Low concentration atropine and myopia: a narrative review of the evidence for United Kingdom based practitioners

Low Concentration Atropine and Myopia: A Narrative Review of the Evidence for United Kingdom Based Practitioners

Short title: Low concentration Atropine and Myopia

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Abstract

The prevalence of myopia is increasing across the world. Controlling myopia progression would be beneficial to reduce adverse outcomes such as retinal detachment and myopic maculopathy which are associated with increased axial length. Pharmacological control of myopia progression with atropine has been investigated since the 19th century and the benefits of slowing myopia progression are considered against the side-effects of near blur and photophobia. More recently, randomised trials have focused on determining the optimum concentration of atropine leading to low-concentration atropine being used to manage myopia progression by practitioners across the world. Currently, in the United Kingdom, there is no licensed pharmacological intervention for myopia management. The aim of this review is to interpret the available data to inform clinical practice.

We conducted a narrative review of the literature and identified peer-reviewed randomised controlled trials using the search terms 'myopia' and 'atropine', limited to the English language. We identified two key studies, which were the Atropine in the Treatment Of Myopia (ATOM) and Low-concentration Atropine for Myopia Progression (LAMP). Further studies were identified using the above search terms and the references from the identified literature.

Atropine 0.01% has a modest effect on controlling axial length progression. Atropine 0.05% appears to be superior to atropine 0.01% in managing myopia progression. There is a dose-dependent rebound effect when treatment is stopped. Atropine is a well-tolerated, safe and effective intervention. Treatment would be needed for several years and into adolescence, until axial length progression is stable.

Low Concentration Atropine and Myopia

An aspirational aim for pharmacological control of myopia progression is the development of a safe, effective, well tolerated, and affordable eyedrop to use once daily or less frequently than that.

Atropine and pirenzepine—both muscarinic antagonists—have shown favourable results for slowing myopia progression(1,2). As topical administration is generally preferable over systemic administration for purely ocular conditions, atropine eyedrops have been the subject of randomised controlled trials in East Asia, Europe, India, Australia and the United States of America. Atropine has been the drug of most interest and will be the focus of this review.

The optimum concentration of atropine is still unknown; the benefit of higher efficacy in terms of slowing myopia progression needs to be balanced against potential adverse effects such as near blur and light sensitivity. It is not clear whether eyes with blue iris would experience the same effects with lower concentrations as those with brown iris using higher concentrations.

Atropine 0.01% has been advocated as a recommended treatment for myopia (3) and this has been found to be the most popular choice of therapeutic agent when paediatric ophthalmologists were surveyed worldwide (4). This may be because pharmacological treatments are easier to prescribe than spectacle and contact lens options for this cohort of practitioners.

However, since the first studies highlighting the benefits of other atropine concentrations and treatment protocols have shown greater efficacy and equivalent safety.

In this paper we will discuss the use of atropine for myopia management, focussing on mechanisms of action and evidence for its efficacy alongside what we still need to learn about atropine and myopia.

Mechanism

The exact mechanism of action for atropine in reducing myopia progression is still unknown. One pathway is inhibition of accommodative function via muscarinic receptors, but as atropine also prevents experimental myopia in chicks, who have striated muscle, other pathways are likely to be involved as well (5). Indeed, there are several hypotheses regarding atropine's mode of action with sites of action in the sclera, retinal pigment epithelium and choroid but no consensus has been reached at present (6).

Changes in the sclera

If a constant load is applied, the tissue extends over time and this biomechanical property is called the 'creep rate'. Posterior and equatorial sclera from myopic eyes have greater creep values than non-myopic eyes (7), meaning that they have poorer biomechanical stability. This promotes axial elongation and formation of staphyloma (8).

Myopic eyes also have thinner sclera with reduced glycosaminoglycans, reduced collagen content and disorganised fibrils (8–10).

Muscarinic receptors 1-5 have been detected in human scleral fibroblasts. In cell culture, atropine has been shown to abolish the carbachol-induced activation of scleral fibroblasts cell proliferation in a concentration-dependent manner (11). In chicks, atropine reduces cellular proliferation and extra-cellular matrix production in whole sclera predominantly via the M1 receptor (12).

Atropine is a reversible competitive antagonist for all 5 muscarinic receptors. However, atropine also influences α-2A -adrenergic receptors(13), Υ-aminobutyric acid receptors (GABA-R)(14) and tyrosine kinase receptors (TKRs)(11). Epidermal Growth Factor (EGF) is from the family of TKRs and has been shown to influence scleral fibroblast proliferation. As such, atropine may exert it's influence through more than the recognised muscarinic receptor pathways(6).

Changes in the choroid

The retina can sense defocus and signal the eye to grow or stop growing, possibly via changes to choroidal thickness (15). The choroid can modulate its thickness and move the retina to the focal plane – this is termed choroidal accommodation (6,16). Concave lenses move the image backwards and place it on the focal plane at the macula, but at the same time, due to the posterior curvature of the eye, place the mid-peripheral image behind the retina, this is termed "hyperopic defocus". Myopic children have thinner choroidal thickness values compared to those with no refractive error or hyperopia (17). Atropine has been shown to abolish choroidal thinning induced by hyperopic defocus in the human eye without changing baseline choroidal thickness (18,19), suggesting that atropine inhibits the signals caused by hyperopic defocus, such as that resulting from accommodative lag during near work (18).

The RPE and choroid secrete a variety of growth factors, including transforming growth factor-β (TGF-β)and basal fibroblast growth factor (bFGF) (6). Atropine blocks the secretion of TGFβ2 via muscarinic receptors in RPE cells(6,20) and increases bFGF production – a factor which is responsible for scleral fibroblast proliferation (6,21).

In children, measures of choroidal thickness have shown that low dose atropine causes a thickening of the choroid in a concentration-dependent response (0.01% to 0.05%) (22). Those children who demonstrated thickening of the choroid with atropine use also showed slower myopia progression, suggesting that choroidal response may serve as a useful surrogate marker for treatment monitoring and dosing (22).

Alongside the biological mechanisms outlined above there is some evidence to suggest a change in relative peripheral refraction with relative peripheral hyperopia in the temporal retina being alleviated with 0.01% atropine (23).

Our understanding of the mechanisms of action for atropine and myopia progression is incomplete. However, it is likely that atropine modulates scleral fibroblast activity and promotes choroidal thickening.

Atropine and myopia control

Donders was the first to advocate use of atropine in myopia in 1864, suggesting its use for accommodative spasm and myopia (24,25). Pollock presented his successful experience of using atropine for myopia control in a case-series of school children in 1916 (25,26). Children were also taken out of school and prevented from all near tasks. Atropine was then used by Gostin in the early 1960s for the treatment of myopia (27). Bedrossian published results of a unilateral crossover study in 1979 which evaluated the use of 1% atropine in controlling myopia progression (28). Ninety children were prescribed 1% atropine to be used in 1 eye and then switched to the fellow eye 12 months later. During the first-year myopia regressed +0.22 D in treated eyes as compared to a mean progression of -0.82 D in the control eyes. During the second year, (after cross-over), the treated eyes regressed a mean +0.18D versus -0.99 D of mean myopia progression in the previously treated (now un-treated) eyes (28). Kennedy conducted a retrospective study of 214 myopic patients treated with atropine 1% between 1967 and 1974 (29). They were matched for age and refractive error with controls. A mean myopia progression of -0.05 D/year was found for those treated with atropine versus -0.36 D/year for controls (29). This finding was consistent with other studies in this era suggesting a control effect of +0.21 D to -0.12 D over the first year of 1% atropine treatment (28,30–33). Brodstein (32) further demonstrated the myopia control benefits of 1% atropine but found significant rebound once treatment was stopped; as well as high rates of drop-out due to non-adherence to treatment (32). Yen and colleagues (34) compared atropine to cyclopentolate and saline. Atropine was superior to both in slowing myopia but high rates of drop-out were noted, particularly in the 1% atropine group (34).

The modern atropine era began with a study by Shih et al. (35). They recruited 186 children, aged 6 to 13 years of age, who were treated each night with either 0.5%, 0.25%, 0.1% atropine eye drops or a control treatment for up to 2 years. The mean myopic progression was -0.04 ± 0.63 D/year in the 0.5% atropine group, -0.45 ± 0.55 D/year in the 0.25% atropine group, and -0.47 ± 0.91 D/year in the 0.1% atropine group. All atropine groups showed significantly less myopic progression than the control group (-1.06 ± 0.61 D/year) ($p<0.01$). Thus overall, the 0.5% concentration was the most effective in slowing myopia.

There are two key randomised clinical trials that have formed much of our current understanding on the safety and efficacy of low-dose atropine(36–39) which we will discuss in detail.

Atropine 1% was re-visited and comprehensively investigated in the ATOM (Atropine for the Treatment Of childhood Myopia) trial (40). Here, 400 children aged 6-12 years with a spherical equivalent (SE) refraction of -1 to -6 D and less than -1.5 D of astigmatism were randomised to one eye per patient receiving 1% atropine or a placebo drop. After 2 years, the mean progression of myopia in the placebo control group was −1.20 ± 0.69 D and axial elongation 0.38 ± 0.38 mm. In the atropine-treated eyes, mean myopia progression was only −0.28 ± 0.92 D, and the axial length remained essentially unchanged from baseline (−0.02 ± 0.35 mm).

After cessation of atropine drops(41), however, the mean progression in the atropine-treated group was -1.14 ± 0.80 D over 1 year, whereas the progression in placebo-treated eyes was -0.38 ± 0.39 D ($P<0.0001$). Axial elongation, whilst constrained by atropine during the two years of treatment, also showed significant rebound. Over the 3 years (2 years of treatment and 1 year of treatment withdrawal), the increase in axial length of the atropine-treated eyes was 0.29 ± 0.37 mm compared with 0.52 ± 0.45 mm in the placebo-treated eyes ($P<0.0001$) (41). Rebound eye growth and myopia progression was most marked in the first 6 months following cessation of atropine treatment.

The results of ATOM reinforced the earlier findings of studies throughout the later part of the 20th century (28,29,32,34). Nonetheless, 1% atropine is a potent cycloplegic and mydriatic drug that will invariably cause blurred near vision due to loss of accommodation and photophobia due to pharmacological dilatation. These unpleasant effects can lead to poor compliance. Given this and the rebound following treatment cessation, interest grew in lower doses of atropine.

The potential that lower doses of atropine were effective in myopia control with less risk of rebound and deleterious effects on pupil size, accommodation and near vision led to the development of the ATOM 2 study (38). Here, 400 children aged 6-12 years with myopia <-2.00 DS and astigmatism <1.50 D were randomised 2:1:1 to bilateral, nightly, atropine 0.5%, 0.1% or 0.01% treatment groups. The

mean myopia progression after 2 years was -0.30 ± 0.60, -0.38 ± 0.60, and -0.49 ± 0.63 D in the atropine 0.5%, 0.1%, and 0.01% groups, respectively. The mean increase in axial length was 0.27 ± 0.25, 0.28 ± 0.28, and 0.41 ± 0.32 mm in the 0.5%, 0.1%, and 0.01% groups, respectively. Atropine 0.01% had a negligible effect on accommodation and pupil size, and no clinical effect on near visual acuity. Given that there was negligible clinical difference in myopia progression between these doses over 2 years, 0.01% atropine was proposed as an effective dose for myopia control. This proposal overlooks the fact that 0.01% atropine had no effect on axial elongation when compared to the control eyes in ATOM.

At the end of the first 2 years (phase 1) of the ATOM 2 trial patients underwent a 12-month wash-out period (phase 2). After withdrawal, any child that progressed at more than -0.50 D was re-commenced on 0.01% atropine once daily for a further 24 months (phase 3). During phase 2 there was an inverse relationship between atropine dose in phase 1 and myopia progression. Of those children originally on 0.01% atropine 24% were re-commenced on atropine during phase 2 compared with 68% of children in the 0.5% group. As a result, atropine 0.01% demonstrated the strongest efficacy in reducing myopia over 3 years (2 years treatment and 1 year of no treatment) due to a combination of treatment effect and less rebound.

Of the original 400 children 345 were enrolled into phase 3. Of these, 192 children were re-started on atropine 0.01% as they had progressed by more than -0.50 DS in phase 2. Of these, 17 were originally in the 0.01% group, 82 in the 0.1% group and 93 in the 0.5% group. Younger age at baseline was a risk for progression in phase 2 in addition to the original atropine group. Amongst the re-treated children, mean progression was lower in phase 3 across all three atropine groups (-0.38 to -0.52 D/year) than in phase 2 (-0.62 to -1.09 D/year). Overall, after 5 years (39), while the higher concentrations of atropine had the strongest effect on myopic progression and axial elongation, the total mean myopia progression was less in the 0.01% group (-1.38 $\pm$ 0.98 D) than in the 0.1% (-1.83 $\pm$ 1.16 D, $P = 0.003$) and 0.5% (-1.98 $\pm$ 1.10 D, $P < 0.001$) groups. Average axial length change over 5 years was 0.75 $\pm$ 0.48 mm, 0.85 $\pm$ 0.53 mm, and 0.87 $\pm$ 0.49 mm in the 0.01%, 0.1%, and 0.5% groups, respectively ($P = 0.185$)(39). There was no direct control group in ATOM 2 but a useful proxy is available from ATOM 1, in which the axial length of placebo untreated eyes had increased by 0.52 ± 0.45 mm at 3 years (41). Thus the mean annual elongation was between 0.15 and 0.17 mm in all groups.

ATOM 2 was limited by the lack of a direct control group and relied on a retrospective cohort from ATOM 1. Most importantly changes in axial length with 0.01% atropine were no different from the placebo eyes in ATOM 1 (42). Furthermore, no concentrations between 0.01% and 0.1% were evaluated. Thus, the optimal concentration remained unclear and a further randomised control trial, the Low dose Atropine for Myopia Prevention (LAMP) study (36,37,43) was commenced to evaluate the efficacy and tolerability of intermediate concentrations.

LAMP enrolled 438 Hong Kong Chinese Children aged 4-12 years with myopia of at least -1 D and astigmatism of -2.5 D or less. Children were randomised 1:1:1:1 to 0.01%, 0.025%, 0.05% atropine or placebo, stratified by age. At the end of year 1 (37) mean change was −0.27 ± 0.61 D, −0.46 ± 0.45 D, −0.59 ± 0.61 D, and −0.81 ± 0.53 D in the 0.05%, 0.025%, and 0.01% atropine groups, and placebo groups, respectively ($P < 0.001$), with a corresponding mean increase in axial length of 0.20 ± 0.25 mm, 0.29 ± 0.20 mm, 0.36 ± 0.29 mm, and 0.41 ± 0.22 mm ($P < 0.001$). Consistent with ATOM2, the 0.01% group did not show statistically significant slowing of axial elongation at year 1. In contrast, atropine 0.05% slowed axial elongation by a robust 0.21mm. In year 2 (36) 383 of the original 438 children continued in the trial. Those previously randomised to placebo were moved to the 0.05% atropine arm. Two-year mean progression was -0.55 ± 0.86 D, -0.85 ± 0.73 D, and -1.12 ± 0.85 D in the 0.05%, 0.025%, and 0.01% atropine groups, respectively (P = 0.015, P < 0.001, and P = 0.02, respectively), with mean axial length changes over 2 years of 0.39 ± 0.35 mm (0.05%), 0.50 ± 0.33 mm (0.025%), and 0.59 ± 0.38 mm (0.01%) (P = 0.04, P < 0.001, and P = 0.10, respectively).

Of the original 438 children, 350 entered phase 3 where each of the original 3 groups: 0.05%, 0.025% and 0.01% were randomised 1:1 to treatment or 'washout' (treatment withdrawn) (43). As expected, children assigned to the washout groups demonstrated faster myopia progression and axial elongation than children continuing to use atropine, regardless of concentration (Table 1).

240 Table 1: Change in spherical equivalent refractive error and axial length over 12 months (phase 3)
241 amongst children continuing atropine treatment and those for whom treatment was withdrawn.
242 Statistically significant differences between groups are indicated by p-values <0.05.

Original treatment group (years 1 and 2)	Phase 3 randomisation group (year 3)	MYOPIA PROGRESSION during phase 3 Mean change in SE ± standard deviation	P-value	AXIAL LENGTH CHANGE phase 3 Mean ± standard deviation	P-value
0.05% atropine	0.05%	-0.28 ± 0.42 D	P<0.001	0.17 ± 0.14mm	P<0.001
	'washout'	-0.68 ± 0.49 D		0.33 ± 0.17mm	
0.025% atropine	0.025%	-0.35 ± 0.37 D	P<0.004	0.20 ± 0.15mm	P=0.001
	'washout'	-0.57 ± 0.38 D		0.29 ± 0.14mm	
0.01% atropine	0.01%	-0.38 ± 0.49 D	P=0.04	0.24 ± 0.18mm	P=0.13
	'washout'	-0.56 ± 0.40 D		0.29 ± 0.15mm	

243

244 Overall, at the end of 3 years of treatment with 0.05% there was mean myopia progression of -0.73 D
245 and axial length elongation of 0.50mm. This level of myopia progression was seen in the first year of
246 those on placebo (-0.81 D), although the children in the placebo group would have been younger in
247 the first year of the trial. In other words, three years of treatment yields the same progression as one
248 year of no treatment. Three years of continued 0.05% use slowed progression by 0.9 D more and
249 elongation by 0.4 mm more than 0.01% atropine (43). A recent report estimated the 3-year slowing
250 of progression in the LAMP study to be 1.36, 0.78, and 0.49 D for 0.05%, 0.025%, and 0.01% atropine,
251 respectively and the corresponding reduction in axial elongation to be 0.55, 0.31, and 0.16 mm.

252 The LAMP study reports a small concentration-dependent rebound during phase 3. There was a
253 slightly larger axial elongation of 0.33 mm in those previously treated with 0.05% compared with 0.29
254 mm among those previously treated with the lower concentrations. Differences in myopia progression
255 across the three groups previously treated with 0.05%, 0.025%, and 0.01% (–0.68, –0.57, and –0.56 D,
256 respectively) were not statistically significant. Supplementary data, not in the main body of the paper
257 suggests that younger children treated with 0.05% show significantly greater rebound.

258

259

Table 2: Summary of efficacy of varying atropine concentrations in retarding myopia progression over 2 years in relation to spherical equivalent refractive error change and axial length change as reported in the ATOM and LAMP studies.

Atropine concentration	Study	Mean ± SD age of participants at baseline	MYOPIA PROGRESSION ± SD at 2 years	AXIAL ELONGATION ± SD at 2 years
1%	**ATOM1**	9.2 years	-0.28 ± 0.92 D	-0.02 ± 0.35 mm
0.5%	**ATOM2**	9.7 ± 1.5 years	-0.30 ± 0.60 D	0.27 ± 0.25 mm
0.1%	**ATOM2**	9.7 ± 1.6 years	-0.38 ± 0.60 D	0.28 ± 0.27 mm
0.05%	**LAMP**	8.45 ± 1.8 years	-0.55 ± 0.86 D	0.39 ± 0.35 mm
0.025%	**LAMP**	8.54 ± 1.7 years	-0.85 ± 0.73 D	0.50 ± 0.33 mm
0.01%	**ATOM2**	9.5 ± 1.5 years	-0.49 ± 0.63 D	0.41 ± 0.32 mm
	LAMP	8.23 ±1.83	-1.12 ± 0.85 D	0.59 ± 0.38 mm

Risk factors for progression

Within the ATOM and LAMP studies there were a cohort of children that still progressed rapidly despite being in the most effective arm of the trial.

In ATOM 2, at the end of 2 years, 18% of those in the 0.01% group had progressed by ≥2 D and approximately 32% had progressed between 0.5-0.99 D (38). This is very similar to the rates of progression in the LAMP study at 2 years for 0.01% Atropine, where 19.2% progressed by >2 D and 36% progressed by 1-1.9 D (36).

In LAMP 13% of the 0.05% group progressed by between >1 D – <1.9 D and 1% progressed by >2 D in the first year (36). After 2 years 19% had progressed by >1-1.9 D and 9% progressed by > 2D (36). After 3 years of continued treatment in LAMP approximately 77% (0.05% atropine) and 48% (0.01% atropine) progressed less than -1.50 D. Conversely, 5% and 12% of children on 0.05% and 0.01% atropine respectively, progressed more than -3 D.

A retrospective analysis of ATOM 1 (44) concluded that risk factors for myopia progression were younger age (8.5 ± 1.4 years vs 9.3 ± 1.5 years; *P* = .023), higher myopic spherical equivalent at baseline

(−3.6 ± 1.3 D vs −2.8 ± 1.4 D; *P* = .015) and having two myopic parents compared with no myopic parents (77% vs 48%; *P* = .012).

A retrospective analysis from the LAMP study noted that mean myopia progression was the same in 6 year old children on 0.05% (-0.90 D, 95% CI -0.82 to -0.99 D), 8 year old children on 0.025% atropine (-0.89 D, 95% CI -0.83 to -0.94 D) and 10 year old children on 0.01% atropine (-0.92 D, 95% CI -0.85 to -0.99 D) (45). The authors state that "younger children required the highest 0.05% concentration to achieve similar reduction in myopic progression as older children receiving lower concentrations. The statement ignores the fact that older children progress more slowly than younger children, with 10-year-olds progressing at around half the rate of 6 year olds. Their conclusion is thus an artefact of considering progression in relative terms. When considering progression in absolute terms the efficacy of different concentrations is *independent* of age. In other words, the difference in axial elongation and myopia progression across different concentrations are similar for all ages.

Given that younger age of onset of myopia is a risk factor for high myopia development (46) and the dose-dependent response seen in the LAMP trial (45) younger children could be offered higher concentrations of atropine (0.05% cf. 0.01%). Indeed, a retrospective analysis from LAMP Phase 3 results reinforce these findings, revealing that younger age (6-8 years) and higher concentrations of atropine (0.05%) lead to higher levels of rebound progression when treatment is withdrawn, indicating the need for continued treatment, or possibly tapering, in younger children.

Safety

Low dose atropine appears to be well tolerated. It has been suggested in a very small study that 0.02% is the highest concentration of atropine that does not result in adverse symptoms (47). In ATOM 2, only 7% of children required either photochromatic or progressive addition lenses to mitigate photophobia and accommodative challenge (39) however, none of the children who re-commenced atropine treatment required additional spectacle lenses to help with glare or near vision blur. A very small proportion (4%) of children developed allergic conjunctivitis(38). All 3 doses were well tolerated, and 0.01% atropine was associated with a 1mm increase in photopic pupil size and a loss of 2-3 D of accommodation, which is clinically insignificant for this age-group, and which returned to normal 2 months after stopping atropine.

In LAMP, only 16 children (<5%) were prescribed progressive addition lenses, with the number being similar across all concentrations. A higher number (<25%) were prescribed photochromic lenses, but again, the proportion was very similar across the three concentrations (43).

Atropine 0.125% and 0.25% concentrations does not elevate intra-ocular pressure over a 12 month period (48). Atropine does not impact retinal function in myopic children (49,50).

Overall, these studies suggest that low dose atropine is well tolerated and symptoms of photophobia and near vision problems can be controlled, as necessary, with the use of photochromic and progressive addition lenses.

Further studies using low-dose atropine

The ATOM and LAMP studies evaluated efficacy, tolerability and rebound effects of a range of atropine concentrations using daily dosing in East Asian children. Additional studies have shown modest findings for 0.01% atropine in Indian and Japanese populations (51,52) and when comparing 0.02% vs 0.01% atropine(53,54). Most recently an Australian placebo controlled muti-racial study compared atropine 0.01% to placebo and reported 2 year data(55). They found no significant difference at 2 years between placebo and 0.01% atropine Spherical equivalent progression at 2 years in the atropine group was -0.64 D and in the placebo group -0.78 D. Axial length elongation at 2 years in the atropine group was 0.34mm and in the placebo group was 0.38mm (55). The authors argue that these findings could be explained by higher rates of drop-out in the placebo group due to faster progression.

Most recently, 3 year results from the Childhood Atropine for Myopia Progression (CHAMP) study have been published(62). The study recruited 576 children at 27 centres across North America and 5 countries in Europe. Children were randomised to placebo vs preservative free 0.01% atropine and preservative free 0.02% atropine (2:2:3). Those aged between 6 and 10 at randomisation were included in the modified intention to treat analysis. The primary outcome of this study was <0.50 D progression at 3 years, which was defined as response to therapy. At 3 years, those progressing <0.50 D were 17.5%, 28.5% and 22.1% in the placebo, 0.01% and 0.02% arms respectively. The results were reported as least squares mean (LSM) which is used where there are unequal observations amongst groups to account for this unbalance (63). From baseline to 3 years the change in LSM SER was −1.28 D (95% CI, −1.37 to −1.19 D), −1.04 D (95% CI, −1.14 to −0.94 D) and −1.18 D (95% CI, −1.26 to −1.10 D) in the placebo, atropine 0.01% and atropine, 0.02%, groups respectively.

For axial length progression the LSM change from baseline at month 36 was 0.81 mm (95% CI, 0.76-0.85 mm), 0.68 mm (95% CI, 0.63-0.72 mm) and 0.73 mm (95% CI, 0.69-0.76 mm) in the placebo, atropine 0.01% and atropine, 0.02%, groups (62). LAMP 3 year results showed axial length changes from baseline of 0.50 ± 0.40mm and 0.89 ± 0.53mm for 0.05% and 0.01% atropine respectively (43).

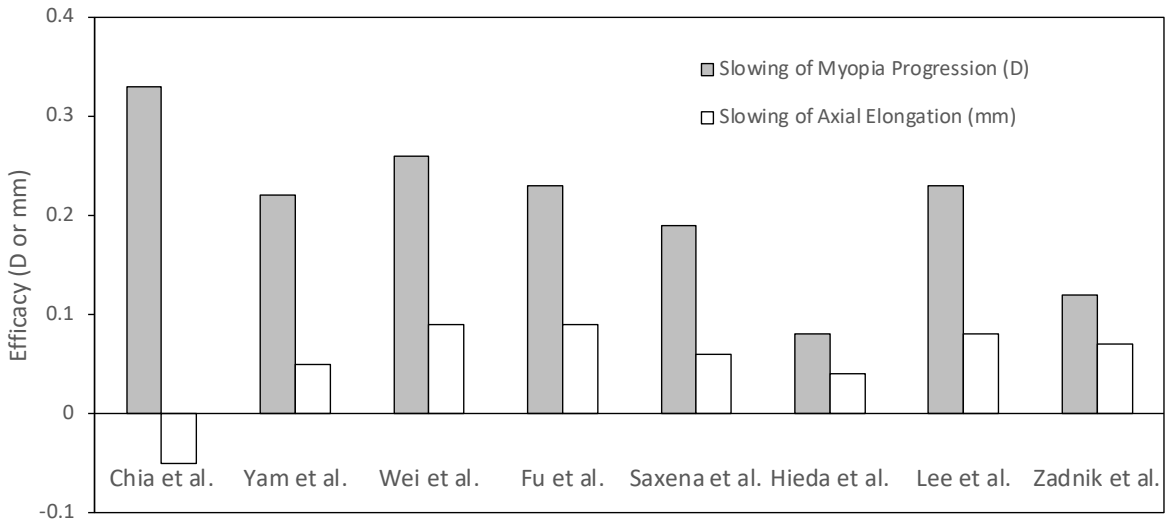
~~It appears that 0.01% is more efficacious in the CHAMP study population than in the LAMP study but falls below the efficacy of atropine 0.05%.~~

Figure 1 summarises the one-year slowing of myopia progression and axial elongation from these and previous clinical trials of atropine 0.01%. The six trials with a concurrent control group show a mean slowing of axial elongation of 0.07 mm (range: 0.04 to 0.09 mm) and a mean slowing of myopia progression of 0.20 D (range: 0.08 to 0.26 mm), which are of questionable clinical importance.

Many trials (56–59) utilising varying concentrations of low-dose atropine are currently on-going around the world. A recent meta-analysis confirmed the benefits of low dose atropine and re-affirmed a dose dependent response (60). A further meta-analysis showed that 0.05% atropine is likely to be the optimal dose (61).

At present, the optimal concentration of atropine for optimal control is unclear, although in the populations studied it appears that 0.05% atropine offers greater myopia control when compared with 0.01% atropine (43).

Figure 1: A summary of 8 studies utilising Atropine 0.01% demonstrating the one-year slowing of axial elongation (mm) and myopia progression (D)



Combination treatments

A companion paper reviews the efficacy of optical interventions for myopia control. There is currently limited evidence for combining atropine with optical myopia management strategies. However, there has been some interest in combing orthokeratology and low dose atropine. Kinoshita and colleagues combined 0.01% atropine with orthokeratology and found a positive effect especially in children with low initial myopia, but no additional benefit at -4.00 DS or worse (64,65). Further studies have found a benefit of adding low dose atropine to orthokeratology (66–69). However, the indications for using this intervention and the subset of patients for which this may be most beneficial is still unclear.

Summary

Atropine is a well-tolerated, safe and effective intervention and has a dose-dependent impact on reducing myopia progression (60). Thus atropine 0.05% is more effective for myopia control when compared with atropine 0.01% in East Asian children. Data on atropine 0.05% in other populations are lacking, although Figure 1 suggests that the efficacy of atropine 0.01% is similar across races.

Retrospective studies have shown 0.01% atropine to be effective and well tolerated in a European population (70,71), although, Joachimson and colleagues reported greater reduction in amplitude of accommodation and larger pupil size when comparing 0.05% and 0.01% atropine in German school children compared with previously published data for East Asian children (72). We await outcomes from key randomised controlled trials to understand in greater detail the efficacy and safety of low dose (0.01%) atropine in a UK and European population (73,74).

We are still searching for a definitive concentration for low-dose atropine. It is likely that we will need more than one concentration for patients and mitigate the tolerability of side effects against the need to prevent myopia progression and the risk of complications that each dioptre poses (75). Advances in our understanding of the mechanism of action of atropine and outcomes from on-going, large, well-designed, randomised control trials will help to guide our management of children with myopia. One clear conclusion is that atropine 0.01% is too low for young children.

We are unclear for how long we should treat patient. It seems sensible to utilise the existing literature and offer at least two-years of treatment. Nonetheless, myopia is a progressive condition with stabilisation reached, on average, at 15 years (76). Given that the risk of eye disease and visual impairment later in life increases with every dioptre (75) and the slowing accrues with each additional year of treatment (77), it makes sense to plan on controlling myopia into the teenage years. If atropine

is to be discontinued, it should be replaced with optical modalities of myopia control and we await trial evidence confirming the optimal strategy for this.

The LAMP phase 3 results show that the risk of rebound for concentrations 0.05% and lower is low and that patients who do rebound respond well to recommencing treatment. Given that younger children progress faster and are more likely to reach higher levels of myopia, children under 9 years should be treated with 0.05% atropine. The decision to continue will depend upon the rate of progression, level of myopia reached, tolerability of treatment and patient and parent expectations. Accordingly, decisions at such time-points should be individualised. An example of such a protocol in a European population was developed by Klaver and colleagues in the Netherlands (78). Those children above the 75th percentile on axial length growth curves are commenced on 0.5% atropine. Alongside this, they suggest prescribing photochromic progressive addition spectacle lenses to mitigate against the side effects of photophobia and near blur. A reasonable target is to slow axial length growth to <0.1mm/year at which point the atropine concentration may be tapered. It is stopped when growth reduces to <0.05mm/year (78). This may require treatment beyond the age of 15 years. Once treatment is stopped children are monitored. However, it is likely that a significant subgroup of children will need treatment for many years, given data showing significant progression of myopia in early adult life in a proportion of myopes (79).

Further work is needed to address the reasons why some children do not respond well to low-concentration atropine. In the LAMP study 9.1% of children on 0.05% and 19.2% on 0.01% progressed by >2 D over 2 years of treatment. In other words, almost 1 in 5 children using 0.01% atropine and almost 1 in 10 children using 0.05% atropine will progress rapidly despite treatment. Furthermore, 5.1% of children using 0.05% atropine and 11.9% using 0.01% atropine progressed more than -3 D over 3 years in the LAMP trial. The reasons for this are likely to be multifactorial; we know that age of myopia onset, parental myopia levels and prior rates of progression influence this outcome. Further, there is some evidence that 0.01% atropine has greater efficacy in European children compared with those of Chinese ethnicity (80), although we cannot be definitive without results to on-going trials in such populations. Of course, apparent failure to respond may just mean that the child was or would have been progressing faster than average and is still receiving some benefit from treatment.

Given the aforementioned risk factors, studies have been conducted and are underway to evaluate the efficacy of low dose atropine in warding off high myopia in those children at high risk but who are emmetropes or low hyperopes to determine if early application can delay the onset and progression of myopia(81–83). A recent 2-year clinical trial randomized 474 nonmyopic children aged 4 to 9 years

with refractive errors between plano and +1.00 D to 0.05% atropine, 0.01% atropine or placebo. Compared with placebo, 0.05% atropine reduced the incidence of myopia from 53% to 28%, but 0.01% had no significant effect (46%) It is important that future studies explore strategies for managing children with unacceptable progression despite being offered low concentration atropine. Measures may include higher concentrations, combination treatments or more novel treatments and strategies. Such studies are needed because these children are most at risk of developing high myopia and the sight-threatening consequence associated with each dioptre of myopia (75).

Challenges remain in interpreting data from some studies. Not all measure axial length and the characteristics of study participants are sometimes poorly described and accounted for. Further, it can be difficult to make comparisons between sub-groups and across studies. Data can be presented as absolute or relative measures, or both. Often, differences between the treated and untreated group are presented as a percentage. However, percentage representation is often misleading as it is absolute change that is most meaningful (77). Brennan *et al*. (77) propose the use of CARE (Cumulative Absolute Reduction in axial Elongation) as the preferred metric when reporting results. This provides a mean value and when using this metric the maximum reported CARE measurement is 0.44mm (approximately 1D) (77). There are differences in the length of time some interventions have been investigated compared to others and so the CARE measurement ceiling may change (77).

Concentration and physiochemical stability of low dose atropine is a key target when ensuring effective, repeatable and stable dosing for children receiving low dose atropine treatment. There is considerable variability in the compounding of atropine, storage and beyond-use recommendations (84), predominantly due to the lack of commercially available formulations. Atropine 0.1mg/ml (0.01%) with a pH of around 6 has been shown to be stable for 6 months when stored at 25°C in low density polyethylene multi-dose bottles, with and without preservatives (85).

In conclusion, atropine is a safe and effective treatment for myopia with promising data for slowing myopia progression when applied at 0.025% and 0.05% concentrations. In East Asian populations, 0.01% atropine does not slow elongation, and higher concentrations are preferable; the optimal concentration in other populations remains unknown.

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