



# Role of Atropine in the control of Myopia Progression- A Review

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## Introduction

With an unprecedented global increase in the prevalence rates, myopia is reaching epidemic proportions and emerging public health challenges (1). Recent estimate projects that by 2050, almost 5 billion (50%) individuals of the world population will suffer from myopia (2). The prevalence of myopia, particularly in East Asia, is very high and ever increasing and similar trends have been shown in other parts of the world but with less extent (3-8). The alarming increase of myopia prevalence has alerted eye health experts and several collaborative work to control the onset and delay the progression of myopia is underway. While several risk factors have been identified concerning myopia development and rate of progression, the etiopathology remains unclear.

The impact that myopia possesses is not just limited to ocular health but has a long-term burden on the health-care system, impact on the global economy, and quality of life (1,9-12). With the majority of myopic individuals to face inevitable myopic maculopathies which are mostly sight threatening; there is an increased global burden of visually impaired (13). The importance of research to control myopia cannot

be overemphasized when one considers the potential complications of high myopia, increasing the cost of health care, and global loss of productivity associated with it (14,15).

Control of myopia progression has become an important clinical goal because of concerns about significantly increased risks of pathologic myopia in those with high myopia (13). Therefore, numerous methods have been applied to achieve myopia control. At present, options for retarding myopia progression include progressive addition of executive bifocal spectacle lenses, (16-20) peripheral defocusing lenses, (21-23) contact lenses, (24) orthokeratology, (25-28) multifocal soft contact lenses, (29) outdoor activities, (30-33) and pharmacological agents (34-39). The growing evidence from high-quality studies has a remarkable impact; myopia management, particularly in children, is becoming a part of routine ophthalmic practice. In this review, we discuss the pharmacological intervention for myopia control in the context of evolving research and development in this area. In this review, we discuss the pharmacological intervention using atropine for myopia control in the context of evolving research and development in this area.

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## Atropine

Atropine is the most effective medication that has been demonstrated to be consistently effective in slowing myopia progression (40). Atropine is a natural alkaloid occurring in plants of the Solanaceae family and is mostly extracted from *Atropa belladonna*.

It is antimuscarinics, blocking the muscarinic receptors from stimulation by the neurotransmitter acetylcholine, as a competitive antagonist. However, anticholinergic drugs do not undergo any chemical reaction with acetylcholine or affect its release or rate of hydrolysis, (41) that is, it does not interfere with the release of acetylcholine in the nerve endings. The action takes place at nerve endings without blocking the transmission of impulses along the nerve fibers (41) Furthermore, it is non-selective, meaning it cannot distinguish between M1, M2, and M3 receptors. It is absorbed mostly in the gut and is distributed widely in the body. It is metabolized in the liver and excreted in urine (60%). Atropine inhibits secretions, reduces tones and relaxes smooth muscles, increases heart rate, depth, and rate of respiratory rate.

In the eye, atropine is used for cycloplegia and mydriasis. In the eye, atropine induces mydriasis by blocking contraction of the circular pupillary sphincter muscle, which is normally stimulated by acetylcholine release, thereby allowing the radial iris dilator muscle to contract and dilate the pupil. Atropine induces cycloplegia by paralyzing the ciliary muscles, whose action inhibits accommodation to allow accurate refraction in children, helps to relieve pain associated with iridocyclitis, and treats ciliary block (malignant) glaucoma. However, both pupil dilation and cycloplegia represent problematic side effects without therapeutic benefit for myopia control.

## Side Effects

The side effects of atropine are not uncommon. They cause inconvenience but are rarely serious and are caused due to facets of its action other than for which it is being used (42). The toxic effects of atropine are termed as “Belladonna poi-

soning” whose severity of the symptoms may vary from mild to moderate to severe, depending on the dose and source. The side effects of atropine are listed in Table I.

## Atropine in Myopia Control

### History

The optical and surgical corrections of myopia only concern improvement in the visual acuity, but these measures have nothing to do with control of myopia progression. Topical atropine in myopia control dates back early in history, starting with early studies by Bedrossian in the 1960s and 1970s (51-53). However, Bedrossian studies were deficient, particularly his studies could not distinguish between reductions in myopia due to long-term cycloplegia and those due to reduced axial elongation, questioning the conclusion that myopia progression could be controlled by topical atropine application. Although the desired outcome was achieved, the pathological complications could not be limited. To establish the efficacy of atropine in myopia control, Kelly et al. (54) also performed a retrospective study among controlled groups and two atropine groups. However, his studies were not randomized and also the treatment regimens varied significantly among groups. The first anti-myopia effect of atropine limited to duration was first suggested by Gimbel (55). However, his study lacked controlled groups, and the treatment regimens were also supplemented by spectacle use. This led Gimbel’s study to be deficient in utility. In 1989, Yen et al.(49) conducted the first randomized placebo-controlled trial of 1% atropine for myopia control.

### Mechanism of Action

Topical atropine has shown to delay myopic progression and axial elongation (56) in a dose-dependent manner, (36,37) but till date, the exact mechanism of action has not been elucidated fully. Initially, it was thought that the drug acted through accommodative mechanisms. Later evidence suggested that the mechanism was through non-accommodative pathways, although atropine causes accommodation block.

**Table I.** Side effects of atropine

Systemic side effects	Ocular side effects
<ul style="list-style-type: none"> <li>• Dry mouth(43,44)</li> <li>• Difficulty in swallowing and talking (43,44)</li> <li>• Dry, flushed, and hot skin (especially over face and neck)(43,44)</li> <li>• Difficulty in micturition, decreased bowel sounds(43,44)</li> <li>• Excitement, ataxia, agitated delirium, acute psychosis (42,45)</li> <li>• Hypotension, weak and rapid pulse, cardiovascular failure with respiratory depression (45-47)</li> <li>• Convulsions and coma occur only in severe poisoning (42)</li> </ul>	<ul style="list-style-type: none"> <li>• Dilated pupil (48-50)</li> <li>• Dreadful visual hallucination (42,45)</li> <li>• Photophobia (48-50)</li> <li>• Accommodation paralysis.(48-50)</li> <li>• Local allergic response (40-50)</li> </ul>

(57) Atropine has been shown to increase choroidal thickness in children (58). The plausible mechanism is thought to be through modulation of dopamine release, (59) which has been correlated with a reduction in the rate of axial eye growth (60) Atropine exerts its action on retinal amacrine cells and dopamine; when atropine binds to mAChR on the cells, they could release dopamine, which is considered to play a role in slowing myopia (61-63). It has also been postulated that the up- and down-regulation of retinal and scleral muscarinic receptors have influence on the scleral matrix (64,65). Inhibition of myopia induction has been shown in both mammalian and avian eyes (66,67). Different to the mammalian eye, the avian eye contains striated ciliary muscle innervated by nicotinic receptors rather than muscarinic receptors (57). Therefore, atropine might have function at a relatively lower dose, through M1/M4 receptors in the retina, not through the accommodation system. On the other hand, a non-muscarinic and a direct influence of atropine on the scleral fibroblasts could also contribute to the effect (68). The scleral muscarinic receptors might modulate the function of scleral fibroblasts and interfere with the scleral remodeling that accompanies progressive myopia (64). Atropine could be directly acting on sclera (69) and might play a possible mechanism in inhibiting glycosaminoglycan production and, thus, eye growth (70). The actual mechanism may include a combination of effects, but determination of the primary mechanism of action may allow more targeted therapy and/or alternative therapies for children who continue to demonstrate rapid myopic progression on treatment (71).

### Dose

Topical atropine of varying concentrations has been administered in children with myopia in an attempt to prevent myopia progression. There have been a number of studies that have evaluated the relationship of concentration of atropine to the reduction of myopic progression. Studies have been performed administering high-dose atropine of concentration 1% or lower than that. The efficacy of 1% atropine was studied by Bedrossian et al. (1966), (51,52) Gimbel (1973), (55) Gruber (1985), (72) Yen et al. (1989), (49) Romano et al. (2000), (73) Chiang et al. (2001), (74) Syniuta et al. (2001), (75) Chua et al. (2006), (36) and Fan et al. (2007). (35) Nightly instillation of one drop of 1% atropine effectively halts the progressive increase in myopic refractive error and eye elongation relative to untreated eyes (36,49,76). However, adverse side effects, including mydriasis, cycloplegia, and accelerated progression on cessation (rebound), have limited the clinical use of 1% atropine. Consequently, interest has shifted to the use of much lower concentrations, which also appear to reduce myopia progression, although in a dose-dependent manner (38,39). Management of myopia

using low-concentration atropine eye drops, are well-tolerated, and with less rebound following cessation of treatment, unlike those with high-dose atropine. Gong et al. meta-analyzed that the efficacy of atropine is concentration independent from 0.01% to 1% atropine, whereas the adverse effects are concentration dependent (77). The American Academy of Ophthalmology recommends the use of 0.01% of atropine for myopia control (78). At present, 0.01% atropine is the most popular measure for myopia control.

### Clinical Myopia Control Studies

Starting with early studies by Bedrossian in the 1960s and 1970s, there have been numerous studies of atropine's topical effect on myopia progression which includes a number of retrospective studies, prospective studies, and randomized controlled trials. A long list of studies is shown in Table 2.

Earlier studies performed by Bedrossian (51) who concluded that topical atropine could halt myopia progression, but lacked enough evidences. Gimbel's (55) study also pointed toward the similar conclusion, but its utility was limited due to variations among treatment regiments. In 1989, Yen et al. (49) conducted the first randomized placebo-controlled trial of 1% atropine for myopia control, randomizing 96 children aged 6–14 years to 1% atropine, 1% cyclopentolate, and placebo group for 1 year. This study concluded that 1% atropine conferred the best efficacy in myopia control among the three studied groups, with myopia progression of 1% atropine  $-0.22$  (0.54) D/year, 1% cyclopentolate  $-0.58$  (0.49) D/year, and placebo  $0.91$  (0.58) D/year (49). The effect of atropine in axial length could not be ascertained due to unavailability of axial length data. Furthermore, a number of study dropouts were noted attributing to the side effects of atropine (mostly photophobia) among high-concentration groups. Due to the demerits of high dose, interest shifted toward a much lower concentration of atropine. In 1999, a randomized controlled trial was conducted by Shih et al. (50) on 200 children, on 0.5%, 0.25%, 0.1% atropine, and 0.5% tropicamide (as control group). His study proved that all atropine treatment groups were much effective in controlling myopia progression, following a 2-year treatment period with mean myopia progression of  $-0.04$  (0.63) D/year,  $-0.45$  (0.55) D/year, and  $-0.47$  (0.91) D/year in the 0.5%, 0.25%, and 0.1% atropine groups, respectively, and  $-1.06$  (0.61) D/year in 0.5% tropicamide control group. These dosages of atropine were much tolerated, in comparison to previous high dosages, side effects complained with 0.5% atropine only by 22% of the subjects. However, the study was limited by the lack of axial length data and placebo control group. To address the shortcoming, Shih et al. conducted a randomized controlled trial among 227 study population (80). This study compared changes in both the refractive errors

Table 2. Studies on atropine for myopia control

Authors (year)	Study design	No. of subjects	Treatment period	Treatment	Control group	Initial refractive error (in Diopters)	Change in refractive error in treatment versus control group (Diopter/year)	Change in axial length (mm/year)
Bedrossian et al. (1966) (51)	Retrospective	35	1 year	1%Atr or Scop drops	Untreated fellow eye	-0.5—-5	+0.18; -0.91	NA
Gimbel (1973) (55)	Retrospective	594	3 years	1%Atr	Untreated myopes	<0.25	+0.59; -0.61	NA
Brodstein et al. (1984) (79)	Retrospective	399	1-9 years	Atr 1% qhs and BF 2.25	Untreated myopes	<-0.5	-0.01 (0.03); -0.03 (0.02)	NA
Yen et al. (1989) (49)	RCT	96	1 year	1%Atr drops; q.o.d. or 1% Cp drops	Placebo	-0.5—-4.0	-0.22 (0.54); -0.58 (0.49); -0.91 (0.58)	NA
Shih et al. (1999) (50)	RCT	200	2 years	0.5%Atr; or 0.25%Atr; or 0.1%Atr all drops	Placebo	-0.5—-7 D	-0.04 (0.63); -0.45 (0.55)*; -0.47 (0.91); -1.06 (0.61)	NA
Romano et al. (2000) (73)	Retrospective	35	2 years	1%Atr drops + BF always compliant	Partially compliant or never compliant to treatment	NA	+0.07; -0.18; -0.17	NA
Syniuta et al. (2001) (75)	RCT	30	8 years	1%Atr (drops) + BF	Untreated myopes	<-6.0	0.05 (0.67); 0.84 (0.26)	NA
Shih et al. (2001) (80)	RCT	227	1.5 years	0.5%Atr drops + MF	Placebo drops + MF or + SV	-3.3 (average)	-0.42 (0.07); -1.19 (0.07); -1.40 (0.09) (progression after 18 months)	0.22 (0.03); 0.49 (0.03)
Lee et al. (2006) (81)	Non Randomized	57	1 year	0.05%Atr drops	Untreated myopes	-0.5—-5.5	-0.28 (0.26); -0.75 (0.35)	NA
Chua et al. (2006) (36)	RCT	400	2 years	1%Atr drops	Placebo	-1.0—-6.0	-0.28 (0.92); -1.20 (0.69) (progression after 2 years)	0.02 (0.35); 0.38 (0.38) (>2 years)
Liang et al. (2008) (82)	RCT	71	8.82 months	0.5%Atr (23) or 0.25%Atr + acupoints; all drops	0.25%Atr drops	<-0.5	-0.15 (0.15); -0.21 (0.23); -0.38 (0.32)	0.12 (0.12); 0.14 (0.11); 0.16 (0.09)
Fang et al. (2010) (35)	Non randomized	50	> 1 year	0.025%Atr	Untreated premyopes	+1—-1	0.14 (0.24); -0.58 (0.34)	NA
Chia et al. (2012) (37)	RCT	400	2 years	0.5%, 0.1%, 0.01%Atr	-----	<-2.0	-0.30(0.60); -0.38(0.60); -0.49(0.63)	0.27(0.250;0.28(0.27); 0.41(0.63)
Yi et al. (2015) (76)	RCT	132	1 year	1%Atr	Placebo	-0.5—-2.0	0.32 (0.22); -0.85(0.31)	-0.03 (0.07); 0.32(0.15)
Wang et al. (2017) (83)	RCT	126	1 year	0.5%Atr	Placebo	-0.5—-2.0	-0.8; -0.2	23mm at 1 year; 24.3 mm at 1 year
Yam et al. (2018) (39)	RCT	438	1 year	0.05%, 0.025%, 0.01%Atr	Placebo	<-1.0	-0.27(0.61); -0.46(0.45); -0.59(0.61); -0.81(0.53)	0.20 (0.250; 0.29 (0.20); 0.36 (0.29); 0.41 (0.22)
Tan et al. (84) (2019) AOK Study	RCT	68	1 month	0.01%Atr +OrthoK	OrthoK	-1.0—-4.0	NA	-0.05 (0.05); -0.02 (0.03)
Wei et al. (85) (2020)	RCT	220	1 year	0.01%Atr	Placebo	-2.58 (1.39)	-0.49 (0.42); -0.76 (0.50)	0.32 (0.19); 0.41 (0.19)
Pérez-Flores I et al. (86) (2021)	RCT	105	1 year	0.01%Atr	-----	-2.00 D to -6.00 D	-0.44±0.41	0.27±0.20

Atr: Atropine; BF: Bifocal; Cp: Cyclopentolate; MF: Multifocal; NA: Not available; OrthoK: Orthokeratology; qhs: Bed time; qod: Every other day; RCT: Randomized controlled trial; Scop: Scopolamine; SV: Single vision.

and axial lengths of a group wearing multifocal spectacles treated daily with 0.5% atropine with those of two placebo control groups. Over an 18-month treatment period, the atropine-treated group recorded a mean increase in myopia of 0.42 D, which was significantly lower than the changes of 1.2 and 1.4 D for the multifocal and single-vision spectacle-wearing control groups, respectively. A correspondingly smaller increase in axial length was recorded for the atropine-treated group (0.22 vs. 0.49 and 0.59 mm), implying that the intergroup differences in myopia progression were at least partly a consequence of inhibited eye elongation.

The strongest evidence for 1% atropine on myopia control was rendered by "Atropine for the Treatment of Childhood Myopia" (ATOM 1) study, conducted by Chua et al. in 2006 (36). It is a randomized, double-blind, placebo-controlled trial including 400 children, randomizing them into two groups: The treatment group receiving 1% atropine once per night in one eye and no treatment in the fellow eye and the control group receiving placebo in one eye and no treatment to the fellow eye and no treatment was administered to the fellow eye. The mean reduction of myopia progression following 2-year treatment was approximately 77% in the treatment group compared with the placebo group with myopia progression significantly lower in the 1% atropine group ( $-0.28$  (0.92) D/2 years), compared with the control group ( $-1.20$  (0.69) D/2 years). The mean increase in axial remained unchanged ( $-0.02$  (0.35) mm/2 years) in the 1% atropine group compared with significant elongation of axial length (0.38 (0.38) mm/2 years) in placebo eyes. Although only 18% of the subjects complained of side effects, the safety concern of high concentration atropine remains a question. Moreover, a rebound phenomenon (36) was observed following the cessation of atropine eye drops administration. During the 1-year washout period, the subjects of ATOM1 study had mean myopia progression of  $-1.14$  (0.8) D/year in the atropine 1% group and  $-0.38$  (0.39) D/year in the control group, suggestive of myopia rebound in the atropine treatment group. By far, high-concentration atropine remained the most efficacious treatment for myopia progression, but the side effects profile and the rebound following drops cessation limited its widespread use.

In 2012, the ATOM2 study evaluated lower concentration for myopia progression to determine the lower optimal concentration for anti-myopia effect of atropine. Among 400 children, 0.5%, 0.1%, and 0.01% concentration of atropine were randomly allocated in the ratio of 2:2:1. Initially, no placebo was allocated as 0.01% of atropine was considered to be used as a control group. The mean myopia progression over 2-year treatment was  $-0.30$  (0.60) D in 0.5% group,  $-0.38$  (0.60) D in 0.1% group, and  $-0.49$  (0.63) D in 0.01% group while the axial elongation was 0.27 (0.25) mm, 0.28

(0.28) mm, and 0.41 (0.32) mm in the 0.5%, 0.1%, and 0.01% atropine groups, respectively (37). An interesting finding of ATOM2 study was that the children in the atropine 0.01% who had myopia progressed by  $-0.43$  D in the 1<sup>st</sup> year had a significantly slowed down progression during the 2<sup>nd</sup> year which was found to be only 0.06 D. However, the axial elongation was 0.24 mm during the 1<sup>st</sup> year and 0.17 mm during the 2<sup>nd</sup> year, with a total of 0.41 mm increased over the 2 years (37). Thus, ATOM2 study concluded the efficacy of 0.01% atropine based on decrease in mean refractive error, rather than axial elongation. Furthermore, the side effects were much less in comparison to previous high-dose studies. Interestingly, a similar rebound was seen in 0.5% and 0.1% atropine group, but much less with 0.01% with myopic progression in 1-year washout to be  $-0.87$  (0.52) D,  $-0.68$  (0.45) D, and  $-0.28$  (0.33) D in the atropine 0.5%, 0.1%, and 0.01% groups, respectively. With fewer side effects and rebound following atropine cessation, ATOM2 study concluded that 0.01% atropine was better in treatment-to-side effect balance.

Although, the ATOM2 study established the efficacy of low-dose atropine in control of myopia progression, due to lack of placebo-controlled group, the study was limited. Therefore, low-concentration atropine of myopia progression (LAMP)(39) study was conducted, which is a double-blinded, randomized, placebo-controlled trial to evaluate the efficacy and safety of low concentration atropine 0.05%, 0.025%, and 0.01% daily. After 1 year, the mean SE change was  $-0.27$  (0.61) D,  $-0.46$  (0.45) D,  $-0.59$  (0.61) D, and  $-0.81$  (0.53) D, respectively (40). Meanwhile, the mean AL change after 1 year was 0.20 (0.25) mm, 0.29 (0.20) mm, 0.36 (0.29) mm, and 0.41 (0.22) mm, respectively. LAMP study noted a clear concentration-dependent response. Among them, 0.05% atropine was most effective for controlling myopia progression and axial elongation during the study period. Furthermore, 0.01% atropine reduced AL elongation at 12%, compared with the placebo group, along with 27% reduction in mean refractive error progression. The side effects were minimal and the drug was well tolerated. The LAMP study provides the strongest evidence in favor of low concentration of atropine to halt myopia progression. Furthermore, LAMP study has delineated a concentration-dependent response in both the efficacy and side effect profile in the low atropine concentration range from 0.05% to 0.01%, which previously had been a controversial issue.

After ATOM and LAMP, many other studies have established the safety and efficacy of varying doses of atropine in myopia control. In a meta-analysis, Huang et al. (40) reported that the treatment effect of atropine (high, moderate, and low dose) in comparison with placebo or single vision lens was strong and, in particular, high-dose atropine (1%



and 0.5%) was significantly superior ( $p < 0.05$ ) to other interventions, except for moderate-dose atropine (0.1%) and low-dose atropine (0.01%). Similarly, Wang et al. (83) compared 0.5% atropine eye drop with a placebo in this study the administration of 0.5% ATE led to less progression in LM, as measured by spherical equivalent, and less increase in AL ( $p < 0.01$ ). In addition, no serious adverse events occurred in both the groups. Beside monotherapies, Tan et al. (84) has also compared efficacy of atropine as a monotherapy and efficiency of combined atropine therapy with orthokeratology. At the end of the study period, dual therapy resulted in a significantly slower change in axial length.

In a randomized clinical trial, Shifei Wei et al., (85) a total of 220 children aged 6–12 years with myopia of  $-1.00$  D– $-6.00$  D in both eyes were enrolled. It was a randomized, placebo-controlled, double-masked study, in which subjects randomly assigned in a 1:1 ratio to atropine, 0.01%, or placebo groups to be administered once nightly to both eyes for 1 year. This study reported the mean myopia progression of  $-0.49$  (0.42) D and  $-0.76$  (0.50) D in the atropine, 0.01%, and placebo groups (mean difference, 0.26 D; 95% CI, 0.12–0.41 D;  $p < 0.001$ ), with a relative reduction of 34.2% in myopia progression. The mean (SD) axial elongation in the atropine, 0.01%, group was 0.32 (0.19) mm compared with 0.41 (0.19) mm in the placebo group (mean difference, 0.09 mm; 95% CI, 0.03–0.15 mm;  $p = 0.004$ ), with relative reduction of 22.0% in axial elongation. Fifty-one percent and 13.2% of children progressed by at least 0.50 D and 1.00 D in the atropine, 0.01%, group, compared with 69.9% and 34.9% in the placebo group. This study concluded that 0.01%, eye drops can slow myopia progression and axial elongation in children.

Recently, a Spanish study “Group of Atropine Treatment for Myopia Control (GTAM)” (86) evaluated the efficacy and safety of atropine 0.01% eye drops for myopia control in a multicentric pediatric Spanish cohort including children aged between 6 and 14 years, with myopia between  $-2.00$  D and  $-6.00$  D, astigmatism  $< 1.50$  D, and documented previous annual progression  $> -0.5$  D. The subjects were prescribed with once nightly atropine 0.01% eye drops in each eye for a period of 12 months. This study reported the mean spherical equivalent and axial length changes to be  $-0.44 \pm 0.41$  D and  $0.27 \pm 0.20$  mm, respectively. Mean SE progression was lower than the year before treatment ( $-0.44 \pm 0.41$  D vs.  $-1.01 \pm 0.38$  D;  $p < 0.0001$ ). An inverse correlation between SE progression and AL progression ( $r: -0.42$ ;  $p < 0.0001$ ) was found. The adverse effects were mild and infrequent, and decreased over the time. With these findings, Barrio-Barrio et al. concluded that atropine 0.01% is effective and safe for myopia progression control in Spanish cohorts and speculated that this could be projected to the world population.

## Safety of Atropine

Several anti-myopia drugs have been known and extensively studied in animal models, human trials remain murky owing to their potential side effects and adverse events on the dose, frequency, and tenure of study. The US-FDA has permitted the clinical trials of only three anti-myopia drugs – atropine, pirenzepine, and 7-MX but has not been approved for prescription yet. In many Asian countries, where the global burden of myopia exists, these drugs are used off-labeled. Off-label use of topical atropine is currently the only treatment used for slowing myopia progression. Despite known inevitable side effects like photophobia, accommodation dysfunction, no alternative to atropine has been approved so far, therefore it is necessary to establish an antimyopia drug with minimal to no side effects but maximum efficacy.

Several routes of absorption are possible for an ophthalmic drug including those acting as anti-myopia agents like atropine. Even when correctly applied, the excess amounts can sometimes cause an unwanted systemic bioavailability of the drops when not completely absorbed into the eye, leading to systemic side effects such as dry mouth, psychological disturbances, and flushing as observed in topical atropine usage. Furthermore, the concentration of active ingredients in such topical ophthalmic preparations is usually very high, so that despite the correct application of the recommended dose, considerable amounts may be absorbed in an unwanted manner through various routes causing adverse ocular and systemic reactions. Moreover, these anti-myopia drugs are not weight adjusted, making children vulnerable to adverse reactions. Lack of pediatric dosing remains a major hindrance. Similarly, the drug delivery for anti-myopia drugs has been limited only to the topical application either on solution or gel form, except for oral methylxanthine. It is known that high myopia primarily affects the posterior vitreous chamber specifically, its outer scleral coat, but no drug delivery system that primarily targets these areas has been established yet.

Moreover, despite extensively studied, what concentration of drug to be prescribed is still questionable. Effectiveness of topical 1% atropine is well established but at the cost of side effects. Hence, interest shifted toward a less concentration with minimal to no side effects. Topical ophthalmic atropine must not be used in patients with a known history of belladonna poisoning and high blood pressure. Narrow-angle glaucoma is an absolute contraindication as there is an increased likelihood of producing complete obstruction of the outflow of aqueous humor, resulting in an acute increase in intraocular pressure in response to relaxation of the ciliary muscle. It must be used with caution in a breast-feeding woman.

## Research Gap

In spite of the plethora of studies in myopia control, the exact etiology of myopia and mechanism of myopia progression is not completely established and understood. The questions on how the pharmaceutical agents retard myopia progression; its pharmacodynamics and pharmacokinetics remain unanswered. At present, no treatment is considered to be 100% effective although dozens of myopia control trials are ongoing.

Moreover, facts established so far are mostly either from non-randomized studies or those from retrospective studies conducted in less sample size. There have been fewer prospective controlled human clinical trials except for those in East-Asian countries. Hence, of the anti-myopic effect of atropine in different regions and ethnicities is yet to be established. Moreover, the treatment regimen so far has been similar for all subjects and no individualized treatment approaches have been explored. There are no guidelines in the selection criteria for the amount of myopia, optimal age to commence myopia control option, or ideal myopia control treatment option for an individual child. Furthermore, even for certain established anti-myopia drugs like atropine, the optimal concentration for longer duration usage with safety in controlling myopia progression and axial length elongation is yet to be answered.

Several pharmaceutical agents are studied for myopia control, but no known drug controls myopia progression efficiently and without side effects; each drug has its own merits and limitations. At present, combination of atropine treatment options with other means of myopia control is being explored. Future studies should also make efforts to individualize myopia control treatment options. The “one size fits all” approach could affect outcome measures for different demographic characteristics. Further research to identify those individuals who are most likely to benefit from different pharmaceutical drugs are necessary. Similarly, the aftermath of drug cessation, for example, rebound phenomenon following atropine cessation should be further investigated. Researches that primarily focus on patient’s safety should be considered. Encouraging large multicenter collaborative researches on the etiology of myopia and its management should continue with ultimate goals to prevent the development of myopia.

## Conclusion

The growing global burden of myopia and its inevitable impacts urges the need to establish an effective intervention to halt myopia progression. Despite global efforts, the most effective treatment strategy is yet to be identified (87). It is necessary to note that myopia can render an otherwise fully healthy person visually challenged. Atropine has demonstrat-

ed its beneficial anti-myopia effect, but there is a need to establish a full-fledged drug amplifying the pros and lessening the cons. In the future, axial length growth graphics by ethnicity, age, and gender, genetic risk scores, objective assessment of time spent outdoors and in near-vision tasks, and responsiveness to different atropine concentration, might help us in the decision of when start the treatment and how evaluate its efficacy (85). With myopia control becoming a mainstream clinical practice for us eye care practitioners, our goal must not just be limited to developing a slowing down measure, but to discover a method to prevent the development of myopia.

## Disclosures

**Peer-review:** Externally peer-reviewed.

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## References

1. Dolgin E. The myopia boom. *Nature* 2015;519:276–8.
2. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, San- karidurg P, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology* 2016;123:1036–42.
3. Morgan IG, Ohno-Matsui K, Saw SM. Myopia. *Lancet* 2012;379:1739–48.
4. Fan DS, Lam DS, Lam RF, Lau JT, Chong KS, Cheung EY, et al. Prevalence, incidence, and progression of myopia of school children in Hong Kong. *Invest Ophthalmol Vis Sci* 2004;45:1071–5.
5. Fan DS, Lai C, Lau HH, Cheung EY, Lam DS. Change in vision disorders among Hong Kong preschoolers in 10 years. *Clin Exp Ophthalmol* 2011;39:398–403.
6. Lam CS, Lam CH, Cheng SC, Chan LY. Prevalence of myopia among Hong Kong Chinese schoolchildren: Changes over two decades. *Ophthalmic Physiol Opt* 2012;32:17–24.
7. Morgan IG. What public policies should be developed to deal with the epidemic of myopia?. *Optom Vis Sci* 2016;93:1058–60.
8. Wu PC, Chuang MN, Choi J, Chen H, Wu G, Ohno-Matsui K, et al. Update in myopia and treatment strategy of atropine use in myopia control. *Eye (Lond)* 2019;33:3–13.
9. Vitale S, Cotch MF, Sperduto RD. Prevalence of visual impairment in the United States. *JAMA* 2006;295:2158–63.
10. Zheng YF, Pan CW, Chay J, Wong TY, Finkelstein E, Saw SM. The economic cost of myopia in adults aged over 40 years in Singapore. *Invest Ophthalmol Vis Sci* 2013;54:7532–7.
11. Liang YB, Wong TY, Sun LP, Tao QS, Wang JJ, Yang XH, et al. Refractive errors in a rural Chinese adult population the Handan eye study. *Ophthalmology* 2009;116:2119–27.

12. Morgan IG, Ohno Matsui K, Saw SM. Myopia. *Lancet* 2012;379:1739–48.
13. Gwiazda J, Hyman L, Hussein M, Everett D, Norton TT, Kurtz D, et al. A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. *Invest Ophthalmol Vis Sci* 2003;44:1492–500.
14. Cooper J, Schulman E, Jamal N. Current status on the development and treatment of myopia. *Optometry* 2012;83:179–99.
15. Holden B, Sankaridurg P, Smith E, Aller T, Jong M, He M. Myopia, an underrated global challenge to vision: Where the current data takes us on myopia control. *Eye (Lond)* 2014;28:142–6.
16. Hasebe S, Ohtsuki H, Nonaka T, Nakatsuka C, Miyata M, Hamasaki I, et al. Effect of progressive addition lenses on myopia progression in Japanese children: A prospective, randomized, double-masked, crossover trial. *Invest Ophthalmol Vis Sci* 2008;49:2781–9.
17. Leung JT, Brown B. Progression of myopia in Hong Kong Chinese schoolchildren is slowed by wearing progressive lenses. *Optom Vis Sci* 1999;76:346–54.
18. Correction of Myopia Evaluation Trial 2 Study Group for the Pediatric Eye Disease Investigator Group. Progressive-addition lenses versus single-vision lenses for slowing progression of myopia in children with high accommodative lag and near esophoria. *Invest Ophthalmol Vis Sci* 2011;52:2749–57.
19. Fulk GW, Cyert LA, Parker DE. A randomized trial of the effect of single vision vs. bifocal lenses on myopia progression in children with esophoria. *Optom Vis Sci* 2000;77:395–401.
20. Berntsen DA, Sinnott LT, Mutti DO, Zadnik K. A randomized trial using progressive addition lenses to evaluate theories of myopia progression in children with a high lag of accommodation. *Invest Ophthalmol Vis Sci* 2012;53:640–9.
21. Walline JJ, Lindsley K, Vedula SS, Cotter SA, Mutti DO, Twelker JD. Interventions to slow progression of myopia in children. *Cochrane Database Syst Rev* 2011;12:CD004916.
22. Kanda H, Oshika T, Hiraoka T, Hasebe S, Ohno-Matsui K, Ishiko S, et al. Effect of spectacle lenses designed to reduce relative peripheral hyperopia on myopia progression in Japanese children: A 2-year multicenter randomized controlled trial. *Jpn J Ophthalmol* 2018;62:537–43.
23. Lam CS, Tang WC, Tse DY, Lee RP, Chun RK, Hasegawa K, et al. Defocus incorporated multiple segments (DIMS) spectacle lenses slow myopia progression: A 2-year randomised clinical trial. *Br J Ophthalmol* 2019;104:363–8.
24. Grosvenor T, Perrigin J, Perrigin D, Quintero S. Use of silicone-acrylate contact lenses for the control of myopia: Results after two years of lens wear. *Optom Vis Sci* 1989;66:41–7.
25. Cho P, Cheung SW. Retardation of myopia in orthokeratology (ROMIO) study: A 2-year randomized clinical trial. *Invest Ophthalmol Vis Sci* 2012;53:7077–85.
26. Hiraoka T, Kakita T, Okamoto F, Takahashi H, Oshika T. Long-term effect of overnight orthokeratology on axial length elongation in childhood myopia: A 5-year follow-up study. *Invest Ophthalmol Vis Sci* 2012;53:3913–9.
27. Sun Y, Xu F, Zhang T, Liu M, Wang D, Chen Y, et al. Orthokeratology to control myopia progression: A meta-analysis. *PLoS One* 2015;10:e0124535.
28. Chan DK, Fung YK, Xing S, Hagger MS. Myopia prevention, near work, and visual acuity of college students: Integrating the theory of planned behavior and self-determination theory. *J Behav Med* 2014;37:369–80.
29. Kang P, McAlinden C, Wildsoet CF. Effects of multifocal soft contact lenses used to slow myopia progression on quality of vision in young adults. *Acta Ophthalmol* 2017;95:e43–53.
30. Xiong S, Sankaridurg P, Naduvilath T, Zang J, Zou H, Zhu J, et al. Time spent in outdoor activities in relation to myopia prevention and control: A meta-analysis and systematic review. *Acta Ophthalmol* 2017;95:551–66.
31. He M, Xiang F, Zeng Y, Mai J, Chen Q, Zhang J, et al. Effect of time spent outdoors at school on the development of myopia among children in China: A randomized clinical trial. *JAMA* 2015;314:1142–8.
32. Rose KA, Morgan IG, Ip J, Kifley A, Huynh S, Smith W, et al. Outdoor activity reduces the prevalence of myopia in children. *Ophthalmology* 2008;115:1279–85.
33. Wu PC, Chen CT, Lin KK, Sun CC, Kuo CN, Huang HM, et al. Myopia prevention and outdoor light intensity in a school-based cluster randomized trial. *Ophthalmology* 2018;125:1239–50.
34. Gwiazda J. Treatment options for myopia. *Optom Vis Sci* 2009;86:624–8.
35. Fan DS, Lam DS, Chan CK, Fan AH, Cheung EY, Rao SK. Topical atropine in retarding myopic progression and axial length growth in children with moderate to severe myopia: A pilot study. *Jpn J Ophthalmol* 2007;51:27–33.
36. Chua WH, Balakrishnan V, Chan YH, Tong L, Ling Y, Quah BL, et al. Atropine for the treatment of childhood myopia. *Ophthalmology* 2006;113:2285–91.
37. Chia A, Chua WH, Cheung YB, Wong WL, Lingham A, Fong A, et al. Atropine for the treatment of childhood myopia: Safety and efficacy of 0.5%, 0.1%, and 0.01% doses (atropine for the treatment of myopia 2). *Ophthalmology* 2012;119:347–54.
38. Chia A, Lu QS, Tan D. Five-year clinical trial on atropine for the treatment of myopia 2: Myopia control with atropine 0.01% eyedrops. *Ophthalmology* 2016;123:391–9.
39. Yam JC, Jiang Y, Tang SM, Law AK, Chan JJ, Wong E, et al. Low-concentration atropine for myopia progression (LAMP) study: A randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control. *Ophthalmology* 2019;126:113–24.
40. Huang J, Wen D, Wang Q, McAlinden C, Flitcroft I, Chen H, et al. Efficacy comparison of 16 interventions for myopia control in children: A network meta-analysis. *Ophthalmology* 2016;123:697–708.



41. AMBACHE N. The use and limitations of atropine for pharmacological studies on autonomic effectors. *Pharmacol Rev* 1955;7:467–94.
42. Berdai MA, Labib S, Chetouani K, Harandou M. Atropa belladonna intoxication: A case report. *Pan Afr Med J* 2012;11:72.
43. Caksen H, Odabaş D, Akbayram S, Cesur Y, Arslan S, Uner A, et al. Deadly nightshade (*Atropa belladonna*) intoxication: An analysis of 49 children. *Hum Exp Toxicol* 2003;22:665–8.
44. Fidan T, Kirpinar I. Psychiatric aspects of a case with deadly nightshade intoxication. *J Acad Emerg Med* 2011;10:86–8.
45. Joshi P, Wicks AC, Munshi SK. Recurrent autumnal psychosis. *Postgrad Med J* 2003;79:239–40.
46. Mirakhur RK, Dundee JW. Cardiovascular changes during induction of anaesthesia. Influence of three anticholinergic premedicants. *Ann R Coll Surg Engl* 1979;61:463–9.
47. Diaz DM, Diaz SF, Marx GF. Cardiovascular effects of glycopyrrolate and belladonna derivatives in obstetric patients. *Bull N Y Acad Med* 1980;56:245–8.
48. Mitchelson F. Muscarinic receptor agonists and antagonists: Effects on ocular function. *Handb Exp Pharmacol* 2012;208:263–98.
49. Yen MY, Liu JH, Kao SC, Shiao CH. Comparison of the effect of atropine and cyclopentolate on myopia. *Ann Ophthalmol* 1989;21:180–2, 7.
50. Shih YF, Chen CH, Chou AC, Ho TC, Lin LL, Hung PT. Effects of different concentrations of atropine on controlling myopia in myopic children. *J Ocul Pharmacol Ther* 1999;15:85–90.
51. Bedrossian RH. Treatment of Progressive Myopia with Atropine. Munich, Germany: Presented at: The XX International Congress of Ophthalmology; 1966. p. 14–9.
52. Bedrossian RH. The effect of atropine on myopia. *Ann Ophthalmol* 1971;3:891–7.
53. Bedrossian RH. The effect of atropine on myopia. *Ophthalmology* 1979;86:713–9.
54. Kelly TS, Chatfield C, Tustin G. Clinical assessment of the arrest of myopia. *Br J Ophthalmol* 1975;59:529–38.
55. Gimbel HV. The control of myopia with atropine. *Can J Ophthalmol* 1973;8:527–32.
56. McBrien NA, Moghaddam HO, Reeder AP. Atropine reduces experimental myopia and eye enlargement via a nonaccommodative mechanism. *Invest Ophthalmol Vis Sci* 1993;34:205–15.
57. McBrien NA, Stell WK, Carr B. How does atropine exert its anti-myopia effects? *Ophthalmic Physiol Opt* 2013;33:373–8.
58. Zhang Z, Zhou Y, Zie Z, Chen T, Gu Y, Lu S, et al. The effect of topical atropine on the choroidal thickness of healthy children. *Sci Rep* 2016;6:34936.
59. Dhillon B, Armani J, Nickla DL. The ocular growth inhibition effected by dopamine agonists and atropine is associated with transient increases in choroidal thickness in chicks. *Invest Ophthalmol Vis Sci* 2008;49:1732.
60. Read SA, Alonso-Caneiro D, Vincent SJ, Collines MJ. Longitudinal changes in choroidal thickness and eye growth in childhood. *Invest Ophthalmol Vis Sci* 2015;56:3103–12.
61. Ashby R, McCarthy CS, Maleszka R, Megaw P, Morgan IG. A muscarinic cholinergic antagonist and a dopamine agonist rapidly increase ZENK mRNA expression in the form-deprived chicken retina. *Exp Eye Res* 2007;85:15–22.
62. Schwahn HN, Kaymak H, Schaeffel F. Effects of atropine on refractive development, dopamine release, and slow retinal potentials in the chick. *Vis Neurosci* 2000;17:165–76.
63. Iuvone PM, Tigges M, Fernandes A, Tigges J. Dopamine synthesis and metabolism in rhesus monkey retina: Development, aging, and the effects of monocular visual deprivation. *Vis Neurosci* 1989;2:465–71.
64. Barathi VA, Beuerman RW. Molecular mechanisms of muscarinic receptors in mouse scleral fibroblasts: Prior to and after induction of experimental myopia with atropine treatment. *Mol Vis* 2011;17:680–92.
65. Barathi VA, Weon SR, Beuerman RW. Expression of muscarinic receptors in human and mouse sclera and their role in the regulation of scleral fibroblasts proliferation. *Mol Vis* 2009;15:1277–93.
66. Tigges M, Iuvone PM, Fernandes A, Sugrue MF, Mallorga PJ, Laties AM, et al. Effects of muscarinic cholinergic receptor antagonists on postnatal eye growth of rhesus monkeys. *Optom Vis Sci* 1999;76:397–407.
67. Schmid KL, Wildsoet CF. Inhibitory effects of apomorphine and atropine and their combination on myopia in chicks. *Optom Vis Sci* 2004;81:137–47.
68. Lind GJ, Chew SJ, Marzani D, Wallman J. Muscarinic acetylcholine receptor antagonists inhibit chick scleral chondrocytes. *Invest Ophthalmol Vis Sci* 1998;39:2217–31.
69. Wang LZ, Syn N, Li S, Barathi VA, Tong L, Neo J, et al. The penetration and distribution of topical atropine in animal ocular tissues. *Acta Ophthalmol* 2019;97:e238–47.
70. Gallego P, Martinez-Garcia C, Perez-Merino P, Ibares-Frías L, Mayo-Iscar A, Merayo-Llodes J. Scleral changes induced by atropine in chicks as an experimental model of myopia. *Ophthalmic Physiol Opt* 2012;32:478–84.
71. Larkin GL, Tahir A, Epley KD, Beauchamp CL, Tong JT, Clark RA. Atropine 0.01% eye drops for myopia control in American children: A multiethnic sample across three US sites. *Ophthalmol Ther* 2019;8:589–98.
72. Gruber E. Treatment of myopia with atropine and bifocals. *Ophthalmology* 1985;92:985.
73. Romano PE, Donovan JP. Management of progressive school myopia with topical atropine eyedrops and photochromic bifocal spectacles. *Binocul Vis Strabismus Q* 2000;15:257–60.
74. Chiang MF, Kouzis A, Pointer RW, Repka MX. Treatment of childhood myopia with atropine eyedrops and bifocal spectacles. *Binocul Vis Strabismus Q* 2001;16:209–15.
75. Syniuta LA, Isenberg SJ. Atropine and bifocals can slow the

- progression of myopia in children. *Binocul Vis Strabismus Q* 2001;16:203–8.
76. Yi S, Huang Y, Yu SZ, Chen XJ, Yi H, Zeng XL. Therapeutic effect of atropine 1% in children with low myopia. *J AAPOS* 2015;19:426–9.
  77. Gong Q, Janowski M, Luo M, Wei H, Chen B, Yang G, et al. Efficacy and adverse effects of atropine in childhood myopia: A meta-analysis. *JAMA Ophthalmol* 2017;135:624–30.
  78. Pineles SL, Kraker RT, VanderVeen DK, Hutchinson AK, Galvin JA, Wilson LB, et al. Atropine for the prevention of myopia progression in children: A report by the American academy of ophthalmology. *Ophthalmology* 2017;124:1857–66.
  79. Brodstein RS, Brodstein DE, Olson RJ, Hunt SC, Williams RR. The treatment of myopia with atropine and bifocals. A long-term prospective study. *Ophthalmology* 1984;91:1373–9.
  80. Shih YF, Hsiao CK, Chen CJ, Chang CW, Hung PT, Lin LL. An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression. *Acta Ophthalmol Scand* 2001;79:233–6.
  81. Fang PC, Yang IH, Lee JJ, Chen CH, Lin PW, Lin SA, et al. Prevention of myopia progression with 0.05% atropine solution. *J Ocul Pharmacol Ther* 2006;22:41–6.
  82. Liang CK, Ho TY, Li TC, Hsu WM, Li TM, Lee YC, et al. A combined therapy using stimulating auricular acupoints enhances lower-level atropine eyedrops when used for myopia control in school-aged children evaluated by a pilot randomized controlled clinical trial. *Complement Ther Med* 2008;16:305–10.
  83. Wang YR, Bian HL, Wang Q. Atropine 0.5% eyedrops for the treatment of children with low myopia: A randomized controlled trial. *Medicine (Baltimore)* 2017;96:e7371.
  84. Tan Q, Ng AL, Cheng GP, Woo VC, Cho P. Combined atropine with orthokeratology for myopia control: Study design and preliminary results. *Curr Eye Res* 2019;44:671–8.
  85. Wei S, Li S, An W, Du J, Liang X, Sun Y, et al. Safety and efficacy of low-dose atropine eyedrops for the treatment of myopia progression in chinese children: A randomized clinical trial. *JAMA Ophthalmol* 2020;138:1178–84.
  86. Pérez-Flores I, Macías-Murelaga B, Barrio-Barrio J, Multicenter Group of Atropine Treatment for Myopia Control (GTAM). A multicenter Spanish study of atropine 0.01% in childhood myopia progression. *Sci Rep* 2021;11:21748.
  87. Kaiti R, Shyangbo R, Sharma IP, Dahal M. Review on current concepts of myopia and its control strategies. *Int J Ophthalmol* 2021;1:606–15.