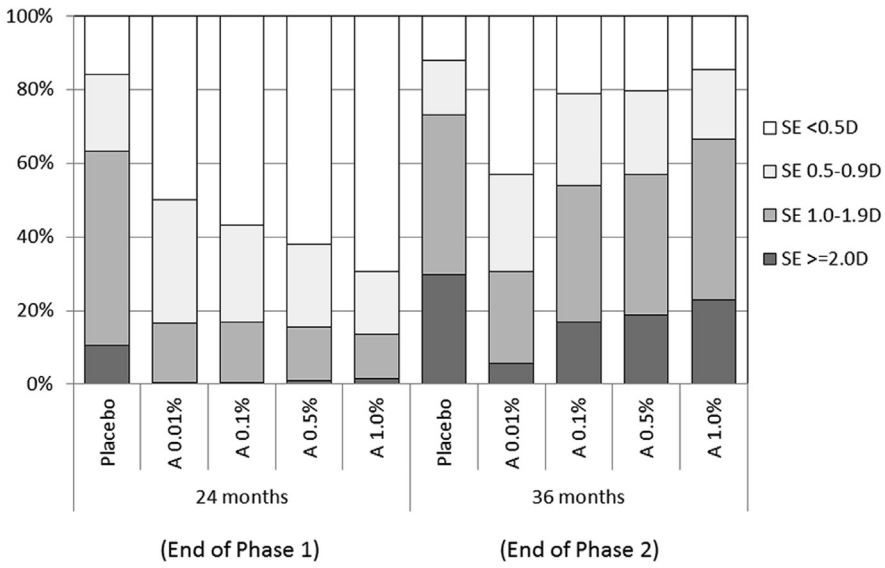


**FIGURE 3. Proportional change in myopia (spherical equivalent, SE) in Atropine for the Treatment Of Childhood Myopia study 1 (ATOM1) eyes that received 1.0% atropine and placebo, and Atropine for the Treatment of Childhood Myopia study 2 (ATOM2) eyes that received 0.5%, 0.1% and 0.01% atropine at 24 and 36 months.**

## DISCUSSION

IN THIS SECOND PHASE OF OUR ATOM2 STUDY, WHEN atropine was ceased after 2 years of treatment, there was an increase in myopia that was greater in eyes treated with higher dosages of atropine. This was associated with a corresponding increase in AL in the atropine 0.1% and 0.5% eyes. Pupil size, accommodation and near vision recovered after atropine was stopped, but recovery was quicker in eyes treated with lower doses of atropine.

These results support the trend seen in the ATOM1 study, in which there was a myopic rebound after cessation of atropine.[16,18] Combining the ATOM1 and ATOM2 results, a dose-related response was noted; the myopic rebound in the atropine 1.0% eyes was larger than that in

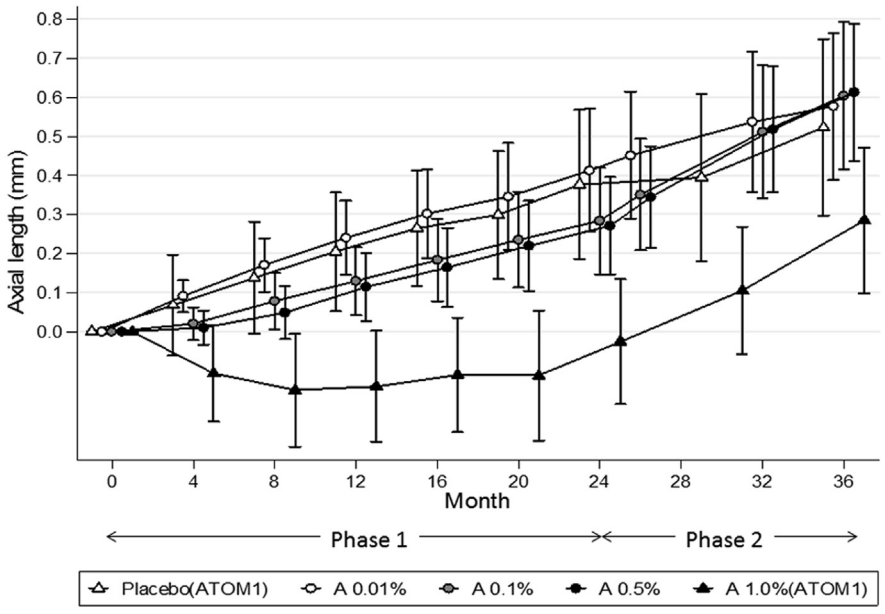


**FIGURE 4. Change in axial length in Atropine for the Treatment Of Childhood Myopia study 1 (ATOM1) eyes that received 1.0% atropine and placebo, and Atropine for the Treatment of Childhood Myopia study 2 (ATOM2) eyes that received 0.5%, 0.1% and 0.01% atropine. Error bars indicate standard deviation (SD).**

the 0.5%, 0.1% and 0.01% eyes (Fig. 2). As a result, the subsequent progression of myopia at 36 months was paradoxically larger in the atropine 1.0%, compared to the 0.5%, 0.1% and 0.01% eyes.

The AL in the atropine 0.1% and 0.5% groups (from the ATOM2 study) and the 1.0% group (from the ATOM1 study) also increased more rapidly after cessation of atropine (Fig. 4), mirroring the increase in myopia. There was a more steady increase in the 0.01% (ATOM2) and ATOM1 placebo group. However, direct comparisons of AL between the 2 ATOM studies was difficult because AL was measured using the A-scan in ATOM1 and IOLmaster in ATOM2. A plot of SE vs AL at the screening visit suggests that AL measurements were lower when using the IOLmaster compared to the A-scan for any spherical equivalent and that this difference increased with lower spherical equivalence.

It is interesting that during the washout period, the change in SE was greater than the change in AL in the groups receiving higher atropine: 3.5 D/mm in the 0.5% group, 2.1 D/mm in the 0.1% group, and 1.5 D/mm in the 0.01% atropine groups; ie, the change in SE during the rebound period was not directly associated with the change in AL alone. However, SE could also be associated with changes in other ocular parameters (eg, corneal curvature, lens thickness or the ratio of posterior vitreous to anterior chamber depth), a possibility that warrants further investigation.

The dose-specific differences in rebound of SE and AL may be explained partially by the pharmaceutical reactions of the eye to atropine. It is known that all 5 forms of muscarinic receptors are present in the sclera and retina, and specific muscarinic receptors are also present in the cornea, iris and lens.[21–23] Although it is not certain how atropine slows myopia progression, it is thought to upregulate or downregulate muscarinic receptors in the retina and sclera, which then either directly or indirectly alter the sclera matrix and thus the degree of scleral creep and ocular elongation.[21–26] It is possible that lower dosages of atropine act at a different site (more anteriorly) or affect various muscarinic receptors to different degrees, resulting in a more modulated adaptive response than occurs with higher dosages of atropine.

Also of clinical interest was whether near visual acuity, pupil size and accommodation recovered fully after cessation of atropine. In the ATOM2 study, all 3 doses had minimal long-term effects on best-corrected distance and near visual acuity. Pupil size and accommodation took several months to recover, with recovery being quicker and more complete in 0.01% eyes, as could be expected with this lowest dosage. Accommodation amplitudes at 36 months were, however, 2.56 D lower than those recorded at the first pre-atropine screening visit. This, too, was not unexpected because amplitudes are expected to be less at 11 years than at 8 years of age. Indeed, at their baseline screening visit, the mean accommodation amplitude in children 8 to 9 years of age (n = 76) was 1.38 D more than that in those between 11 and -12 years of age (n = 61) (16.48 D vs 15.10 D, $P = 0.011$). Of note, however, was that accommodative amplitude in the 0.5% eyes (13.24 ± 2.72 D) was lower than that in the 0.1% eyes (14.45 ± 2.60D) and

**TABLE 2.** Pupil Size, Accommodation and Visual Acuity Values Over Time in the Atropine 0.01%, 0.1% and 0.5% Groups

| | ICC | Atropine 0.01% mean (SD) | Atropine 0.1% mean (SD) | Atropine 0.5% mean (SD) | *P* value |
|---|---|---|---|---|---|
| Pupil size (mesopic) (mm) | | | | | |
| Screening (pre-atropine) | 0.64 | 4.66 (0.71) | 4.58 (0.69) | 4.58 (0.68) | 0.6353 |
| 24 months | 0.93 | 5.50 (0.80) | 6.89 (0.99) | 7.76 (1.10) | <0.0001 |
| 26 months | 0.81 | 4.39 (0.65) | 4.49 (0.81) | 4.62 (0.78) | 0.0507 |
| 32 months | 0.76 | 4.33 (0.79) | 4.20 (0.64) | 4.29 (0.67) | 0.3177 |
| 36 months | 0.81 | 4.19 (0.74) | 4.20 (0.72) | 4.23 (0.64) | 0.8894 |
| Pupil size (photopic) (mm) | | | | | |
| Screening (pre-atropine) | 0.94 | 3.90 (0.57) | 3.94 (0.63) | 4.03 (0.66) | 0.2117 |
| 24 months | 0.96 | 5.07 (0.92) | 6.66 (1.07) | 7.55 (1.20) | <0.0001 |
| 26 months | 0.95 | 3.91 (0.74) | 4.00 (0.67) | 4.16 (0.67) | 0.0245 |
| 32 months | 0.96 | 3.85 (0.70) | 3.83 (0.76) | 3.90 (0.64) | 0.6453 |
| 36 months | 0.94 | 3.76 (0.59) | 3.69 (0.55) | 3.75 (0.58) | 0.6089 |
| Accommodation (D) | | | | | |
| Screening (pre-atropine) | 0.86 | 16.17 (3.38) | 16.83 (3.00) | 15.81 (3.43) | 0.0128 |
| 24 months | 0.95 | 11.78 (3.20) | 6.81 (3.38) | 4.10 (2.60) | <0.0001 |
| 26 months | 0.91 | 14.65 (3.19) | 13.85 (3.41) | 12.42 (3.52) | <0.0001 |
| 32 months | 0.90 | 14.48 (3.10) | 14.25 (2.88) | 13.50 (3.23) | 0.0401 |
| 36 months | 0.91 | 14.04 (2.90) | 14.45 (2.60) | 13.24 (2.72) | 0.0006 |
| Distance logMAR visual acuity | | | | | |
| Screening (pre-atropine) | 0.72 | 0.02 (0.05) | 0.01 (0.06) | 0.02 (0.06) | 0.3872 |
| 24 months | 0.76 | 0.00 (0.06) | 0.01 (0.05) | 0.01 (0.06) | 0.2468 |
| 26 months | 0.71 | −0.01 (0.05) | 0.00 (0.06) | 0.01 (0.05) | 0.1499 |
| 32 months | 0.73 | −0.01 (0.05) | 0.00 (0.06) | 0.01 (0.06) | 0.0300 |
| 36 months | 0.67 | −0.01 (0.05) | −0.01 (0.05) | 0.00 (0.05) | 0.3822 |
| Near logMAR visual acuity | | | | | |
| Screening (pre-atropine) | 0.66 | 0.04 (0.09) | 0.05 (0.08) | 0.04 (0.07) | 0.5648 |
| 24 months | 0.74 | 0.02 (0.07) | 0.11 (0.17) | 0.29 (0.18) | <0.0001 |
| 26 months | 0.83 | −0.02 (0.07) | 0.00 (0.08) | 0.02 (0.08) | 0.0004 |
| 32 months | 0.72 | −0.01 (0.05) | −0.01 (0.06) | −0.01 (0.07) | 0.8660 |
| 36 months | 0.74 | −0.01 (0.05) | −0.02 (0.06) | −0.01 (0.06) | 0.3947 |

that in the 0.01% eyes (14.04 ± 2.90 D) eyes at 36 months. Although this had no clinical effect on near vision, it is questionable whether this difference will persist and result in an earlier onset of presbyopia in the future.

The strengths of this study lie in its randomized, double blinded design and relatively low loss-to-follow-up rates. The study, however, is limited by the lack of a true placebo or control group in the ATOM2 study, necessitating the use of a historical control from ATOM1, which had almost identical study methodologies.[19] Although study design was largely similar in the 2 studies, we acknowledge a temporal difference in the studies; ATOM1 was performed between 1999 and 2004, and ATOM2 between 2006 and 2012. In addition, ATOM1 placebo subjects were slightly younger (9.2 vs 9.7 years) and had lower degrees of myopia (−3.5 vs −4.7 D) at screening. AL was measured by differing devices in the 2 studies.

In conclusion, cessation of 0.1% and 0.5% atropine resulted in greater degrees of myopic rebound, with a negative effect on both SE and AL. In contrast, the lower dosage of 0.01% atropine appears to result in less myopic rebound, which led to a more sustained effect of myopia retardation and overall reduction of myopia. Coupled with the fact that 0.01% atropine also showed the least amount of pupil dilation and accommodative loss, and consequently the fastest recovery from these side effects after cessation, we conclude that atropine eye drops at the lowest dosage of 0.01% results in an optimal balance between efficacy and safety and could represent a clinically viable approach to myopia retardation in children.

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## Biosketch

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