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Atropine: Updates on myopia pharmacotherapy

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Abstract:

The prevalence of myopia has rapidly increased over the last 30 years, with the World Health Organization estimating a worldwide incidence of 23%, projected to increase to 50% by 2050. The myopia epidemic has prompted a reincarnation in efforts to overcome this challenge. The exploration of atropine use in myopia was a result due to a lack of treatment in effect. This study aimed at reviewing the role of atropine in the management of myopia worldwide based on currently available findings. A literature search was conducted using PubMed/MEDLINE and Google Scholar for studies published up to April 2022 inclusive. Articles with high or medium clinical relevance were selected for this review. Multiple studies have demonstrated the relevance and efficacy rates of different concentrations of atropine, despite still insufficiently explained the exact site and mechanism of action of atropine in slowing myopia progression. Currently available findings highlight that topical atropine opened a new page in pharmacotherapy of myopia and have shown a high therapeutic effect on myopia progression in Asian and European child population, irrespective of ethnicity. There is potential for myopia control with fewer side effects using lower concentrations but still exists a room for improvement, underscoring the requirement of modified atropine topical preparations with increased bioavailability, potentially with nanoparticle formulations, to enable the effective management of myopia.

Keywords:

High concentration atropine, low-concentration atropine, myopia, pharmacotherapy, refractive error, topical atropine

The prevalence of myopia has rapidly increased over the last 30 years, with the World Health Organization estimating a worldwide incidence of 23%, projected to increase to 50% by 2050.[1-3] The increased incidence (myopia in 50% of young adults in the USA and Europe and 90%–95% in many East Asian countries) naturally begs the questions as to what is driving this epidemic and if there is something that can be done to stop it.[3-5]

What can we do about the exponentially growing incidence of myopia in young people?

The myopia epidemic has started to attract the attention of researchers once again to overcome this challenge.

This study aimed at reviewing the role of atropine in the management of myopia worldwide based on the currently available findings. A literature search was conducted using PubMed/MEDLINE and Google Scholar for studies published up to April 2022 inclusive.

Articles with high or medium clinical relevance were selected for this review.

The exploration of atropine use in myopia was a result due to a lack of treatment in effect.

The exact site and mechanism of action of atropine in slowing myopia progression are still insufficiently understood.[6] One of the proposed mechanisms is an impact of atropine on choroidal thickness. Multiple other mechanisms have been proposed: atropine binding to muscarinic receptors

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on scleral fibroblasts and interfering with scleral remodeling; increased dopamine release by atropine binding to muscarinic receptors of amacrine cells; and reduction of γ-aminobutyric acid levels. Besides, it is feasible that atropine may indirectly affect the retina due to the release of dopamine or other neurotransmitters,[7] causing an increase in choroidal thickness,[8] specifically by dopamine.

As researchers and practitioners considered the properties of atropine outside of the accommodative mechanism of action, it became reasonable to conduct clinical trials in myopia subjects.[9]

The landmark Atropine in the Treatment of Myopia (ATOM) study[10] performed their large randomized clinical trial in 400 children of Asian ethnicity and found a beneficial effect for 1% atropine. The ATOM2 study[11] was conducted in a Singaporean pediatric population (6–12 years of age), which significantly differed from European one racially and in terms of the pattern of myopic progression [Table 1]. Chia *et al*.[11] randomly assigned myopic children to 0.5%, 0.1%, and 0.01% atropine eye drops. Over 2 years, myopia progressed − 0.30 ± 0.60 D for the 0.5% group, −0.38 ± 0.60 D for the 0.1% group, and − 0.49 ± 0.63 D for the 0.01% groups. All were significantly slower than the historical placebo control group. It was evidenced that the clinical efficacy of low-concentration 0.01% atropine in the 2nd year is much better than in the 1st year resulting in clinically not significant results between 0.01%, 0.1%, and 0.5% atropine.

Atropine is the preferred practice pattern for progressive myopia in Taiwan.[12] As early as the year 2000, the Ophthalmological Society of Taiwan advised to use atropine to slow down myopia progression. This treatment is prescribed to nearly 50% of Taiwanese children with progressive myopia. Although topical use of atropine is known to cause photophobia and accommodation lag, these adverse events do not appear to hamper its implementation in Taiwanese children. By contrast, the lighter iris color in Europeans is generally considered a barrier for its use in the Western world.[13]

Table 1: Two-year efficacy of atropine in the treatment of myopia 2 study

	ATOM2 study		
	0.5% atropine	0.1% atropine	0.01% atropine
Change of SE (D)			
1st year	−0.17	−0.31	−0.43
2nd year	−0.13	−0.07	−0.06
Total 2 years	−0.3	−0.38	−0.49
Change of AL (mm)			
1st year	0.11	0.13	0.24
2nd year	0.16	0.15	0.17
Total 2 years	0.27	0.28	0.41

ATOM2=Atropine in the treatment of myopia 2, SE=Spherical equivalent, AL=Axial length

A meta-analysis conducted by Gong *et al*.[14] suggests that the efficacy of atropine is dose independent within this range (0.01%, 0.1%, and 0.5% concentrations), whereas the adverse effects are dose dependent.

The first randomized placebo-controlled trial on low-concentration atropine (0.05%, 0.025%, and 0.01%) was conducted by Yam *et al*.[15] Researchers have found that all concentrations were well tolerated and effective comparing to placebo, despite concentration-related response [Table 2]. It was highlighted that 0.05% atropine is most effective at 1-year follow-up.

Continued LAPM study with 2-year follow-up[16] [Table 3] reconfirmed that 0.05% atropine is the most efficacious concentration showing the similar efficacy and toleration between the 1st and 2nd years. This study[17] assessed whether the low-concentration atropine could cause ocular biometry changes. The results did not demonstrate any change in corneal or lens power; however, retardation of axial elongation was observed in all treatment groups, compared to placebo, thus highlighting an antimyopic effect.

Taken into account an age effect on treatment responses as a secondary analysis from a randomized trial,[18] it was documented that younger children required the highest 0.05% concentration to achieve a similar reduction in myopic progression as older children on lower concentrations.

A recent study of Yam *et al*.[19] evaluated low-concentration atropine impact on choroidal thickness and have evidenced choroidal thickening induction associated with retardation of axial length increase in all treatment groups, despite concentration-dependent response.

The impact of 0.01% atropine on axial length growth in a real life was assessed by Kaymak *et al*.[20] The observed atropine effects were not very distinctive: statistical analysis confirmed that atropine reduced axial length growth but to an extent of minor clinical relevance. It was also shown that beneficial effects of 0.01% atropine may not be obvious in each single case.

The recent randomized trial conducted by Wang *et al*.[21] reconfirmed the safety of 0.01% atropine with no impact on the retinal and choroidal structure and vasculature.

The latest report from LAMP study[22] concluded that for Asian children over 3 years, the optimal concentration of atropine is 0.05%, with only minor rebound effects.

Table 2: Atropine (different concentrations) efficacy compared with placebo group in low-concentration atropine for myopia progression study

	Mean change in SE	Percentage reduction in myopia progression	AL change	Percentage reduction in AL elongation
Atropine 0.05%	−0.27 (0.61)	67	−0.20 (0.25)	51
Atropine 0.025%	−0.46 (0.45)	43	0.29 (0.20)	29
Atropine 0.01%	−0.59 (0.61)	27	0.36 (0.29)	12
Placebo	−0.81 (0.53)	-	0.41 (0.22)	-

SE=Spherical equivalent, AL=Axial length

Table 3: Two-year efficacy of atropine in low-concentration atropine for myopia progression study

	LAMP study			
	0.05% atropine	0.025% atropine	0.01% atropine	Placebo
Change of SE				
1st year	−0.25	−0.46	−0.64	−0.82
2nd year	−0.30	−0.39	−0.48	
Total 2 years	−0.55	−0.85	−1.12	
Change of AL (mm)				
1st year	0.20	0.29	0.35	0.43
2nd year	0.18	0.22	0.25	
Total 2 years	0.39	0.50	0.59	

SE=Spherical equivalent, AL=Axial length, LAMP=Low-concentration atropine for myopia progression

Table 4: Efficacy of atropine 0.01% in European patients

Myopic progression rate (D/year)	Treatment group atropine 0.01%	Control group	*P*
Baseline (between visit 1 and visit 2), mean±SD	−1.20±0.64	−0.80±0.38	<0.0001
After 12 months (from visit 2), mean±SD	−0.54±0.61	−1.09±0.64	<0.0001
P	<0.0001	<0.0001	

SD=Standard deviation

Taken into account that there are well-recognized differences in the effect of atropine between heavily pigmented Asian eyes and Caucasian eyes, Loughman and Flitcroft[23] initiated the study aimed to determine the acceptability and tolerability of 0.01% atropine (by measuring visual performance and quality of life) as a treatment for myopia control in a Caucasian population exhibiting light irides. The authors evidenced that overall, 0.01% of atropine was generally well tolerated bilaterally and no serious adverse effects were observed, concluding that this dose appears to provide a viable therapeutic option for myopia control among Caucasian eyes. Multiple further research studies[24-29] have shown efficacy and safety of 0.01% atropine, among which is the first randomized double-masked, placebo-controlled clinical trial based on findings of predominantly European population – The Myopia Outcome Study of Atropine in Children.[26]

Efficacy of atropine 0.01% in European patients was assessed by Sacchi *et al*.[25] [Table 4].

Another group of researchers in Rotterdam investigated the effect of a higher concentration of topical atropine (0.5%) daily during 1 year[30] and 3 years, respectively,[31,32] in progressive myopia up to − 6.6 D. The obtained results demonstrate atropine potential to slow down the progression rate of spherical equivalent, however adverse events (photophobia and difficulties with reading) rate is high [Table 5]. However, comparing the high concentration atropine (0.5%) to the lowest one (0.01%), researchers from this group evidenced that "the balance between efficacy and acceptable side effects makes this (0.01%) concentration attractive when less tight control is acceptable."[32]

Recently, Austermann *et al*.[33] conducted an *ex vivo* study of freshly enucleated pig eyes to assess corneal penetration of atropine as 0.01%, 0.1%, and 0.5% drops in different preserved and preservative-free formulations obtained from pharmacies. Ten minutes lately after instilled, eye drop aqueous humor sample was taken and atropine concentrations were measured by high-performance liquid chromatography–tandem mass spectrometry. This study showed good, dose-dependent penetration of atropine 0.01% "into the cornea and anterior chamber, which was not significantly affected by additives and preservatives."

Lately, Gan *et al*.,[34] based on a meta-analysis of different atropine concentrations used in trials, concluded that despite dose-dependent effect, low-dose atropine 0.01% has shown an efficacy in a longer follow-up period, and has been found to induce minimal clinical symptoms for myopia control in children.

Another network meta-analysis conducted by Ha *et al*.[35] highlighted 0.05% atropine as the most beneficial concentration taking into account the relative risk of myopia progression.

In summary, there is a growing body of evidence supporting atropine use as a therapeutic agent in myopia; however, there are still unanswered questions such as "the optimal dosage and treatment regimen."[36]

Concluding, currently available findings highlight that topical atropine opened a new page in pharmacotherapy of myopia, and have shown a high therapeutic effect

Table 5: Three-year efficacy of atropine for progressive myopia in Europeans

	Continued therapy (*n*=8; 71.8%)			Ceased therapy (*n*=35), from which lost to follow-up (*n*=9; 28.2%)	
	Increased dose (*n*=32)	Decreased dose (*n*=26)	Same dose (*n*=31)	Allergy stop (*n*=9)	Adverse events (*n*=17)
Median change of SE (D/year)					
First	−0.4 (0.6)	+0.2 (0.7)	+0.1 (0.5)	−0.4 (0.7)	−0.7 (1.1)
Second	−0.6 (0.7)	−0.3 (0.4)	−0.3 (0.6)	−0.9 (1.3)	−0.8 (0.9)
Third	−0.5 (0.8)	−0.3 (0.3)	−0.3 (0.5)	−0.4 (1.4)	−0.9 (1.1)
Median change of AL (mm/year)					
First	0.3 (0.2)	0.0 (0.2)	0.0 (0.1)	0.2 (0.3)	0.3 (1.0)
Second	0.3 (0.3)	0.1 (0.1)	0.1 (0.2)	–	–
Third	0.2 (0.3)	0.1 (0.1)	0.1 (0.1)	–	–

SE=Spherical equivalent, AL=Axial length

on myopia progression in Asian and European child population irrespective of ethnicity. There is potential for myopia control with fewer side effects using lower concentrations but still exists a room for improvement, underscoring the requirement of modified atropine topical preparations with increased bioavailability, potentially with nanoparticle formulations, to enable the effective management of myopia.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

The author declares that there are no conflicts of interest in this paper.

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