Review

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Review

Randomized and Controlled Studies on Atropine Efficacy for Preventing Myopia Progression from 2017 to 2023

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Abstract: Myopia has become a major health problem around the world. The development of myopia is starting to appear at an earlier age than in previous generations and its consequences have prompted multiple studies, particularly regarding topical atropine treatment aiming at preventing or slowing myopia progression. Our objective is to review randomized and controlled studies on the efficacy and safety of topical atropine to prevent myopia progression in children. This was a narrative review compiled from literature of PubMed and Cochrane Library, including randomized and controlled clinical trials of atropine eye drops for myopia progression published within 2017 - 2023. Fourteen clinical trials were found in the 7 year-period analyzed. All study atropine concentrations were effective in reducing the progression of myopia compared to the placebo. The highest dose of atropine (1%) showed the best efficacy in reducing the spherical equivalent progression and axial elongation over the lower dose (0.01%). Side-effects were mild or moderate. The use of atropine eye drops to prevent myopia progression has shown benefits without involving serious adverse effects. Higher doses of atropine (0.5% and 1%) have been shown to have more efficacy in preventing myopia progression than lower doses (0.01%), so starting intervention with those doses of atropine could be considered for preventing myopic children from becoming severe myopia patients later in life.

Keywords: myopia; atropine; myopia sequelae; myopia health problem; myopic children

1. Introduction

Myopia can be due to an excessive axial length, especially due to the lengthening of the vitreous chamber or an excessive dioptric power of the refractive [1]. Axial length generally increases during childhood and can result in more severe myopia in adolescence and adulthood, sometimes leading to high myopia [2] or pathological myopia [3], which is an important cause of low vision worldwide [4]. Therefore, the concern about the increase of myopia in children arises from the fact that the prevalence of pathological signs increases abruptly with more severe myopia, defined as 6 diopters or more [5–7].

Myopia has become an alarming health problem that is on the rise, with studies estimating that myopia and high myopia will show a significant increase in prevalence worldwide, affecting almost 5 billion people and one billion people by 2050, respectively [8]. The evident contribution of pathological myopia to low vision or blindness [4] and the considerable impact on the quality of life push the search for new treatment strategies to slow down its progressive development and prevent the pathologies associated with high myopia. In fact, significant progress has been made from a pharmacological point of view with the use of topical atropine in clinical studies. The ability of this topical antimuscarinic drug to delay myopia progression has been demonstrated in several clinical trials over the years [9]. It has also been considered the most efficient treatment among multiple therapies. In 2011, the Cochrane Database Review evaluated the published evidence for several treatments that aimed to slow down myopia progression in children and concluded that the topical antimuscarinic medication was the most effective [10]. Then in 2020, a new review was carried out,

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finding again consistent evidence of a significant benefit when using antimuscarinic drugs to slow myopia progression in children [11].

Atropine is a nonspecific antimuscarinic receptor antagonist, which causes mydriasis and cycloplegia. Muscarinic receptors are widely distributed in different ocular tissues in mammals. They are found in the cornea, iris, ciliary body and ciliary muscles, lens epithelium, retina, retinal pigment epithelium, choroid, and sclera [12]. Although the exact mechanism by which this drug acts to slow myopia progression remains unexplained, there are multiple animal studies that show the possible effects of atropine on the ocular structures [12]. It was originally hypothesized that the excessive accommodation of the eye was responsible for myopia and that is why it was understood why atropine was used to temporarily paralyze the smooth ciliary muscle and block accommodation [13]. But later studies showed that the effect of atropine could be through a non-accommodative pathway as atropine was seen to reduce axial elongation in chickens, which are known to have only striated ciliary muscles with nicotinic receptors [14]. In addition, other findings suggested that atropine might have an indirect effect on the sclera or retina, possibly by causing the secretion of dopamine or other neuromodulators [15]. Extensive evidence has supported dopamine as one of the retinal neurotransmitters involved in the signaling cascade that controls eye growth [16].

The excessive axial elongation of the eye can also be attributed to scleral thinning due to increased scleral tissue remodeling [12]. During myopia development, changes in the scleral biochemistry and structure have been shown to impact the biomechanical behavior of the sclera [17], especially due to changes in scleral collagen content since 90% of the scleral dry weight is collagen. There has been demonstrable evidence of active tissue remodeling in myopic eyes, with an increase in matrix degradation [18] and slowed production of the new extracellular matrix [19]. As a result, this increases the susceptibility of the sclera to distending and consequently enlarging under physiological forces inside the eye [20]. Therefore, multiple factors governing the scleral biomechanical properties are being targeted to prevent the progression of myopia. Atropine is believed to act on this fibrous connective tissue [21] and this is supported by the presence of subtypes of muscarinic acetylcholine receptors in human scleral fibroblasts, suggesting that the sclera may be an important site for the action of antagonist muscarinic receptors [22].

In this review, we aim to evaluate the efficacy and safety of atropine for myopia progression in children. We found it convenient to include double-blind randomized placebo-controlled studies. First, the randomized design of these trials will ensure that there will be equal variables in the placebo and atropine groups, thus limiting the selection bias. Secondly, as neither participants nor researchers are aware of group allocations, blinding and the use of a placebo diminish the effect of participants and researchers on procedures and outcome interpretation.

2. Materials and Methods

A literature search using PubMed and Cochrane Library was conducted from January 2017 to December 2023. The following keywords and MeSH terms were used: “Myopia” in combination with “prevention”, “progression”, “children”, “atropine”, “outdoor activities”, “epidemiology”, “genetics”, “pathogenesis”, and “ethnicity”. All the pertinent articles were thoroughly assessed, and their reference lists were also carefully read to identify studies that could not be in the search. The eligibility of the studies was initially assessed on titles and abstracts. Full manuscripts were achieved for all chosen studies and a call for final inclusion was created once a thorough examination of the papers.

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Inclusion Criteria

a. Randomized placebo-controlled trials of atropine eye drop for myopia progression published between 2017 and 2023 were included.
b. All participants in the trials were children aged 4 to 14 years, with a confirmed diagnosis of myopia and a spherical equivalent, ranging from -0.50 to -8.00 diopters in both eyes, measured under cycloplegia.
c. The main efficacy outcome assessed should have been determined as a change in the spherical equivalent of refraction, measured by cycloplegic autorefraction, and a change in ocular axial length. Studies must have shown the safety profile of atropine, either through the size of pupils, accommodation, and the presence or not of adverse effects (eg. photophobia, blurred vision, allergic conjunctivitis).

Exclusion criteria

a. Treatment follow-up less than one year.
b. Clinical trials including combined treatments with topical atropine.
c. Children with other ocular diseases
d. Previous or current treatment with atropine or any other antimuscarinic receptor antagonist.
e. Baseline data of the experimental and control groups not well balanced between groups

3. Results

Fourteen studies were found to fulfill our review study criteria. Tables 1–9, show a summary of the results of randomized controlled trials (RCTs) on atropine for myopia progression.

3.1. Low-Concentration Atropine for Myopia Progression (LAMP) Study

From January 2016 to November 2017 the "Study on low-concentration atropine for the progression of myopia", also called LAMP, was carried out at the Eye Center of the Chinese University of Hong Kong (CUHK) [23]. A total of 438 subjects were recruited into the study; children aged 4 to 12 years with myopic refraction of at least -1.0 D in both eyes, with astigmatism of less than -2.5 D, and documented myopic progression of at least -0.5 D in the past year were enrolled in this single-center, double-blind clinical trial. Study participants were randomly assigned to receive 0.05%, 0.025%, or 0.01% atropine eye drops, or placebo eye drops once nightly for 1 year in both eyes in an allocation ratio of 1: 1:1:1 in 6 strata defined by sex and age groups of 4 to 6 years, 7 to 9 years, and 10 to 12 years, respectively. In this way gender and age could be balanced across the four treatment arms. Side effect parameters included changes in accommodation amplitude, in distant and near best visual acuity (BCVA) and in mesopic and photopic pupil sizes. A questionnaire was administered to all subjects to determine the impact of different treatment groups on the vision-related quality of life. There was no significant difference among groups in demographics, baseline near work and outdoor time, baseline refractive error, accommodation, pupil diameter, BCVA, parental spherical equivalents (SE), and axial elongation (AL). After 1 year, the mean accommodation amplitudes were different among all 4 groups at 24 months, -1.98 in the 0.05% atropine group, - 1.61 in the 0.025%, -0.26 in the 0.01% and -0.32 in the placebo group ($P < 0.001$). The pupil sizes under photopic and mesopic conditions were increased, respectively, by 1.03 +/- 1.02 mm and 0.58 +/- 0.63 mm in the 0.05% atropine group, 0.76 +/- 0.90 mm and 0.43 +/- 0.61 mm in the 0.025% atropine group, 0.49 +/- 0.80 mm and 0.23 +/- 0.46 mm in the 0.01% atropine group, and 0.13 +/- 1.07 mm and 0.02 +/- 0.55 mm in the placebo group ($P < 0.001$). Further results are shown in Table 1.

3.2. Safety and Efficacy of Low-Dose Atropine Eye Drops for the Treatment of Myopia Progression in Chinese Children

This study was a randomized, placebo-controlled, double-masked study. Participants were children with myopia who visited Beijing Tongren Hospital in Beijing, China, from April 2018 to July

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2018 [24]. The range of the study subjects was from 6 to 12 years, with a refractive error of spherical equivalent (SE) range of −1.00 D to −6.00 D in both eyes, and astigmatism of −1.50 D or less in both eyes. All children were recruited and randomized to receive either 0.01% atropine or placebo eyedrops in both eyes once daily for 1 year at an allocation ratio of 1:1. A total of 76 children (69%) and 83 children (75%) allocated into the atropine and placebo groups, respectively, returned for the 1-year primary outcome assessment visit. At baseline, there were no relevant differences identified in demographics, initial SE, initial AL, intraocular pressure (IOP), age at myopia onset, parental myopia, time outdoors, and near across the two groups.

Table 1. Study carried out at the Eye Centre of the Chinese University of Hong Kong, Hong Kong, China.

Author(s)	**Yam et al, 2019 [23]**				**P Value**	
					Group Overall	**(1 vs. 0, 2 vs. 0, 3 vs. 0, 1 vs. 2, 1 vs. 3, 2 vs. 3)**
Treatment	3) 0.05% (n = 109)	2) 0.025% (n = 108)	1) 0.01% (n = 110)	0) Placebo (n = 111)	--------	--------
Baseline Spherical equivalent (D) Mean (SD)	-3.98 (1.69)	-3.71 (1.85)	-3.77 (1.85)	-3.85 (1.95)	--------	--------
Change in Spherical equivalent (D) Mean (SD)	-0.27 (0.61)	0.46 (0.45)	-0.59 (0.61)	-0.81 (0.53)	<0.001	(0.006, <0.001, <0.001, 0.05, <0.001, 0.01)
Baseline Axial length (mm) Mean (SD)	24.85(0.90)	24.86 (0.95)	24.70 (0.99)	24.82 (0.97)	--------	---------
Change in Axial length (mm) Mean (SD)	0.20 (0.25)	0.29 (0.20)	0.36 (0.29)	0.41 (0.22)	<0.001	(0.18, <0.001, <0.001, 0.02, <0.001, 0.006)

3.3. Atropine 0.5% Eye Drops for the Treatment of Children with Low Myopia

This study was conducted at The People's Hospital of Yan'an and Affiliated Hospital of Yan'an Medical University from January 2014 to December 2016 [25]. Study subjects were children, between 5 and 10 years old, with a diagnosis of low myopia defined as a spherical equivalent (SE) ranging from -0.50 to -2.00 diopters (D), as measured by cycloplegic autorefraction. One hundred twenty-six eligible children were randomly divided into the placebo group (0.5%) or a control group at a ratio of 1:1. Children of both groups were administered eye drops once daily at night for a total duration of 1 year. For each participant, one eye alone was assessed: the eye with more severe myopia. There were no significant differences in age, race, ethnicity, sex, SE, and AL at baseline between the two groups.

3.4. Efficacy and Safety of 0.01% Atropine for Prevention of Childhood Myopia in a 2-Year Randomized Placebo-Controlled Study

This multicenter, randomized, double-masked, placebo-controlled, parallel-arm study was conducted at 7 university hospitals in Japan from December 2014 through September 2019 [26]. Study subjects were Japanese school children, aged 6 to 12 years with mild to moderate myopia, defined as cycloplegic objective spherical equivalence from −1.00 to −6.00 D in both eyes, and astigmatism of ≤ 1.50 D who reportedly experienced myopia progression in the past year. The subjects were randomized to receive either 0.01% atropine eye drop, or atropine-matched placebo eye drops at the ratio of 1:1. In all subjects, 1 drop of a randomly allocated drug was instilled in each eye once per night for 24 months. One hundred and fifty-eight children completed the study, 77 subjects were from the placebo group. Safety endpoints were incidence of treatment-emergent adverse events (TEAEs) and study drug-related TEAEs, abnormal findings on the ocular surface, cornea, retina and accessory visual structures, accommodative function, intraocular pressure (IOP) and pupil diameter throughout the 24-month treatment period. Baseline characteristics such as gender and age were similar in both groups. In the atropine group, the photopic pupil diameter shows a significant increase at the 2-week (baseline) and 12-month observation periods, but then it decreases at 24 months, showing only an increase in the early phase. No changes in the mesopic pupil diameters were observed at 24 months in either group. Near-distance visual impairment did not occur in the 0.01% atropine group.

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Table 2. Results of studies performed in Beijing Tongren Hospital, Beijing, China; The People's Hospital of Yan'an, Shaanxi, China; Multicenter University Hospitals, Japan.

Author(s)	Wei et al, 2020 (24)		Difference	P Value
Treatment	0.01% (n = 110)	Placebo (n=110)		
Baseline Spherical equivalent (D) Mean (SD)	-2.52 (1.33)	−2.64 (1.46)		
Change in Spherical equivalent (D) Mean (SD)	−0.49 (0.42)	−0.76 (0.50)	0.26 (0.07)	<.001
Baseline Axial length (mm) Mean (SD)	24.50 (0.76)	24.69 (0.97)		
Change in Axial length (mm) Mean (SD)	0.32 (0.19)	0.41 (0.19)	0.09 (0.03)	<.004
Author(s)	**Wang et al, 2017 (25)**		**Difference**	**P Value**
Treatment	0.5% (n=63)	Placebo (n=63)		
Baseline Spherical equivalent (D) Mean (SD)	-1.3 (0.4)	-1.2 (0.3)		
Change in Spherical equivalent (D) Mean (SE)	-0.8 (-1.1, -0.4)	-2.0 (-2.5, -1.6)	1.2 (0.8, 1.5)	<.01
Baseline Axial length (mm) Mean (SD)	24.1 (1.0)	23.8 (0.9)		
Change in Axial length (mm) Mean (SE)	23.0 (20.7, 25.5)	24.3 (21.2, 26.8)	-1.3 (-1.6, -0.9)	<.01
Author(s)	**Hieda et al, 2021 (26)**		**Difference**	**P Value**
Treatment	0.01% (n=84)	Placebo (n=84)		
Spherical equivalent (D) Baseline (2-week) LS Mean (95% CI)	−2.91 (−3.20, −2.62)	−2.98 (−3.27, −2.69)		
Change in Spherical equivalent (D) LS Mean (95% CI)	−1.26 (−1.35, −1.17)	−1.48 (−1.57, −1.39)	0.22 (0.09, 0.35)	<0.001
Axial length (mm) Baseline (2-week) LS Mean (95% CI)	24.43 (24.27, 24.60)	24.51 (24.34, 24.68)		
Change in Axial length (mm) LS Mean (95% CI)	0.63 (0.59, 0.67)	0.77 (0.73, 0.81)	−0.14 (−0.20, −0.08)	<0.001

Table 3. Results of multicenter trial in India; prospective study in a Hospital, Valencia, Spain; prospective study in a Hospital, Madrid, Spain.

Author(s)	Saxena et al, 2021 [27]		Difference	P Value
Treatment	0.01% (n = 47)	Placebo (n=45)		
Baseline Spherical equivalent (D) Mean (SD)	-3.5 (1.3)	-3.7 (1.3)		
Change in Spherical equivalent (D) Mean (SD)[95% CI]	-0.16 (0.38) [0.05 to 0.26]	-0.35 (0.4) [0.23 to 0.48]	0.19	0.02
Baseline Axial length (mm) Mean (SD)				
Change in Axial length (mm) Mean (SD)[95% CI]	0.22 (0.2) [0.16-0.27]	0.28 (0.28) [0.21-0.37]	0.06	0.19
Author(s)	**Diaz-Llopis & Pinazo-Durán, 2018 [28]**		**Difference**	**P Value**
Treatment	0.01% (n=100)	Placebo (n=100)		
Baseline Spherical equivalent (D) Mean (SD)	-1.1 (0.50)	-1.2 (0.40)		
Change in Spherical equivalent (D)	-0.14 (0.35)	-0.65 (0.54)		<0.01
Author(s)	**Moriche-Carretero et al, 2021 [29]**		**Difference**	**P Value**
Treatment	0.01% (n=171)	Placebo (n=168)		
Baseline Spherical equivalent (D)	-2.13 (0.63)	-2.16 (0.62)		
Change in Spherical equivalent (D)	-0.51 (0.39)	-0.76 (0.37)	-0.24 (0.04)	<0.001
Baseline Axial length (mm)	24.22 (0.66)	24.26 (0.91)		
Change in Axial length (mm)	0.20 (0.20)	0.37 (0.27)	0.17 (0.02)	<0.001

3.5. Atropine for the Treatment of Childhood Myopia in India: Multicentric Randomized Trial

This multicentric, double-blinded, placebo-controlled, randomized clinical trial was conducted at 3 tertiary centers to evaluate the 1-year efficacy of 0.01% atropine in myopic children of Indian ethnicity [27]. A total of 100 children aged 6 to 14 years with -0.5 diopters (D) to -6 D of myopia on cycloplegic refraction and -1.5 D of astigmatism were enrolled. The participants were randomized in 1:1 ratio to the atropine or placebo group.

The mean change in the anterior chamber depth, lens thickness, and vitreous chamber depth, was not significantly different in the 2 groups. Mesopic and photopic pupil size, accommodation amplitude, distance, and near vision remained stable on follow-up and did not change significantly between the groups.

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3.6. Superdiluted Atropine at 0.01% Reduces Progression in Children and Adolescents. A 5-Year Study of Safety and Effectiveness

A total of 200 children, 9-12 years of age, with a bilateral myopia of −0.5 to −2 diopters, and less than 1.5 astigmatism, were included in this 5-year study that took place in Spain [28]. The children were randomized into the 0.01% atropine group, or a control group and the main outcome was the change in the spherical equivalent.

3.7. Myopia Progression and Axial Elongation in Spanish Children: Efficacy of Atropine 0.01% Eye-Drops

This study was conducted in an outpatient clinic in Spain, 339 subjects participated in this randomized study to assess the efficacy of low-dose atropine treatment on myopia progression in Spanish children [29]. Caucasian myopic children between the ages of 5 and 11 years, with a cycloplegic spherical equivalent (SE) between −0.50 and −4.50 D in each eye and astigmatism ≤ 1.50 D in both eyes, were randomly divided into a treatment arm, receiving atropine (0.01%), and an untreated control arm. The treatment group was made up of 171 eyes and the control group of 168 eyes. Two groups were established through randomization. After 2 years of follow-up, data were collected for only one randomly selected eye.

3.8. Efficacy and Safety of 1% Atropine on Retardation of Moderate Myopia Progression in Chinese School Children

A randomized, controlled study evaluating atropine and placebo in myopic Chinese children [30]. The study included 660 participants between the ages of 6 to 12 years. Initial myopic spherical equivalent ranged from -2.0D to -8.00D, and astigmatism ≤ 1.0D. In phase I, the children received topical 1% atropine eye. drops at bedtime once a month (one eye received treatment at day 1, the other eye received treatment at day 16 for 24 months. n phase II, the frequency of the medication was reduced to once two-months, for 12 months. Finally, in phase III, no atropine was applied to the children for 12 months (withdrawal of atropine). Spherical equivalent, axial length, intraocular pressure, and atropine-related side effects were examined at 6, 12, 24, 36 and 48 months for all children. All control cases were matched with the experimental cases in terms of age, sex, and initial SER (±0.50 D).

3.9. Effect of Low-Dose Atropine on Myopia Progression, Pupil Diameter and Accommodative Amplitude: Low-Dose Atropine and Myopia Progression

This double-blind and randomized controlled study carried out between June 2016 and June 2017 recruited a total of 400 children aged 6 to 14 who visited the First Affiliated Hospital of Zhengzhou University [31]. Their spherical equivalent refractive error (SER) ranged from −1.25 to −6.00 D, with an astigmatism of less than 2.0 D. The subjects of the study were randomly divided into three groups, 138 children in the 0.02% atropine group, 142 in the 0.01% atropine group, and 120 children made up the control group. Repeated measurements of spherical equivalent refractive errors (SERs), axial length (AL), pupil diameter and accommodative amplitude were performed at baseline, and 4, 8 and 12 months after treatment.

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3.10. Atropine Ophthalmic Solution to Reduce Myopia Progression in Pediatric Subjects: The Randomized, Double-Blind Multicenter Phase II APPLE Study

The purpose of this double-blind, randomized, controlled study was to assess the dose-response effects of low-dose atropine on myopia progression and safety in pediatric patients [32]. The subjects were children between the ages of 6 and 11 years old with a spherical equivalent (SE) between -1.00 and -6.00 D in both eyes and astigmatism of <-1.5. Participants who met all eligibility criteria were stratified by age group (ages 6-7, 8-9 and 10-11) and randomized in a 1:1:1:1 ratio, randomly dividing the subjects into four groups: 0.0025%, 0.005%, 0.01% and placebo. Out of the 99, 24 made up the atropine 0.0025%, 24 made up the 0.005% group, 25% made up the 0.01% and 26 made up the placebo group. Pupil size did not change in the placebo and the 0.0025% groups, but children treated 0.005% and 0.01% atropine experienced changes in pupil size of 0.26 and 0.31 mm respectively.

3.11. Myopia Progression after Cessation of Low-Dose Atropine Eye Drops Treatment: A Two-Year Randomized, Double Masked Placebo-Controlled, Cross-Over Trial

220 children participated in this randomized, double-masked, placebo controlled study, the purpose was to evaluate myopia progression after ceasing treatment with 0.01% atropine eye drops through a 2 year cross-over study [33] . The subjects were 6- to 12-year-old children with spherical equivalent refraction range of -1.00 to 6.00D in both eyes, astigmatism of less than 1,50D in both eyes and intraocular pressure of less than 21mmHg. Out of the 220 participants 66 did not attend the follow up during phase I and 26 of them were lost to follow up in Phase 2. Leaving 133 subjects. During Phase I the participants were randomly divided into 2 groups, 0.01% and placebo. 65 children were allocated atropine and 68 were allocated placebo. The SE baseline in the atropine placebo group was -2.65 +/- 1.29D and the baseline in the placebo-atropine group was -2.74+/- 1.48D. AL baseline was 24.62 +/- 0.80mm in the placebo atropine group and 24.72+/- in the atropine-placebo group.

Table 4. Studies carried out at Second People's Hospital of Yunnan Province, China; First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.

Author(s)	**Zhu et al, 2020 (30)**		**Difference**	
Treatment	1% (n=262)	Placebo (n=308)		
Baseline Spherical equivalent (D)	-3.82±0.44	-3.74±0.51		
Change in Spherical equivalent (D)	-0.31±0.29	-0.80±0.66		0.008
Baseline Axial length (mm)	24.93±0.21	24.91±0.18		
Change in Axial length (mm)	0.14±0.09	0.39±0.14		<0.001
Withdrawal of 1% atropine				
Change in Spherical equivalent (D)	-0.41±0.23	-0.75±0.64		0.012
Change in Axial length (mm)	0.19±0.13	0.40±0.16		<0.001

Author(s)	**Fu et al, 2020 (31)**			**0.02% vs. 0.01% atropine**	**P Value**	**0.01% atropine vs. control**	**P Value**
Treatment	0.02% (n=117)	0.01% (n=119)	Control group (n=100)				
Baseline Spherical equivalent (D) Mean (SD)	−2.76±1.47	−2.70±1.64	−2.68±1.42				
Change in Spherical equivalent (D) Mean (95% CI)	−0.11 (−0.17 to −0.05)	−0.15 (−0.21 to −0.09)	-0.23 (−0.28 to −0.17)	0.04 (0.01 to 0.07)	0.04	0.09 (0.02 to 0.16)	0.01
Baseline Axial length (mm)	24.60±0.72	24.58±0.74	24.55±0.71				
Change in Axial length (mm) Mean (95% CI)	0.30 (0.25 to 0.35)	0.35 (0.31 to 0.39)	0.49 0.43 to 0.55)	0.04 (0.01 to 0.07)	0.03	0.14 (0.19 to 0.09)	0.004

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3.12. Safety and Efficacy of 0.01% and 0.1% Low-Dose Atropine Eye Drops Regimens for Reduction of Myopia Progression in Danish Children: A Randomized Clinical Trial Examining One Year of Effect and Safety

This study was conducted by the Department of Ophthalmology at Aarhus University Hospital, and it took place in various hospitals of Denmark [34]. Ninety-seven children from ages 6 to 12 were selected and randomly divided into three groups: the first group received a a 0.1% loading dose for 6 months later switching to 0.01% atropine for 6 months (N=33), the second group received 0.01% for twelve months (N=32), and the third group received placebo for 12 months (N=32). Children from 6 to 9 inclusion criteria had spherical power of <-1D and children from age 10 to 12 had spherical power of < -2D. For both age groups, maximum allowed astigmatism at inclusion was less than -1.5D. Mean baseline Axial Length was 24.54 (SD: 0.90) 24.60 (SD: 0.86) and 24.68 (SD: 0.78) for the placebo, 0.01% loading dose and 0.01% group respectively. Mean baseline SER was -3.04D (SD: 1.04), -2.97D (SD: 1.59) and -2.94 (SD: 1.13) for the placebo, 0.1% loading dose and 0.01% groups respectively.

3.13. Low-Dose 0.01% Atropine Eye Drops vs. Placebo for Myopia Control A Randomized Clinical Trial

This multicenter randomized, double masked placebo-controlled study was conducted from June 2018 to September 2022 [35]. One hundred eighty-seven children were selected, each child was randomly assigned to one of the following groups: atropine group who received 0.01% atropine drops and placebo. Each group applied their drops nightly. Treatment lasted 24 months followed by a 6-month observation period.

Children between the ages 5 to 12 years old were selected from different institutions across the United States. The subjects had low to moderate bilateral myopia −1.00D to −6.00 D spherical equivalent refractive error. A total of 187 children were included in the study 125 received atropine 0.01% and 66 received placebo. The SR mean baseline was −2.83 (sd 1.17) and −2.83 (sd 0.97) for the atropine and the placebo group respectively. The AL mean baseline for the atropine group was 24.4 (sd 0.8) and for the placebo group 24.4 (sd 0.8).

Table 5. Multicenter Phase II APPLE Study, Singapore.

Author(s)	**Chia et al, 2023 (32)**				**P Value**		
Treatment	Placebo % (n=26)	0.0025% (n=24)	0.005% (n=24)	0.01% (n=25%)			
Baseline Spherical equivalent (D) Mean (SD)	−3.93 (1.31)	−3.00 (1.1)	−3.8 (1.4)	−3.25 (1.1)	0.020		
Change in Spherical equivalent (D) LS mean	−0.6	−0.49	−0.37	−0.35	Placebo vs. 0.0025%	Placebo vs. 0.005%	Placebo vs. 0.01%
					0.2463	0.0090	0.0056
Baseline Axial length (mm) Mean (SD)	24.79 (0.8)	24.35 (0.8)	24.64 (0.8)	24.77 (0.7)	0.174		
Change in Axial length (mm) LS mean	0.36	0.3	0.27	0.25	Placebo vs. 0.0025%	Placebo vs. 0.005%	Placebo vs. 0.01%

Table 6. Study performed at Beijing Tongren Hospital, Capital Medical University, Beijing, China.

Author(s)	**Wei et al, 2023 (33)**				
Treatment	**Phase 1**				
	Completed 2 years (*n* = 133)	**Not completed 2 years (*n* = 87)**	**P Value**		
Baseline Spherical equivalent (D) Mean ± SD	−2.67 ± 1.41	−2.44±1.36	0.237		
Baseline Axial length (mm) Mean ± SD	24.65 ± 0.89	24.50 ± 0.83	0.227		
	Phase 2-Crossover				
	Atropine-placebo group (n = 65)	**Placebo-atropine group (n = 68)**	**Difference**	**95% CI**	***p*-value**
Change in Spherical equivalent (D) Mean ± SD	−1.26 ± 0.66	−1.25 ±0.70	0.01 ± 0.12	−0.24-0.23	0.954
Change in Axial length (mm) Mean ± SD	0.68 ±0.31	0.72 ±0.32	0.04 ± 0.06	−0.08-0.15	0.537

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Table 7. Study carried out at the following hospitals in Denmark: Aarhus University Hospital, Hospital of Southern Denmark, Copenhagen University Hospital.

Author(s)	Hansen et al, 2023 [34]			P Value	
Treatment	**Placebo (n=29)**	**0.1% loading dose (n=33)**	**0.01% (n=32)**		
Baseline Spherical equivalent (D)	−3.04 D	-2.97	−2.94		
Standard deviation (SD)	(SD: 1.04)	(SD: 1.59)	(SD: 1.13)		
Baseline Axial length (mm)	24.54 mm	24.60 mm	24.68 mm		
Standard deviation (SD)	(SD): 0.90)	(SD: 0.86)	(SD: 0.78)		
Change in Spherical equivalent (D)	−3.64 (−4.19; −3.09)	0.24 (0.05; 0.42)[a]	0.19 (0.00; 0.38) [b]	0.1% loading dose vs. placebo	0.01% vs. placebo
				0.06	0.14
Change in Axial length (mm) LS mean	24.94 (24.62; 25.26)	−0.10 (− 0.17; −0.02)[a]	−0.07 (− 0.15; 0.00)[b]	0.06	0.16

Table 8. Multicenter study performed in the United States.

Author(s)	Repka et al. 2023 (35)						P value
Treatment(s)	**Atropine 0.01%**			**Placebo**			
Baseline Spherical equivalent (D) Mean (SD)	-2.83 ±1.17			−2.83±0.97			>0.05
Change in Spherical equivalent (D) LS mean	12 Months	24 months	30 months	12 Months	24 Months	30 months	
	-0.39 ±0.36	-0.78±0.64	-0.94±0.77	-0.45±0.35	-0.74± 0.60	-0.88± 0.71	>0.05
Baseline Axial length (mm) Mean (SD)	24.4 ±0.8			24.4 ±0.8			>0.05
Change in Axial length (mm) LS mean	12 Months	24 Months	30 Months	12 Months	24 months	30 Months	
	0.22 ±0.17	0.42±0.29	0.51±0.35	0.25 ±0.16	0.41±0.27	0.49 ±0.32	>0.05

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3.14. Low Dose Atropine in Preventing the Progression of Childhood Myopia: A Randomized Controlled Trial

This double blind randomized controlled clinical trial studied the effects of 0.01% atropine eye drops in 100 children [36]. The first group was administered 0.01% atropine eye drop once at bedtime and the second group was administered a placebo.

Table 9. Study carried out at Guru Teg Bahadur Hospital (GTBH), UCMS, University of Delhi, India.

Author (s)	**Sharma et al (36)**		**P Value**
Treatments(s)	Atropine 0.01%	Placebo	
Change in Spherical equivalent (D) LS mean	0.31 ± 0.55	0.80 ± 1.65	0.003
Change in Axial length (mm) LS mean	0.11 ± 0.22	0.23 ± 0.44	

Adverse effects.

In the LAMP study, symptoms of photophobia were predominant across groups at the 2-week visit ($P < 0.001$) but decreased over time in the first year ($P = 0.27$) (23). Photophobia at 2 weeks after starting the treatment, was seen in 34 children (31.2%) of the 0.05% atropine group, in 20 children (18.5%) of the 0.025% atropine group, in 6 children (5.5%) of the 0.01% atropine group and in 14 children (12.6%) of the placebo group (<0.001) (23). Visual acuity and vision-related quality of life were not affected in each group [23].

In the study conducted at Beijing Tongren Hospital [24], five children (4.5%) reported photophobia in the atropine 0.01% group compared with one child (0.9%) in the control group. Four children experienced allergic conjunctivitis; one of them was in the control group. None of the children in either group reported near-blurred vision.

The study conducted at The People's Hospital of Yan'an, an Affiliated Hospital of Yan'an Medical University [25], showed no serious adverse events, such as eye itching and distention, in any of the groups during the study period.

In the study conducted in Japan [26], the incidence of mild allergic conjunctivitis side effects in the 0.01% atropine group was low (2.4%), and quite similar to the placebo group (1.2%).

In the Indian study, none of the patients reported experiencing blurred vision, photophobia, or the need to stop therapy [27].

In the 5-year study conducted in Spain [28], side effects that forced discontinuation of treatment occurred in only 2%. Those side effects included photophobia, difficulty reading, mydriasis, and headache. Mild photophobia, difficulties in very close reading, and excessive mydriasis were also recorded in 5%. On the contrary, in the second study conducted also in Spain [29], participants did not report any side events, and no patient had to quit treatment due to poor tolerance.

In the only study that used 1% of atropine [30], no serious adverse events related to atropine were noted. Adverse events in children who maintained and ceased therapy in the treatment group were photophobia 205/330 (62.12%), blurred near vision 65/330 (19.70%), allergic reaction 3/330 (0.9%) eye irritation 61/330 (18.5%), and infections (conjunctivitis, blepharitis) 18/330 (5.451%).

In the APPLE study, 4 subjects reported eye pruritus, 2 from the 0.0025% and 2 from the 0.01% dose; 4 subjects reported blurry vision, 2 from the 0.0025%, 1 from the 0.005%, 1 from the 0.01% dose, one patient reported allergic conjunctivitis. One child in the atropine 0.0025% group experienced eye pain that resulted in discontinuation and withdrawal from the study (32)

In the cross over trial, four children (5.4%) complained of photophobia in the switch to using atropine group, and allergic reactions were also uncommon, with 3 children occurring with allergic conjunctivitis (33).

In the Danish study, 14 adverse events were reported. All were deemed mild except 2 which were unrelated to the drug. Most frequently AE reported were photophobia, blurred near vision and eye irritation (34).

Finally, the study that took place at the First Affiliated Hospital of Zhengzhou University [31] showed photophobia as the only discomfort symptom, which was resolved by wearing sunglasses or

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sun hats during outdoor activities. Mild near-vision blur was another symptom that appeared in 7 children for 2 to 4 weeks and gradually disappeared over time.

4. Discussion

This review included data from fourteen clinical trials carried out in Denmark, Spain, United States and China within 2017 - 2023. Seven of the clinical trials used the 0.01% dose of atropine. This dose has already shown efficacy and safety for slowing myopia progression in children, with minimal impact on visual function in a previous study, the ATOM2 Study [37]. All these studies proved that this minimal dose of atropine was well tolerated and that no serious adverse effects were observed. Even though the minimal dose of 0.01% has been shown to attenuate myopia progression, there were differences with this dose in the results of the axial elongation within the 1-year follow-up studies and the 2-year follow-up study. At the end of the year, the LAMP study showed no significant improvement in the axial length (0.36 mm for 0.01% atropine versus 0.41 mm for the placebo; P=0.18). In the study that took place in India [27], the difference in axial length change between the 0.01% dose of atropine and the placebo (0.06 mm P = 0.19) did not reach statistical significance at the end of the year, even when there was a greater elongation in the placebo group. In contrast, the 1-year study from Beijing Tongren Hospital [24] successfully demonstrated a reduced mean advancement of axial length in the 0.01% atropine group as compared to the placebo group (0.32 mm for 0.01% atropine versus 0.41 mm for the placebo; mean difference 0.09; SD: 0.03; P=.004). But it was the 2-year follow-up study that showed a more notable difference in the axial length progression between the atropine and the placebo group (0.63 mm for 0.01% atropine versus 0.77 mm for the placebo; mean difference − 0.14; 95% CI: − 0.20, − 0.08; P< 0.001) [26]. The study conducted at the Second People's Hospital in Yunnan show that after one year of treatment, the axial length in the control group and experimental group do not have a significant statistical difference but after 18 months of treatment, there was a statistical difference between both (25.10±0.15for the 1% atropine group and 25.57±0.14 for the placebo group (p=0.018).

At the end of the 12-month period, the cross-over study showed significant improvement in the axial length (0.30+/- 0.20 mm for 0.01% atropine- placebo versus 0.37+/- 0.18 mm for the placebo-atropine group; P=0.033). The APPLE study showed that lower concentrations of atropine although well tolerated are not as effective as the 0.01% atropine eye drops.

The results of these studies are consistent with a previous study, the ATOM 2 study, where the efficacy of 0.01% atropine was mainly based on the second year, with a significantly less axial elongation and also less spherical equivalent progression [37], proving that it can take more time, more than one year, to evidence a greater effect, particularly in the axial length elongation with the minimal dose of atropine. It has been discussed that the better efficacy of the 0.01% atropine dose during the second year of the treatment can be the result of a cumulative effect over time [38]. The therapeutic effect of atropine may have taken longer to reach its peak since it may not have reached its concentration threshold at 0.01% during the first year [38].

The efficacy of a higher dose of atropine has also been proven to slow the progression of myopia with greater magnitude [39]. Two of the 14 studies reviewed showed evidence that the efficacy observed for 0.01% atropine was less than for higher concentrations. In the LAMP study across all the concentrations, 0.05% atropine was the most efficient dose in reducing the progress of myopia compared to the lower dose (-0.27 +/- 0.61 D for 0.05% atropine versus -0.59 +/- 0.61 D for the 0.01% atropine; P<0.001) [23]. Results of the LAMP study phase 2 also showed that 0.05% atropine is the optimal concentration over a 2-year period [38]. The study that took place at the First Affiliated Hospital of Zhengzhou University showed that 0.02% dose of atropine had the best myopia progression effect over the 0.01% (−0.38±0.35D for 0.02% atropine versus −0.47±0.45D for the 0.01% atropine P <0.01) [31]. And across the nine studies described the one that used the higher dose of atropine, 1%, also showed a significant improvement in the spherical equivalent compared to the placebo group at the end of the 4-year study (-4.96±1.22 D for 1% atropine versus -7.28±1.26 D in the control group, P<0.001) (30). Another study with a high concentration of atropine, 0.5%, and good outcomes was the study conducted at The People's Hospital of Yan'an and Affiliated Hospital of

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Yan'an Medical University [25], however, there are some limitations in this study such as not reporting the mean difference of score for axial elongation. Even though higher concentrations of atropine seem promising, the myopic rebound observed in previous studies, where the treatment of atropine has been stopped abruptly, made physicians reconsider the idea of using high doses of atropine because the myopic rebound is usually greater at higher doses [40,41]. The study conducted at the Second People's Hospital of Yunnan Province [30] took into consideration this myopic rebound and provided evidence that this can be prevented by administering atropine with a modified regimen and withdrawing atropine eye drops progressively. During the first phase of the study, 1% atropine was used periodically and alternatively. In the second stage, there is a gradual reduction leading to the elimination of topical atropine eye drops in the third phase. In the end, after withdrawal of 1% atropine for 1 year, the mean progression of myopia in this study was significantly decreased when compared to those from 1%, 0.5%, and 0.1% atropine groups in which atropine eye drops were used daily and withdrew abruptly.

The LAMP study [23], the study performed at the First Affiliated Hospital of Zhengzhou University [31] and the APPLE study reaffirmed what was seen in the ATOM2 study, where changes in spherical equivalent and axial length followed a concentration-dependent response. They proved that the higher the dose, the greater the effectiveness in reducing the spherical equivalent progression and axial elongation over the 1-year period. But, in the study conducted at the First Affiliated Hospital of Zhengzhou University, there was no dose-dependent response regarding the accommodative amplitude and pupil diameter change in the 0.01% and 0.02% atropine-treated groups. In contrast in the LAMP study the accommodation amplitude and pupil size did follow a dose-dependent response, the changes within the 0.01% group were less compared with the higher doses of atropine 0.025% and 0.05%. Nevertheless, these changes were clinically small in all groups and remained stable over time. Therefore, in terms of pupil dilatation, accommodation loss, near vision, and best-corrected distance vision, the children tolerated all 3 concentrations of atropine without any issues.

The strengths of all the studies included in this review were their randomized, double-masked, placebo-controlled design. There were no significant differences in the baseline factors that could influence the outcome between the placebo and the atropine groups in any of the studies. The children in all these studies were assigned to each group in a balanced and equal manner, the 1:1 ratio seen in seven studies,1:1:1 in one study, and 1:1:1:1 ratio in the last study demonstrate the equilibrium of data among the 14 studies. Other factors also contributed to the strengths of these studies; in the case of the LAMP study, the comparison of low dose and high dose in terms of atropine effectiveness and visual side effects remained the trial's more crucial finding. It has been proven that environmental factors have the potential to affect myopia progression [42], two of the fourteen studies took into consideration the time outdoors and the near work of children in both the atropine group and placebo group [23,24], showing no relevant differences between them. Therefore, to demonstrate a probable risk factor, it seems vital to gather comprehensive lifestyle data.

The duration of the treatment in three studies was a strength, in the Japanese study [26] and in the study that took place in Spain [28]; the 0.01% atropine eye-drop administration was found to be effective and tolerable at 2 and 5 years of use. While the duration of the study conducted at the Second People's Hospital of Yunnan Province [30] showed the efficacy of the 1% atropine treatment at 2 years of use. In all the studies, the reported adverse effects were like those seen in previous clinical trials [37,39]. However, the side effects weren't specifically assessed in one study [25]. The most observed side effects in these studies were photophobia and allergic conjunctivitis. Blur near vision was a side effect that although it was annoying at first for the participants, as the days went by it became more tolerable, until it disappeared [30].

Finally, there were individuals in the studies that use 0.01% that under the same dose of atropine treatment progressed more than others in terms of spherical equivalent. The possibility of performing the treatment at higher maximum doses in the subgroup of individuals who did not respond so favorably despite treatment with 0.01% atropine could be considered now that it has been proved that a myopic rebound can be prevented.

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5. Conclusion

In conclusion, the use of atropine eye drops to prevent myopia progression has shown benefits without involving serious adverse effects related to the antimuscarinic drug at higher and lower doses. Also, gradually withdrawing the frequency of atropine eye drops can prevent the myopic rebound seen especially in higher doses of atropine. Higher doses of atropine, like 0.5% and 1% have been shown to have more efficacy in preventing myopia progression than lower doses (0.01%), so starting intervention with these doses of atropine should be considered for preventing myopic children from becoming severe myopia patients later in life.

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