# Topical Atropine in the Control of Myopia

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**Abstract:** Efforts to reduce myopia progression in childhood are driven by the increasing incidence of high myopia and its attendant health risks. Interventional approaches to reduce myopia progression in childhood have included the use of spectacles, contact lens, and pharmacological methods, of which the latter appear to be most promising. We review the use of topical atropine eye drops in the retardation of myopia progression in children and discuss the efficacy and safety profiles when used at different concentrations (1.0%, 0.5%, 0.1%, and 0.01%). Topical atropine reduces myopia progression and axial elongation in children in a dose-related manner, but a rebound phenomenon occurs with higher doses. Its use has been shown to be safe, but higher doses cause pupil dilation, loss of accommodation and near vision. Atropine 0.01% has the best therapeutic index, with clinically insignificant amounts of pupil dilation, near vision, and accommodation loss but remains as effective as higher doses.

**Key Words:** atropine, myopia, control, prevention

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Myopia is a refractive disorder of the eye that poses a significant burden on global health systems.[1] Aside from the obvious visual disability, which is correctable with spectacles, contact lenses, or refractive surgery, high or pathological myopia is associated with significant ocular morbidity and is an important cause of blindness, including choroidal neovascularization, cataract, glaucoma, retinal tears, and detachment.[1] It has also been shown to be associated with a lower quality of life.[2] Prevalence of myopia varies with geographical, socioeconomic, and ethnic factors; however, data show that it is increasing worldwide.[3–6] In Asia, the prevalence of myopia is estimated to be 47.3% for people in their third decade of life.[7] Furthermore, there has been an increase in the prevalence of high myopia, with up to 20% of secondary school children in East Asian populations being affected.[8–10] Myopia occurring at an earlier age in childhood has also been shown to be associated with a higher degree of myopia in adult life.[11,12]

In 2011, Walline et al[13] published a Cochrane database meta-analysis of 23 randomized controlled trials (RCTs) of interventions to slow the progression of myopia in children. They evaluated a range of therapies targeted at limiting myopic progression, which included spectacle undercorrection, progressive and bifocal spectacles, topical cyclopentolate, and rigid gas-permeable contact lenses, but found the greatest myopia-retarding efficacy with topical antimuscarinic medications, with topical pirenzepine slowing progression by 0.31 diopters (D) and atropine by 0.80 D at 1 year compared with placebo.

More recently, in another network meta-analysis by Huang et al[14] that involved 30 RCTs to determine the effectiveness of different interventions in slowing down the progression of myopia in children, the authors found that the most effective intervention that showed a marked reduction in myopia progression was atropine, followed by pirenzepine, orthokeratology, and peripheral defocus–modifying contact lenses showing moderate effects and progressive addition spectacle lenses showing minimal effects.

Since then, further studies on the use of varying doses of topical atropine have shown both efficacy and reduction of adverse effects. The aim of this article is to discuss the studies involving antimuscarinic agents (ie, pirenzepine and atropine) in the control of myopic progression in young children.

## PIRENZEPINE

Topical pirenzepine gel is a selective antimuscarinic (M1) agent that has been used in myopia progression trials in the form of a 2% ophthalmic gel. Two RCTs have shown an approximately 50% reduction in myopia progression with a corresponding reduction in axial length after 12 months of follow-up in patients who used pirenzepine gel twice a day.[15,16] In the first study, which was performed in Asia (Singapore, Hong Kong, and Thailand), the increase in axial length was 0.33 and 0.20 mm for patients who had placebo in both eyes versus pirenzepine gel, respectively. The mean increase of myopia was also lower in the pirenzepine group (0.47 D/y) compared with the placebo group (0.84 D/y, $P < 0.01$). The second study, which was conducted in the United States for 2 years, also showed a lower mean increase in myopia in the pirenzepine group compared with placebo (0.58 and 0.99 D, respectively; $P = 0.008$). These accounted for a 31% to 41% reduction of myopia. Although it was hoped that a more selective antimuscarinic agent would result in less cycloplegia, the authors noted that children receiving pirenzepine encountered difficulties with accommodation and mild mydriasis. Although it induced less pupil dilation compared with 1% atropine, pupil dilation was still present with a mean change in pupil diameter of up to 1.5 mm in the pirenzepine group 1 hour after instillation. A significant percentage of children also experienced difficulty with accommodation (between 44% and 47% of patients in the pirenzepine groups vs between 2% and 6% in the placebo groups). Further trials and registration of this drug were subsequently not pursued, and pirenzepine gel is no longer available.

## ATROPINE

Atropine is a nonspecific muscarinic acetylcholine receptor antagonist, which has long been used for pupil dilation and amblyopia therapy as a 1% topical solution. It has also been used off-label to reduce myopia progression. Its exact mechanism of action in myopia control is unclear. Atropine prevents myopia in chicks that possess a striated ciliary muscle, which is innervated by nicotinic receptors rather than muscarinic receptors. This demonstrates that atropine does not slow myopia progression by blocking accommodation but via a nicotine receptor pathway.[17] There are currently 2 theories to explain this: (1) atropine functions at a relatively low dose via a neurochemical cascade, which begins at M1/4 receptors in the retina (possibly in amacrine cells); (2) atropine has a direct effect on scleral fibroblasts by inhibiting glycosaminoglycans synthesis via a nonmuscarinic mechanism.

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As early as the 1960s, the use of atropine eye drops in the treatment of childhood myopia was studied and shown to be safe and effective in reducing the progression of myopia, and since then, many studies have confirmed its efficacy.[18] In a cohort study conducted in Minnesota, 214 children between the ages of 6 and 15 years received atropine from 1967 to 1974 over a mean treatment period of 3.5 years. Compared with matched controls, the mean progression of myopia in the group treated with atropine 1% every night was significantly lower (0.05 vs 0.36 D/y, $P < 0.001$). There were no serious adverse effects reported, although patients frequently complained of photophobia and blurred near vision.[19]

Subsequently, several other retrospective and case-controlled studies evaluating the use of atropine 1% daily with bifocal spectacles also showed a reduction in the rate of myopia progression in those children treated.[20–23] Romano and Donovan,[20] in a retrospective review of 35 patient records over a follow-up period of 5 years, showed a decrease in the rate of myopia in the group compliant with treatment (atropine 1% daily and bifocals) of +0.07 D/y compared with the mean annual change in refractive error in the general population (aged 8–15 years) of −0.24 D/y ($P < 0.02$). In another small case-controlled study by Syniuta and Isenberg[21] consisting of 15 children in the United States, similar findings were noted with atropine and bifocals in retarding myopia progression, where the mean annual myopic progression in the atropine and bifocal group was 0.05 ± 0.67 D vs 0.84 ± 0.26 D in the control group ($P = 0.00021$) over a mean follow-up period of 29.3 months. In addition to similar findings, Brodstein et al[22] also reported that the fastest rate of myopic progression occurred between 8 and 12 years of age, with the slowest rate of myopic progression occurring in patients over the age of 18 years.

A 3-arm trial of 247 children from Taiwan compared the use of different cycloplegic eye drops in controlling myopia progression for 1 year and found that the effect of atropine 1% every other night was more effective at reducing myopia progression compared with cyclopentolate 1% every night.[24] Children were aged 6 to 14 years and were randomized to receive 1% atropine eye drops every other night and bifocal spectacles prescribed after 2 weeks of treatment, 1% cyclopentolate eye drops every night and single vision lenses (SVLs) prescribed if necessary, or normal saline eye drops every night and SVLs prescribed if necessary. The mean myopic progression was −0.219 D in the atropine group, −0.578 D in the cyclopentolate group, and −0.914 D in the saline group.

The use of lower concentrations of atropine has also been studied with the intention of reducing the adverse effects of photophobia and near vision blur and improving compliance in children with myopia. Overall, results from these studies have shown that atropine, even at lower doses, slow the progression of myopia significantly, with a lower incidence of adverse effects reported.

A prospective study conducted in Taiwan in the 1990s in children with high myopia (−6.0 D or higher) showed a reduction in the mean myopia progression rate with the use of atropine 0.5% eye drops once a night compared with prior treatment with tropicamide 0.5% (−0.01 ± 0.04 vs −0.12 ± 0.09 D/mo, $P < 0.05$) and prior nontreatment (−0.04 ± 0.06 vs −0.14 ± 0.07 D/mo, $P < 0.05$).[25] Another RCT conducted in Taiwan further showed that even lower doses of atropine were effective in reducing myopia progression.[26] A group of 186 children aged 6 to 13 years were randomized to 1 of 3 atropine treatment groups (atropine 0.5%, 0.25%, or 0.1% daily) or to a control group for up to 2 years. The mean myopic progression in each of the groups (0.04 ± 0.63 D/y in the atropine 0.5% group, 0.45 ± 0.55 D/y in the atropine 0.25% group, and 0.47 ± 0.91 D/y in the atropine 0.1% group) was less than in the control group (1.06 ± 0.61 D/y, $P < 0.01$). Three adverse events were reported, all of which occurred in the group receiving the highest dose of atropine (0.5%). Two patients complained of photophobia, and 1 patient had allergic blepharitis. The authors also found that a number of children demonstrated fast progression (higher than −1.0 D/y) despite receiving treatment, with the highest percentage in the 0.1% group (4% of children in the 0.5% atropine group, 17% in the 0.25% atropine group, and 33% in the 0.1% atropine group). Similarly, another retrospective case-controlled study evaluating the use of atropine 0.05% and 0.1% found that these lower concentrations were also effective in slowing the rate of myopia progression.[27] Children were first started on 0.05% atropine every night and subsequently switched to 0.1% atropine if their myopia progressed more than 0.50 D in the first 6 months (45% of patients). Compared with those who were untreated, the progression of myopia was slower in the atropine group (−0.23 vs −0.86 D/y, $P < 0.01$), although 20% of those treated still progressed at higher than 0.50 D/y (compared with 100% of patients treated with placebo). Hence, although low concentrations of atropine are not as effective compared with higher doses at arresting the progression of myopia, their effect in retarding myopia progression is still clinically significant compared with no treatment. Furthermore, one can expect patients to be more compliant to these low concentrations of atropine as a result of a lower incidence of adverse effects.

## The Atropine for the Treatment of Childhood Myopia Studies

Atropine for the treatment of childhood myopia (ATOM1) was one of the first placebo-controlled, double-masked RCTs that compared daily atropine 1% eye drops with placebo in the treatment of childhood myopia.[28] We conducted this study in Singapore from 1999 to 2004, which involved 400 children aged 6 to 12 years with mild to moderate myopia (−1 to −6 D). In the treatment group, patients received 1% atropine once per night in 1 eye and no treatment in the fellow eye. In the control group, vehicle eye drops were used in 1 eye and no treatment was administered to the fellow eye. Photochromic progressive glasses were prescribed to all study subjects. The study comprised 2 years of treatment and 1 washout year (where treatment was ceased). Parameters measured at follow-up included cycloplegic autorefraction, axial length by A-scan, and intraocular pressure. Slit lamp examination with lens and fundi examination was performed at each visit. Multifocal electroretinogram at 12 months was also performed in a subset of patients. The ATOM1 trial showed a 77% reduction in myopia progression between atropine-treated eyes and placebo-treated eyes (progression of −1.20 ± 0.69 D in the placebo group and −0.28 ± 0.92 D in the atropine group). There was a strong correlation with a decrease in axial elongation of the eye. There were no serious adverse effects associated with the drug, and 4.5% of subjects withdrew from the study because of allergic symptoms, 1.5% for glare, 1% for blurred near vision, and 3.5% for logistical difficulties. In the washout period (24–36 months), there was, however, a significant rebound phenomenon for both axial elongation and myopia progression upon cessation of the 1% atropine drops[29] (Figs. 1, 2).

ATOM2, which immediately followed ATOM1, was designed to compare the safety and efficacy of 3 lower doses of atropine (0.5, 0.1, and 0.01%).[30] This 5-year study was conducted from 2006 to 2012 and involved 400 Singaporean children aged from 6 to 12 years with myopia of −2 D or higher. They were randomized to 3 groups treated with 0.5% atropine (n = 161), 0.1% atropine (n = 155), or 0.01% atropine (n = 84). Compared with ATOM1, children in this study were slightly older (9.7 vs 9.2 years) and had higher baseline myopia (−4.7 vs −3.5 D).

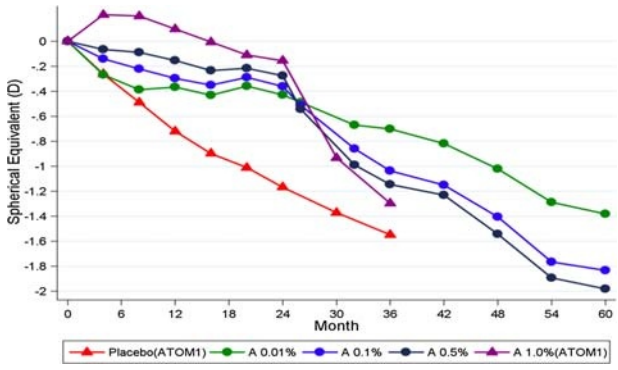


**FIGURE 1.** Summary of mean SE change over time in patients treated with differing doses of topical atropine. A indicates atropine. Reprinted with permission from *Ophthalmology* 2016; 123:391–399.

Unlike ATOM1, we did not include a placebo group in ATOM2 because we hypothesized that the 0.01% arm might represent a pseudo–placebo group because of its ultralow concentration. This 5-year study included 2 years of treatment followed by 1 year of washout. Those who continued to progress were restarted on treatment after the third year for 2 further years, receiving just 1 of the 3 concentrations, which was to be determined after efficacy and safety studies over the first 2 years.

The results of ATOM2 showed that there was a dose-related response for myopia control with atropine; however, these differences were clinically small (Figs. 1, 2). If data from ATOM1 using 1% atropine and the above data from ATOM2 are combined, the lowest dose (0.01% atropine) has a similar clinical efficacy that was not statistically significant compared with the higher doses when compared with placebo, which was encouraging.

ATOM2 clearly showed the advantage of lower concentrations of atropine in reducing visual adverse effects. In the 0.01% group, the mean pupil size was just 0.8 mm larger than at baseline in photopic conditions and 1.2 mm in mesopic conditions; in comparison, the difference was 2.3 and 3.1 mm (photopic) and 2.7 and 3.6 mm (mesopic), respectively, in the 0.1% and the 0.5% atropine treatment groups. The mean residual accommodation was 11.8 D in the 0.01% atropine group versus 6.8 and 4.0 D in the 0.1% and 0.5% atropine groups, respectively. This suggested a clinically insignificant amount of accommodation loss at the lowest concentration. The mean baseline accommodation was 16.2 D. Therefore, only 6% of children in the 0.01% group asked for photochromic progressive spectacles as compared with 61% in the 0.1% group and 70% in the 0.5% group. As accommodation was minimally affected, the visual acuity for near sight was also excellent in the group treated with 0.01% atropine, with a mean value of 20/20, J1. These findings confirmed that 0.01% atropine did not significantly affect near visual function and caused minimal pupil dilation.

Importantly, both ATOM1 and 2 found that topical atropine use was very safe.[27,29] The most common adverse side effect in ATOM2 was allergic conjunctivitis (4%), although no cases occurred in the 0.01% atropine group. Glare was a symptom in only 1% of subjects. There was no loss of best-corrected visual acuity or change in intraocular pressure. After cessation of drops, there was no loss of accommodation or permanent pupil dilation and there was no cataract formation. Electrophysiology did not show any abnormalities related to atropine use.[31,32]

During the washout period in ATOM2, 365 children (89% of the original cohort) were still present in this third year of study.[33] A similar rebound phenomenon was observed as for ATOM1, but this was inversely related to the dose. The group treated with 0.01% atropine showed minimal rebound (Fig. 1). Figure 2 shows the corresponding rebound effects on axial length elongation during the washout period (24–36 months). The rebound phenomenon was only observed at higher doses, and the group that received 0.01% eventually had the lowest axial elongation.

In the last phase of the ATOM2 trial, which had 345 (86%) patients still enrolled, patients who progressed more than 0.5 D after the cessation of atropine treatment were all restarted on atropine 0.01% for 24 months.[34] Seventeen (24%) children in the 0.01% group, 82 (59%) children in the 0.1% group, and 93 (68%) children in the 0.5% group were retreated under this criterion, suggesting that the least progression had occurred in the original 0.01% group. Children who required retreatment were also found to be younger, with less myopia at baseline, and had a greater increase in myopia during the first 2 years.

The overall changes in myopia progression are summarized in Figure 1. At the end of 5 years, the change in myopia was lowest in the 0.01% atropine group at −1.4 D; in comparison, the placebo group achieved this progression in half the amount of time at 2.5 years. Figure 2 illustrates the corresponding changes of axial length elongation over the 5 study years.[34]

## Subsequent Studies Involving Low-Dose Atropine 0.01%

In a recent retrospective case-controlled study conducted in the United States evaluating atropine 0.01% in the control of childhood myopia, the authors similarly found that atropine 0.01% significantly reduced the rate of myopic progression with minimal adverse effects in a mostly white population.[35] However, this study was only conducted over a 1-year period and included 60 children aged 6 to 15 years with initial myopic spherical equivalents (SE) from −0.25 to −8.00. Those who were on atropine had significantly lower rates of myopic progression (−0.1 ± 0.6 D/y) compared with the controls (−0.6 ± 0.4 D/y, $P = 0.001$), and 75% of children in this group showed slow progression (≤−0.25 D/y) compared with only 18% of controls. Three patients on atropine still had a rapid progression of −1.00 D/y or higher. Eighty-two percent of children with low initial myopia (−1.00 D or lower) who received atropine had plano or slightly hyperopic refractive changes after 1 year, whereas 100% of the controls were more myopic. Only 3 children in the atropine group complained of intermittent blur or light sensitivity, but they did not find it symptomatic enough for treatment to be discontinued.

In evaluating the efficacy of low-dose atropine in the prevention of myopia onset, a retrospective cohort study conducted in Taiwan by Fang et al[36] compared 50 children aged from 6 to 12 years who were premyopic (SE lower than +1.0 D) and

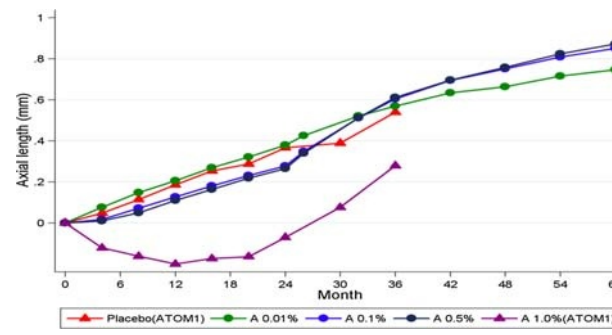


**FIGURE 2.** Summary of mean axial length change over time in patients treated with differing doses of topical atropine. A indicates atropine.

received atropine 0.025% at bedtime with those who did not over a period of 12 months. The mean spherical refraction myopic shift in the atropine group was −0.14 ± 0.24 D/y, significantly lower than that in the control group [−0.58 ± 0.34 D/y ($P < 0.0001$)], and only 21% of children receiving atropine became myopic compared with 54% of those who did not ($P = 0.016$). A lower percentage of children (8%) in the atropine group also experienced fast myopic shift (higher than −0.5 D/y) compared with the control group (58%, $P = 0.0002$). There were no reports of near vision blur in either group and no significant differences between the 2 groups regarding complaints of photophobia (16% vs 8%, $P = 0.41$).

## SUMMARY

Atropine eye drops have been shown to be safe and efficacious in reducing the progression of myopia in several clinical trials and retrospective studies. From the ATOM trials, atropine reduced myopia progression and axial elongation in children in a dose-related manner, but a rebound phenomenon occurred with higher doses. Atropine eye drops are safe with no serious adverse events, but in higher doses, they have limited practical use because they cause pupil dilation, loss of accommodation, and near vision.[28–30,33,34] Atropine 0.01% has the best therapeutic index with clinically insignificant amounts of pupil dilation, near vision, and accommodation loss but is still as effective as higher doses.[29] In children aged 6 to 9 years, the mean increase of myopia under treatment of 0.01% atropine was 2.0 D for 5 years; in comparison, 7-year-old children with myopia in Singapore increased by 3.8 D during this time, indicating that atropine 0.01% reduces myopia progression by 50%.[37]

As a result of these findings and the minimal adverse effects associated with low-dose atropine, further studies with a longer period of follow-up should be considered to evaluate the use of low-dose atropine in preventing the onset of myopia, especially in high-risk populations. There are some questions yet to be answered. There is still uncertainty regarding the exact pharmacological effect of atropine and whether it has longer-term effects on eyeball growth and development. Crucially, we need to evaluate whether this treatment can, in the long run, reduce the future incidence of high myopia and its attendant health risks. More studies need to be done to evaluate the appropriate duration of treatment and the best times to start, stop, and restart treatment.

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*I can't change the direction of the wind, but I can adjust my sails to always reach my destination*
***— William Shakespeare***