



## Atropine for the Prevention of Myopia Progression in Children

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**Purpose:** To review the published literature on the efficacy of topical atropine for the prevention of myopic progression in children.

**Methods:** Literature searches were last conducted in December 2016 in the PubMed database with no date restrictions, but were limited to studies published in English, and in the Cochrane Library database without any restrictions. The combined searches yielded 98 citations, 23 of which were reviewed in full text. Of these, 17 articles were deemed appropriate for inclusion in this assessment and subsequently were assigned a level of evidence rating by the panel methodologist.

**Results:** Seventeen level I, II, and III studies were identified. Most of the studies reported less myopic progression in children treated with atropine compared with various control groups. All 8 of the level I and II studies that evaluated primarily myopic progression revealed less myopic progression with atropine (myopic progression ranging from  $0.04 \pm 0.63$  to  $0.47 \pm 0.91$  diopters (D)/year) compared with control participants (myopic progression ranging from  $0.38 \pm 0.39$  to  $1.19 \pm 2.48$  D/year). In studies that evaluated myopic progression after cessation of treatment, a rebound effect was noted. Several studies evaluated the optimal dosage of atropine with regard to myopic progression, rebound after treatment cessation, and minimization of side effects. Lower dosages of atropine (0.5%, 0.1%, and 0.01%) were found to be slightly less effective during treatment periods of 1 to 2 years, but they were associated with less rebound myopic progression (for atropine 0.01%, mean myopic progression after treatment cessation of  $0.28 \pm 0.33$  D/year, compared with atropine 0.5%,  $0.87 \pm 0.52$  D/year), fewer side effects, and similar long-term results for myopic progression after the study period and rebound effect were considered. The most robust and well-designed studies were carried out in Asian populations. Studies involving patients of other ethnic backgrounds failed to provide sufficient evidence of an effect of atropine on myopic progression.

**Conclusions:** Level I evidence supports the use of atropine to prevent myopic progression. Although there are reports of myopic rebound after treatment is discontinued, this seems to be minimized by using low doses (especially atropine 0.01%). *Ophthalmology* 2017;124:1857-1866 © 2017 by the American Academy of Ophthalmology

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy, effectiveness, and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee Pediatric Ophthalmology/Strabismus Panel is to review the published

literature on the efficacy of topical atropine for the prevention of myopic progression in children.

### Background

Myopia is a common treatable ocular condition that occurs in up to 50% of the adult population in the United States.<sup>1,2</sup> Although it is less common in children, the prevalence of myopia in the United States is increasing, and between 1971 and 1999, it rose from 25% to 42%.<sup>3</sup> In Asian countries, myopia is more common, and it is increasing in prevalence at an even more rapid rate. Up to 90% of young adults

have myopia in Taiwan, Singapore, and Hong Kong.<sup>4-7</sup> Additionally, myopia seems to be increasing in younger age groups as well, with an increased prevalence from 5.8% in 1983 to 21% in 2000 in 7-year-old children in Taiwan.<sup>6</sup>

The cause and underlying mechanism of myopia progression remain unclear; therefore, its increasing prevalence is not well understood. Several theories have been proposed to explain the recent increase and its earlier onset in children, including a decrease in outdoor activity, an increase in time spent doing near work, and an increase in urbanization.<sup>8,9</sup> Despite these theories and studies showing that increasing outdoor activity and decreasing near work may help to retard myopic progression,<sup>8,9</sup> other treatments have been sought. The prevention of myopia progression has been prioritized largely because the risks of increasing axial myopia include glaucoma, cataract, myopic macular degeneration, and retinal detachment.<sup>10,11</sup>

A 2011 Cochrane database review<sup>12</sup> evaluated the published evidence for various treatments aimed at slowing the progression of myopia in children. The treatment methods included eyeglasses that undercorrect, multifocal eyeglasses, novel lens eyeglasses, various contact lens therapies such as bifocal or multifocal contact lenses or orthokeratology, topical timolol, and topical antimuscarinic agents, including pirenzepine and atropine. The conclusion of the Cochrane review was that antimuscarinic agents are “the most likely effective treatment to slow myopia progression.”<sup>12</sup> The most commonly used and studied antimuscarinic agent for slowing myopic progression is atropine. Although there is much interest in its use, how atropine exerts antimyopia effects is not well understood. Atropine initially was used on the premise that accommodation was the causative factor in myopia progression, and therefore, cycloplegia may retard myopic advancement. However, because atropine prevents myopic progression even in animals that have striated ciliary muscles and because nonpharmacologic mechanisms for decreasing accommodation (i.e., bifocals) do not seem to retard myopic progression, researchers have shifted away from hypotheses of accommodation as the primary factor in progression.<sup>13,14</sup> Current theories about the primary factor include a local retinal effect that may retard myopia progression or a potential biochemical change brought about by binding muscarinic receptors,<sup>14</sup> which have been shown to be present in the sclera of certain animals.<sup>15</sup> Two newer theories suggest that pupillary dilation may result in increased ultraviolet A exposure, which may limit axial elongation,<sup>16</sup> or that myopia may be associated with increased chronic inflammation in the eye, which may be downregulated by atropine.<sup>17</sup> Given the broad interest in preventing myopia and numerous more recent studies evaluating atropine, we set out to review the current evidence for the use of atropine to retard the progression of myopia.

## Questions for Assessment

The purpose of this assessment is to address the following questions: (1) Does topical atropine prevent the progression

of myopia in children? and (2) Does this effect vary with atropine dosage?

## Description of Evidence

Literature searches were conducted last in December 2016 in the PubMed database with no date restrictions, but were limited to studies published in English, and in the Cochrane Library database without any restrictions. The following terms were used, along with publication and language filters:

(*Myopia*[mh] OR *myop*\* OR *shortsight*\* OR *nearsight*\*) AND (*Eyeglasses*[mh] OR *spectacle*\* OR *glasses* OR *contact lens*\* OR *atropine*[mh] OR *atropine sulfate* OR *usp* OR *atropa belladonna* OR *atropen* OR *tropic acid*) AND (*Refractive errors*[mh] OR *Refraction, Ocular*[mh] OR *Accommodation, Ocular*[mh] OR *Visual Acuity*[mh] OR *accommodat*\* OR *acuity* OR *progress*\* OR *slow*\* OR *retard*\* OR *function*\* OR *delay*\*) AND (*Infant* [MeSH] OR *Infant*\* OR *infancy* OR *Newborn*\* OR *Baby*\* OR *Babies* OR *Neonate*\* OR *Preterm*\* OR *Pre-matur*\* OR *Postmatur*\* OR *Child*[MeSH] OR *Child*\* OR *Schoolchild*\* OR *School age*\* OR *Preschool*\* OR *Kid* OR *kids* OR *Toddler*\* OR *Adolescent*[MeSH] OR *Adoles*\* OR *Teen*\* OR *Boy* OR *boys* OR *Girl*\* OR *Minors*[MeSH] OR *Minors*\* OR *Puberty*[MeSH] OR *Pubert*\* OR *Pubescen*\* OR *Prepubescen*\* OR *Pediatrics* [MeSH] OR *Paediatric*\* OR *Schools*[MeSH] OR *Nursery school*\* OR *Kindergar*\* OR *Primary school*\* OR *Secondary school*\* OR *Elementary school*\* OR *High school*\* OR *Highschool*\*).

The combined searches yielded 98 citations, and the panel reviewed 23 articles in full text. Of these, 17 articles were deemed appropriate for inclusion in this assessment (including 4 articles that are not clinical trials) and subsequently were assigned a level of evidence rating by the panel methodologist (R.T.K.). The 75 articles that were not reviewed consisted of editorials, review articles, and research that was not directly related to this assessment. The rating scale was based on that developed by the Oxford Centre for Evidence-Based Medicine.<sup>18</sup> A level I rating was assigned to well-designed and well-conducted randomized clinical trials; a level II rating was assigned to well-designed case-control and cohort studies and lower-quality randomized studies; and a level III rating was assigned to case series, case reports, and lower-quality cohort and case-control studies. Six studies met level I criteria and 6 studies met level II criteria. In addition, 6 studies that met level III criteria were included because of their impact on the use of atropine for the prevention of myopia, particularly in non-Asians.

## Published Results

The treatment evaluated for this assessment involves the administration of atropine ophthalmic solution of varying concentrations in children with myopia in an attempt to prevent myopia

progression. The articles that were reviewed examined the effect of atropine with respect to several different metrics, including the rate of progression of myopia; the rebound of myopia after cessation of treatment; the impact of atropine on biometric characteristics; the effect on accommodation and pupil size; the effect on astigmatism, intraocular pressure, and electroretinography parameters; and the occurrence of side effects. A summary of the results for level I and II studies is presented in Table 1, and a summary for the results for level III studies is presented in Table 2.

## Outcomes

**Effect on Progression of Myopia.** Progression of myopia is the primary outcome of most of the reviewed studies. In 1989, Yen et al<sup>19</sup> reported a randomized controlled trial of atropine for the treatment of myopia progression. This study compared atropine 1% dosed every other day in both eyes with 2 control groups (cyclopentolate 1% dosed nightly and a placebo drop dosed nightly). In the 247 Taiwanese children included in the study, the mean myopic progression over 12 months was  $-0.22 \pm 0.54$  diopter (D),  $-0.58 \pm 0.49$  D, and  $-0.91 \pm 0.58$  D per year in the atropine 1%, cyclopentolate 1%, and placebo groups, respectively ( $P < 0.01$  for all comparisons). Although atropine 1% was found to reduce myopic progression, there were several intolerable side effects and dropouts, and only 96 of the 247 enrolled participants completed the 1-year study. In the atropine 1% group, 100% of patients reported photophobia, but the reason for the 151 study dropouts was not specifically discussed in the report.

Because the atropine 1% was poorly tolerated, several years later a second group of Taiwanese children was evaluated in a randomized trial<sup>20</sup> comparing the following 3 groups with a control group receiving tropicamide with full single-vision distance eyeglass correction: (1) lower-dose atropine 0.5% with bifocals, (2) atropine 0.25% with partially undercorrected (0.75 D) single-vision distance eyeglasses, and (3) atropine 0.1% with full eyeglass correction. In this study, 200 children were enrolled and 186 children were followed up for the entire 2 years. The findings of this study showed that lower dosages of atropine also could slow myopic progression; the progression was  $-0.04 \pm 0.63$  D/year,  $-0.45 \pm 0.55$  D/year,  $0.47 \pm 0.91$  D/year, and  $-1.06 \pm 0.61$  D/year in the atropine 0.5%, atropine 0.25%, atropine 0.1%, and tropicamide groups, respectively ( $P < 0.01$  for all atropine groups compared with tropicamide). The authors noted that atropine 0.5% had the least myopic progression and significantly fewer (4%) of the children in that group showed rapid ( $>1$  D/year) myopia progression during the study compared with 17%, 33%, and 44% in the atropine 0.25%, atropine 0.1%, and control groups, respectively. This study was useful in understanding the potential efficacy of lower-strength atropine, but it was marred by the potential bias of differing refractive correction between groups, with no indication of masking. Two years later, Shih et al<sup>21</sup> evaluated 227 Taiwanese children, comparing the atropine 0.5% group plus multifocal (progressive) lenses with 2 control groups (multifocal progressive lenses and single-vision lenses). At 18 months, 188 participants were available for follow-up and had a mean myopic progression of  $-0.42 \pm 0.07$  D,  $-1.19 \pm 0.07$  D, and  $-1.4 \pm 0.09$  D for the atropine 0.5% plus multifocal progressive lenses, multifocal progressive lenses only, and single-vision lenses only groups,

respectively ( $P < 0.0001$  for the atropine group compared with both control groups).

In 2006, the Atropine for the Treatment of Myopia (ATOM) 1 study<sup>23</sup> was reported in Singapore. This study enrolled 400 Asian children and randomized them to either atropine 1% or a placebo eyedrop in 1 eye. Three hundred forty-six children completed the 2-year follow-up, resulting in a reported myopic progression of  $0.28 \pm 0.92$  D in the atropine 1% group compared with  $-1.2 \pm 0.69$  D in the placebo group over 2 years. The difference in myopia progression between the 2 groups at 2 years was  $-0.92$  D (95% confidence interval, 1.10 to  $-0.77$  D;  $P < 0.001$ ). Because of the known side effects of atropine 1% (such as photophobia and blurred near vision), the ATOM 1 group then initiated a second study that was reported in 2012 (ATOM 2),<sup>26</sup> which compared lower doses of atropine with historical controls. In this study, 400 children were assigned randomly in a 2:2:1 ratio to atropine 0.5%, 0.1%, or 0.01% nightly for 2 years. The mean myopic progression at 2 years in the 355 participants who completed the entire follow-up was  $-0.30 \pm 0.60$  D,  $-0.38 \pm 0.60$  D, and  $-0.49 \pm 0.63$  D in the atropine 0.5%, 0.1%, and 0.01% groups, respectively ( $P = 0.02$ , atropine 0.01% vs. atropine 0.5% groups;  $P = 0.05$ , between other concentrations). By comparison, myopia progression in ATOM 1 study was  $-1.20 \pm 0.69$  D in the placebo group and  $0.28 \pm 0.92$  D in the atropine 1% group. As an extension of the ATOM 2 study, after a 1-year washout, children who had myopia progression of at least  $-0.5$  D during the washout period then were restarted on atropine 0.01%.<sup>35</sup> For this study, 192 children (24%, 59%, and 68% of children originally randomized to atropine 0.01%, 0.1%, and 0.5%, respectively) were started on atropine 0.01% and followed up for an additional 2 years. In these 3 groups, the overall myopia progression was  $-1.98 \pm 1.1$  D,  $-1.83 \pm 1.16$  D, and  $-1.38 \pm 0.98$  D in the original atropine 0.5%, 0.1%, and 0.01% groups, respectively ( $P = 0.003$ , atropine 0.01% vs. 0.1%;  $P < 0.001$ , atropine 0.01% vs. 0.5%). Therefore, despite initially considering atropine 0.01% to be a control group, the authors believed that not only did it have the least rebound progression during the washout period, but also that it responded best to reinitiation of low-dose atropine after the washout.

Five of the randomized trials reviewed evaluated myopia progression after 1 to 2 years of treatment, and all of them found statistically significantly less progression in children using atropine. In addition, when varying doses were evaluated, most studies found relatively good efficacy of lower doses of atropine. Table 3 summarizes the effects of varying doses of atropine in level I trials to demonstrate the clinical effect of each atropine dose as well as the rebound effect on discontinuation of treatment. The lowest dose of atropine tested (atropine 0.01%) was found to be significantly effective in slowing the progression of myopia. However, during the treatment phase, atropine 0.01% was found to be significantly less effective than higher doses (atropine 0.5% and 1%). Yet, children who were treated initially with atropine 0.01% seemed to respond better when restarted on atropine 0.01% after a washout period.

**Myopia Progression during a Washout Period.** In 2009, Tong et al<sup>24</sup> reported the long-term results of the children initially enrolled in ATOM after a 1-year washout period. Of the 400 children initially enrolled, 333 children completed the 3-year follow-up (2 years on treatment and followed by a 1-year washout period). During the

1-year washout, myopic progression was  $1.14 \pm 0.8$  D/year for the atropine 1% group and  $-0.38 \pm 0.39$  D/year for the control group ( $P < 0.0001$ ). Conversely, over the entire 3-year study, the myopic progression was  $-0.46 \pm 0.26$  D/year and  $-0.52 \pm 0.30$  D/year for the atropine 1% and control groups, respectively ( $P = 0.043$ ). This is statistically significant, but is unlikely to be of clinical relevance for most physicians and patients. Chia et al<sup>28</sup> reported the results of the ATOM 2 study cohort 1 year after discontinuing treatment. Of the 400 children initially enrolled, 356 entered the washout phase. During the 1-year washout, myopic progression was  $-0.87 \pm 0.52$  D,  $-0.68 \pm 0.45$  D, and  $-0.28 \pm 0.33$  D in the atropine 0.5%, 0.1%, and 0.01% groups, respectively ( $P < 0.001$ ). Over the entire 3-year study period, the spherical equivalent became more myopic by  $-1.15 \pm 0.81$  D,  $-1.04 \pm 0.83$  D, and  $-0.72 \pm 0.72$  D in the atropine 0.5%, 0.1%, and 0.01% groups, respectively ( $P < 0.001$ ).

Of the articles reviewed, these 2 were the only ones that evaluated myopia progression after discontinuation of the treatment. In both studies, there seemed to be a dose-dependent rebound effect, with cessation after higher dosages of atropine resulting in increased myopic progression during the washout phase. Despite this finding, there was significantly less myopic progression over the entire study period (treatment and washout) for all participants treated with atropine compared with control participants. In addition, children treated with the lowest dose of atropine (atropine 0.01%) had the least myopic progression over the entire combined treatment and washout periods.

**Effect on Biometric Characteristics.** In 2001, Shih et al<sup>21</sup> evaluated axial length, anterior chamber depth, and lens thickness in their participants who were treated with atropine 0.5%, multifocal eyeglasses, or single-vision eyeglasses. They reported a significant difference in lens thickness: the atropine group had less thickening over the 18-month period compared with the 2 control groups ( $P = 0.01$ ). In addition, the increase in axial length was significantly less in the atropine group compared with the 2 control groups over the 18-month study (mean increase in axial length of  $0.22 \pm 0.03$  mm vs.  $0.49 \pm 0.03$  mm vs.  $0.59 \pm 0.04$  mm in the atropine 0.5% plus multifocal eyeglasses, multifocal eyeglasses, and single-vision eyeglasses groups, respectively;  $P = 0.0001$ ). At the 2-year end point in the ATOM 1 study,<sup>23</sup> participants who were treated with atropine 1% had a mean change in axial length of  $-0.02 \pm 0.35$  mm compared with the placebo group, which had a mean elongation of  $0.38 \pm 0.38$  mm ( $P < 0.001$ ). After the 1-year washout period,<sup>24</sup> the mean elongations were persistently different: the atropine-treated eyes elongated by  $0.29 \pm 0.37$  mm compared with control eyes, which elongated by  $0.52 \pm 0.45$  mm ( $P < 0.0001$ ).

Kumaran et al<sup>29</sup> evaluated the ATOM 1 study cohort to understand better how atropine influences ocular growth. They included 313 children from the ATOM 1 study and measured changes in corneal curvature, anterior chamber depth, lens thickness, vitreous chamber depth, and axial length. Their multivariate analysis of patients in the atropine-treated group showed that at 36 months from study enrollment, there was a significant increase in vitreous chamber depth and axial length, independent of age and gender. The authors suggested that their data indicate that atropine slows myopic progression by reducing vitreous chamber growth and elongation.

In the ATOM 2 study,<sup>26</sup> the mean increase in axial length was  $0.27 \pm 0.25$  mm,  $0.28 \pm 0.28$  mm, and  $0.41 \pm 0.32$  mm in the atropine 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). After the 1-year washout period in the ATOM 2 study, the axial length growth was greater in the atropine 0.5% ( $0.35 \pm 0.20$  mm) and atropine 0.1% ( $0.33 \pm 0.18$  mm) groups compared with the atropine 0.01% group ( $0.19 \pm 0.13$  mm;  $P < 0.001$ ). However, the overall change in axial length from baseline to the 36-month end point was not significantly different among groups ( $P = 0.787$ ). Additionally, in the 2-year extension period in which 192 children received atropine 0.01% after progressing during the washout period, there was less axial elongation in the group originally randomized to atropine 0.01% ( $0.19 \pm 0.18$  mm) than in the groups initially randomized to atropine 0.5% ( $0.26 \pm 0.23$  mm;  $P = 0.013$ ) and atropine 0.1% ( $0.24 \pm 0.21$  mm;  $P = 0.042$ ).<sup>35</sup>

**Effect on Accommodation and Pupil Size.** After the first 6 months of the 1-year washout, the children enrolled in the ATOM 1 study did not show any significant differences in the amplitude of accommodation or near visual acuity between the atropine-treated and placebo-treated groups within 6 months of discontinuing treatment.<sup>24</sup> In the ATOM 2 study, there was significantly less effect on accommodative amplitudes (11.3 D for atropine 0.01%, 3.8 D for atropine 0.1%, and 2.2 D for atropine 0.5%;  $P < 0.01$ ) and pupillary enlargement under photopic and mesopic conditions (1 mm for atropine 0.01% vs. 3 mm for atropine 0.1% and 0.5%;  $P < 0.001$ ) for atropine 0.01% compared with the higher doses of atropine 0.1% and 0.5%.<sup>26</sup> At 36 months in the ATOM 2 trial, which included the 1-year washout after the 2 years of treatment,<sup>28</sup> accommodation was less in the patients treated with atropine 0.5% ( $13.24 \pm 2.72$  D) compared with the atropine 0.1% group ( $14.45 \pm 2.61$  D) and atropine 0.01% group ( $14.01 \pm 2.9$  D;  $P < 0.001$ ). In all 3 groups, accommodation was significantly less than that measured at the baseline visit by an average of  $-2.56$  D ( $P < 0.001$ ). The diminished accommodative amplitude after the 1-year washout in all 3 groups is concerning for a permanent decrement of accommodative ability, which may be greatest with higher doses of atropine; however, a longer follow-up period is necessary to determine the true long-term effects.

**Effect on Astigmatism, Intraocular Pressure, and Electroretinography Parameters.** In 2001, Shih et al<sup>21</sup> evaluated the change in astigmatism over the 18-month period of their study comparing atropine 0.5% with multifocal and single-vision eyeglasses. They did not find a significant difference between groups in the change in astigmatism. In the ATOM study,<sup>25</sup> there was also no significant difference in the amount of astigmatism change between the atropine-treated group and the control group ( $P = 0.182$ ). In both groups, astigmatism increased by 0.12 to 0.16 D/year, "mirrored by an increase in corneal astigmatism of 0.10 to 0.13 D per year, suggesting that most of the change in astigmatism was corneal in nature."<sup>25</sup>

Shih et al<sup>21</sup> also evaluated the change in intraocular pressure over their 18-month study period, and they did not find a significant difference between treatment groups. In the ATOM 1 study,<sup>23</sup> there were no significant changes in intraocular pressure and no absolute readings of more than 21 mmHg after 2 years of treatment with atropine 1%.

The ATOM 1 group<sup>36</sup> also reported on a cross-sectional cohort of children who were completing the study who consented to undergo multifocal electroretinography at 2- to 3-month intervals after stopping atropine 1% treatment. The study failed to detect any differences between electroretinography parameters in treated



Table 1. Chronological Summary of Included Level I and II Studies

Author(s), Year	Level of Evidence	Premise	Total No., Ethnicity, and Age Range (yrs) of Patients	Baseline Spherical Equivalent (D)	Final Follow-up	Outcomes Evaluated	Results*	Comments
Yen et al, 1989 <sup>19</sup>	II	A1% QOD vs. C1% QHS vs. saline QHS	247, Taiwanese, 6–14	–0.50 to –4.00 (cyl >1 D excluded)	12 mos	Myopia progression	A1%: 0.22±0.54 D C1%: 0.58±0.49 D Placebo: 0.91±0.58 D $P < 0.01$ for all comparisons	Dropouts were excluded, final n = 96
Shih et al, 1999 <sup>20</sup>	II	A0.5% with bifocals vs. A0.25% with partially undercorrected eyeglasses vs. A0.1% with full eyeglass correction vs. tropicamide QHS with full correction	200, Taiwanese, 6–13	–0.50 to –6.75 (cyl >2 D and anisometropia >2 D excluded)	2 yrs	Myopia progression	A0.5%: 0.04±0.63 D/yr A0.25%: 0.45±0.55 D/yr A0.1%: 0.47±0.91 D/yr Tropicamide: 1.06±0.61 D/yr $P < 0.01$ for all atropine groups compared with tropicamide	14 patients lost to follow- up; potential bias with differing refractive correction between groups; no indication of masking
Shih et al, 2001 <sup>21</sup>	I	A0.5% with multifocal lenses vs. multifocal lenses vs. SV lenses	227, Taiwanese, 6–13	Range not reported but mean –3.3	18 mos	Myopia progression	A0.5%: 0.42±0.07 D Multifocal lenses only: 1.19±0.07 D SV lenses only: 1.4±0.09 D over 18 mos $P < 0.0001$ for A0.5% group compared with both control groups	39 patients excluded for failure to meet criteria of progression >2 D
Syniuta and Isenberg, 2001 <sup>22</sup>	II	Case-control study of 15 children treated with A1% matched to 15 controls treated with SV lenses	30, American, 4–13	Range not reported but mean –1.8 in both groups	Mean 30 mos (range 3–96 mos)	Myopia progression	A1%: 0.05±0.67 D/yr Control: 0.84±0.26 D/yr	Case-control study
Chua et al, 2006 <sup>23</sup> (ATOM 1)	I	A1% vs. placebo	400, Asian, 6–12	–1 to –6	2 yrs	Myopia progression	A1%: –0.28±0.92 D Placebo: –1.2±0.69 D $P < 0.001$	54 participants did not complete the 2-yr follow-up
Tong et al, 2009 <sup>24</sup> (ATOM 1)	I	A1% vs. placebo	400, Asian, 6–12	–1 to –6	1 yr after discontinuing A1% or placebo	Myopia progression	A1%: –1.14±0.8 D/yr Control: –0.38±0.39 D/yr $P < 0.0001$ Over the entire 3 yrs: A1%: –0.46±0.26 D/yr Placebo: –0.52±0.3 D/yr $P = 0.043$	67 participants did not complete follow-up
Chia et al, 2009 <sup>25</sup> (ATOM 1)	I	A1% vs. placebo	400, Asian, 6–12	–1 to –6	2 yrs	Change in astigmatism	A1%: 0.3±0.19 Untreated eye: 0.24±0.17 Placebo: 0.33±0.18 Untreated placebo eye: 0.33±1.16 $P > 0.05$	Secondary outcome of ATOM1 study; underpowered to sufficiently detect outcome

(Continued)

Table 1. (Continued.)

Author(s), Year	Level of Evidence	Premise	Total No., Ethnicity, and Age Range (yrs) of Patients	Baseline Spherical Equivalent (D)	Final Follow-up	Outcomes Evaluated	Results*	Comments
Chia et al, 2012 <sup>26</sup> (ATOM 2)	I	A0.5% vs. A0.1% vs. A0.01% (2:2:1 ratio)	400, Asian, 6–12	$\geq -2$	2 yrs	Myopia progression	A0.5%: $-0.3 \pm 0.6$ D over 2 yrs A0.1%: $-0.38 \pm 0.6$ D over 2 yrs A0.01%: $-0.49 \pm 0.63$ D over 2 yrs $P = 0.02$ between the 0.01% and 0.5% groups; $P = 0.05$ between other concentrations	No control group, but included historical controls; 45 participants did not complete the study
Chia et al, 2013 <sup>27</sup> (ATOM 2)	II	A0.5% vs. A0.1% vs. A0.01% (2:2:1 ratio)	35, Asian, 6–12	$\geq -2$	32 mos	Electroretinography changes during and after treatment	Gradual decline in cone function over time that was not influenced by atropine treatment	Exploratory study
Chia et al, 2014 <sup>28</sup> (ATOM 2)	I	A0.5% vs. A0.1% vs. A0.01% (2:2:1 ratio)	400, Asian, 6–12	$\geq -2$	1 yr after discontinuing atropine	Myopia progression	A0.5%: $-0.87 \pm 0.52$ D A0.1%: $-0.68 \pm 0.45$ D A0.01%: $-0.28 \pm 0.33$ D $P < 0.001$	Exploratory study; 44 participants did not complete the study
Kumaran et al, 2015 <sup>29</sup> (ATOM 1)	II	A1% vs. placebo	400, Asian, 6–12	-1 to -6	2 yrs	Analysis of multiple biometric outcomes	Atropine seemed to slow myopia progression by reducing growth in vitreous chamber depth and thereby reducing axial length	Underpowered to sufficiently detect multiple outcomes

A = atropine; ATOM = Atropine for the Treatment of Myopia; C1% = cyclopentolate 1%; cyl = cylinder; D = diopter; D/yr = diopter per year; QHS = nightly; QOD = every other day; SD = standard deviation; SV = single vision.  
\*Mean  $\pm$  SD unless otherwise noted.

Table 2. Chronological Summary of Included Level III Studies

Author(s), Year	Premise	Total No., Ethnicity, and Age Range (yrs) of Patients	Baseline Spherical Equivalent (D)	Final Follow-up	Outcomes Evaluated	Results	Comments
Brodstein et al, 1984 <sup>30</sup>	A1% vs. controls	253, American, 8–12	<−0.5	Up to 9 yrs (mean, 4.25 yrs)	Myopic progression	Control: 0.30±0.02 D/mo Treated (during treatment): −0.01±0.03 D/mo P < 0.0001 (during treatment vs. control + pretreatment)	Nonrandomized; variable control group
Chiang et al, 2001 <sup>31</sup>	A1% plus bifocals (compared fully vs. partially compliant groups)	706, American, 6–16	<−0.5	Variable	Myopic progression	Fully compliant: 0.08 D/yr Partially compliant: 0.23 D/yr P < 0.001	Retrospective and nonrandomized; patients analyzed in groups based on compliance
Cooper et al, 2013 <sup>32</sup>	3×3 phase I trial design to determine maximum tolerated dose of atropine	12, American, 8–16	−1.75 to +0.75	1 wk	Insufficient accommodation or excessive pupillary dilation	0.02% was determined to be maximal tolerated dose	
Polling et al, 2016 <sup>33</sup>	A0.5%	77, white, Asian, and African, <18	<−3	1 yr	Myopic progression	Before treatment: −1.0±0.7 D/yr After treatment: −0.1±0.7 D/yr Patients who ceased therapy: −0.5±0.6 D/yr P = 0.03	Prospective case series with no comparison group
Loughman and Flitcroft, 2016 <sup>34</sup>	A0.01% daily	14, white, >18	Plano to −6	5 days	Pupil size and responsiveness, accommodative amplitude, visual acuity, reading speed	Significant change in pupil size and reactivity but no other significant changes	5-day study to evaluate tolerability of A0.01% in non-Asian population with light iris color
Chia et al, 2016 <sup>35</sup> (ATOM 2)	A0.5% vs. A0.1% vs. A0.01% (2:2:1 ratio)	192, Asian, 6–12	≥−2 at baseline; those who progressed −0.5 or more in the first yr after ATOM2	3 yrs after discontinuing atropine	Myopia progression	A0.5%: −1.98±1.1 D A0.1%: −1.83±1.16 D A0.01%: −1.38±0.98 D P = 0.003, A0.01% vs. A0.1%; P < 0.001, A0.01% vs. A0.5%	Comparisons between groups over 5 yrs were difficult to interpret because only a select group was retreated at 3 yrs; possible bias because only those responding poorly were retreated

A = atropine; ATOM = Atropine for the Treatment of Myopia; D = diopter; D/yr = diopter per year.

Table 3. Effect of Varying Doses of Atropine on Myopic Progression in Level I Clinical Trials

Atropine Dose	Myopia Progression on Treatment in Level I Trials	Myopia Progression 1 Year after Discontinuing Treatment in Level I Trials
No treatment or placebo participants	1.4±0.09 D over 18 mos <sup>21</sup> 1.2±0.69 D over 2 yrs <sup>23</sup>	0.38±0.39 D/yr <sup>24</sup>
1%	0.28±0.92 D over 2 yrs <sup>23</sup>	1.14±0.8 D/yr <sup>24</sup>
0.5%	0.42±0.07 D over 18 mos <sup>21</sup> 0.3±0.6 D over 2 yrs <sup>26</sup>	0.87±0.52 D/yr <sup>28</sup>
0.1%	0.38±0.6 D over 2 yrs <sup>26</sup>	0.68±0.45 D/yr <sup>28</sup>
0.01%	0.49±0.63 D over 2 yrs <sup>26</sup>	0.28±0.33 D/yr <sup>28</sup>

D = diopter; D/yr = diopter per year.

participants compared with control participants. However, the study may not have been powered to detect a difference, because no discussion of sample size was included.

The ATOM 2 study group<sup>27</sup> evaluated 35 children who consented to undergo full-field electroretinography at baseline, 24 months, and 32 months (8 months after treatment ended). All 3 electroretinography examinations were completed by 29 of the participants. Data from sequential electroretinography testing revealed a statistically significant reduction in the 30-Hz flicker and photopic A- and B-waves in the cohort over time. However, multivariate analysis revealed that these changes were independent of atropine dose and that they correlated statistically more with increases in axial length.

**Side Effects.** The use of atropine has been approved by the United States Food and Drug Administration for the treatment of amblyopia, but not for its use in preventing the progression of myopia. The most frequently reported side effects in the reviewed studies of topical atropine included light sensitivity, allergic reaction, and blurred near vision.<sup>12</sup> Although these were short-term side effects, there is also concern about the long-term use of atropine and increased exposure of the lens and retina to ultraviolet light.

Many of the patients in the study by Yen et al<sup>19</sup> dropped out (151 of 247), most of whom were part of the atropine 1% group and had symptoms related to light sensitivity (100% of the atropine 1% group reported light sensitivity). Shih et al<sup>20</sup> reported that 22% of children assigned to atropine 0.5% reported photophobia within the first 3 months of treatment. In the ATOM 1 study,<sup>23</sup> 34 participants (17%) using atropine 1% dropped out of the study for the following reasons: allergic reactions (4.5% of the total sample), glare (1.5% of the total sample), blurred near vision (1% of the total sample), and logistical difficulties (3.5% of the total sample). There were no serious adverse effects. In the ATOM 2 study,<sup>26</sup> 4.1% of children demonstrated allergic conjunctivitis in the atropine 0.5% and 0.1% groups only. There were no major adverse events related to the use of atropine at any concentration.

## Studies on Non-Asian Populations

Given the recent increase in the prevalence of myopia in Asian countries, much of the interest and research has originated in Asia. However, a recent meta-analysis by Li et al<sup>37</sup> revealed that atropine seemingly has more effect in slowing myopic progression in Asian

children compared with white children. However, this finding requires further study. It is unclear whether there are truly differences among the populations or if there are simply fewer data in non-Asian groups, because no randomized controlled trials have been performed outside of Asia. However, several non-randomized (and mostly retrospective) studies have been reported. In 1984, Brodstein et al<sup>30</sup> evaluated patients who were treated with atropine 1%. This study compared myopic progression in 253 treated patients who were followed up for up to 9 years with a control group of 146 patients who declined the atropine treatment. This study found that there was a statistically significant slowing of myopic progression in the treated group. However, it is difficult to draw strong conclusions from this study given its nonrandomized nature.

In 2001, Chiang et al<sup>31</sup> reported the results of a retrospective cohort of patients in Wisconsin who were treated with atropine 1% and bifocals. These patients received atropine 1% until the age of 16 years, with variable follow-up. The study divided the patients into 2 groups based on their compliance (partial vs. complete), which potentially biased the results that revealed statistically significantly less myopic progression in the fully compliant group (0.08 D/year) compared with the partially compliant group (0.23 D/year;  $P < 0.001$ ). Similarly, Syniuta and Isenberg<sup>22</sup> in 2001 also reported a study comparing 15 myopic children from Los Angeles, California, receiving atropine 1% with 15 control participants. This study revealed a statistically significant difference ( $P = 0.0002$ ) in myopic progression in the atropine 1% group (0.05±0.67 D/year) compared with the control group (0.84±0.26 D/year), but the study's small sample size, potential for selection bias, and differing follow-up limits its conclusiveness on the efficacy of atropine 1%.

In 2013, Cooper et al<sup>32</sup> studied 12 participants in New York to evaluate the maximum dose of atropine that could be tolerated in white eyes without creating symptoms of insufficient accommodation or excessive pupillary dilation. This dose was found to be 0.02% in their participants. In 2016, Polling et al<sup>33</sup> performed an effectiveness study of 77 children in Rotterdam, the Netherlands, including children of European ( $n = 53$ ), Asian ( $n = 18$ ), and African ( $n = 6$ ) descents. Children in this study were prescribed atropine 0.5% for 1 year. Sixty of the 77 patients (78%) complied with the therapy, and the mean progression rate diminished from  $-1.0 \pm 0.7$  D/year in the year before therapy to  $-0.1 \pm 0.7$  D/year in the year of the treatment. This study was not randomized or controlled, and very few conclusions can be drawn from it.



Finally, in 2016, Loughman and Flitcroft<sup>34</sup> studied the acceptability of atropine 0.01% in a white population in Ireland. In their study, 14 university students were given atropine 0.01% daily, and the effect on pupil size, accommodative amplitude, and visual acuity was assessed. Although the mean pupil size and responsiveness were statistically significantly affected by the atropine 0.01%, in their small white population, the atropine 0.01% generally was well tolerated and did not adversely affect reading speed or visual acuity at distance or near.

## Conclusions

This review of the level I and II and select level III evidence demonstrated a reduction in myopic progression in children treated with atropine by as much as 1 D/year during treatment. Most of the evidence is from patients residing in Asian countries, and it may not be generalizable to other populations. Varying doses of atropine all have been demonstrated to retard myopic progression, presumably by limiting axial elongation. Although higher doses seem to have a stronger effect, myopic rebound after treatment cessation seems to be greater. In addition, lower doses seem to be associated with fewer side effects, such as light sensitivity and accommodative insufficiency. Given the more sustained effect of atropine 0.01% coupled with the lower incidence of adverse effects, this review suggests that it may represent the most reasonable approach to myopia retardation in children; however, the optimal time to initiate and discontinue therapy is still not known. Clinicians, patients, and families must decide whether the effects of this treatment are clinically significant enough to warrant their use.

## Future Research

Future research related to the use of atropine with respect to the progression of myopia is necessary to address several topics. First, it would be useful to form a better understanding of the exact mechanism of myopic progression and the underlying effect of atropine on this pathogenesis. Alternative forms of drug delivery should be sought to improve compliance. Importantly, studies of children in non-Asian ethnic groups are required to determine whether atropine treatment is as effective for non-Asians as it has been reported to be for Asian children. In addition, the optimal dosage for various patient subgroups still requires further study. Given the myopic rebound associated with all doses of atropine, it will be crucial to delineate optimal duration of treatment and how best to discontinue or taper treatment safely and to minimize regression. Because this treatment is relatively simple to use, additional studies combining atropine with other optical treatments, such as bifocals or contact lenses, are necessary to optimize the potential treatment effect fully. Finally, future studies should focus on optimal ages as well as refractive errors and changes to target while also evaluating risk factors for treatment failure. If risk factors for atropine failure can be

determined, targeted therapy with increased doses of atropine or other nonatropine treatments can be considered and studied in those groups.

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Abbreviations and Acronyms:

**ATOM** = Atropine for the Treatment of Myopia; **D** = diopter.

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