COMMENTARY

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Interpretation of expert consensus on the application of low-concentration atropine eye drops in the prevention and control of myopia in children and adolescents

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INTRODUCTION

The application of atropine in the prevention and control of myopia was reported as early as the 1970s.[1] In recent years, low-concentration atropine has drawn the attention of clinicians and parents of children because of its excellent efficacy and safety. Currently, although the national drug regulatory authority has not officially sanctioned the application of low-concentration atropine eye drops in clinical myopia prevention and control, some provincial drug regulatory departments have permitted their use in the form of hospital preparations or obtained through a doctor's prescription on Internet hospitals. However, there is a lack of unified guidance on the selection of atropine eye drop concentrations and usage specifications in China. Therefore, the Optometry Group of the Ophthalmology Branch of the Chinese Medical Association and the Ophthalmology and Optometry Committee of the Ophthalmologist Association of Chinese Doctor Association have formulated the "Expert Consensus on the Application of Low-Concentration Atropine Eye Drops in the Prevention and Control of Myopia in Children and Adolescents (2024)" (hereinafter referred to as the "consensus").[2] This consensus deliberates on the effectiveness, safety, and applicable population of low-concentration atropine eye drops and standardizes the usage specifications. The interpretation is as follows.

EFFICACY OF ATROPINE

The consensus indicates that atropine eye drops are the sole drug verified by evidence-based medicine to be capable of effectively delaying the progression of myopia.[3] Moreover, the myopia control effect exhibits an obvious concentration-dependent phenomenon.[4,5] High-concentration atropine (1% and 0.5%) eye drops possess myopia prevention and control efficacy of up to 60%–96%. However, there are obvious adverse reactions, mainly severe photophobia and decreased near vision, and a rebound effect occurs after drug withdrawal.[4–6] Considering the safety and effectiveness of clinical use, 0.01% atropine eye drops are currently the research focus of most scholars.

A large-scale randomized controlled clinical trial conducted in Singapore (Atropine for the Treatment of Myopia 2 [ATOM 2]), which lasted for 5 years and was divided into three stages, was designed to explore the efficacy and safety of atropine eye drops of different concentrations

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TABLE 1 Retardation rates of spherical equivalent and axial length growth following the administration of low-concentration atropine eye drops in published randomized controlled trials

Atropine concentration (%)	Study time (years)	Retardation rate of spherical equivalent (%)	Retardation rate of axial length growth (%)
0.01[5,8,12–18]	1–5	15–59	12–47
0.02[14–16]	1–3	9–46	10–39
0.025[5]	5	43	29
0.05[5,19]	2–5	66–73	51–65

(0.5%, 0.1%, and 0.01%) in 400 myopic children.[4] The results indicate that: 1) Atropine eye drops of 0.5%, 0.1%, and 0.01% are all effective in controlling the progression of myopia, and 0.01% atropine eye drops have the fewest adverse reactions. 2) The rebound effect of 0.01% atropine eye drops was the mildest after drug withdrawal. 3) There is a cumulative effect of delaying the progression of myopia; that is, as the use of atropine eye drops continues, the effect of controlling the progression of myopia improves progressively.[4] Other similar studies also suggested that 0.01% atropine eye drops are at the optimal balance point of efficacy and safety. These studies have led to an increasing amount of research on and use of 0.01% atropine eye drops in clinical practice.[5,7–10] Meanwhile, research on the effectiveness of atropine eye drops of different concentrations (0.05%, 0.025%, 0.02%, and 0.01%) is also in progress.[11] A study from Hong Kong (Low-Concentration Atropine for Myopia Progression [LAMP] Study) evaluated the efficacy and safety of low-concentration atropine eye drops (0.05%, 0.025%, and 0.01%) compared with placebo within 1 year and found that all concentrations are well tolerated and delay the progression of myopia in a concentration-dependent manner.[5] Table 1 lists the retardation rates of the four concentrations of atropine eye drops on the spherical equivalent (SE) degree of myopia and axial length growth. Based on previous authoritative research findings, the consensus holds that since 0.01% atropine eye drops have a good effect in delaying myopia progress, have the fewest adverse reactions, and have the mildest rebound effect, it is a reasonable concentration for delaying the progression of myopia in children and adolescents at this stage. In March 2024, 0.01% low-concentration atropine sulfate eye drops were officially approved by the Chinese national drug regulatory authorities for myopia prevention and control in children and adolescents, enhancing the legality and authority of its application.

Currently, there is a controversy regarding the use of low-concentration atropine eye drops in myopia prevention. In 2023, the same research team in Hong Kong conducted the LAMP2 study. It was demonstrated that among non-myopic children aged 4–9 years (with cycloplegic SE ranging from 0.00 to +1.00 D), compared with the placebo group, the incidence of myopia was significantly reduced in those using 0.05% atropine eye drops every night. However, there was no significant difference between the group using 0.01% atropine and the placebo group.[20] In addition, other studies evaluated the preventive effect of 0.025% atropine on children in the pre-myopia stage. The refractive changes in the medication group were significantly lower than those in the control group, suggesting that 0.025% atropine eye drops are also effective in myopia prevention.[21] Therefore, further research is still needed to clarify the preventive effect of low-concentration atropine on myopia.

MECHANISM

The consensus holds that the mechanism by which atropine eye drops retard myopia progression remains unclear. There are mainly the following hypotheses: (1) Accommodative paralysis hypothesis: Initially, researchers believed that atropine can paralyze the M receptor of the ciliary muscle and relax accommodation, thus delaying the progression of myopia.[22] (2) Site of action hypothesis: Studies on birds innervated by N receptors in the ciliary muscle found that atropine is also effective. After injecting atropine and 0.9% sodium chloride solution, there was no difference in the accommodative response of the chicks. This suggests that atropine does not delay the progression of myopia through the accommodation of the ciliary muscle but may act on the M receptor of other tissues in the eye.[23,24] For instance, atropine can act on the scleral M receptor to thicken the scleral fibrous layer and thereby control the progression of myopia.[25] (3) Scleral hypoxia hypothesis: Recent studies have revealed that choroidal ischemia leading to scleral hypoxia remodeling is an important mechanism for the occurrence of myopia.[26] Moreover, many studies have found that after atropine treatment, the choroid thickens and choroidal blood flow increases, thereby alleviating scleral hypoxia and inhibiting axial length growth, suggesting that atropine may act on choroidal tissue.[27–29] (4) Others: Some studies have discovered that the delaying effect of nitric oxide (NO) on myopia is dose-dependent, and atropine can induce the synthesis of NO in a certain way to delay myopia progress[30]; atropine can promote the generation of endogenous dopamine, and dopamine can effectively inhibit the development of form-deprivation myopia in chicks.[31] Regarding the mechanism of atropine eye drops in delaying the progression of myopia, further research is still required.

SAFETY AND MANAGEMENT OF ADVERSE REACTIONS

The consensus indicates that the adverse reactions to atropine also exhibit a concentration-dependent pattern.[4,5] Atropine is an anticholinergic drug and an M receptor

TABLE 2 Adverse reactions and treatment methods that may occur with 0.01% atropine eye drops

Adverse reactions	Clinical manifestations and changes	Treatment
Photophobia	Due to pupil dilation, this may occur in a bright environment. The symptoms can disappear.	For those who are intolerant, wearing a hat or photochromic glasses can alleviate the symptoms.
Increased intraocular pressure	In very few cases, there is a transient elevation.	–
Decreased near vision	Due to ciliary muscle paralysis, the accommodative amplitude decreases by 2.00–3.00 diopter and recovers after drug withdrawal.	For those who are intolerant, wearing near addition glasses, or doing accommodative function training.
Allergic reaction	Relatively rare. Manifested as ocular itching, burning sensation, eyelid swelling, and redness around the eyes.	Stop taking the drug immediately; local application of hormones can accelerate recovery.
Irritating reaction	A few cases of ocular stinging discomfort.	–

blocker; thus, it can be used for mydriasis and paralysis of the ciliary muscle. Atropine ophthalmic gel (1%) is often used for slow mydriatic optometry to diagnose myopia, which can cause ocular symptoms such as photophobia, irritation, and blurred vision,[32] and may also lead to systemic symptoms such as facial flushing, increased heart rate, fever, and abdominal distension.[33] As the concentration decreases, systemic symptoms almost vanish and ocular symptoms also continuously decline. Due to the mydriatic effect of atropine, although the concentration is continuously reduced to 0.01%, photophobia (6.3%) remains the most common adverse reaction.[34] In the ATOM study, after 2 weeks of medication by the subjects, the pupil diameters of each group all changed significantly, and the change in pupil diameter in the 0.01% group was much smaller than that in the other two groups. During the first year (1a) and the second year (2a), the pupil diameters did not change much compared with that after 2 weeks.[4] Pupil dilation resulted in an increase in ultraviolet and blue light entering the eye. Long-term exposure to harmful light can increase the risk of retinal photodamage. A study selected 35 subjects from the ATOM study for retinal electrophysiological examination and found no abnormalities in the three groups (0.5%, 0.1%, and 0.01%).[35] The ciliary muscle paralysis effect of atropine reduced accommodative capacity in the eye, leading to blurred near vision. The incidence of decreased near vision in 0.01% atropine is 2.3%.[34] In the ATOM study, the accommodative amplitude of the 0.01% group decreased by 4.90 D in 2 weeks, which was much lower than that of the other two groups (12.90 and 13.60 D), and recovered during 1a and 2a.[4] In the LAMP study, the reduction in accommodative amplitude was very small in the four groups of 0.05%, 0.025%, 0.01%, and placebo. In the 0.01% group, it was 0.26 ± 3.04 D, and in the control group, it was 0.32 ± 2.91 D, which had almost no impact on near vision tasks.[5] At present, in all studies on 0.01% low-concentration atropine for myopia prevention and control, there are no serious systemic adverse reactions. The incidence of ocular adverse reactions is low, the symptoms are mild, and they are gradually becoming easier to tolerate. The consensus lists the possible adverse reactions and treatment methods for 0.01% atropine eye drops, as shown in Table 2.

CLINICAL APPLICATION OF LOW-CONCENTRATION ATROPINE

User groups of low-concentration atropine

The consensus indicates that low-concentration atropine eye drops are suitable for myopic individuals aged 6–12 years, with a diopter of spherical power from −4.00 to −1.00 D, diopter of astigmatism ≤1.50 D, and anisometropia diopter ≤1.50 D. For children under 6 years of age, medication should be administered with caution, and strict follow-up is necessary. For myopic people with risk factors for rapid progression of myopia, such as a family history of high myopia,[36] early onset age,[37] high initial degree,[38] high intensity of near vision use,[39] and short outdoor activity time,[40] drug treatment and intervention can be implemented at an early stage. Moreover, a combined regimen of low-concentration atropine with orthokeratology lenses or defocus spectacle lenses can be adopted.[41,42]

Usage specifications of low-concentration atropine

1. Baseline assessment: After diagnosing myopia, in addition to considering the adverse reactions of atropine, examinations of the eye's accommodative ability, anterior segment health status, intraocular pressure, pupillary light response, pupil diameter, axial length, and fundus should be conducted. Corneal topography can be selectively examined. For patients with risk factors for the rapid progression of myopia, emphasis should also be placed on myopia prevention and control.
2. Education before medication: The consensus indicates that patients or their guardians should have a certain understanding of the mechanism and efficacy of low-concentration atropine eye drops and that compliance

TABLE 3 Follow-up time and content of low-concentration atropine

Follow-up time	Follow-up content
First within 1–2 weeks	Intraocular pressure, anterior segment health status, subjective reaction after medication
Every 3 months	Best corrected visual acuity (including distant and near vision), accommodative function, intraocular pressure, diopter, axial length, pupil examination, anterior segment examination
Every 6 months	Add fundus examination compared to the examination every 3 months
Every 12 months	Add assessment of related systemic symptoms (flushed face, headache, heart disease, urinary system, etc.) compared to the examination every 6 months

TABLE 4 Drug withdrawal management of low-concentration atropine

Drug withdrawal	Response type	Other situations	Treatment
Regular drug withdrawal	Good response	–	Consider drug withdrawal and observe the rebound effect
	Moderate response	Young age, rapid progression	Continue to use it and conduct strict follow-up
Abnormal drug withdrawal	Poor response	Refuse to increase the concentration; Refuse to combine with other measures	It is recommended to stop using
	Adverse reactions occur	Intolerance	It is recommended to stop using

is of great importance. Doctors need to conduct health education before medication, mainly regarding the efficacy of atropine supported by evidence-based medicine, individualized efficacy, handling of inability to improve vision and adverse reactions, necessary myopia correction, and good eye use habits. Regular reexamination should be performed to avoid affecting the actual efficacy due to unauthorized drug discontinuation or irregular medication.

3. Medication process and follow-up: Based on the response degree and adverse reactions to low-concentration atropine in myopia patients, the consensus provides recommendations for different strategies regarding follow-up and reexamination as well as the timing of drug withdrawal, as shown in Tables 3 and 4. The recommended usage is one drop at a time once a night before bed. According to the annual myopia progression, it is divided into: (i) Good response: progression $\leq$ 0.25 D or progression decreases by at least 50%; (ii) Moderate response: progression 0.25–0.75 D; (iii) Poor response: progression $\geq$ 0.75 D or the annual increase in axial length is greater than or equal to 0.2 millimeters. The management process with 0.01% atropine eye drops to prevent and control the progression of myopia is shown in Figure 1.

The ATOM study demonstrated that for myopic children aged 6–12 years, 0.01% atropine had an extremely good effect in the first 2 years. The second year was superior to the first year. Hence, it is recommended that the treatment should last for 2 years if possible.[4] The LAMP study holds that 0.05% atropine can be directly administered until the third year,[5] and a younger age can influence the efficacy.[43] This might be because myopia develops rapidly before the age of 12 years and then gradually stabilizes. It is suggested that, for younger children taking the medicine, the atropine concentration can be appropriately increased to achieve a good response. The European Society of Ophthalmology indicated in the myopia management guidelines in 2021 that the concentration and frequency of use of low-concentration atropine can be customized individually. For instance, for those with moderate or poor responses, the drug can be administered twice a day or a higher concentration of atropine can be used.[44] The consensus also believes that for children and adolescents who do not have a good response, under the condition of no other myopia risk factors and in accordance with medication specifications, they can take the drug once in the morning and once in the evening, increase the concentration (such as 0.02%)[10] or combine prevention and control measures.[11]

Rebound effect and reuse after drug withdrawal

After discontinuation of the atropine eye drops, the growth rate of the diopter and axial length exhibits a rebound increase, which is known as the rebound effect. This makes it difficult to determine the timing of drug withdrawal for clinical applications. The lower the concentration of atropine eye drops, the older the age at drug withdrawal, the smaller the progression of myopia during medication, the higher the diopter and longer the axial length before medication, and the smaller the rebound effect after drug

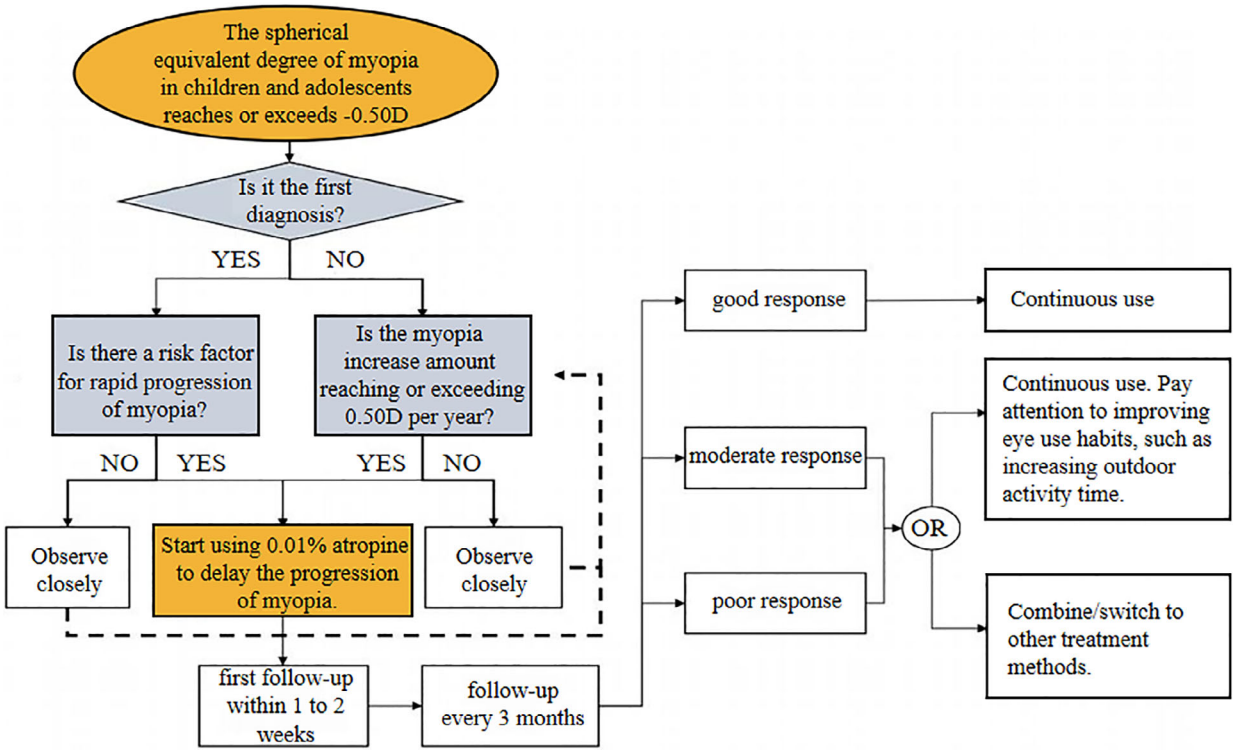

FIGURE 1 Management process of applying 0.01% atropine eye drops to prevent and control the progression of myopia (quoted from "Consensus", 2024).[2]

withdrawal.[4,5,43] These results suggest that continuous use of 0.01% atropine eye drops until adolescence when myopia is relatively stable may have a better effect on myopia prevention and control. However, considering that there is currently no high-level evidence-based proof for the long-term safety of atropine, the relatively safe and effective continuous medication duration recognized by most studies is 5–10 years.[17,45] For those with obvious rebound effects after drug withdrawal ($\triangle$DS $\geq$ 0.50 D), re-medication can be considered. The ATOM study holds that the efficacy of 0.01% atropine reuse after drug withdrawal is the best.[4]

Contraindications for the use of low-concentration atropine

Absolute contraindications for atropine eye drops: allergy to hyoscyamine components; suffering from glaucoma or having a tendency toward glaucoma (shallow anterior chamber, narrow chamber angle, etc.).

Cautionary situations for atropine eye drops: Patients with low accommodative power; hypopigmentation (such as albinism), craniocerebral trauma, heart diseases (especially arrhythmia, congestive heart failure, coronary heart disease, mitral stenosis, etc.) should use it with caution. Some eye diseases accompanied by photophobia symptoms (such as keratitis) can be treated after recovery.

PRECAUTIONS

Physicians should strictly determine whether to recommend low-concentration atropine treatment for children with myopia according to the indication range. They should instruct the children and guardians to purchase them from a standardized institution with a prescription. Self-preparation is not advisable.

In conclusion, the "Consensus" provides scientific discussions and recommendations for the use of low-concentration atropine in the prevention and control of myopia in children and adolescents and offers an important reference basis for the prevention and control of myopia in children and adolescents in China. Through continuous scientific research and clinical practice in the future, the consensus will be continuously updated and refined.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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