Use of Atropine for Prevention of Childhood Myopia Progression in Clinical Practice

Kendrick Co Shih, M.R.C.S.Ed., Tommy Chung-Yan Chan, F.R.C.S.Ed., Alex Lap-Ki Ng, M.R.C.S.Ed., Jimmy Shiu-Ming Lai, F.R.C.Ophth., Walton Wai-Tat Li, M.D., Arthur Chak-Kwan Cheng, F.R.C.S.Ed., and Dorothy Shu-Ping Fan, F.R.C.S.Ed.

Objective: The most effective strategy to reduce myopia-related complications is to prevent myopia progression during childhood. This review article examines the latest published evidence on the use of atropine in childhood myopia control and discusses practical aspects of applying the findings to clinical practice. Future directions including possible forms of combination therapy are examined.

Methods: A literature search with a focus on randomized controlled trials (RCTs) and meta-analyses on the subject was conducted. Observational studies with control groups were also reviewed to discuss issues regarding feasibility of using atropine for myopia control in clinical practice.

Results: Five RCTs and 2 meta-analyses were found. The studies all found beneficial effects of atropine in myopia control, as well as a clear but perhaps clinically insignificant dose-response relationship between atropine and myopia progression rates. Available evidence however is focused on predominantly Chinese populations, and there is a current lack of guidance on timing of therapy initiation, duration of therapy, and treatment cessation. For future directions, combining atropine with other forms of myopia control would be worth considering.

Conclusions: Atropine is robust option for childhood myopia control. Further evidence including RCTs in different populations as well as the upcoming 5-year atropine for the treatment of myopia 2 trial results will provide much needed answers for wider acceptance of its use.

Key Words: Atropine—Myopia progression control—Childhood myopia—RCTs—Meta-analysis.

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From the Department of Ophthalmology (K.C.S., T.C.-Y.C., A.L.-K.N., J.S.-M.L., W.W.-T.L., A.C.-K.C., D.S.-P.F.), LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China; Department of Ophthalmology (T.C.-Y.C.), Hong Kong Eye Hospital, Hong Kong, China; Department of Ophthalmology (W.W.-T.L., A.C.-K.C., D.S.-P.F.), Hong Kong Sanatorium and Hospital, Hong Kong, China; and Department of Ophthalmology and Visual Sciences (A.C.-K.C., D.S.-P.F.), The Chinese University of Hong Kong, Hong Kong, China.

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Address correspondence to Dorothy Shu-Ping Fan, F.R.C.S.Ed., Department of Ophthalmology, Hong Kong Sanatorium and Hospital, 2 Village Road, Happy Valley, Hong Kong, China; e-mail: dorothyfan@hksh.com

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Myopia, or near-sightedness, is an ocular condition where there is a mismatch between the optical power and length of the eye. Here, the combined optical power of the eye is too strong for its corresponding axial length, causing incoming light to focus in front of the retina. Myopia is the most common abnormality in human eyes and is a significant public health problem, affecting 20% to 50% of the population older than 12 years of age in the United States.[1–3] The prevalence is even higher in certain Asian countries, such as Singapore, Hong Kong, and Taiwan, reaching up to 80% to 90% of the young adult population in published studies.[4–7] Recent evidence points toward an increasing prevalence of myopia as well as earlier onset over the last 20 to 30 years.[4,8,9] Although the refractive error can be effectively corrected with either concave lenses or refractive surgery, the associated increased axial length remains and significantly increases the risk of blinding diseases, including retinal detachment, myopic retinopathy, and glaucoma.[10–12] Myopia has been implicated as the sixth leading cause of vision loss and more significantly, most these myopia-related complications begin to manifest in young adults.[13]

The most common form of myopia worldwide is secondary to elongation of the axial length of the eye, termed axial myopia. Axial lengthening begins in childhood and is most marked during the adolescent growth period. The risk of myopia-related complications increases proportionately with axial length. As such, the most effective strategy to reduce myopia-related complications is to prevent myopia progression during childhood. Currently, the underlying mechanism for myopia development and progression remains unclear; however, it is understood that the resultant axial length is determined by a complex interplay between individual genetics and environment.[14] Although gene therapy may eventually have a role to play, recent evidence has pointed to the visual environment being a strong factor in determining axial length.[15,16] The Sydney Myopia Study determined that outdoor activity was protective against myopia progression, whereas near-work activity showed a detrimental effect, even when adjusted for parental myopia and ethnicity.[17,18] However, increasing urbanization worldwide as well as rising academic demands imposed on children mean that it is impractical to expect the burden of myopia to be solved solely through encouragement of outdoor activities.

From existing literature, a several options for slowing progression of myopia have been proposed and evaluated (Table 1). The devices studied include bifocal lenses, progressive lenses, peripheral defocusing lenses, contact lenses, and orthokeratology, whereas pharmacological agents, predominantly muscarinic antagonists, have also

TABLE 1. *Randomized Comparative Clinical Studies of Atropine to Prevent Myopia Progression*

Modality	Mechanism	Published RCTs	Mean Increase in Myopia, D	Mean Change in Axial Length, mm	Reported Adverse Events	Recommendation
Atropine	Unknown	Chia et al.[19] (0.5%)	1.15 (3 yr, no control)	0.61 (3 yr, no control)	Allergic conjunctivitis Decreased visual acuity Light sensitivity Impaired accommodative amplitude Logistical difficulties	Promising Needs RCTs in non-Asian populations Mechanism and site of action remains to be understood
		Chia et al.[19] (0.1%)	1.04 (3 yr, no control)	0.60 (3 yr, no control)		
		Chia et al.[19] (0.01%)	0.72 (3 yr, no control)	0.58 (3 yr, no control)		
		Chia et al.[19] (0.5%, without washout)	0.15 (2 yr, no control)	0.27 (3 yr, no control)		
		Chia et al.[19] (0.1%, without washout)	0.19 (2 yr, no control)	0.28 (3 yr, no control)		
		Chia et al.[19] (0.01%, without washout)	0.25 (2 yr, no control)	0.41 (3 yr, no control)		
		Chua et al.[20] (1%)	0.46 vs. 0.54 (3 yr)	0.29 vs. 0.52 (3 yr)		
		Chua et al.[20] (1%, without washout)	0.28 vs. 1.20 (2 yr)	0.02 vs. 0.38 (2 yr)		
		Shih et al.[21] (0.5%)		0.22 vs. 0.59 (18 mo)		
		Shih et al.[22] (0.5%)	0.04 vs. 1.06 (1 yr)	—		
		Shih et al.[22] (0.25%)	0.45 vs. 1.06 (1 yr)	—		
		Shih et al.[22] (0.1%)	0.47 vs. 1.06 (1 yr)	—		
		Yen et al.[23] (1%)	0.22 vs. 0.91 (1 yr)	—		
Cyclopentolate	Unknown	Yen et al.[23]	0.58 vs. 0.91 (1 yr)	—	No additional adverse effects	Clinical efficacy lower than atropine
Pirenzipine	Unknown	Siatkwoski 2008 (BD dose)	0.26 vs. 0.53 (1 yr)	—	Impaired accommodative amplitude Allergic conjunctivitis Medication residue Decreased visual acuity Eye discomfort Mydriasis	Clinical efficacy lower than atropine
		Tan et al.[24] (BD dose)	0.47 vs. 0.84 (1 yr)	—		
		Tan et al.[24] (daily dose)	0.70 vs. 0.84 (1 yr)	—		
Orthokeratology lens	Peripheral defocus	Cho et al.[25] (low-to-mod myopia)	—	0.36 vs. 0.63 (2 yr)	Intolerance/discomfort Conjunctival hyperemia Increased tearing and discharge Corneal abrasions Impaired mesopic contrast Increased higher-order aberrations	Promising Also corrects refractive error Needs studies on whether effect remains after treatment cessation High dropout rate (24% in Cho et al.[25] and 46% in Charm et al.[26]) is a source of concern Lack of reported cases of infective keratitis is in contrast to known risk in existing literature
		Charm et al.[26] (high myopia)	—	0.19 vs. 0.51 (2 yr)		
Progressive additional lenses	Reduced accommodation	Gwiazda et al.[27] (+2.00 D)	1.28 vs. 1.48 (3 yr)	0.64 vs. 0.75 (3 yr)	Intolerance/discomfort	Clinically insignificant efficacy

been extensively investigated.[24–33] A Cochrane Database Systematic Review in 2011 concluded that clinical trials on bifocals, progressive addition lenses, and contact lenses have yielded disappointing long-term results for myopia control.[34] Recently, there have been encouraging results from well-designed clinical trials from Hong Kong using orthokeratology for myopia control.[35] The added bonus to patients with this option is being spectacle free during the daytime. However, there remains a lack of evidence on whether the observed axial length control is a transient or permanent effect if orthokeratology is stopped. Furthermore, there is a concern among physicians on the increased risk of infective keratitis related to overnight contact lens wear.[36] Another treatment with strong supporting evidence from well-conducted clinical trials is the daily topical use of the nonselective muscarinic antagonist atropine. The perceived benefits of using atropine for myopia control are its clinical efficacy from major trials conducted largely in Taiwan and Singapore, as well as its minimal side effects at low concentrations.[19–23] The same 2011 paper from the Cochrane Database concluded that pharmacological interventions with atropine appeared to have the most consistent preventive effect on the progression of childhood myopia.[34] This review examines the use of atropine in the control of childhood myopia progression and will emphasize recent results from well-designed randomized controlled trials (RCTs) as well as examine the practical aspects of applying such findings to daily clinical practice.

TOPICAL ATROPINE THERAPY

Atropine is an alkaloid from derived from Atropa belladonna and acts as a nonselective competitive muscarinic acetylcholine

receptor antagonist. It has demonstrated high affinity for all 5 muscarinic receptors. It paralyzes the ciliary and iris muscles, causing loss of accommodation and pupil dilation. Typically in the office setting, a 1% solution is used for this purpose. The frequently reported side effects are light sensitivity and blurred near vision. Whereas light sensitivity is usually transient in nature, long-term exposure to increased levels of ultraviolet light may theoretically pose risks to the lens and retina. Therefore, an ultraviolet filter by means of photochromic lenses is recommended to reduce such risk. The blurred near vision often requires progressive additional lenses for symptomatic relief. Again, long-term use of atropine poses a theoretical risk of premature loss of accommodation. However, this effect has not yet been seen in existing literature.

Currently the United States Food and Drug Administration (FDA) only approves of atropine use in amblyopia treatment and not in myopia control. Despite this, interest in atropine as a method of preventing myopia progression has been reported for almost 200 years. The site of action of atropine was initially believed to be the receptors in the ciliary muscle, consistent with the prevailing hypothesis back then that frequent and excessive accommodation led to myopia progression. However, a several findings from animal studies have subsequently refuted this hypothesis. In the landmark paper by McBrien et al., intravitreal injection of atropine was shown to be effective in preventing myopia in chicks, which have a striated ciliary muscle with nicotinic receptors. This suggested that atropine controlled myopia through a nonaccommodative mechanism.[37] This in part may explain why optical approaches to reduce accommodation have proven to be ineffective at stopping myopia. Further studies have pointed to the sclera or the retina to be potential sites of action for atropine in myopia control, but the evidence is conflicting. At the moment, current available evidence cannot fully explain the site and mechanism of action of atropine in myopia control. Despite this, in Asian countries, where myopia has become epidemic, it is widely studied and prescribed. There has been an understandable general resistance to its adoption in the United States and Europe, where myopia prevalence figures are lower and greater weight is given to the risk of side effects. This has, however, not stopped interest from researchers in the Western world. In 1984, Brodstein et al.[38] published one of the largest studies on the subject, a prospective cohort study that compared myopia progression rates in 253 subjects on daily 1% atropine solution with 146 controls. Subjects were followed up to 9 years, with the average follow-up period at 4 years. The study stratified subjects into 2 age groups for analysis, with the first group aged 8 to 12 years having a mean myopia progression rate of −0.07 diopter (D) (0.73) compared with −0.624 D (0.42) in age-matched controls, and the second group aged 12 to 15 years having a mean myopia progression rate of −0.14 D (0.29) compared with −0.34 D (0.43) in age-matched controls. This study established that myopia progression rates varied according to age, with the fastest progression before the 12 years of age with subsequent slowing thereafter. As such, the beneficial effect of atropine on myopia progression was most marked for the 8- to 12-year-old group. Furthermore, the study demonstrated that stopping atropine treatment subsequently caused myopia progression to resume.

METHODS

The review focused on results from meta-analyses and RCTs on atropine in the control of myopia progression in human subjects. A literature search was conducted using the US FDA Web site, PubMed, clinicaltrials.gov, and the Cochrane library for English-language RCTs and meta-analyses on human subjects up to April 27, 2015. We used the following as key words: myopia, atropine, RCTs, meta-analysis, and humans. References within the retrieved studies were searched for additional clinical trials. The primary outcome extracted from the studies was the mean progression rate of myopia (D per year). Secondary outcomes included systemic and local adverse effects. Observational studies with control groups were also reviewed for evidence of feasibility in clinical practice.

SUMMARY OF EVIDENCE FROM CLINICAL STUDIES

The literature search revealed 5 RCTs and 2 recently published meta-analyses. To date, atropine has the most number of RCTs conducted among all options for myopia control (Table 2). Here, the methodology and results from published studies are discussed and compared.

Randomized Controlled Trials

The first RCT on the use of atropine in childhood myopia was reported by Yen et al.[23] from Taiwan in 1989. The study randomized 96 patients, aged 6 to 14 years, into one of the 3 groups: 1% atropine alternate nights, 1% cyclopentolate every night, or normal saline every night. The 3 groups demonstrated similar baseline demographics and clinical parameters, although neither subjects nor investigators were masked during the trial. The baseline refraction was −1.52. The subjects were followed up for 1 year with mean myopia progression at the end of the study reported at −0.22 in the atropine group compared with −0.91 in the control group. Some atropine-treated eyes in the study even showed decreases in myopia, although this is likely because of its cycloplegic effect and unlikely permanent. The reported clinical efficacy was however much tempered by the significant adverse effects experienced by the subjects on 1% atropine solution. It was noted that a significant number of these patients suffered photophobia resulting in less time being spent outdoors and restricting the subjects from activities, suggesting difficulty in its use as a long-term agent. A decade later, investigators of a different center in Taiwan conducted an RCT examining the clinical efficacy in a series of lower concentrations of atropine solution.[22] Shih et al. compared the efficacy of 0.5%, 0.25%, and 0.1% atropine solution and followed up the subjects for 2 years. Each group contained at least 40 subjects, compared with 32 subjects in the study by Yen et al. The subjects in the study by Shih et al. were aged between 6 and 13 years, with significantly higher baseline myopia of −4.41 than that of the study by Yen et al. It is also important to note that Shih's group used tropicamide solution in the place of a placebo control. Mean progression rate was −0.04, −0.45, and −0.47 for 0.5%, 0.25%, and 0.1% solutions, respectively. This study demonstrated 2 important findings. First, that atropine showed an obvious dose-dependent effect on myopia progression. Shih et al. effectively demonstrated that the ability of atropine solution to control myopia was related to its concentration. Second, lower concentrations produced significantly less adverse effects. Only 2 patients (of 41) exhibited intolerable photophobia in the 0.5% solution group, whereas no adverse effects were experienced in the 0.25% and 0.1% groups. Armed with the knowledge that the 0.5% solution

TABLE 2. *Summary of Available Modalities of Myopia Progression Control With Consistent Protective Effects From Randomized Comparative Trials*

Authors	Country	Eyes	Masking	Age	Baseline Refraction	Intervention (Control)	Follow-up	Rate
Chia et al.[19]	Singapore	400	Double	6–12 yr	−4.7 ± 1.6 D	0.5% atropine	2 yr	−0.15 ± 0.30 D/yr
						0.1% atropine		−0.19 ± 0.30 D/yr
						0.01% atropine		−0.25 ± 0.32 D/yr
Chua et al.[20]	Singapore	400	Double	6–12 yr	−3.4 ± 1.4 D	1% atropine	2 yr	−0.14 ± 0.46 D/yr[a]
						0.5% hydroxylpropyl methycellulose		−0.60 ± 0.35 D/yr
Shih et al.[21]	Taiwan	227	Double	6–13 yr	−3.3 ± 0.1 D	0.5% atropine + multifocal glasses	18 mo	−0.28 ± 0.05 D/yr[a]
						Multifocal glasses		−0.79 ± 0.05 D/yr
						Single vision spectacles		−0.93 ± 0.06 D/yr
Shih et al.[22]	Taiwan	200	Single	6–13 yr	−4.4 ± 1.5 D	0.5% atropine	2 yr	−0.04 ± 0.63 D/yr[a]
						0.25% atropine		−0.45 ± 0.55 D/yr[a]
						0.1% atropine		−0.47 ± 0.91 D/yr[a]
						0.5% tropicamide		−1.06 ± 0.61 D/yr
Yen et al.[23]	Taiwan	247	No	6–14 yr	−1.5 ± 0.9 D	1% atropine	1 yr	−0.22 ± 0.54 D/yr[a]
						1% cyclopentolate		−0.58 ± 0.49 D/yr[a]
						Normal saline		−0.91 ± 0.58 D/yr

[a]Significant difference between the intervention and control group.

group showed the largest mean difference from the control group, Shih et al.[21] conducted a second RCT randomizing 227 subjects into 3 groups: 0.5% atropine with multifocal glasses, multifocal glasses alone, and single vision glasses. The study was named the Myopia Intervention Trial. The follow-up period was 18 months and baseline myopia was −3.28. At the end of the study, the atropine and multifocal glasses group showed a mean progression of −0.41, compared with −1.19 in the multifocal glasses alone group and −1.40 in the single vision glasses group. Although the results further confirmed that atropine showed beneficial effects on myopia progression, it failed to show any significant impact of combining multifocal glasses with atropine. There were 2 important unanswered questions in the RCTs conducted in Taiwan. First, whether the use of atropine solution resulted in long-term adverse effects including cataract formation and retinal toxicity. Second, whether the clinical effect of atropine would last after cessation of therapy. Both these questions were later to be answered by the atropine for the treatment of myopia (ATOM) trial.

In 2006, Chua et al.[20] published the results from the first atropine for the treatment of childhood myopia study (ATOM1) conducted in Singapore on a predominantly ethnic Chinese population. ATOM1 tested monocular treatment with daily topical 1% atropine, with saline solution serving as a placebo in a cohort of 400 children aged 6 to 12 years with mean baseline myopia of −3.36 (1.38). The primary outcome measures included the degree of myopia progression by cycloplegic autorefraction and the change in axial length as measured by ultrasound. Patients were followed for 2 years while on treatment, as well as a subsequent year after treatment cessation to assess the permanency of the treatment effect. The results from the ATOM1 trial were as follows: monocular, daily instillation of 1% atropine reduced the progression of myopia by 77% compared with placebo-treated controls. In fact, the efficacy of 1% atropine meant that subjects were anisometric at the end of the treatment period. Unfortunately, there was a clear rebound effect after treatment cessation, where posttreatment, atropine-treated eyes progressed at a significantly higher rate than placebo-treated eyes. At the end of the 3 years however, the atropine-treated eyes were still less myopic than the untreated controls (mean, −4.29 vs. −5.22 D).[39]

The 2012 atropine for the treatment of myopia 2 (ATOM2) study by Chia et al. used a similar treatment protocol as ATOM1. The main difference was binocular administration of a lower concentration of atropine (0.01%, 0.1%, and 0.5%).[19] ATOM2 was conducted to address the limitations of the ATOM1 study, chiefly the side effects of impaired visual acuity and light sensitivity as a result of pupil dilation and decreased accommodative amplitude. For the ATOM2 trial, children were given the option of using photochromic glasses with a reading addition should they have difficulty with glare or reading while on treatment. Furthermore, the study investigated the effects of reduced atropine concentration administration on the subjects' visual acuity, pupil size, and accommodative amplitude. Primary outcome measures were again cycloplegic refraction and axial length, but this time laser interference biometry instead of ultrasound was used to determine the latter parameter because of its higher accuracy. As a result of the positive findings from the ATOM1 trial, it was determined no longer ethical to have a true placebo-control group. Instead, the investigators used historical progression data from ATOM1 to serve as a control. Although there were differences in the baseline parameters of between the subjects of ATOM1 and ATOM2, with ATOM2 having a slightly older mean age (9.7 vs. 9.2 years) and higher baseline myopia (−4.7 vs. −3.5 D), the differences were deemed not significant enough to prevent comparison.

The results of the ATOM2 trial suggested a clear dose-response relationship between atropine and myopia progression. The eyes treated with lower concentrations of atropine demonstrated the greatest myopia progression, although this result was deemed not clinically significant. The most significant finding for the investigators though was the relative clinical efficacy of 0.01% atropine. This concentration was initially included in the study to serve as a control for the other concentrations. Although there was most myopia progression in the 0.01% atropine-treated group, their accommodative amplitudes, visual acuities, and pupil sizes were least affected. This was reflected by the number of subjects needing photochromic lenses with reading addition during the study: 70% and 61% of the children treated with 0.5% and 0.1% atropine requested spectacles with a reading addition, whereas only 6% of children treated with 0.01% atropine requested to do so. A similar result to ATOM1 was observed in the 1-year posttreatment washout period, with all eyes rebounding and accelerating in their myopia progression compared with when the eyes were on treatment.[40] The eyes treated with higher concentrations of atropine showed the greatest rates of myopia progression, whereas the eyes

treated with 0.01% atropine progressed at a slower rate, but still faster than when the eyes were on treatment. Thus, from the ATOM2 trial, the 0.01% atropine solution achieved the best balance of clinical efficacy and side-effect profile.

Meta-Analysis

In 2011, Song et al.[41] reported a meta-analysis with a focus on evidence from RCTs. The article included 5 RCTs and 1 interventional controlled study without randomization. The justification for inclusion of the latter study by Fan et al.[42] was that the control group was closely matched to the treatment group in subject demographics. Although the study found a combined effect size of 0.733 D/year for the daily use of atropine in myopia control, as well as a dose-response relationship between atropine and myopia progression rates, it did not add anything new to the table, given that the findings were already confirmed from the RCTs published at the time. The study was only able to examine the clinical efficacy of atropine while the patients remained on treatment without accounting for the rebound effect after treatment cessation. Nor were the findings from the study generalizable, as it included only studies on predominantly Chinese populations. This was unavoidable though, given the lack of RCTs conducted on the subject in other populations.

In 2014, Li et al.[43] conducted a different meta-analysis, this time including evidence from both RCTs and observational studies for analysis. The study included 4 RCTs and 7 observational studies with a total of 1,815 children between the ages of 5 to 15 years. This meant that studies on white populations were examined as well, improving the generalizability of the findings of the study. Although the findings of the ATOM2 trial were compared in the author's discussion, the analysis did not involve data from the trial. Results from both RCTs and observational studies consistently showed a beneficial role of atropine in myopia control. More crucially though, the study was able to examine and compare the pooled effects of studies in Asian children and white children, with weight mean differences in myopia progression in RCTs of Asian children, observational studies of Asian children, and observational studies of Caucasian children being 0.55, 0.54, and 0.35 D per year, respectively. The findings suggested that atropine was more effective in myopia control in Asian children; however, the significant differences in baseline myopia levels between the 2 populations may have accounted for this effect. Although it may be difficult to find a white population with similarly high baseline myopia level, RCTs are still needed before a comparison between the 2 populations is fair. It is also important to note that this study did not include other populations other than the predominantly Chinese populations in the Asian studies and the Caucasian populations in the Western studies.

APPLICATION TO CLINICAL PRACTICE

With recent evidence from well-designed clinical trials supporting the use of topical atropine, the main issues when applying to clinical practice is the starting dosage to be used, the optimum timing of therapy, and the treatment protocol for stepping up or weaning off treatment.

From a safety perspective, it was evident from the ATOM1 trial that if photochromic bifocal glasses were prescribed to every subject, even at 1% concentration, atropine solution was safe, with no serious adverse effects attributable to the drug during the study period.[20] This was in contrast to the findings of Yen's study where no such glasses were offered. The most common adverse effect in both ATOM1 and ATOM2 trials was allergic conjunctivitis.[19,20] In the ATOM2 trial, none of the patients on 0.01% solution demonstrated allergic conjunctivitis. There was no change in intraocular pressure or cataract formation in the subjects. In a subset of ATOM1 subjects who underwent multifocal electroretinography assessment at the end of the study, none showed significant maculopathy.[44] In a subset of ATOM2 subjects who underwent full field electroretinography assessment at the end of the study, the 35 subjects were noted to have reduced retinal sensitivity. However, this was in keeping with the features of myopic eyes and was not attributable to atropine.[45] Subjects who lost more than 1 line of best-corrected visual acuity or experienced glare recovered on cessation of drops. No patient suffered permanent loss of accommodation or exhibited permanent pupil dilation after cessation of the eye drops. Other interventional studies using 1% atropine solution included the article by Fan et al.[42] on 23 subjects and 23 matched controls showed that this concentration showed good efficacy in clinical practice with tolerable side effects. Unlike the RCTs, Fan et al. used 1% atropine ointment to reduce systemic absorption through the lacrimal system, whereas photochromic progressive glasses were prescribed for all patients as in the ATOM1 study. Her study population was children with moderate to severe myopia, as such it had the highest baseline myopia of all published studies at −5.18 D. The study showed significant slowing of myopia progression (+0.06 vs. −1.19) and axial lengthening (0.09 vs. 0.70) with only 1 subject developing an adverse event, which was allergic conjunctivitis. There were no other adverse events during the 1-year study period. Thus, the choice of concentration will be dependent on clinical efficacy, rebound effect, and just as importantly, convenience.

Aside from the RCTs, several interventional studies also successfully used lower concentrations of atropine in clinical practice. Wu et al.[46] examined the efficacy of prescribing 0.05% atropine solution as the initial dosage for all patients, with those having more than −0.5 D progression after 6 months being switched to a 0.1% solution. This group showed a progression rate of −0.23 D per year compared with −0.86 in controls.

With an adequate balance of side effects, least amount of rebound and clinical efficacy, the 0.01% atropine solution seems to be best suited as the starting treatment for parents considering atropine therapy for myopia progression control. Although from ATOM2, differences between 0.01%, 0.01%, and 0.5% concentrations were deemed clinically insignificant, there is a clear dose-response relationship regarding clinical efficacy of atropine solution.[19,40] A study by Cooper et al.[47] examined the maximum tolerated dose of atropine without clinical signs or symptoms. The study team found that patients could tolerate up to 0.02% solution without significant effects on visual acuity, light sensitivity, and near vision. However there are currently no studies comparing the clinical efficacy of 0.02% atropine with other concentrations.

Regarding the optimal time point for starting treatment, it is evident from the published RCTs that all patients undergoing treatment had significant myopia before enrolment. As none of the studies were able to stop myopia progression, it is important to note that patients treated with atropine will continue to have myopia progression, albeit at a slower rate. Thus, there are those who argue for early treatment in premyopic patients in at-risk populations.

Fang et al.[48] demonstrated the clinical efficacy of 0.025% solution in 24 children between 6 and 12 years of age with mean baseline myopia of −0.31 (0.45). It could be argued that such patients with low baseline myopia are less at risk of fast progression. However, it should be noted that the control group for the study showed a myopia progression rate of −0.58 D per year, which is similar to the placebo controls of the ATOM1 trial. The feasibility of convincing parents to start treatment in premyopic children will be dependent on the side-effect profile and motivation. It may, therefore, be offered if 0.01% to 0.02% solution is used, and at-risk populations are targeted (family history of severe myopia).

Another clinical question that requires answering is the frequency of follow-ups and the parameters to be measured each visit. For adequate and accurate documentation, cycloplegic refraction and axial length through laser interference biometry are essential parameters. A questionnaire on side effects should also be included. The myopia progression rate at which clinical efficacy has been achieved also remains to be defined.

Finally, treatment must be stopped at some point. This will likely depend on the stability of the patient's refractive error as well as the patient's age. Although 0.01% atropine solution has been shown to have the least rebound effect among all concentrations, the ATOM2 trial still demonstrated a faster myopia progression rate after stopping 0.01% atropine solution than while the patient was on the treatment.[40] More importantly, the soon to be published 5-year results of the ATOM2 study will likely yield further information to aid us in planning long-term treatment.

Adoption of atropine in myopia control will ultimately be dependent on the societal burden of myopia and parents' motivation for myopia control. In Taiwan, where myopia prevalence in young adults reach up to 80%, in a national cross-sectional study Fang et al. demonstrated the widespread routine use of atropine in myopia control. In the year 2000, when 1% and 0.5% atropine solution were the only forms prescribed, already up to 37% of myopic children attending an ophthalmologist was under treatment with atropine.[49] With the introduction of lower concentrations of atropine, this rate increased to 50% in 2007.

In conclusion, the authors recommend treatment with daily topical application of 0.01% atropine solution. The lack of adverse effects with this concentration of atropine means that the treatment can be recommended to pediatric patients with any degree of ongoing myopia progression on serial cycloplegic refraction. After an initial period of close monitoring (1 week and then 1 month after starting treatment) of treatment intolerance and compliance issues, patients on treatment should have 6-monthly to annual follow-ups for compliance, side effects/adverse effects, axial length monitoring through intraocular lens master and cycloplegic refraction. For patients with demonstrated fast myopia progression (equal to or more than −1.0 D progression over 12 months), higher concentrations of atropine should be considered, starting with the 0.1% solution. However, parents of such patients should be warned about adverse effects with higher concentrations of atropine and photochromic glasses with reading additions should be prescribed routinely for such patients. For those with slow myopic progression while on 0.01% atropine solution (less than −0.5 D progression over 12 months), treatment can be stopped without tapering because of the negligible rebound effect with this concentration. For patients on higher concentrations of atropine, a tapering off period is needed to counter the known rebound effect. There remain no published studies on an effective protocol for tapering off atropine therapy. However, a safe method would be a slow and stepwise decrease of frequency of application from daily to alternate days to biweekly, and then finally to weekly treatment before stopping therapy, while monitoring for fast progression during the weaning off period.

FUTURE DIRECTIONS FOR RESEARCH

Perhaps the most interesting future direction for atropine therapy is that given the simplicity of its treatment, especially at lower doses, there is potential for combining this with other forms of myopia control.

One major disadvantage of using atropine is that myopic patients will still require spectacles or contact lenses for good distant vision. Naturally, to solve this, an interesting strategy would be to combine atropine with overnight orthokeratology lenses to allow the patients to be free of glasses during the daytime. There is growing evidence that continued use of overnight orthokeratology lenses may slow myopia progression and axial lengthening in myopes, with 2 recently published RCTs from Hong Kong showing beneficial effects.[25,26] The retardation of myopia in orthokeratology (ROMIO) study was conducted on subjects with mild to moderate myopia, whereas the high myopia-partial reduction orthokeratology (HM-PRO) study was conducted on those with severe myopia. It is important to note that both studies on orthokeratology in myopia control exhibited high dropout rates, with 24% in the ROMIO study and 46% in the HM-PRO study, meaning there may be questions on its long-term feasibility. However, there remains a lack of evidence on whether this is a transient effect that disappears after the lenses are stopped or whether it is a permanent effect. Nevertheless, further research into the potential effects of combination therapy is worthwhile and already trials are currently being planned to combine low-dose atropine with overnight orthokeratology for myopia control.

Another interesting area for combination therapy with atropine is alternate therapies such as acupuncture. In 2011, the Cochrane Database published a systematic review that examined 2 RCTs conducted from Taiwan on the subject. As the 2 studies were examining different outcomes, their results could not be pooled for meta-analysis, and no conclusions were made from the results alone. However, it was important to note that both studies showed a significant number of dropouts because of intolerable pain from acupuncture, suggesting this to be an important issue to be considered by clinicians for this approach.[50] A recent single-blind RCT compared 0.125% atropine alone with 0.125% atropine and auricular acupoint therapy.[51] Although the study concluded that subjects using combination therapy exhibited slower myopia progression rates (−0.41 vs. −0.66 D per year) and axial lengths (0.24 vs. 0.32 mm) compared with those in the atropine-only group, the study was marred by a high dropout rate of almost 40% at 6 months. The differences in myopia progression rates and axial length, although statistically significant, may not be clinically significant. It is important to note that the myopia progression rate in the combination group was still higher than other reported studies using atropine solution alone. More crucially though, the baseline myopia was significantly higher in the atropine alone group than in the combination therapy group (−2.42 vs. −1.75 D), making a fair comparison of both groups impossible.

Despite this, combining atropine with alternate therapies is worth exploring in future studies.

CONCLUSIONS

There is strong evidence that myopia is a significant and increasing public health problem, especially in Asia over the past 10 to 20 years as a result of rapid urban expansion. It is also apparent that there are safe and effective ways to slow myopia progression, with the optimal timing during childhood. To date, atropine has the most number of RCTs conducted among treatment strategies for myopia control in children. However, it is important to note that atropine has yet to receive FDA approval for this purpose.

The results from well-designed RCTs show encouraging signs that low-dose atropine solution will be an effective and well-tolerated long-term strategy for childhood myopia control. In particular, the robust methodology of the ATOM1 and ATOM2 trials provided strong evidence due to their double-blind design and large cohort of subjects (400 in each study) with a relatively low dropout rate during the study period. However, the generalizability of their results was hindered by the ethnic make-up of the study population, which in both cases was overwhelmingly Chinese. Thus further, well-designed RCTs in other ethnic populations are still required. Furthermore, considering that myopic rebound was seen in treated participants at all concentrations, further work is needed to elucidate how long a treatment interval is needed and the time point at which it is safe to stop therapy. Finally, myopia progression in childhood and adolescence is typically associated with axial elongation and control of myopia results in slower axial lengthening. Although it is reasonable to assume that retarding the axial elongation of a child will result in a lower risk of glaucoma, cataract, retinal detachment, and myopic retinopathy, this has yet to be established.

The main limitation of our review is that it included only trials in English and studies that were published, which may lead to a potential publication bias. Second, our emphasis on reporting RCTs meant that while the findings were derived from well-controlled conditions, they were dependent on very stringent inclusion and exclusion criteria, thus perhaps making these results only applicable in an ideal world. Myopic children in the real world may be more likely to receive multiple other interventions before and during atropine use, including orthokeratology and alternative medicine like acupuncture.

Given the significant public health problem of myopia, low-dose atropine therapy should be a serious consideration for every ophthalmologist managing pediatric patients. Atropine can be considered in children at high risk of development of high myopia, including those with a higher degree of myopia at a young age, rapid progression of myopia, and family history of high or pathological myopia. However, regardless of the concentration used systemic and ocular side effects should be carefully monitored.

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