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A Meta-Analysis Assessing Change in Pupillary Diameter, Accommodative Amplitude, and Efficacy of Atropine for Myopia Control

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Purpose: To determine the effect of atropine on pupillary diameter, accommodative amplitude as well as myopia progression.

Methods: Medical databases and Cochrane Library were systematically searched for studies from 1980 until June 2020. The primary and secondary outcomes were: a) change in pupillary diameter (PD) and accommodative amplitude (AA) and b) annualized mean change in spherical equivalent and axial length with various concentrations of atropine compared to control.

Results: Thirteen trials (6 RCTs, 7 observational studies) that studied 9 atropine concentrations (0.01−1.0%) were included. The relation between atropine and change in PD and AA was nonlinear; at < 0.10% atropine, the slope of the curve was steep but the change in PD (+0.7 mm; 95% CI: +0.1 to +1.4) and AA (−1.6D; 95% CI: −3.9 to +0.7) was smaller whereas at ≥0.10% atropine, the slope plateaued but change in PD (+3.2 mm, 95% CI: +2.8 to +3.5) and AA (−10.7D; 95% CI: −12.2 to −9.2) was high.

Reduction in myopia progression with atropine at <0.10% and ≥0.10% as compared to controls was 0.37D (95% CI: 0.16 to 0.58) versus 0.75D (95% CI: 0.17 to 1.33) for spherical equivalent and −0.10 mm (95% CI: −0.24 to 0.05) versus −0.23 mm (95% CI: −0.34 to −0.13) for axial length.

Conclusions: A nonlinear dose-response relationship exists between atropine and PD and AA. Further work is warranted to determine the concentration that provides maximal efficacy with tolerable side effects.

Key Words: accommodative amplitude, atropine, muscarinic antagonists, myopia control, pupillary diameter

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Myopia

Considered to be the most common cause of distance vision impairment,[1] myopia is estimated to affect half of the population worldwide by 2050.[2] In addition to resulting in a significant economic burden,[3] high myopia (−5.0D or worse) may also induce pathologic changes that result in vision impairment and/or blindness. Data from many countries, especially from East Asia, show that myopic macular degeneration is one of the leading causes of blindness.[4,5] Additionally, any level of myopia is associated with the risk of visual impairment[6], which is significantly higher with high myopia.[7] Given the rising burden, there has been an increasing interest in solutions to better manage and control myopia.

Atropine

Presently, of all the known strategies to slow or reduce myopia progression, atropine, a nonselective antimuscarinic agent, is considered superior and widely used despite the lack of understanding relating to its mode of action as well as lack of clarity with respect to the efficacy of 0.01% atropine.[8] Although other pharmaceutical agents, such as Pirenzepine, a selective antimuscarinic agent, and 7-methylxanthine, showed promise in early clinical trials,[9,10] presently atropine is the only pharmaceutical agent that is broadly adopted for myopia control. It was reported that, in Taiwan, up to 50% of ophthalmologists nationwide prescribe atropine for children with myopia.[11] However, the use of atropine is not without issues. Despite no reports of serious side effects to date, photophobia and difficulty with near-work remain the major concerns for the application of atropine at higher concentrations. Another significant concern is the "rebound" of myopia that occurs on ceasing treatment.[12] There are other concerns related to the unknown effects of long-term use on pupils, macula, and/or retina, although some data shows that the accommodative amplitude (AA) and near vision recovered to pretreatment within months after cessation of atropine.[13]

Although previous meta-analyses[8,14,15] have considered the effect of various concentrations of atropine on axial elongation and refractive error, its effect on pupillary diameter (PD) and amplitude of accommodation has not been considered so far. In this meta-analysis, we considered the effect of various concentrations of atropine on pupillary dilation and AA as well as for efficacy in myopia control (change in spherical equivalent and axial length).[16–19]

METHODS

Design

We searched the electronic medical databases, including PubMed, EMBASE, Scopus, ProQuest, and Cochrane library.

A combination of keywords and Boolean operators using search terms "myopia", "myopia progression", "myopia control", "atropine", "atropine eye drops", along with the main Boolean operators "AND", "OR" were used. Databases were searched for articles from 1980 until June 2020 following the PRISMA guidelines (Fig. 1).

Inclusion/Exclusion Criteria

To be included in the meta-analysis, the articles had to meet the following criteria:

a) participants were myopic;
b) age 16 years or younger;
c) the data was from a randomized clinical trial (RCT) or an observational study;
d) a control group or a historical control group was included in the trial or study;
e) at entry, participants had myopia with spherical equivalent of 0.50 Diopter (D) or worse;
f) participants were followed for at least 12 months; and
g) the full-text article was published in English language.

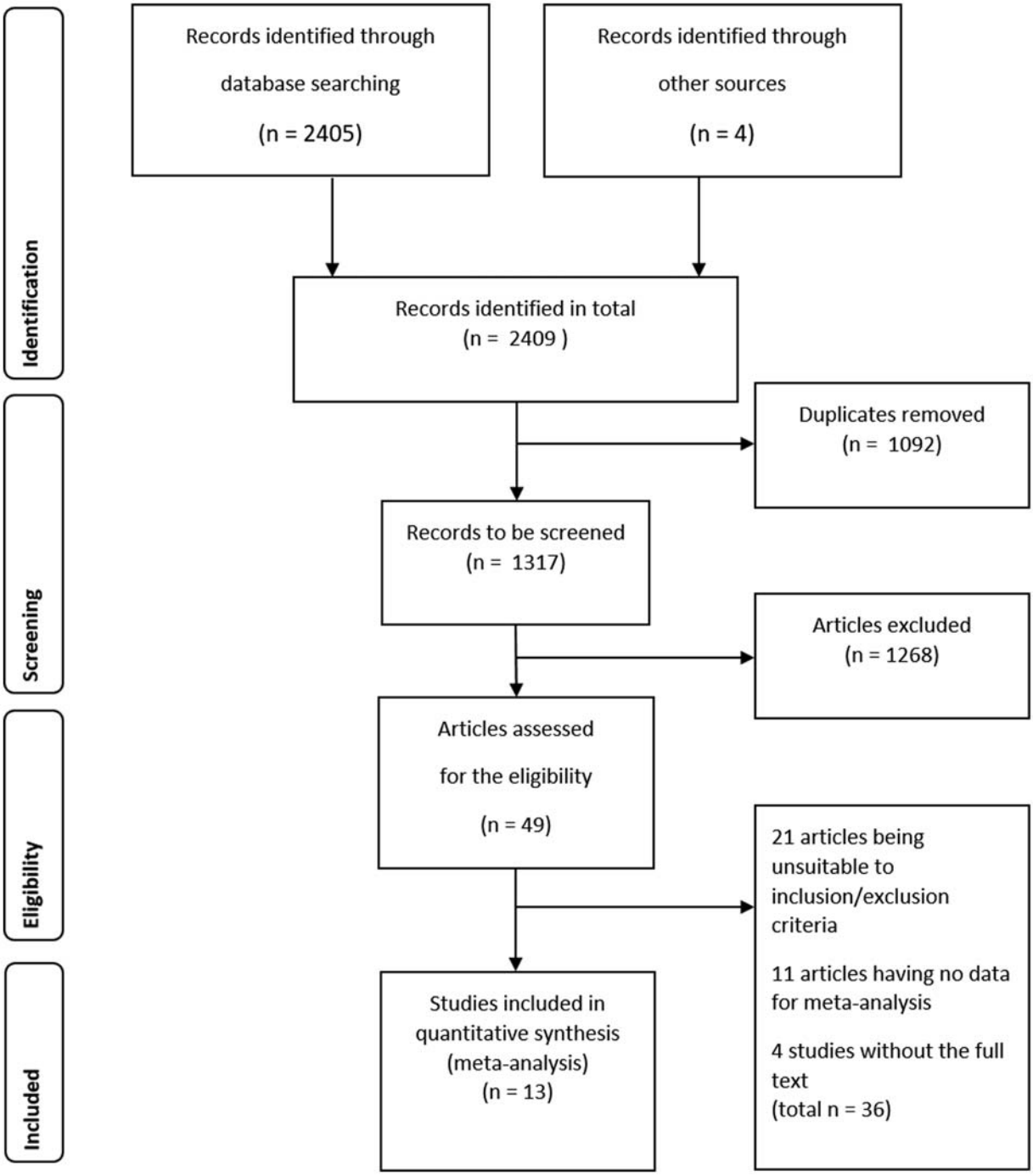

FIGURE 1. Process outlining search and selection of articles in the meta-analysis.

TABLE 1. Characteristics of the Articles Included

Author and Year	Country	Age	Follow-up	Concentration investigated	Participants in the treatment arms	Type of study	Spherical equivalent	Axial length	Pupil size	Amplitude of accommodation
Randomized clinical trials (6)										
Yam 2019[33]	Hong-Kong	4–12	1 year	0.05%	109	RCTs	x	x	x	x
				0.025%	108					
				0.01%	110					
Yi 2015[26]	China	7–12	1 year	1%	68	RCTs	x	x		
Chia 2012[22]	Singapore	6–12	2 year	0.5%	161	RCTs	x	x	x	x
				0.1%	155					
				0.01%	84					
Chua 2006[23]	Singapore	6–12	2 year	1%	200	RCTs	x	x		x
Shih 1999[25]	Taiwan	6–13	1.5 year	0.5%	41	RCTs	x			
				0.25%	47					
				0.1%	49					
Yen 1989[19]	Taiwan	6–14	1 year	1%	32	RCTs	x			
Observational studies (7)										
Fu 2020[44]	China	6–14	1 year	0.02%	117	Observational study	x	x	x	x
				0.01%	119					
Sacchi 2019[45]	Italia	5–16	1 year	0.01%	52	Observational study	x			
Larkin 2019[46]	USA	6–15	2 year	0.01%	100	Observational study	x			
Lee CY 2016[47]	Taiwan	6–12	1 year	0.25%	12	Observational study	x			
				0.125%	32					
Clark 2015[27]	USA	6–15	1 year	0.01%	32	Observational study	x			
Fan 2007[48]	Taiwan	5–10	1 year	1%	23	Observational study	x	x		
Lee JJ 2006[29]	Taiwan	6–12	2 year	0.05%	21	Observational study	x			

Articles were excluded if:

a) at baseline, participants had spherical equivalent refractive error of −0.25D or better;
b) were 17 years old or older;
c) each of the participants was on multiple concentrations of atropine during the observation period;
d) participants were treated with a combination of atropine and other myopia control treatment methods.

In our review, we considered control groups as those that were treated with either single-vision spectacles, 0.50% tropicamide or placebo eye drops.

Data Collection and Extraction

Two of the authors (HTDM and PS) individually reviewed the extracted data using the inclusion/exclusion criteria. Initially, the titles and abstracts were reviewed, and ineligible articles and duplicated data were removed. All selected articles were assessed using the "Newcastle–Ottawa" scale for the observational studies and the "Cochrane" risk of a bias evaluation tool for randomized clinical trials.[20] The following data were extracted from selected articles: authors, year of publication, country of research, study design, age of participants, baseline spherical equivalent and axial length, and prescribed concentration of atropine. Additionally, we also collected PD, AA, annual change in spherical equivalent, and annual change in axial length. If there were multiple articles reporting data of a single study, we extracted in priority the data from the earliest published publication that provided the annual change.

Statistical Analysis

The primary outcomes were the change in PD and AA with various concentrations of atropine compared to control. The secondary outcomes included the annual mean change in spherical equivalent refractive error and axial elongation with atropine compared to control. Statistical analysis was conducted using Review Manager (version 5.3 by Cochrane Collaboration),

TABLE 2. Quality assessment of the observational studies using the Newcastle-Ottawa Scale

	Representativeness	Control definition	Ascertainment of exposure	Outcome not present at the start	Comparability	Assessment of outcome	Follow-up length	Adequacy of follow-up
Fu 2020	**	**	*	*	**	**	*	*
Sacchi 2019	*	*	*	*	**	**	*	*
Larkin 2019	*	*	*	*	**	*	*	*
Lee CY 2016	*	*	*	*	*	*	*	*
Clark 2015	*	*	*	*	**	*	*	*
Fan 2007	*	*	*	*	*	*	*	*
Lee JJ 2006	*	*	*	*	*	*	*	*

*represents score, each individual feature can be labelled a maximum of one star, except the comparability can be given up to 2 stars.

GraphPad Prism 8 (version 8.4.3 by GraphPad Software, LLC), and Microsoft Excel (version 2016 Microsoft Office by Microsoft Co.).

To calculate the effect size, the difference in AA and PD with various concentrations of atropine compared to control was pooled. Similarly, the mean annual change in myopia progression, that is, spherical equivalent and axial length with the use of atropine compared to control, was assessed. Cohen d formula along with the random effect model was applied. The I^2 statistical test was used to quantify the heterogeneity and the risk of bias evaluation for all the included studies and trials. Positive effect size for spherical equivalent and pupil dilation, as well as the mean difference, represented that the atropine was superior to the control, whereas it was the converse for axial length and AA.[21] For the analysis related to side effects, that is, change in PD and the AA, baseline data before instillation of atropine was used as the control except for the randomized clinical trial conducted by Chia et al[22] where a historical control group was used. Further analysis was conducted to determine the relationship between the change in PD and AA to the various concentrations of atropine. The relation between weighted data from the meta-analysis versus different concentrations of atropine was determined using linear, logarithmic, inverse, quadratic and cubic fits; R^2 and standardized residual errors were used to determine the model that best fits the data. Cubic, quadratic and logarithmic fits had high R^2 values. However, both quadratic and cubic fits were found to either estimate values beyond the range of the observed data or have significant standardized residual errors, and therefore, a dose-response curve was generated using only the logarithmic fit.

RESULTS

Characteristics of Studies

The search yielded a total of 2405 scientific items. After removing duplicates and completing the eligibility assessment, a total of 13 eligible articles (6 RCTs and 7 observational studies) remained (Fig. 1). These comprised data from 2907 participants aged 4 to 16 years old and with at least one year of follow-up. A total of 9 different concentrations of atropine were used in these trials.

Table 1 presents the basic characteristics of the trials/studies included in the meta-analysis. The trials were from various countries and/or regions across the world. The quality of the trials/studies were assessed using features presented in Table 2 for observational studies and Figure 2 for the randomized clinical trials. Of the 13 trials/studies that were eligible, the study of Chia et al[22] lacked a control group, however, was a well-conducted clinical trial using a historical control group, and therefore included in the analysis.[23]

Effect of Atropine on Pupillary Diameter and Amplitude of Accommodation

Only 3 of the 13 studies included data on pupil diameter and AA. A further single study, Chua et al[23] reported only the change in AA. The effect of seven concentrations of atropine was extracted from these studies. All concentrations excepting for 0.01% atropine resulted in a reduction in AA (mean change −4.67 D, 95% CI, −7.44 to −1.89D, $P < 0.001$; $I^2 = 99\%$) and an increase in PD (mean increase 1.33 mm, 95% CI, 0.57 to 2.09 mm, $P < 0.001$; $I^2 = 99\%$) (Figs. 3 and 4).

Figure 5 presents the relation between the weighted data for change in amplitude of accommodation and increase in PD to various concentrations of atropine using a logarithmic equation and is given by "Effect size for change in PD = 8.151 + 0.849 × LN (atropine concentration)" and "Effect size for the amplitude of accommodation e = −23.131 − 2.389 × LN (atropine concentration) where LN is the natural log of atropine. The curve indicates a non-linear dose-response; the curve was steep for lower concentrations and seems to slow/plateau for points at ≥0.10% atropine. Therefore, we categorised the effect sizes for concentrations < 0.10% and ≥0.10% atropine and the data is presented in Table 3.

At concentrations of <0.10% atropine, the mean change in PD and AA was 0.7 mm (95% CI, 0.1 to 1.4) and −1.6D (95% CI, −3.9 to 0.7) whereas for ≥0.1% atropine concentrations it increased to 3.2 mm (95% CI, 2.8 to 3.5) and −10.7 D (95% CI, −12.2 to −9.2) respectively. These differences for change in PD and AA between the two groups, i.e. <0.10% and ≥0.10%, were significant (Table 3).

Efficacy of Atropine for Myopia Control

A total of 9 concentrations of atropine were assessed in 21 treatment arms and were as follows: 0.01% (6 treatment arms), 0.02% (1), 0.025% (1), 0.05% (2), 0.10% (2), 0.125% (1), 0.25%

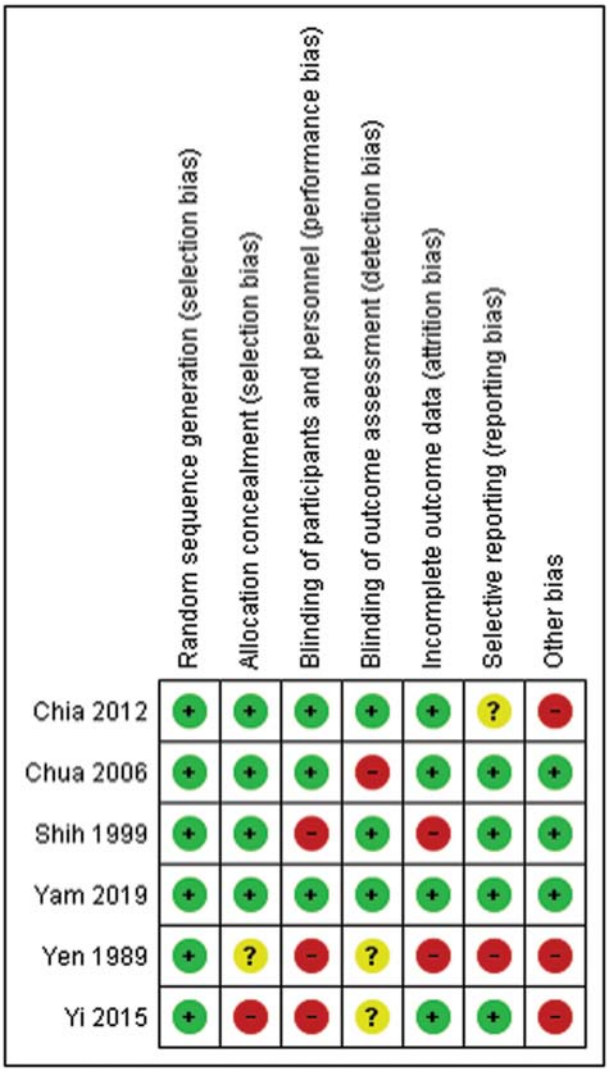

FIGURE 2. Quality assessment of the RCTs using the 6 domains risk of bias assessment.

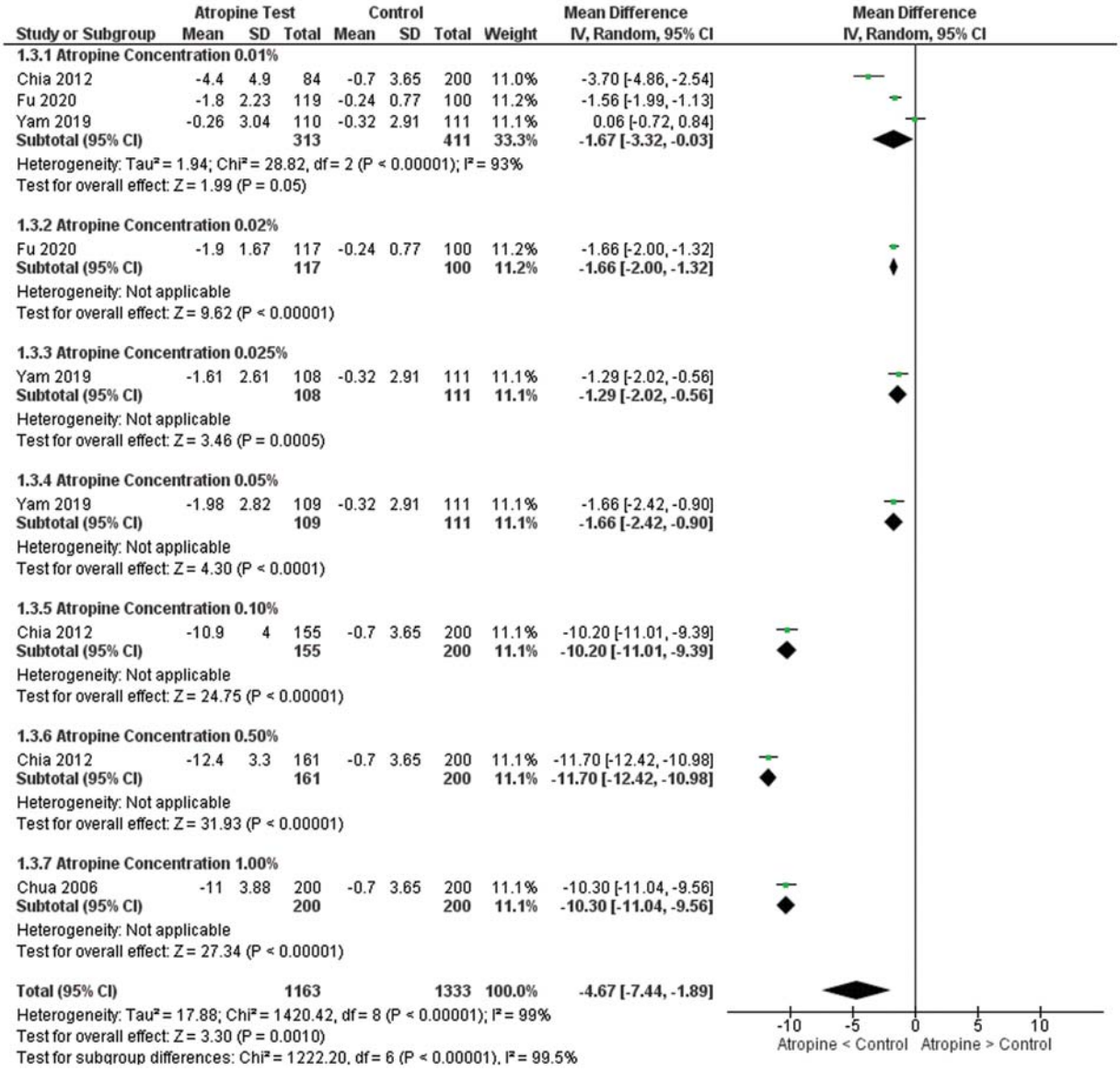

FIGURE 3. Effect of various concentrations of atropine on accommodative amplitude.

(2), 0.50% (2) and 1.00% (4). The pooled estimates suggest that, compared to the control, reduction in annual progression of spherical equivalent with 0.01% atropine was 0.34D (95% CI, 0.25 to 0.44), 0.02% was 0.32D (95% CI, 0.19 to 0.45), 0.025% was 0.35D (95% CI, 0.22 to 0.48), 0.05% was 0.51D (95% CI, 0.40 to 0.62), 0.10% was 0.46D (95% CI, 0.37 to 0.56), 0.125% was 1.00D (95% CI, 0.20 to 1.80), 0.25% was 0.64D (95% CI, 0.41 to 0.86), 0.50% was 0.79D (95% CI, 0.37 to 1.21), 1.00% was 0.92D (95% CI, 0.63 to 1.21), and overall was 0.57D (95% CI, 0.43 to 0.71) (Fig. 6). The differences between groups were significant ($P < 0.001$). The data was highly heterogeneous ($I^2 = 93\%$, $P < 0.001$). The reduction in spherical equivalent with atropine compared to controls for concentrations <0.10 and $\geq 0.10\%$ was 0.37D (95% CI, 0.16 to 0.58) versus 0.75D (95% CI, 0.17 to 1.33) and not significant between the 2 groups. However, the mean difference was 0.38 D/year and considered to be clinically relevant (Table 3).

Similarly, atropine was statistically superior to the controls in slowing axial elongation with a pooled difference in annual mean of -0.17 mm (95% CI -0.25 to -0.08, $P < 0.001$) (Fig. 7). The data was highly heterogeneous ($I^2 = 95\%$, $P < 0.001$) and the efficacy varied across concentrations with 0.01% atropine statistically insignificant compared to the control (mean difference of -0.03D, 95% CI, -0.11 to 0.05, $P = 0.45$). The reduction in axial length for concentrations of <0.10 and $\geq 0.10\%$ atropine compared to controls was -0.10 mm (95% CI, -0.24 to 0.05) and -0.23 mm (95% CI, -0.34 to -0.13) respectively (Table 3).

DISCUSSION

None of the previous meta-analyses had systematically reviewed the data for the two common side effects related to the use of atropine, that is, an increase in PD and a reduction in AA.[19,24–26] Since these 2 factors seem to be mostly responsible for the initial choice of concentration of atropine in myopia management,[22,27–29] they were analyzed and reported as the primary outcomes in the current meta-analysis. Since data on PD and AA with the use of atropine was not always reported in efficacy

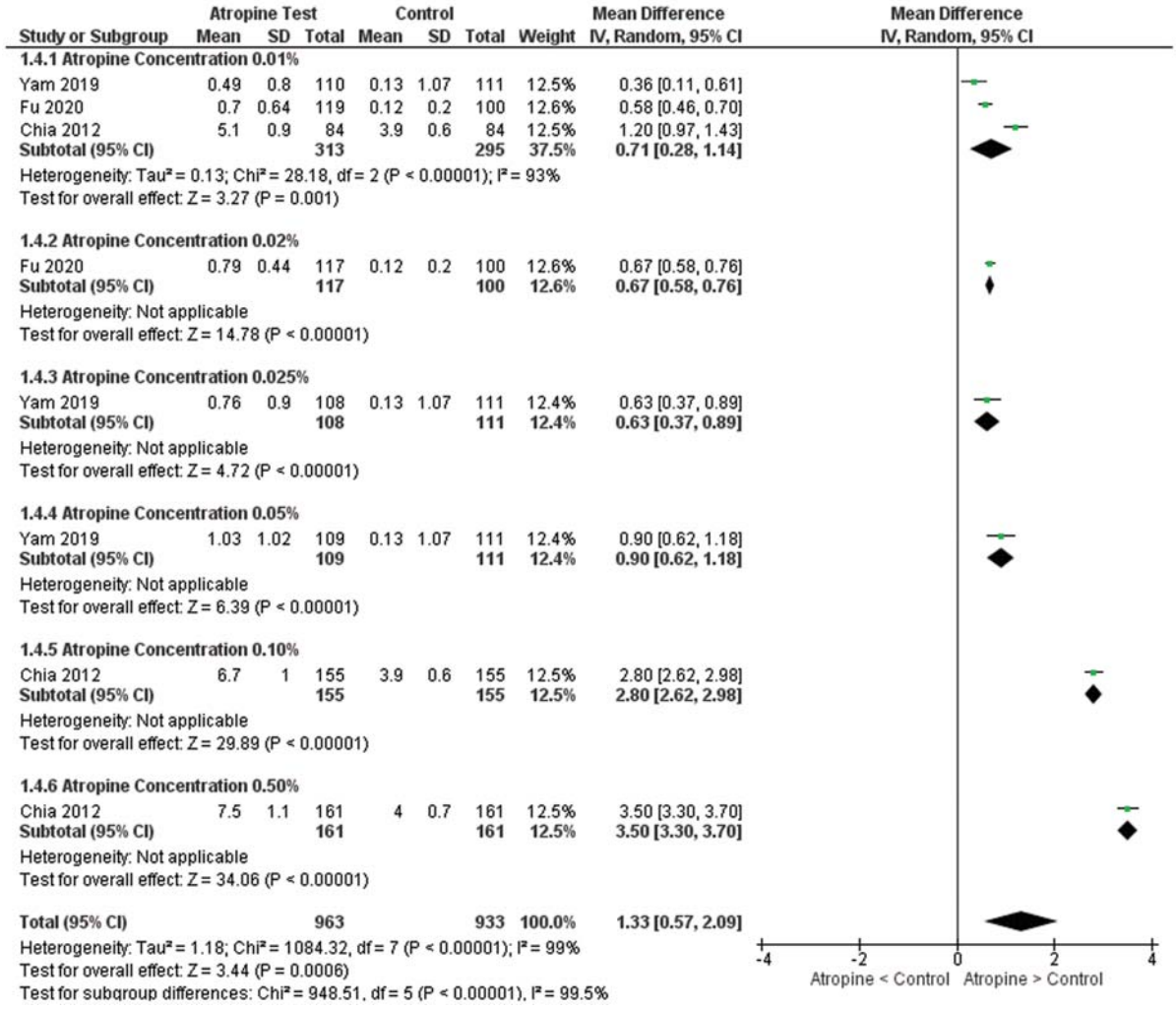

FIGURE 4. Effect of various concentrations of atropine on pupil size.

trials, the data is somewhat limited. Furthermore, where information was available on the effect of atropine on pupillary size and AA, there was no information on efficacy.[30,31] Notwithstanding the above, a quantification of the effect size for an increase in PD and a reduction in AA indicates a greater effect or an increased magnitude of these side-effects at higher concentrations (Figs. 3 and 4). This relationship was examined further (Fig. 5) and the data highlights a non-linear dose response relationship characterized by: a) a steep increase in the effect versus dose at concentrations <0.10% atropine and b) a higher effect but a slower rise or some plateauing of the curve for concentrations ≥0.10% atropine and c) the trend is similar for both the side effects. Our findings align with published reports wherein the majority of the reports of photophobia or near work problems were with the use of 0.50% atropine and infrequent in those using ≤0.10% atropine.[22,25,32] However, although the relationship indicates a steep increase for concentrations <0.10% atropine, previous reports also found no significant difference in the rate of side-effects with the use of 0.05% and 0.025% atropine.[28,33] More data is needed to better understand and confirm this relationship. In addition to the lack of sufficient data, other factors that may be confounding include a possible variability in the stability of atropine as well as the time of measurement versus instillation. Atropine is mostly available as a compounded product that is diluted for use; thus ensuring that the stability and therefore appropriate strength is important especially for the lower concentrations of atropine. In this respect, although there are some reports of atropine being unstable at certain conditions, others have not found an issue.[34–36] Furthermore, the side-effects may be time-related and may peak for example, within certain hours after instillation of drop and may reduce in intensity thereafter. Therefore, the time at which the measurements were collected post-instillation might also influence the results.

Although there have been a number of meta-analyses reporting on the efficacy of atropine in slowing myopia,[14,15,37] since the last reported analysis in 2017, there have been a further 4 studies that have assessed the efficacy of 0.01% atropine. Therefore, we also considered the efficacy of atropine in controlling the progression of myopia. In comparison to controls, all concentrations were observed to slow myopia when the spherical equivalent refractive error was considered as the outcome measure. Similarly, all except 0.01% atropine had a significant effect in slowing axial length. Utilising the cut-off criteria of <0.10% and ≥0.10% atropine, compared to controls, the reduction in progression was 0.37D (95% CI, 0.16 to 0.58) versus 0.75D (95% CI, 0.18 to 1.33)

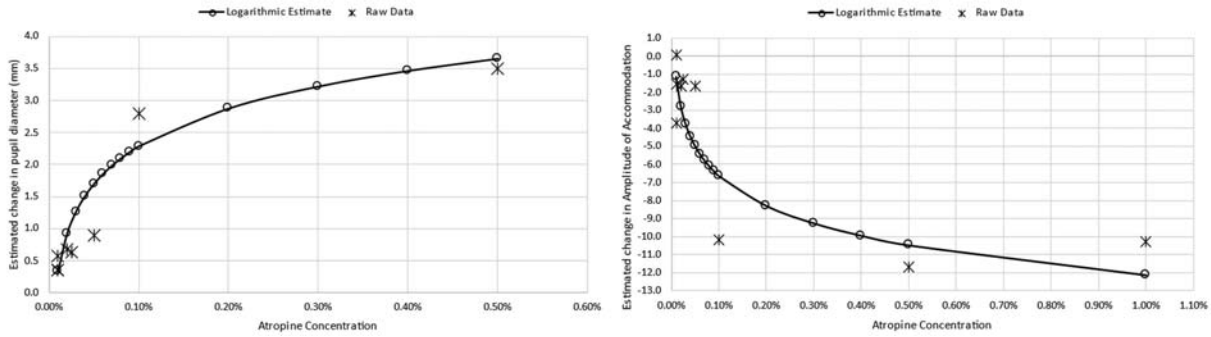

FIGURE 5. Relation between the concentration of atropine to change in a) pupillary size and b) accommodative amplitude.

for spherical equivalent refractive error and −0.10 mm (95% CI, −0.24 to 0.05) versus −0.23 mm (95% CI, −0.34 to −0.13) for axial length. Although there was lesser control of myopia at the lower concentrations, the overlap of CI indicates that the groups were not significantly different. Evidence indicates that the younger the age of onset, the faster the progression of myopia, and thus interventions should be considered as early as possible.[38] Furthermore, the second-year data of the low-concentration atropine for myopia progression (LAMP) study indicated that the progression of myopia in those that were not treated in the first year (controls) and treated using 0.05% atropine in the second year was clinically and statistically equivalent to the group using 0.01% atropine over 2 years, suggesting a more aggressive approach early on may be a useful strategy.

Additionally, although our analysis found some differences between the various concentrations for the reduction in spherical equivalent refractive error and/or axial length, two of the previous meta-analyses did not find significance between the various

TABLE 3. Sub-group Analysis: <0.10% and ≥0.10% Atropine Concentration on Pupillary Size, Accommodative Amplitude, Change in Spherical Equivalent and Change in Axial Length Compared to Controls

Outcome	Sub-group	Atropine Concentration	Effect Estimate (Diff: Test - Control)	95% CI	Subgroup Estimate (Diff: Test vs Control)	95% CI
Amplitude of accommodation [D]	Conc <0.10%	0.01%	−1.7	−3.3 to 0.0	−1.6	−3.9 to 0.7
		0.02%	−1.7	−2.0 to −1.3		
		0.03%	−1.3	−2.0 to −0.6		
		0.05%	−1.7	−2.4 to −0.9		
	Conc ≥ 0.10%	0.10%	−10.2	−11.0 to −9.4	−10.7	−12.2 to −9.2
		0.50%	−11.7	−12.4 to −11.0		
		1.00%	−10.3	−11.0 to −9.6		
Pupil size [mm]	Conc < 0.10%	0.01%	0.7	0.3 to 1.1	0.7	0.1 to 1.4
		0.02%	0.7	0.6 to 0.8		
		0.03%	0.6	0.4 to 0.9		
		0.05%	0.9	0.6 to 1.2		
	Conc ≥ 0.10%	0.10%	2.8	2.6 to 3.0	3.2	2.8 to 3.5
		0.50%	3.5	3.3 to 3.7		
Spherical equivalent progression [D]	Conc < 0.10%	0.01%	0.34	0.25 to 0.44	0.37	0.16 to 0.58
		0.02%	0.32	0.19 to 0.45		
		0.03%	0.35	0.22 to 0.48		
		0.05%	0.51	0.40 to 0.62		
	Conc ≥ 0.10%	0.10%	0.46	0.37 to 0.56	0.75	0.17 to 1.33
		0.125%	1.00	0.20 to 1.80		
		0.25%	0.64	0.41 to 0.86		
		0.50%	0.79	0.37 to 1.21		
		1.00%	0.92	0.63 to 1.21		
Axial elongation [mm]	Conc < 0.10%	0.01%	−0.03	−0.11 to 0.05	−0.10	−0.24 to 0.05
		0.02%	−0.16	−0.24 to −0.08		
		0.03%	−0.12	−0.18 to −0.06		
		0.05%	−0.21	−0.27 to −0.15		
	Conc ≥ 0.10%	0.10%	−0.07	−0.12 to −0.02	−0.23	−0.34 to −0.13
		0.50%	−0.09	−0.14 to −0.04		
		1.00%	−0.36	−0.41 to −0.30		

CI indicates confidence of interval.

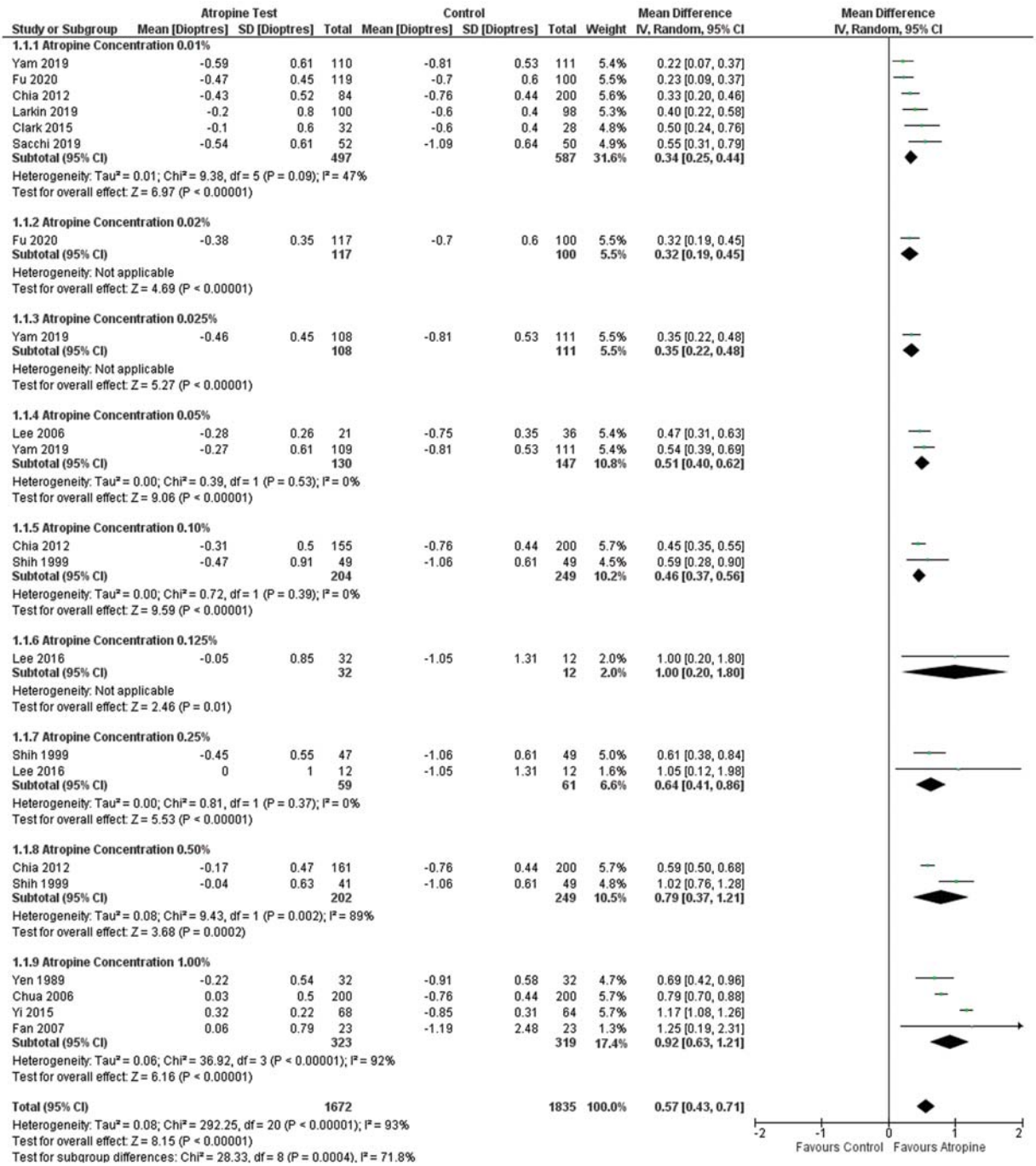

FIGURE 6. Annual change in spherical equivalent refractive error: atropine compared to control.

doses/concentrations.[8,14] The differences may be related to variation between the studies with respect to the articles considered for the meta-analysis as well as the categorization. For example, Gong et al[14] considered the results of a 3-year follow-up study of ATOM 1 study for 1% atropine,[13,23] whereas we had considered only the original ATOM 1 study.[23] With respect to categorization, Huang et al[8] had combined both 1% and 0.5% into high dose, 0.1% as moderate, and 0.01% as low dose, and had considered only 5 articles. Furthermore, although the previous articles had considered the efficacy over the study period (eg, 24 months), we have provided the annualized difference in progression to ensure uniformity across the studies.

In addition to concerns related to dilation of pupil and significant decrease of AA, there are other concerns related to long-term use of atropine. The importance of these is the rebound of myopia that occurs on discontinuation of atropine, which is said to occur especially with high dose atropine.[12,13] However, the data is limited and was not explored further. Other concern is retinal damage due to long-term exposure to ultraviolet light. In this regard, there have been some trials that have followed participants using atropine for 10 years or more with no adverse events,[18,39,40] and recent evidence indicates no damage to the retinal layers.[41,42] However, the available information is inadequate to analyze this data systematically. Although the data support the role of

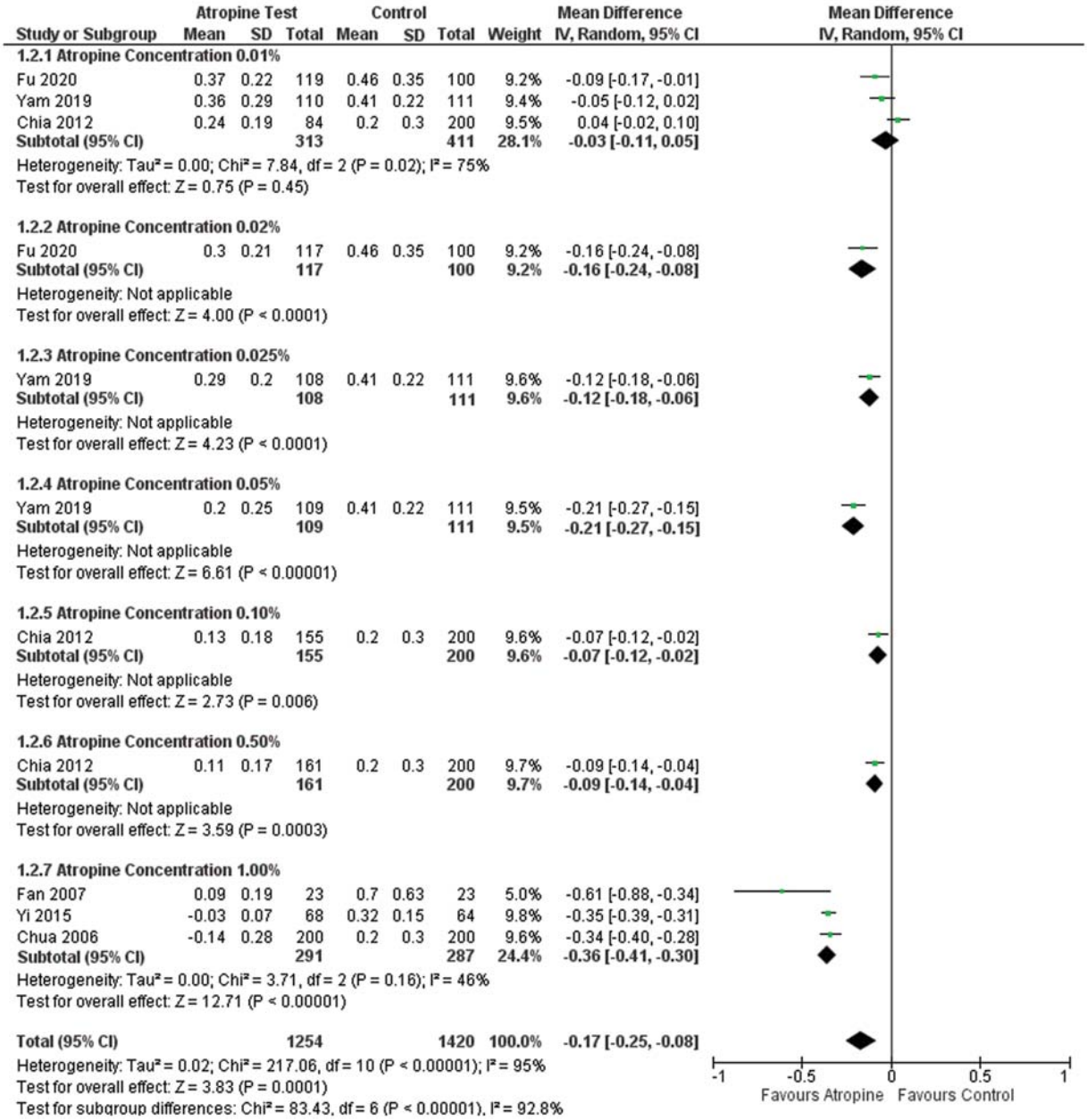

FIGURE 7. Annual change in axial elongation: Atropine compared to control.

atropine, including low dose atropine, in myopia management, the effect of the lowest dose, that is, 0.01% atropine remains inconclusive as its effect on axial length was not significantly different.[22]

There are several limitations associated with this meta-analysis. Although there were enough studies, most of these studies used low concentrations of atropine, and only a few had reported on pupil size and AA. Therefore, there was limited information on the use of higher concentrations of atropine where there was a greater risk of side effects. Additionally, there is variation in the techniques used to measure AA and PD between studies. However, rather than absolute values, we reported changes in PD and AA, comparing them to the control used in those studies. Therefore, the effects of such variation are likely minimized. Furthermore, although the change in pupil size and AA was considered, the functional outcomes of these structural variations, such as loss of vision or glare or photophobia was not explored, as these were not always available or easily quantifiable due to the variation in subjective questionnaires between studies.[22,25,33] Except for the LAMP study and the Atropine for the Treatment of Myopia (ATOM2) study, subjective symptoms were not evaluated systematically.[22,33] Despite a robust study design and conduct of the trial, the use of a historical control group is a source of bias.[22] Nonetheless, it was considered reliable as both studies were conducted in a similar population and with comparable designs. Finally, all of the studies that reported on pupil size and accommodation were from Asian eyes; the effects of mydriatics and cycloplegics on pigmented versus non-pigmented or lesser pigmented eyes are well known.[24] Therefore, although the current meta-analysis found little variation in pupillary size and AA for concentrations of atropine <0.10%, it is possible that there may be a greater variation in eyes with lesser pigmentation.

In summary, the data indicate that at concentrations of <0.10%, the effect on the pupillary size and AA was small with

insignificant variation between the various concentrations. On average, the change in pupil size was <1 mm, and the change in AA was <2.0D. Despite some discomfort due to the increase in pupil size, the loss of a small amount of AA is unlikely to have resulted in any significant symptoms as children have large reserves of accommodation.[22,33,43] Similarly, the ability to slow myopia progression was lower for concentrations <0.10%. Although higher concentrations of atropine (≥0.10%) can significantly slow ocular elongation, they are accompanied by large increases in PD and AA that limit their use. Further work needs to be conducted to determine the concentration of atropine that achieves the maximal efficacy without a significant increase in PD and AA.

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