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Efficacy and Adverse Effects of Atropine in Childhood Myopia
A Meta-analysis

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IMPORTANCE Some uncertainty about the clinical value and dosing of atropine for the treatment of myopia in children remains.

OBJECTIVE To evaluate the efficacy vs the adverse effects of various doses of atropine in the therapy for myopia in children.

DATA SOURCES Data were obtained from PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials, from inception to April 30, 2016. The reference lists of published reviews and clinicaltrials.gov were searched for additional relevant studies. Key search terms included *myopia*, *refractive errors*, and *atropine*. Only studies published in English were included.

STUDY SELECTION Randomized clinical trials and cohort studies that enrolled patients younger than 18 years with myopia who received atropine in at least 1 treatment arm and that reported the annual rate of myopia progression and/or any adverse effects of atropine therapy were included in the analysis.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently abstracted the data. Heterogeneity was statistically quantified by Q, H, and I^2 statistics, and a meta-analysis was performed using the random-effects model. The Cochrane Collaboration 6 aspects of bias and the Newcastle-Ottawa Scale were used to assess the risk for bias.

MAIN OUTCOMES AND MEASURES The primary outcome was a difference in efficacy and the presence of adverse effects at different doses of atropine vs control conditions. The secondary outcomes included the differences in adverse effects between Asian and white patients.

RESULTS Nineteen unique studies involving 3137 unique children were included in the analysis. The weighted mean differences between the atropine and control groups in myopia progression were 0.50 diopters (D) per year (95% CI, 0.24-0.76 D per year) for low-dose atropine, 0.57 D per year (95% CI, 0.43-0.71 D per year) for moderate-dose atropine, and 0.62 D per year (95% CI, 0.45-0.79 D per year) for high-dose atropine ($P < .001$), which translated to a high effect size (Cohen *d*, 0.97, 1.76, and 1.94, respectively). All doses of atropine, therefore, were equally beneficial with respect to myopia progression ($P = .15$). High-dose atropine were associated with more adverse effects, such as the 43.1% incidence of photophobia compared with 6.3% for low-dose atropine and 17.8% for moderate-dose atropine ($\chi^2_2 = 7.05$; $P = .03$). In addition, differences in the incidence of adverse effects between Asian and white patients were not identified ($\chi^2_1 = 0.81$; $P = .37$ for photophobia).

CONCLUSIONS AND RELEVANCE This meta-analysis suggests that the efficacy of atropine is dose independent within this range, whereas the adverse effects are dose dependent.

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Supplemental content

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Myopia is a relatively prevalent and increasing public health concern, particularly in East Asia, where it has already reached a pandemic level.[1] An estimated 2.5 billion people will be affected by myopia in 2020.[2] The prevalence has been reported to be 80% or higher in the young adult population in certain Asian countries or areas, such as Singapore, Hong Kong, and Taiwan.[3-5] Similarly, in the United States, the prevalence of myopia is 20% to 50% among the population older than 12 years.[6] This silent epidemic should not be ignored.[7] The worldwide prevalence of myopia and high myopia is estimated to increase substantially, affecting nearly 5 billion and 1 billion people, respectively, by 2050.[8] In addition, the cost of uncorrected refractive error is a very real existing problem, affecting as many as 88% of children with myopia, and thus, the implications of increasing myopia prevalence worldwide are significant.[8,9] Apart from the substantial socioeconomic cost, severe sight-threatening complications associated with high myopia substantially compromise quality of life.[10] An excellent review by Flitcroft[11(p622)] clearly demonstrates that no safe threshold for myopic refractive errors exists, which suggests that no such thing as "physiological myopia" exists. A recent study[12] reported that axial lengths of 26 mm or greater and refractive errors of −6 diopters (D) or greater are significantly associated with an increased lifetime risk for visual impairment. Therefore, an effective treatment to slow or even stop myopia progression in young children is urgently needed. Researchers and clinicians have proposed approaches to treat myopia for many years. However, to date, no ideal approach has been identified as efficacious for the prevention and treatment of myopia with sufficient safety and clinical acceptability.[13]

Atropine, a nonselective muscarinic antagonist, has been studied widely in recent years to prevent worsening of myopia in children.[14] Although the exact mechanism and site of action of atropine are still unknown, different concentrations of atropine (low dose, 0.01%; moderate dose, >0.01% to <0.5%; and high dose, 0.5% to 1.0%) have been widely used topically as eyedrops, with great interest in Asian areas, especially in Taiwan and Singapore.[15] Atropine was thought to have a dose-related efficacy but was also thought to be associated with significant adverse effects. Some studies have reported that 1.0% atropine can stop or even reverse myopia progression, but the treatment was associated with other vision-related adverse effects.[16,17] In a recent 5-year study,[15] 0.01% atropine was shown to be effective, with fewer vision-related adverse effects. Thus far, much uncertainty remains about the clinical use of atropine, such as dosing, safety concerns, and the generalizability of the application of atropine in different ethnic groups.

Previous systematic reviews[18,19] have assessed the efficacy of atropine, but a quantitative assessment of the adverse effects was lacking. Because race and iris color are known factors that influence cycloplegia, the adverse effects of atropine in lightly pigmented eyes of white persons may be more severe.[20] In this follow-up meta-analysis, we aimed to evaluate the overall efficacy of atropine in slowing myopia progression in children in the context of quantitative data about the adverse effects that accompany such treatment. We have also investigated whether there was a difference in the incidence of adverse effects between different ethnicities.

Key Points

Question Do the adverse effects and efficacy of topical atropine support its use in children with myopia, and if so, at what dose should it be administered?

Findings This meta-analysis of 19 studies that included 3137 children found atropine to be effective in slowing progression of myopia; however, no difference in efficacy was identified between different doses of atropine within this range. Higher doses of atropine were associated with more adverse effects.

Meaning Because adverse effects were less frequent at lower doses of atropine and higher doses were not more effective, this meta-analysis supports using atropine at lower doses (0.01%) to reduce progression of myopia.

Methods

Data Sources and Literature Searches

We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials to yield relevant studies from their inception to April 30, 2016, using Medical Subject Headings (MeSH) and free words combined with *myopia*, *refractive errors*, and *atropine*. We also screened clinicaltrials.gov and the reference lists of published reviews to identify additional relevant studies. Only studies published in English were included.

Eligibility Criteria

We included comparative studies (ie, randomized clinical trials [RCTs], non-RCTs, and cohort studies). The studies were selected according to the following criteria: (1) participants were younger than 18 years and had myopia, (2) atropine was used in at least 1 treatment arm, and (3) the study reported at least 1 outcome of interest, including the annual rate of myopia progression and any adverse effects.

Data Collection and Quality Assessment

Two of us (Q.G. and M.L.) screened titles and abstracts to identify potentially eligible articles independently and in duplicate, and then they checked the full text to determine the final inclusions. When more than 1 report used data from the same study, we included only the latest report to avoid duplicate counting of the data. For the included studies, both reviewers independently extracted data regarding study characteristics (author, study design, country or area, intervention and control, and length of follow-up), patient characteristics (sex, age, mean change in cycloplegic spherical equivalent, mean change in axial elongation, and number of adverse events), and outcomes of interest. Discrepancies were adjudicated by a third reviewer (L.L.)

We assessed the risk for bias of RCTs for the following 6 aspects according to the Cochrane Collaboration: allocation sequence generation, allocation concealment, masking of patients and clinicians, masking of outcome assessors, incomplete outcome data, and selective outcome reporting. For observational studies, we applied the Newcastle-Ottawa Scale, which included 8 items within 3 domains to evaluate bias in

patient selection, comparability, and outcome assessments. A study can be awarded a maximum of 1 star for each numbered item among the items that evaluate patient selection and outcome assessments. A maximum of 2 stars could be given for comparability, and the total scores ranged from 0 to 9 points. No case-control studies were included.

Statistical Analysis

Data analyses were performed using Review Manager (version 5.3; Cochrane Collaboration), STATA (version 12.0; StataCorp), and SAS (version 9.4; SAS Institute, Inc) software. We conducted analyses for changes in different concentrations of atropine vs control conditions based on comparative studies. We calculated the weighted mean difference (WMD) and 95% CIs for different doses of atropine in refractive changes and axial elongation vs the control group, as well as the risk ratio for adverse effects between the atropine and control groups. The effect sizes (ESs) were calculated using the Cohen *d* formula. An effect size would be defined as small at 0.20 or greater, medium at 0.50 or greater, or large at 0.80 or greater, which means the treatment effect was low, moderate, or strong, respectively.[21,22] The various concentrations of atropine were also correlated with the WMDs and adverse effects. The extent of heterogeneity was statistically quantified by Q, H, and I^2 statistics across studies. We performed all the meta-analyses using a random-effects model if the Q statistic was significant.

A subanalysis was performed by evaluating the heterogeneity between different ethnicities (Asian vs white individuals). We performed a sensitivity analysis by excluding studies with significantly different characteristics. In addition, publication bias was addressed by a Begg rank correlation, an Egger regression, and a trim-and-fill method.[21]

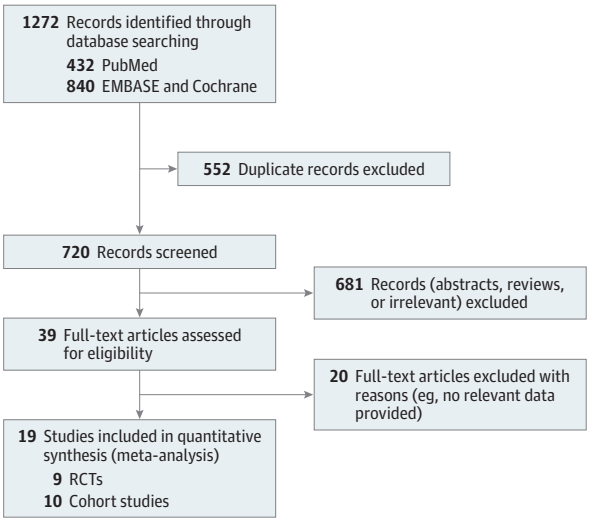
Results

The retrieval identified 720 articles, and ultimately, 19 unique studies constituted the data for analysis (**Figure 1**), including 9 RCTs[17,23-30] and 10 cohort studies.[16,31-39] A total of 3137 unique children younger than 18 years were included in this meta-analysis; 1814 were included in RCTs, and 1323 were included in cohort studies. In addition, 268 Asian and 201 white participants underwent separate analysis in the 1.0% atropine group for ethnic comparison. The study characteristics are listed in the **Table**. Low-dose atropine was investigated in 2 studies,[27,37] moderate-dose atropine in 7 studies,[24,28,29,34,36-38] and high-dose atropine in 13 studies,[17,23-33,35] together resulting in 22 experimental groups in 19 studies. Ten studies were conducted in Taiwan, 3 in the United States, 3 in Singapore, 2 in Mainland China, and 1 in Hong Kong. Among the studies, Liang et al[28] and Chia et al[29] compared different doses of atropine groups without a control group that did not receive atropine. Lin et al[16] conducted a self-control study and compared interocular imbalance. The other studies included atropine vs a control group with no administration of atropine.

Risk of Bias Assessment

The risk for bias for the included RCTs is presented in eTable 1 in the Supplement. The quality of the included cohort studies was generally high according to the Newcastle-Ottawa Scale items (eTable 2 in the Supplement).

Figure 1. PRISM Flow Diagram of the Literature Search Process



RCTs indicate randomized clinical trials.

Refraction

Of the atropine vs control group comparison, 1 study[39] reported data on low-dose atropine; 5 studies,[24,34,36-38] on moderate-dose atropine; and 11 studies,[17,23-27,30-33,35] on high-dose atropine. Seven RCTs[17,23-28] (n = 1349) and 9 cohort studies[31-39] (n = 1308) reported data on refraction. We combined RCT and cohort studies to provide larger samples of the different doses because we found no difference between RCTs and cohort studies (P = .30) (eFigure 1 in the Supplement). The pooled data showed significantly less progression in refraction for low-dose (WMD, 0.50 D per year; 95% CI, 0.24-0.76 D per year; P < .001), moderate-dose (WMD, 0.57 D per year; 95% CI, 0.43-0.71 D per year; P < .001), and high-dose (WMD, 0.62 D per year; 95% CI, 0.45-0.79 D per year; P < .001) atropine groups than control groups after therapy (**Figure 2**). The ES pooling revealed a large treatment effect in the outcome of interest in low-dose (ES, 0.97; 95% CI, 0.43-1.5; P < .001), moderate-dose (ES, 1.76; 95% CI, 1.44-2.07; P < .001), and high-dose (ES, 1.94; 95% CI, 1.22-2.65; P < .001) atropine groups (Figure 2). No statistically significant difference in changes of refraction among various doses of atropine was observed within this range (χ^2_2 = 3.74; P = .15 for interaction; I^2 = 46.5%) (eFigure 2 in the Supplement). We observed no correlation between a dose and treatment effect (r = 0.17; P = .51).

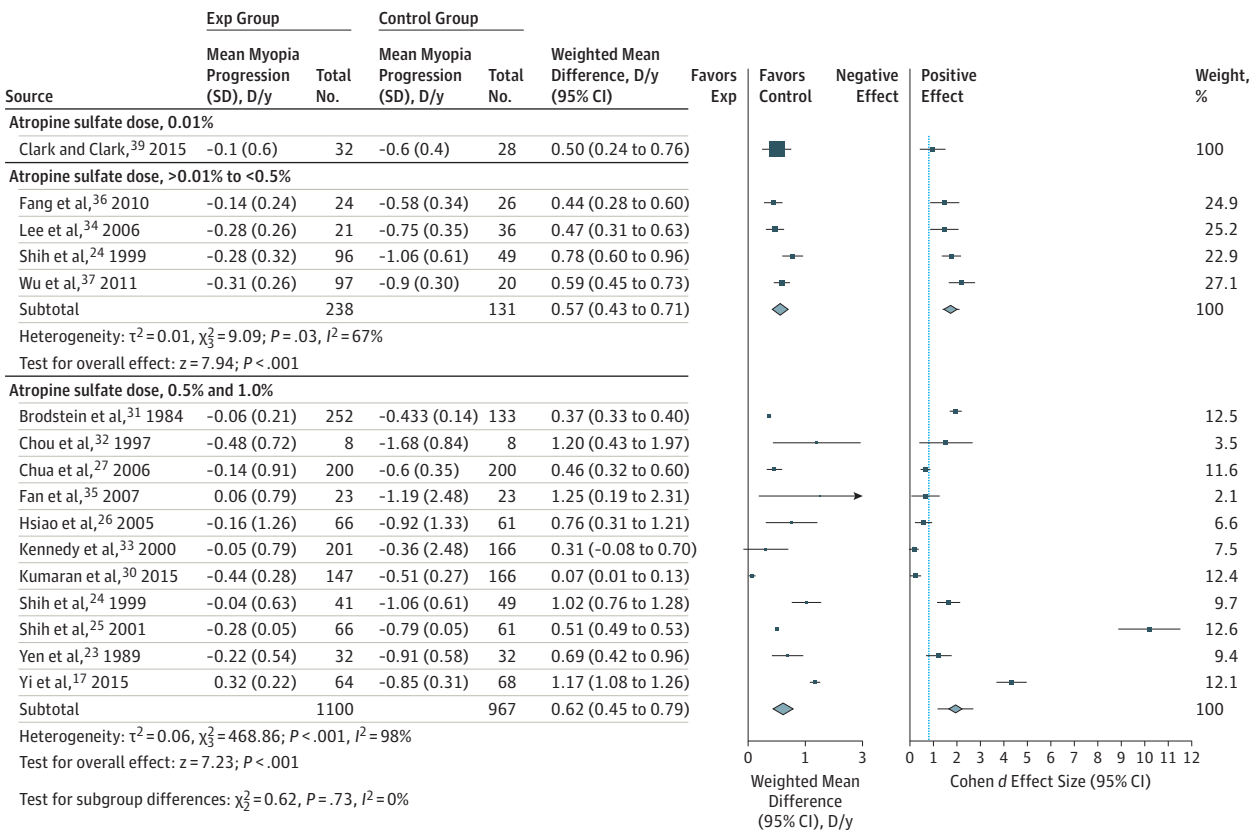
In addition, the ES pooling revealed a large treatment effect in the outcome of interest for RCTs (ES, 2.67; 95% CI, 1.46-3.88) and cohort studies (ES, 1.30; 95% CI, 0.61-1.98). A significant heterogeneity and publication bias was found in the treatment effects for RCTs and no publication bias in cohort studies (eTable 3 in the Supplement). In addition, no significant difference was found in 0.01% and 1.0% atropine treatment between Asian and white individuals (P = .25 and P = .83).

Table. Characteristics of the Studies Included in the Meta-analysis

Source	Study Design	Country/Area	Follow-up, mo	Atropine Dose, %	Age, y	Baseline Refraction, Diopter
Yen et al,[23] 1989	RCT	Taiwan	12	1.0	6-14	Mean (SD), −1.52 (0.92)
Shih et al,[24] 1999	RCT	Taiwan	24	0.5. 0.25, 0.1	6-13	Mean (SD), −4.41 (1.47)
Shih et al,[25] 2001	RCT	Taiwan	18	0.5	6-13	Mean (SD), −3.28 (0.13)
Hsiao et al,[26] 2005	RCT	Taiwan	18	0.5	6-13	Mean, −3.37
Chua et al,[27] 2006	RCT	Singapore	24	1.0	6-12	Mean (SD), −3.36 (1.38)
Liang et al,[28] 2008	RCT	Taiwan	6	0.25, 0.5	6-15	Range, −0.50 or less
Chia et al,[29] 2012	RCT	Singapore	24	0.5, 0.1, 0.01	6-12	Range, −2.00 or less
Kumaran et al,[30] 2015	RCT	Singapore	36	1.0	6-12	Mean, −3.36
Yi et al,[17] 2015	RCT	China	12	1.0	7-12	Mean (SD), −1.23 (0.32)
Brodstein et al,[31] 1984	Cohort	United States	33	1.0	8-15	Not reported
Chou et al,[32] 1997	Cohort	Taiwan	38	0.5	7-14	Range, −6.00 or less
Kennedy et al,[33] 2000	Cohort	United States	144	1.0	6-15	Mean, −1.49
Lee et al,[34] 2006	Cohort	Taiwan	20	0.05	6-12	Mean (SD), −1.58 (1.37)
Fan et al,[35] 2007	Cohort	Hong Kong	12	1.0	5-10	Mean (SD), −5.18 (2.05)
Fang et al,[36] 2010	Cohort	Taiwan	18	0.025	6-12	Mean (SD), −0.31 (0.45)
Wu et al,[37] 2011	Cohort	Taiwan	54	0.05	6-12	Mean (SD), −2.45 (1.63)
Lin et al,[38] 2014	Cohort	Taiwan	36	0.125	7-17	Mean (SD), −4.00 (1.75)
Clark and Clark,[39] 2015	Cohort	United States	13	0.01	6-15	Mean (SD), −2.00 (1.60)
Lin et al,[16] 2013	Cohort	China	11.5	1.0	8-15	Mean (SD), −1.92 (0.91)

Abbreviation: RCT, randomized clinical trial.

Figure 2. Forest Plots of the Mean Difference in Refraction Between the Experimental and Control Groups at Different Doses of Atropine and the Overall Estimates of the Effect of Atropine on Refraction



Vertical interrupted line denotes where the positive effect begins to be large (small, ≥0.20; medium, ≥0.50; and large, ≥0.80). D indicates diopter.

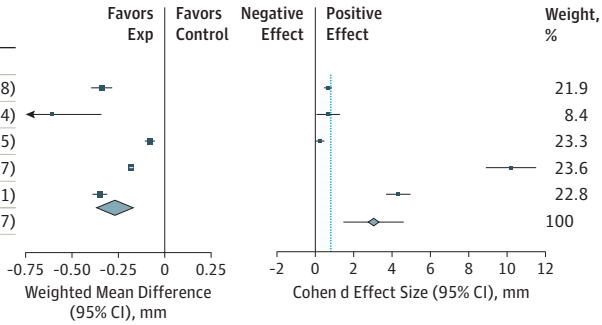
Figure 3. Forest Plot and the Overall Estimates of the Effect of Atropine on Axial Length

Source	Exp Group: Mean Axial Length (SD), mm	Exp Group: Total No.	Control Group: Mean Axial Length (SD), mm	Control Group: Total No.	Weighted Mean Difference (95% CI), mm
Atropine sulfate dose, 0.5% and 1.0%					
Chua et al,[27] 2006	-0.14 (0.28)	200	0.2 (0.3)	200	-0.34 (-0.40 to -0.28)
Fan et al,[35] 2007	0.09 (0.19)	23	0.7 (0.63)	23	-0.61 (-0.88 to -0.34)
Kumaran et al,[30] 2015	0.1 (0.09)	147	0.18 (0.15)	166	-0.08 (-0.11 to -0.05)
Shih et al,[25] 2001	0.15 (0.03)	66	0.33 (0.03)	61	-0.18 (-0.19 to -0.17)
Yi et al,[17] 2015	-0.03 (0.07)	64	0.32 (0.15)	68	-0.35 (-0.39 to -0.31)
Subtotal		500		518	-0.27 (-0.36 to -0.17)

Heterogeneity: $\tau^2 = 0.01$, $\chi^2_4 = 163.36$; $P < .001$, $I^2 = 98\%$

Test for overall effect: $z = 5.37$; $P < .001$

Test for subgroup differences: Not applicable



Vertical interrupted line denotes where the positive effect begins to be large (small, ≥0.20; medium, ≥0.50; and large, ≥0.80).

Axial Elongation

Five studies[17,25,27,30,35] reported changes in axial length between the high-dose atropine and control groups. The study by Lin et al[38] was not included because orthokeratology was used as the control. We also combined RCTs and cohort studies to obtain the results because of the limited number of studies. The analyses showed that the WMD in changes of axial elongation between the atropine groups and control groups was −0.27 mm (95% CI, −0.36 to −0.17 mm; $P < .001$) in high-dose studies (**Figure 3**). The ES pooling for the high-dose studies was 3.05 (95% CI, 1.52-4.57; $P < .001$) (Figure 3). The ES pooling was 3.67 (95% CI, 1.85-5.50; $P < .001$) in RCTs and 0.68 (95% CI, 0.08-1.27) in cohort studies.

Adverse Effects

All atropine arms in RCTs and cohort studies were combined to estimate the difference in the incidence of adverse effects among various doses of atropine (eFigure 3 in the Supplement). In addition, the incidence of adverse effects reported in 12 studies[16,23,24,27-29,33-36,38,39] is summarized in eTable 4 in the Supplement. In total, 308 adverse effect events were reported in 2425 patients in the atropine groups from all included studies, with an incidence of 12.7%. Of those, the most common were photophobia (205 of 816 [25.1%]), followed by poor near visual acuity (48 of 636 [7.5%]), and allergy (20 of 679 [2.9%]). Other adverse effects included headache, chalazion, systemic effects, and those that occurred in fewer than 1% of the patients. Only 2 events of photophobia among 721 patients were reported in the control groups. Therefore, the incidence of any adverse event was significantly greater in the atropine compared with the control groups ($P < .001$). In addition, data for the RCTs and cohort studies were pooled, because of the limited number of studies, to estimate the adverse effects of 1.0% atropine in Asian and white individuals (eFigure 4 in the Supplement).

Photophobia

The incidence of photophobia with low-dose atropine was 6.3% (95% CI, 0.1%-17.9%); with moderate-dose atropine, 17.8% (95% CI, 5.8%-33.9%); and with high-dose atropine, 43.1% (95% CI, 16.2%-71.7%), revealing an increase in the rate of this adverse effect with dose escalation ($\chi^2_2 = 7.05$; $P = .03$). The incidence of photophobia was statistically significant but only moderately correlated with the dose of atropine ($r = 0.56$; $P = .03$).[40] The rates of photophobia were 61.5% (95% CI, 12.0%-111.0%) in Asian and 38.4% (95% CI, 32.0%-45.0%) in white participants ($\chi^2_1 = 0.81$; $P = .37$ for interaction).

Poor Near Visual Acuity

The incidence of poor near visual acuity for low-dose atropine was 2.3% (95% CI, 0.1%-5.5%); for moderate-dose atropine, 11.9% (95% CI, 7.0%-18.5%); and for high-dose atropine, 11.6% (95% CI, 0.8%-27.3%) ($\chi^2_2 = 9.98$; $P = .007$ for interaction). The rates of poor near visual acuity were 4.9% (95% CI, −4.0% to 14.0%) in Asian and 10.7% (95% CI, 6.0%-15.0%) in white individuals ($\chi^2_1 = 1.36$; $P = .24$ for interaction).

Allergy

The incidence of allergy for moderate-dose atropine was 2.9% (95% CI, 0.1%-6.9%); for high-dose atropine, 3.9% (95% CI, 2.0%- 6.2%) ($\chi^2_1 = 0.24$; $P = .62$). The rates of allergy were 3.0% (95% CI, 0%-6.0%) in Asian and 3.7% (95% CI, 1.0%-6.0%) in white individuals ($\chi^2_1 = 0.11$; $P = .74$ for interaction).

Other Adverse Effects

The incidence of other adverse effects for low-dose atropine was 4.8% (95% CI, 1.0%-10.6%); for moderate-dose atropine, 11% (95% CI, 6.5%-16.4%); and for high-dose atropine, 11.2% (95% CI, 3.3%-21.5%) ($\chi^2_2 = 3.57$; $P = .17$ for interaction). The rates of other adverse events (ie, chalazion and systemic effects) were 3.3% (95% CI, −3.0% to 10.0%) in Asian and 12.2% (95% CI, 8.0%-17.0%) in white individuals ($\chi^2_1 = 5.10$; $P = .02$ for interaction).

Discussion

Our meta-analysis confirms that atropine is effective in slowing the progression of myopia in children. No difference was found between various doses of atropine within this range. This finding is in contrast to a 2011 meta-analysis[18] that showed better efficacy at higher doses, but that analysis included only 6 studies available at that time. In addition, those authors evaluated only

the moderate and high doses of atropine, without the low dose. The next meta-analysis[19] published 3 years later included 11 studies and 1815 children and showed a positive effect of atropine, but no stratification by dose or quantification of adverse effects was performed and the 0.01% dose was not included.

In 2016, a network meta-analysis was published[41] that showed that pharmacological intervention, such as atropine, is most effective in slowing myopia progression, and no dose dependence was observed, which was in contrast to previous analyses and was probably related to the further accumulation of clinical trials. Seven studies were included that examined all the high, moderate, and low doses of atropine; however, in the meta-analysis, no quantitative assessment of adverse effects was performed. Our meta-analysis also did not find differences in efficacy among doses within this range.

Our study quantifies adverse effects and has been instrumental in forming practical guidelines for the administration of atropine, including dosing. We have shown that increasing the dose of atropine leads to a growing number of adverse effects. Our analysis also showed that differences in the incidence of adverse effects between Asian and white patients were not identified, but only 1.0% atropine was analyzed because of limited studies on other doses in white patients.

A previous study[42] reported that a lighter iris color in Europeans is generally considered to be a barrier for the use of atropine in the Western world, and the rate of adverse effects may be higher. The study did not identify a difference in photophobia, poor near visual acuity, or allergy between Asian and white children for 0.5% atropine. The study focused on Europeans, with 53 European and 13 Asian patients.[42] We believe there are 2 reasons for the findings. One is that white patients were involved in only 1 study,[33] and thus no pooled data could be gathered; the other is that 1 study involving Asian patients was published in 1989,[23] and all patients reported photophobia, which may be because no strategies existed to alleviate the symptom at that time.

Polling et al[42] reported that, overall, European and Asian children reported a similar prevalence of photophobia and reading problems. However, Asian children, in general, suggest they were able to cope with the adverse effects more easily, and 63.3% of the European children experienced undiminished adverse effects compared with 20% of the Asian children. Therefore, Asian children adapted very quickly.

As Huang et al[41] suggested, clinical decisions about any intervention require information about efficacy, short- vs long-term benefits, and the risks for adverse effects. Therefore, an additional examination of the adverse effects of atropine is important.

No difference in the efficacy of atropine was identified across various doses within this range, but the lowest dose, 0.01%, was administered in only 2 studies.[29,39] Although we recommend using the lowest dose of atropine (0.01%) for therapy, more clinical trials with this dose are needed, and a crossover design would be interesting, with the weakest response from low-dose atropine to the high-dose of atropine, to test whether such a potential clinical scenario might be effective. If adverse effects occur, the discontinuation of the therapy could be considered on a case-by-case basis, depending on how debilitating it is to patients, and this could serve as a basis for the measurement of the rebound effect.

Although the topical application of atropine slows the progression of myopia, the combined approaches might be necessary to better prevent the progression of myopia. Outdoor activities,[43-47] orthokeratology,[48] and bifocals[49] have been shown to be capable of slowing the progression of myopia, and a recent study[50] also raised the possibility of using stem cells to prevent myopia progression.

Limitations

The present study has some limitations. First, because not enough studies examined each atropine concentration, different types of studies were combined in this meta-analysis to investigate the overall effects of different doses, which might be a source of additional heterogeneity. Second, the reports on adverse effects in the included studies were not comprehensive, and some of the differences in rates of symptoms seem quite large, which may have limited a more in-depth analysis. Third, the efficacy of atropine was reported during the duration of the trials; however, the cessation of atropine therapy has been found to lead to a rebound effect and faster progression of myopia,[51] and this very important aspect was not studied in any of the investigated studies. Chia et al[52] found that 0.01% atropine has a lesser rebound effect than 0.5% and 0.1% atropine 1 year after stopping the administration of atropine. Because the 0.01% atropine dose is as effective as higher doses for slowing the progression of myopia, with fewer adverse effects and rebound effects, use of 0.01% atropine should be advocated. Fourth, the poor near visual acuity induced by high-dose atropine may also deter children from close work and thus slow the progression of myopia. This factor was also not controlled for in any of the studies. Fifth, we did not evaluate the axial length across various doses of atropine because such measurements were available only for high-dose atropine groups.

Conclusions

The efficacy of atropine is dose independent, whereas the adverse effects are dose dependent. The low dose of atropine seems to herald a new therapeutic scenario that decreases the adverse effects and seems to decrease the rebound effects. Therefore, this dose should be investigated further, along with the effects of encouraging more outside time for children. In addition, pharmaceutical companies could produce 0.01% atropine commercially to aid further global research.

ARTICLE INFORMATION

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Study concept and design: Gong, Janowski, Liu.
Acquisition, analysis, or interpretation of data: Gong, Janowski, Luo, Wei, Chen, Yang.
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