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# Low-concentration atropine for controlling myopia onset and progression in East Asia

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ABSTRACT

*Purpose:* Over the past few years, there has been a rapid accumulation of data on the use of low-concentration atropine for myopia control, especially in East Asian children, with its effectiveness varying in different studies. This review aims to evaluate the current evidence surrounding the efficacy and safety of low-concentration atropine in the management of myopia onset and progression in East Asia.
*Methods:* Clinical trials involving atropine for myopia control in East Asia were reviewed.
*Results:* Atropine has been shown to reduce myopia progression in East Asian children, compared with placebo. Its efficacy is concentration-dependent, with 1 % atropine yielding the greatest effect in slowing myopia progression by over 70 %, but it is associated with significant rebound and side effects. Lower concentrations also confer significant myopia-control effects while maintaining a more acceptable safety profile, with relative reductions of 67 % and 43 % reported for 0.05 % and 0.025 % atropine, respectively. While 0.01 % atropine showed the least effect compared to 0.05 % and 0.025 %, it still yielded a significant efficacy in slowing myopic refraction. Over two years, 0.05 % atropine reduced the incidence of myopia by nearly 50 %, demonstrating greater effectiveness than 0.01 % atropine. This effect was particularly notable in children with low hyperopic reserves ($< +0.75$ D), but not in those with higher reserves.
*Conclusions:* The current evidence shows that low-concentration atropine plays a crucial role in managing myopia in East Asian children and demonstrates satisfactory safety profiles. Timely administration of the most effective and safest concentration can potentially prevent sight-threatening complications and subsequent vision loss.

## Introduction

Myopia is a prevalent eye condition in which the eye focuses light in front of the retina rather than directly on it, resulting in blurred vision for distant objects[1]. It is now acknowledged as one of the leading causes of preventable blindness worldwide, responsible for about one-third of global uncorrectable visual impairment[2,3]. In regions such as East Asia, it has been reported to have reached epidemic levels[4,5]. The prevalence of myopia has risen dramatically in recent years and is a growing public health challenge. It appears that the percentage of the population affected will continue to rise in the coming decades. In 15-year-old children, a pooled analysis showed a high prevalence of myopia at nearly 70 % in East Asia, reaching over 86 % in Singapore[6], while the prevalence rate in Africa is considerably lower, estimated at 5.5 %[6]. Amidst these extremes, other regions around the world report diverse myopia rates but there is a global increasing trend[6–8].

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Myopia can be associated with progressive abnormal eyeball elongation and resultant mechanical stretching of the outer coats of the eye, increasing the risks of sight-threatening complications such as cataracts, glaucoma, macular degeneration and even blindness[9,10]. There is currently no level of myopia that is considered safe regarding the risk of developing pathologic complications[9]. Even individuals with relatively low levels of myopia face an increased risk of these sight-threatening conditions. However, for those who progress to high myopia, the risks become significantly greater[9]. Although sight-threatening myopia-related pathologies are typically observed in later life, the underlying myopia is mostly developed during childhood. Serious complications such as myopic maculopathy and retinal detachment can also occur in children[11,12]. There has been vigorous research in developing effective interventions to slow myopia progression, delay or even prevent its onset in children. One such intervention that has been the subject of extensive research is low-concentration atropine. In recent years, a substantial amount of data has emerged on using low-concentration atropine for myopia control, showing varying levels of effectiveness across different studies[13]. In this review, we sought to summarize and provide perspectives on evidence from key clinical trials regarding the use of low-concentration atropine for controlling myopia onset and progression in East Asia.

## Clinical trials on atropine for myopia progression and onset

The efficacy of atropine drops in slowing myopia progression in children has been affirmed by the Singaporean studies, Atropine for the Treatment of Myopia (ATOM) 1 and 2. ATOM1 compared 1.0 % atropine with placebo drops administered in one eye[14]. After two years, topical 1.0 % atropine decreased spherical equivalent (SE) progression by –0.28 ± 0.92 diopter (D) versus –1.20 ± 0.69 D in the placebo-treated eyes. The respective reductions in axial length (AL) elongation were –0.14 ± 0.28 mm versus 0.20 ± 0.30 mm. While it produced substantially higher efficacy, it was associated with significant rebound and unwanted side effects[15]. ATOM2 subsequently compared the effects of atropine at concentrations of 0.5 %, 0.1 % and 0.01 %[16]. Initially, the 0.01 % concentration was intended to serve as the placebo group; however, a historical control from ATOM1 was used instead since 0.01 % atropine demonstrated efficacy in ATOM2. After two years, it was found that AL elongation and myopia progression were 0.27 ± 0.25 mm, –0.30 ± 0.60 D with 0.5 %; 0.28 ± 0.28 mm, –0.38 ± 0.60 D with 0.1 %; and 0.41 ± 0.32 mm, –0.49 ± 0.63 D with 0.01 %. Treatment was then discontinued for one year, and any child showing myopia progression of 0.50 D or more in at least one eye was restarted on 0.01 % atropine[17]. A rebound effect was observed during the one-year treatment cessation, with higher concentrations leading to a more significant increase in myopia. Over the three years, a larger proportion of children in the higher concentration groups needed to restart treatment due to progression of 0.50 D or more (24 % in the 0.01 % group, 59 % in the 0.1 % group and 68 % in the 0.5 % group). The five-year results of ATOM2 indicated that the lower rate of myopia progression in the 0.01 % group persisted for an additional two years among children who were still experiencing rapid progression after the one-year break. At the end of five years, overall myopia progression and changes in axial elongation were lowest in the 0.01 % group (–1.38 ± 0.98 D; 0.75 ± 0.48 mm) compared to the 0.1 % group (–1.83 ± 1.16 D; 0.85 ± 0.53 mm) and the 0.5 % group (–1.98 ± 1.10 D; 0.87 ± 0.49 mm). In addition, atropine 0.01 % resulted in minimal pupil dilation, slight loss of accommodation and no near vision loss compared to higher doses.

The use of a historical control group in the ATOM2 study raised questions about the validity of comparing results from different periods and patient groups. Besides, 0.01 % had no effect on AL elongation compared with the historical control[18]. Notwithstanding, its use in clinical practice has grown widely. The 2015 report of the World Health Organization on myopia highlighted that 0.01 % atropine was the most widely used strategy for managing childhood myopia in Asian countries, particularly in Singapore, where it is a licensed therapeutic medication[19]. Many hospitals and ophthalmic clinics in public services and private practice have adopted 0.01 % atropine worldwide, especially in Asia and Australasia[20]. Among pediatric ophthalmologists globally, nearly two-thirds regularly prescribe 0.01 % atropine to mitigate myopia progression[21]. Additionally, the Mumbai Group of Paediatric Ophthalmologists and Strabismologists in India has also endorsed it for treating childhood myopia, with almost two-thirds of pediatric ophthalmologists in the region routinely prescribing it[22].

Recognizing that lower concentrations should be more tolerable while still retaining efficacy, the Low-concentration Atropine for Myopia Progression (LAMP) study was launched in Hong Kong. Over the past five years, the LAMP study has focused on low-concentration atropine (0.05 %, 0.025 % and 0.01 %) for slowing myopia progression. It is a randomized, double-masked, placebo-controlled study that aimed to determine the efficacy and safety of three different low-concentration atropine eye drops, 0.05 %, 0.025 % and 0.01 % compared to 0.9 % sodium chloride[23]. In a cohort of 438 Chinese myopic children aged 4–12 years, four groups were randomly assigned in a 1:1:1:1 ratio to receive one of the three concentrations of atropine or placebo drops each night. In the first phase of the LAMP study, the investigators sought to examine the effectiveness of different low concentrations of atropine in comparison to a placebo, identify any concentration-dependent responses and evaluate the optimal concentration for treatment[23]. The findings demonstrated that compared to the placebo, 0.05 %, 0.025 % and 0.01 % atropine slowed myopia progression by 67 % (–0.27 ± 0.61 D versus –0.81 ± 0.53 D), 43 % (–0.46 ± 0.45 D versus –0.81 ± 0.53 D) and 27 % (–0.59 ± 0.61 D versus –0.81 ± 0.53 D), respectively, indicating a concentration-dependent response after one year (Fig. 1). A concentration-dependent response was also observed in slowing AL elongation, 51 % (–0.20 ± 0.25 mm versus 0.41 ± 0.22 mm), 29 % (0.29 ± 0.20 mm versus 0.41 ± 0.22 mm) and 12 % (0.36 ± 0.29 mm versus 0.41 ± 0.22 mm), respectively, although the difference in AL elongation between the 0.01 % atropine and placebo groups was not significant (Fig. 2). All three concentrations had no clinical effect on corneal or lens power, and their antimyopic effects were observed in their ability to slow AL elongation[24], indicating a potential reduction of the risk of subsequent myopia-related complications. Furthermore, all three concentrations demonstrated satisfactory safety profiles, with the children tolerating them well[23]. The reductions in accommodation amplitude were clinically small across all groups, measuring 1.98 D, 1.61 D, 0.26 D and 0.32 D for the 0.05 %, 0.025 % and 0.01 % atropine groups and the placebo group, respectively[23]. In practical terms, a reduction of less than 2 D in accommodation amplitude corresponds to an increase in near-point distance of approximately 1.7 cm, which is not considered a significant clinical concern. Photopic pupil size also increased by 1.03 mm, 0.76 mm, 0.49 mm and 0.13 mm in the 0.05 %, 0.025 % and 0.01 % atropine groups and the placebo group, respectively. In a study by Cooper et al., 0.02 % atropine was the highest concentration that did not lead to clinical symptoms or findings typically associated with higher doses, with a corresponding pupillary dilation of 3 mm[25]. Consequently, using a threshold of over 3 mm for photopic pupil size, the data from the LAMP study indicate that all three low concentrations of atropine were well tolerated. Additionally, neither distance nor near vision was affected, and symptoms of photophobia, along with vision-related quality of life, were consistent across all groups. It is evident that 0.05 % atropine was the optimal concentration, as it yielded superior efficacy in slowing myopia progression while maintaining minimal side effects. While 0.01 % atropine had a relatively limited efficacy as a standalone treatment in the LAMP study, other studies have shown it may offer enhanced benefits when used in combination with other interventions such as orthokeratology and Defocus Incorporated Multiple Segments (DIMS)[26–28]. The diverse methods of measuring treatment effects and the differing treatment durations in various studies complicate the comparison of various myopia-control

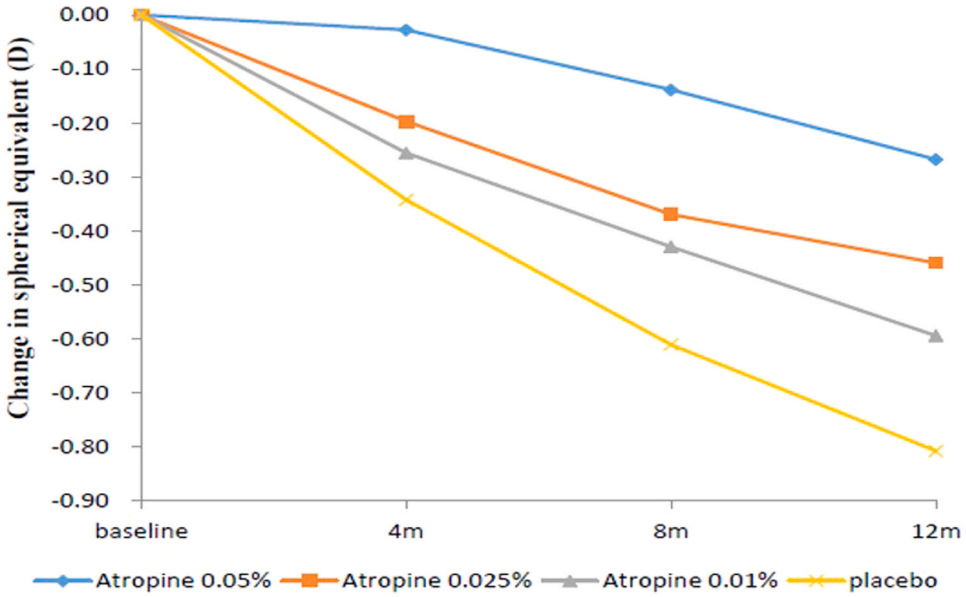


**Fig. 1.** Changes in spherical equivalent (SE) over one year (data from Yam et al., *Ophthalmology*. 2019).

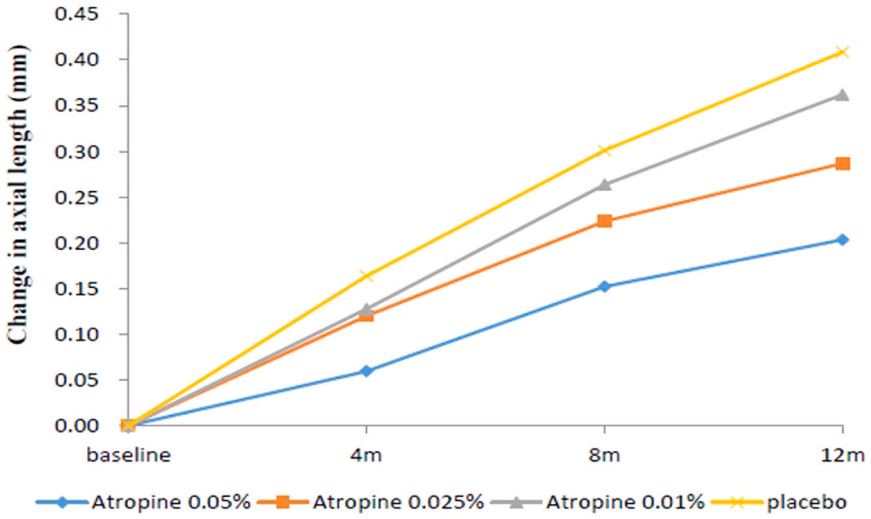


**Fig. 2.** Changes in axial length (AL) over one year (data from Yam et al., *Ophthalmology*. 2019).

interventions. As a result, no single method stands out as clearly superior. However, it is also essential to identify which interventions may potentially prevent the onset of high myopia and its associated sight-threatening complications later in life. The efficacy of 0.05 % atropine is comparable to that of myopia-control spectacle lenses, dual-focus soft contact lenses, orthokeratology, and repeated low-level red-light therapy, all of which also demonstrate at least 50 % efficacy in controlling myopia[29,30].

In phase two, the children who were in the placebo group during the first year were switched to 0.05 % atropine treatment, while those who had received 0.01 %, 0.025 % or 0.05 % atropine in the first year continued with the same treatment for the second year[31]. A total of 383 out of the 438 children completed the two-year follow-up. Over the two years, the mean SE changes were –0.55 ± 0.86 D, –0.85 ± 0.73 D and –1.12 ± 0.85 D for the 0.05 %, 0.025 % and 0.01 % atropine groups, respectively. The corresponding mean AL changes were 0.39 ± 0.35 mm, 0.50 ± 0.33 mm and 0.59 ± 0.38 mm. The efficacies of 0.05 % and 0.025 % atropine in the second year remained consistent with those of the first year, while the 0.01 % atropine group showed a slight improvement. However, it was observed that over the two years, the efficacy of 0.05 % atropine was double that of 0.01 % atropine. For the group that transitioned from placebo in the first year to 0.05 % atropine in the second year, their myopia progression decreased from –0.82 ± 0.49 D, 0.43 ± 0.21 mm in the first year to –0.18 ± 0.49 D, 0.15 ± 0.18 mm in the second year. The effects on accommodation and pupil size for all concentrations in the second year were similar to those observed in the first year. Thus, the data revealed that 0.05 % atropine consistently outperformed 0.025 % and 0.01 % concentrations, with efficacy remaining stable over the two-year period. The substantial improvement in myopia progression observed in children who transitioned from placebo to 0.05 % atropine underscores the promising benefits of early and effective treatment.

In a secondary analysis of the phase two data, an age-dependent treatment response to 0.05 %, 0.025 % and 0.01 % atropine was observed[32]. Notably, the younger children in this cohort aged between 4 and 12 years showed less treatment effectiveness, requiring the higher concentration of 0.05 % atropine to achieve a similar reduction in myopia progression as older children using lower concentrations. This

was attributed to the inherent natural slowing of axial length that occurs with age and implies that while 0.01 % atropine may exhibit diminished efficacy, it could still be a viable option in myopia-control therapy, particularly since tapering off to this concentration at an older age may still provide clinically relevant benefits. It also highlights the importance of personalized approaches to myopia management with low-concentration atropine.

In another study involving 314 children from the LAMP study cohort, subjects were examined for the effects of varying concentrations of atropine on subfoveal choroidal thickness (SFChT) over two years[33]. The two-year changes in SFChT from baseline were significant across the different atropine groups: 21.15 ± 32.99 μm for 0.05 %, 3.34 ± 25.30 μm for 0.025 % and −0.30 ± 27.15 μm for 0.01 %. A concentration-dependent response was noted, with thicker choroids linked to higher atropine concentrations. Of note, significant increases in SFChT were observed at 4 months for the 0.025 % and 0.05 % groups, stabilizing thereafter. Monitoring for this plateau can help determine the optimal duration and concentration of atropine therapy needed to maintain its benefits, as well as the potential need for additional interventions if myopia progression continues despite stable choroidal thickness. This understanding is crucial for maximizing the effectiveness of myopia management strategies in children. Over two years, increased SFChT correlated with slower SE progression and decreased AL elongation, with 18.45 % of the effect of atropine 0.05 % on SE progression observed to be mediated through choroidal thickening. This choroidal response may serve as a biomarker for assessing long-term treatment outcomes and guiding atropine concentration adjustments.

Phase three of the LAMP trial sought to compare the efficacy of continued and stopping treatment for 0.05 %, 0.025 % and 0.01 % atropine during the third year, to evaluate the efficacy of continued treatment over three years and to investigate the rebound phenomenon and its determinants after cessation of treatment[34]. Children in each concentration group were randomized at a 1:1 ratio to a continued treatment group and a washout subgroup. During the third year, SE progression was faster in the washout subgroup than in the continued treatment group across all concentrations: −0.68 ± 0.49 D versus −0.28 ± 0.42 D for 0.05 % atropine, −0.57 ± 0.38 D versus −0.35 ± 0.37 D for 0.025 % atropine and −0.56 ± 0.40 D versus −0.38 ± 0.49 D for 0.01 % atropine (Fig. 3). AL elongation also occurred more rapidly in the washout subgroup than in the continued treatment group across all concentrations, although the difference for 0.01 % atropine was not significant: 0.33 ± 0.17 mm versus 0.17 ± 0.14 mm for 0.05 % atropine, 0.29 ± 0.14 mm versus 0.20 ± 0.15 mm for 0.025 % atropine and 0.29 ± 0.15 mm versus 0.24 ± 0.18 mm for 0.01 % atropine (Fig. 4). Over the three-year duration, 0.05 % atropine remained the optimal concentration. Although 0.025 % atropine yielded a greater efficacy than 0.01 % atropine in the first year, their efficacies in controlling AL elongation were similar in the second and third years, highlighting the clinical advantage of initiating treatment with 0.05 % atropine rather than starting at a lower concentration with the intention of increasing it later. The rebound effect observed after discontinuing 0.05 % atropine was minimal and recognized as “clinically insignificant”. In contrast, the 0.025 % and 0.01 % groups exhibited no rebound effect. This suggests that there may be merit in implementing a tapering strategy before ceasing treatment, particularly for those who have been using the 0.05 % concentration.

The purpose of phase four of the LAMP study was to evaluate: 1) the long-term efficacy of low-concentration atropine over five years, 2) the proportion of children requiring retreatment and associated factors and 3) the efficacy of *pro re nata* (PRN) retreatment using 0.05 % atropine from the third to fifth years[35]. During the fourth and fifth years, all continued treatment subgroups were switched to 0.05 % atropine for continued treatment, while all treatment cessation subgroups followed a PRN retreatment protocol to resume 0.05 % atropine for children with myopic progressions of 0.50 D or more over one year. Over five years, the cumulative mean SE progressions were −1.34 ± 1.40 D for the

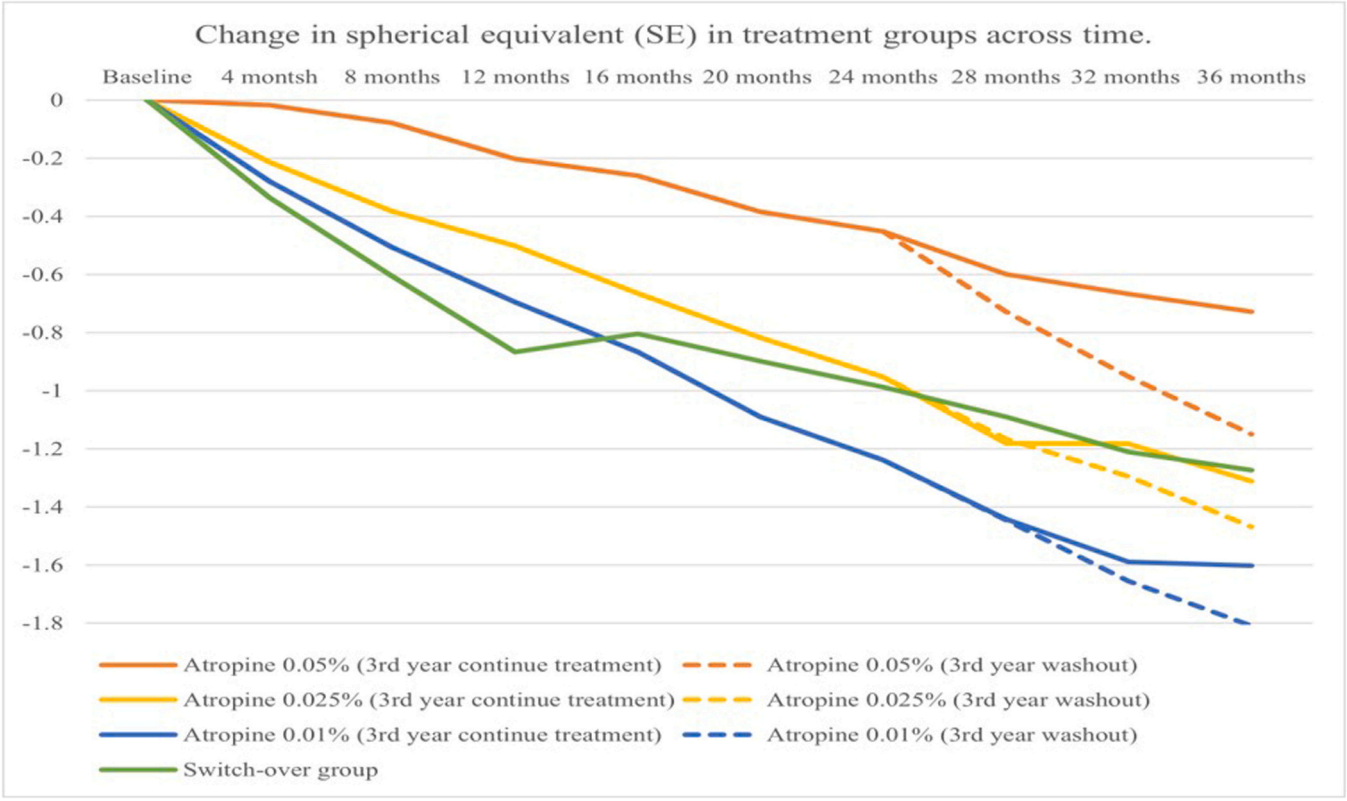


**Fig. 3.** Changes in spherical equivalent (SE) for treatment groups over three years. The switchover group received a placebo during the first year and transitioned to 0.05 % atropine at the start of the second year, continuing with this treatment into the third year (data from Yam et al., *Ophthalmology*. 2022).

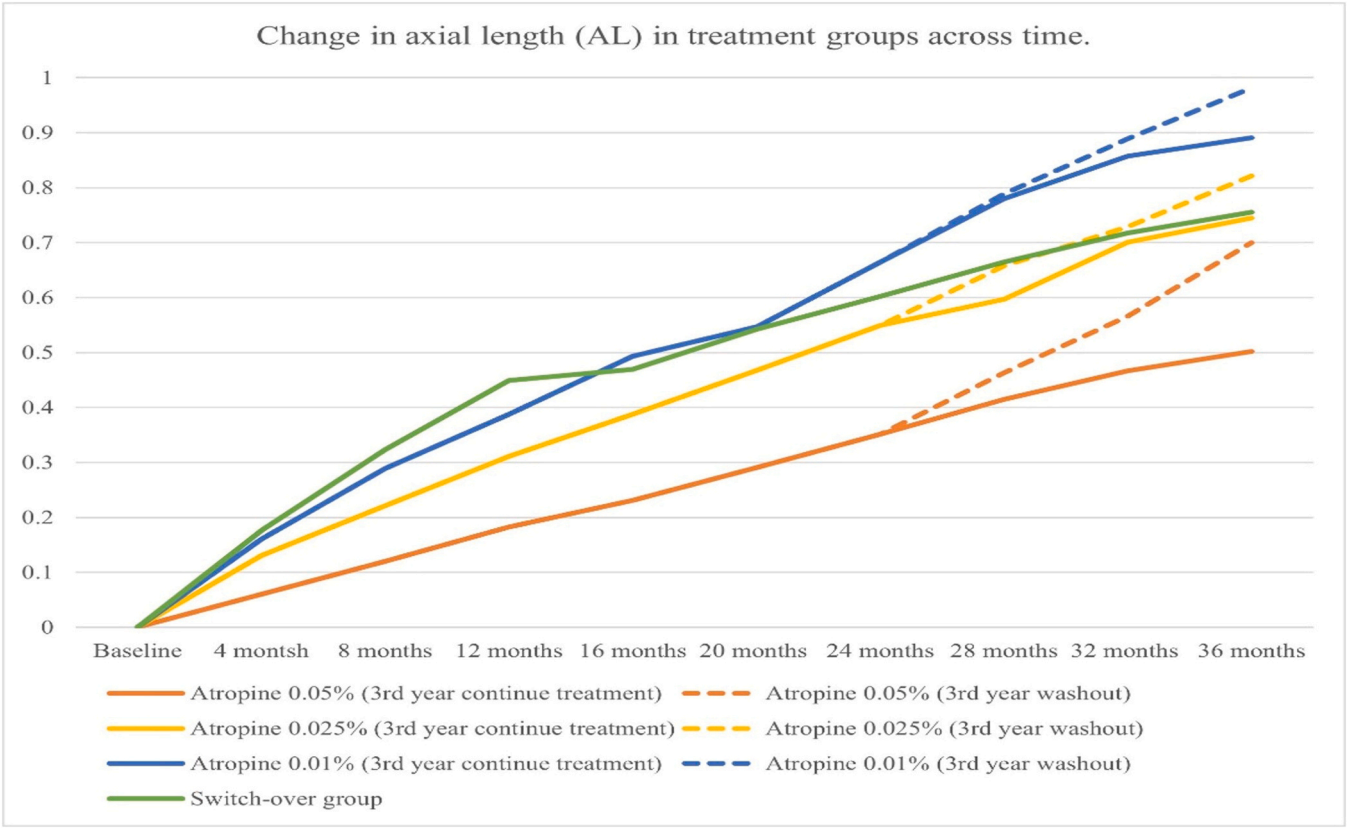


**Fig. 4.** Changes in axial length (AL) for treatment groups over three years. The switchover group received a placebo during the first year and transitioned to 0.05 % atropine at the start of the second year, continuing with this treatment into the third year (data from Yam et al., *Ophthalmology*. 2022).

initial 0.05 % atropine group, −1.97 ± 1.03 D for the initial 0.025 % atropine group and −2.34 ± 1.71 D for the initial 0.01 % atropine group. AL elongation over the five years demonstrated a similar trend among groups: 0.79 ± 0.54 mm, 1.11 ± 0.46 mm and 1.24 ± 0.72 mm for the initial 0.05 %, 0.025 % and 0.01 % atropine subgroups, respectively. Among the PRN retreatment group, 87.9 % (94/107) of children needed retreatment, and the proportion of retreatment across all studied concentrations was similar. Between the third and fifth years, the SE progression for this group was −1.00 ± 0.74 D and AL elongation was 0.51 ± 0.34 mm. For the continued treatment group during those three years, SE progression was −0.97 ± 0.82 D and AL elongation was 0.49 ± 0.32 mm. It was found that for children who restarted treatment, 0.05 % atropine achieved similar efficacy as continued treatment. In summary, two to three years of atropine treatment for children aged 4–12 years at baseline is likely not enough to stabilize myopia, continued 0.05 % atropine treatment is effective in myopia control with good tolerance over five years, and retreatment should be considered for those who experience myopia progression after discontinuing treatment. However, it is advisable to maintain 0.05 % atropine treatment during the first five years for children at high risk of myopia progression.

As myopia rates continue to rise globally, exploring various interventions is crucial for developing comprehensive prevention strategies. The LAMP2 study aimed to evaluate the efficacy of 0.05 % and 0.01 % atropine for delaying myopia onset in children[36]. Nonmyopic, healthy children aged 4–9 years with cycloplegia-confirmed SE refraction between 0.00 and + 1.00 D and astigmatism of no more than 1.00 DC were recruited for the study. Participants were randomly assigned to receive 0.05 % atropine, 0.01 % atropine or saline placebo eyedrops for night application for two years. After two years, the cumulative myopia incidence was found to be 28.4 % for the 0.05 % atropine group, 45.9 % for the 0.01 % group and 53 % for the placebo group. Compared to the 0.01 % atropine and placebo groups, 0.05 % atropine yielded a significantly lower myopia incidence over two years by 17.5 % and 24.6 %, respectively. The percentages of children with a fast myopic shift were 25 % for the 0.05 % atropine group, 45.1 % for the 0.01 % group and 53.9 % for the placebo group. Compared to the 0.01 % atropine and placebo groups, 0.05 % atropine showed reduced myopic shift of 20.1 % and 28.9 %, respectively. No significant difference was observed between the 0.01 % atropine and placebo groups regarding the two-year cumulative incidence of myopia (7.1 %) or the percentage of fast progressors (8.8 %). Changes in SE and AL were found to be −0.46 D, −0.84 D and −1.01 D; 0.48 mm, 0.63 mm and 0.70 mm for the 0.05 % group, 0.01 % group and placebo group, respectively. The 0.05 % atropine was shown to decrease myopic shift and AL elongation compared to the 0.01 % atropine and the placebo. There were similar rates of photophobia in the placebo, 0.01 % and 0.05 % groups, and best-corrected distance and near acuity were not different among the three groups. In essence, atropine 0.01 % was ineffective in delaying myopia onset, whereas atropine 0.05 % reduced the incidence by about half over two years. It was safe and well tolerated, with comparable rates of photophobia observed in the placebo, 0.01 % and 0.05 % groups. The efficacy of 0.05 % atropine in reducing the incidence of myopia is similar to those of repeated low-level and increased outdoor time, which also reduced myopia incidence by up to approximately 50 %[37–39]. Therefore, low concentration of 0.05 % atropine may serve as an additional strategy to help slow refractive changes and axial elongation in children identified as at-risk for myopia.

In a secondary analysis of the LAMP2 study, Zhang et al. observed that 0.05 % atropine was more effective than 0.01 % atropine and placebo for eyes with lower hyperopic reserves. Accordingly, it was recommended that 0.05 % atropine should be targeted at children with hyperopic reserves of < +0.75 D since participants with baseline hyperopic reserves ranging from + 1.0 D to + 0.75 D showed no significant differences in SE change across all treatment groups[40]. This is consistent

with a report by He et al., which noted significantly better efficacy in children with SE of + 0.01 to + 0.50 D compared to those with SE of −0.50 to 0.00 D, showing relative efficacies of 64.0 % versus 14.0 %, respectively, following treatment with repeated low-level red light[37]. He et al. suggested that prophylactic interventions, including repeated low-level red light and increased outdoor time, should be implemented earlier, particularly for those with an SE in the range of + 0.01 to + 0.50 D. Evidence from the secondary analysis of the LAMP2 trial suggests that while children with hyperopic reserves of < +0.75 D may be indicated for prophylactic interventions, those with reserves of at least + 0.75 D may not need treatment yet. This distinction is important to avoid unnecessary treatment in children who are likely to remain emmetropic. Continuous close monitoring will, however, remain essential.

The Atropine Treatment Long-term Assessment Study (ATLAS) conducted in Singapore assessed the 20-year follow-up outcomes and safety for the patients who participated in the ATOM1 study (1 % atropine versus placebo; 1999 through 2003) and the 10-year follow-up outcomes for the patients who took part in the ATOM2 study (atropine 0.01 % versus 0.1 % versus 0.5 %; 2006 through 2012)[41]. The findings showed that the short-term use of atropine in children for a duration of two to four years starting at approximately nine years of age was not associated with differences in SE or AL between treatment and placebo in ATOM1 or different atropine concentrations in ATOM2, 10–20 years after treatment. In the ATOM2 participants, greater myopia progression in ten years after treatment cessation was linked to younger age at treatment initiation and higher atropine concentrations (0.5 % and 0.1 % versus 0.01 %). Younger children have more pronounced eye growth compared to older children[42,43]. Thus, while initiating atropine treatment early can effectively slow eye growth, discontinuing the treatment when they are still relatively young may trigger a rebound effect, resulting in accelerated eye elongation. In contrast, older children, whose eye growth has naturally begun to stabilize[42,43], are less likely to experience such a pronounced rebound after stopping treatment. This indicates that short-term atropine use, especially in younger children, could result in a significant rebound effect, potentially negating the benefits gained during earlier treatment. Moreover, it suggests a more gradual approach to discontinuing treatment with higher concentrations might be necessary. There was no higher incidence of treatment or myopia-related ocular complications in the 1 % atropine-treated group compared to the placebo group[41], indicating its potential for long-term protection against these complications, even with short-term use. Notably, the ATLAS investigators urged caution in interpreting these findings due to the limited number of participants in this observational study. They noted that those who experienced adverse effects might have been less likely to return for follow-up. It was also observed in the ATOM2 participants that a longer AL at baseline in childhood and greater axial elongation during the treatment period of the clinical trial were linked to a higher incidence of early myopic macular degeneration (MMD) in adulthood although most eyes exhibited only grade one MMD[41], implying that AL elongation could be an essential measure in evaluating the response to atropine treatment in childhood and monitoring the risk of developing MMD in adulthood. Overall, the ATLAS study demonstrated the long-term safety of atropine treatment and highlighted that a short treatment duration may not lead to any significant changes in outcomes. Accordingly, when evaluating concentration, it is essential to carefully consider the duration of treatment required to achieve the best long-term results. The ATLAS data lays a foundation for addressing key questions regarding the optimal duration of atropine treatment needed for sustained outcomes. Specifically, it raises important considerations about the appropriate timing for safely discontinuing treatment, as well as whether tapering the concentration or continuing treatment into adolescence is the more effective strategy. These issues will need to be addressed in future studies. Until these questions are resolved, it is crucial to closely monitor patients after treatment is discontinued so that therapy can be restarted promptly if a rebound occurs. The LAMP study has demonstrated that retreatment with 0.05 % atropine is as effective as ongoing treatment[35].

The landmark ATOM1, ATOM2 and LAMP studies discussed in this review are summarized in Table 1. When using low-concentration atropine for myopia management, it is crucial to incorporate lifestyle recommendations. This should include encouraging at least two hours of outdoor time daily, limiting leisure near work time to under two hours, increasing viewing distance and taking regular breaks during close-up tasks[44–48]. A recent study highlighted that reduced outdoor time during COVID-19 lockdowns diminished the efficacy of DIMS spectacle lenses[49]. Furthermore, the Myopia Outcome Study of Atropine in Children (MOSAIC) revealed that participants who faced fewer COVID-19-related restrictions experienced more significant treatment effects with 0.01 % atropine[50]. These findings emphasize the critical role of lifestyle factors in enhancing the efficacy of low-concentration atropine. In East Asia, initiatives have been implemented that may indirectly improve the effectiveness of this treatment when properly enforced. Examples include Taiwan's Tian-Tian 120 program[51] which promotes 120 minutes of daily outdoor activities, and the Sports and Health 150 program[52] advocating for 150 minutes of weekly exercise in schools. Singapore's "Kids for Nature" initiative aims to encourage primary school children and their families to spend more time outdoors through educational programs in national parks. Additionally, the Chinese government's "Double Reduction" policy seeks to decrease homework and after-school tutoring while increasing after-school care[53]. Another promising approach currently under investigation involves creating more naturalistic visual environments or outdoor scenes within classroom settings[4,54].

## Biological mechanisms of atropine in myopia control

Despite its widespread use, the mechanism by which atropine slows eye growth remains inconclusive, with several hypotheses proposed regarding its action. Atropine acts as a nonselective antagonist of muscarinic receptors, competing for binding sites on all types of muscarinic receptors, thereby inhibiting the action of acetylcholine, the natural physiological agonist for these receptors[55]. The initial application of atropine stemmed from the hypothesis that excessive accommodative effort contributed to myopia, with atropine thought to eliminate this accommodative function. However, subsequent studies indicated that atropine likely does not act through the accommodative pathway. This is supported by findings that both atropine and pirenzepine, another muscarinic antagonist, were effective in inhibiting myopia in chicks that do not possess muscarinic receptors in the ciliary muscle[56,57]. Moreover, even in the absence of accommodation, eyes that are functionally hyperopic tend to grow longer[58]. This led to a transition from focusing on accommodative pathways to investigating mechanisms within the retina, choroid and sclera. In most mammalian species, muscarinic receptors (M1 to M5) are known to be distributed throughout these tissues[59]. Evidence has been presented against the sclera as a site of action for atropine in myopia control[60–62], whereas other studies have indicated that atropine might be acting through alteration of retinal neurotransmission. In chicks, both form deprivation and lens-induced myopia significantly reduced retinal *ZENK* messenger ribonucleic acid levels, while atropine administration reversed this downregulation caused by both conditions[63,64]. Additionally, atropine was found to inhibit choroidal thinning induced by hyperopic defocus[65,66] and increased choroidal thickness in myopic subjects[33].

The available evidence suggests that atropine may exert its effects through multiple pathways. Gaining a deeper understanding of these mechanisms will enhance administration strategies and help identify individuals who could benefit most from treatment. Additionally, this knowledge can improve our understanding of potential side effects.

## The rebound phenomenon

The rebound phenomenon refers to the resurgence of myopia

**Table 1**
Summary of ATOM1, ATOM2, and LAMP studies on atropine for myopia control.

| Author, year | Study location | Follow-up (month) | Sample size | Age (y) | Arms and treatments | Baseline SE (D) | Baseline AL | SE control (treatment group /control group) | AL control (treatment group /control group) |
|---|---|---|---|---|---|---|---|---|---|
| Chua et al., 2006 **(ATOM1 study)**[14] | Singapore | 24 | 400 | 6–12 | | –1.0 to –6.0 | | | |
| | | | 200 | 9.2 | 1 % Atropine | –3.36 (1.38) | 24.80 (0.83) | 77 % | –0.02 mm/0.38 mm |
| | | | 200 | 9.2 | Placebo | –3.58 (1.17) | 24.80 (0.84) | | |
| Chia et al., 2012 **(ATOM2 study)**[16] | Singapore | 24 | 400 | 6–12 | | –2.0 or less | | | |
| | | | 161 | 9.70 (1.5) | 0.5 % Atropine | –4.7 (1.8) | 25.2 (0.9) | –0.30 D/–0.49 D | 0.27 mm/0.41 mm |
| | | | 155 | 9.70 (1.6) | 0.1 % Atropine | –4.8 (1.5) | 25.2 (0.8) | –0.38 D/–0.49 D | 0.28 mm/0.41 mm |
| | | | 84 | 9.50 (1.5) | 0.01 % Atropine | –4.5 (1.5) | 25.1 (1.0) | | |
| Yam et al., 2019 **(LAMP study)**[23] | Hong Kong | 12 | 438 | 4–12 | | –1.0 or less | | | |
| | | | 109 | 8.45 (1.81) | 0.05 % Atropine | –3.98 (1.69) | 24.85 (0.90) | 67 % | 51 % |
| | | | 108 | 8.54 (1.71) | 0.025 % Atropine | –3.71 (1.85) | 24.86 (0.95) | 43 % | 29 % |
| | | | 110 | 8.23 (1.83) | 0.01 % Atropine | –3.77 (1.85) | 24.70 (0.99) | 27 % | 12 % |
| | | | 111 | 8.42 (1.72) | Placebo | –3.85 (1.95) | 24.82 (0.97) | | |

AL=axial length; ATOM=Atropine for the Treatment of Myopia; D=diopter; LAMP=Low-concentration Atropine for Myopia Progression; SE =spherical equivalent.

progression following the cessation of the intervention, which can lead to a faster rate of progression in the treatment group compared to the control group, thus negating the accumulated benefits achieved during the active treatment phase[29]. In the three-year results of the LAMP study, AL elongation was more pronounced in the washout groups from 24 to 36 months. Pairwise comparisons revealed that the difference was primarily due to the previously treated 0.05 % group progressing slightly faster—by approximately 0.04 mm—than the 0.01 % group, though clinically small[34]. Younger children (6–8 years) were more likely to show greater rebound, but stopping treatment at an older age and lower concentration was associated with a lesser rebound effect[34]. This implies that tapering off atropine treatment to a lower concentration and eventually stopping at an older age may help reduce the rebound effect. The ATLAS study has illustrated the rebound phenomenon more clearly, showing that the benefits gained in the initial ATOM studies were completely erased[41]. This highlights the importance of close monitoring following cessation of treatment with atropine and points to the fact that treatment for two to four years with the concentrations used in the ATOM studies is probably not sufficient.

## What else do we need to understand?

We now have a substantial amount of data demonstrating the efficacy of low-concentration atropine in slowing myopia progression. However, a common challenge in myopia management is the lack of specific studies tailored to the unique characteristics of individual children. We still need to know whether 0.05 % atropine can control myopia in children of different ages, ethnicities, lifestyles, and locations. In the LAMP studies, all children were of Chinese ancestry and attended a single study site. Besides, it is crucial to understand if there are safety implications for long-term atropine use for controlling myopia onset and whether the effect observed in the LAMP 2 study represents delay or prevention of myopia. The participants in the LAMP2 trial are currently in their fourth year of follow-up, with the total intended follow-up duration of 6 years to evaluate a longer-term effect. Furthermore, public health approaches, enhanced screening methods, and prediction models are needed to understand how premyopes who could benefit from the delaying effect of atropine may be identified since they may not present for eye examinations before myopia onset.

It is important to recognize that other circumstances can lead to myopic refractive errors, including keratoconus, myopia of prematurity, and microspherophakia, which are causes of nonaxial myopia. Congenital glaucoma can also lead to buphthalmos and progressive myopia[67]. In these situations, the use of low-concentration atropine may not be suitable. Therefore, it is essential to carefully evaluate preliminary ocular biometric measures and birth history before initiating treatment. Additionally, the effectiveness of low-concentration atropine in cases of syndromic myopia or familial high myopia, which are likely genetically determined, remains uncertain. Typically, such cases are excluded from clinical trials on myopia progression[67]. The absence of evidence regarding the efficacy of treatments for these conditions complicates the development of evidence-based guidelines. Moreover, several genes have been linked to myopia and related ocular biometric characteristics[68,69], with those contributing to syndromic myopia being involved in diverse biological processes[70]. This suggests that responses to myopia progression interventions may be variable in such cases. Given the rarity of the conditions, conducting clinical trials may be impractical, making the use of animal models for studying syndromic myopia and myopia of prematurity a viable alternative.

## Conclusions and recommendations

Low concentrations of atropine, specifically 0.05 %, 0.025 %, and 0.01 %, have shown significant efficacy in slowing myopia progression while maintaining favorable safety profiles, exhibiting a concentration-dependent response. Among them, 0.05 % atropine consistently demonstrates superior efficacy in slowing myopia progression over five years and delaying its onset over two years. Initiating treatment early and maintaining the most effective concentration before considering discontinuation may be crucial for sustaining efficacy in the long term. Furthermore, since the exact duration of atropine treatment necessary for sustained outcomes is still unknown, it is important to closely monitor patients after treatment is discontinued so that therapy can be restarted promptly if a rebound occurs. In addition, clinical trials involving children with myopia of prematurity, syndromic myopia, and familial high myopia have not yet been conducted; thus, such conditions

should be approached on a case-by-case basis and with caution, as the effects of atropine in these cases are currently unclear. When treating with low-concentration atropine, it is important to take into account the visual environment and lifestyle factors. Given the substantial impact of age, refraction, ethnicity and personal habits, tailoring treatment to the individual is crucial for optimal outcomes.

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