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Atropine for myopia control: An evidence-based review

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Abstract
Atropine eye drops reduce myopia progression during childhood in a dose dependent manner, with greatest effect documented with lower concentrations (0.01-0.05%) and most consistent efficacy with 0.05% in longitudinal RCTs like LAMP and consistent benefits seen in ATOM and CHAMP programs. At low concentrations, the adverse effects are benign, consisting of mild pupil dilation and a small degree of accommodation loss, while higher concentrations are associated with more severe photophobia, more pronounced near fixation blur, and more substantial rebound effects on myopia progression. Continuous treatment is more effective than a treatment break (washout) during the primary school years and rebound effect can be improved by higher ages, lower concentrations, and tapering off. LAMP phase 3 and meta-analytic data provide a rationale for easing and lengthening the intervals between treatments. Practical recommendations from various countries are based on individualized (most often starting at 0.05% for fast progressors) multi-metric treatment plans and prolonged monitoring of refractive myopia and axial length, recognizing country specific regulatory frameworks and off label compounding where it applies.

Keywords: Myopia, atropine, ATOM, LAMP, CHAMP

Introduction
By 2050, close to half the world's population will be myopic, leading to lifetime risks including pathologic myopia blinding complications which increases the need for effective myopia management in childhood. The global increase in myopia, particularly among children, resulting in potentially blinding complications in later years, has prompted the need for myopia management strategies that are evidence based to prevent the escalation in axial myopia as well as the refractive shift. Low-dose atropine has gained widespread acceptance as a component of the pharmacologic management of myopia, and this has been complemented by International Myopia Consensus recommendations, agreeing to the clinical relevance of the lower concentration atropine and the mild side effect profile of atropine. The public and clinical educational materials also emphasize clinic myopia management with atropine as part of a collaborative approach that includes myopic lifestyle changes as well as optical correction and increase outdoor activities [1, 2, 3, 4].

Mechanisms of Action: The atropine myopia-modulating actions are largely non-accommodatory. They involve muscarinic mechanisms in the sclera, choroid, and retina, and altering the pathways that regulate eye growth. The signal functions of scleral hypoxia, choroidal perfusion, and extracellular matrix remodeling have attracted recent attention. Choroidal scleral biomechanics and changes in scleral thickness in children are in accord with experimental work demonstrating effects of atropine on the scleral and choroidal cytoskeletal integrity and regulation of critical scleral-choroidal signaling nodes (P53 and β-catenin). Documentation of dose-dependent scleral choroidal thickening by LAMP clinical imaging also supports the biologic rationale for reduced axial elongation occurring with low-dose atropine treatment. [5, 6, 7].

Pivotal Clinical Trials
- **ATOM (Atropine for The Treatment of Myopia):** The trial in the ATOM program was effective in identifying the concentration where atropine caused significant rebound

effect and adverse effects which warranted a shift toward lower concentration. The five-year observation in ATOM2 was able to identify a dose-response during treatment. In the five-year follow-up, there was greater progression recorded in the five-year period in the progression during the follow-up with the 0.01% concentration in combination with no significant pupillary dilation and slight accommodation. The early phases, however, did not provide a placebo to strengthen the axial outcomes in the debate concerning the 0.01% concentration [8, 9, 4].

- **LAMP (Low Dose Atropine for Myopia Progression):** The foundational RCT showed a clear response that depended on concentration for 0.05%, 0.025%, and 0.01% compared to placebo. The 0.05% concentration achieved the most significant reduction in refractive progression and axial elongation. It maintained its effectiveness over several years of follow-up. Continued therapy worked better than a washout during the third year. The five-year extension also reported lasting effectiveness with continued 0.05% and useful patterns for PRN restarting when progression occurred [10, 11, 12, 13].
- **CHAMP (Childhood Atropine for Myopia Progression):** This was a three-year, placebo-controlled phase 3 study of proprietary 0.01% and 0.02% atropine. 0.01% was associated with clinically meaningful slowing of refractive progression and axial elongation. 0.02% grade of significance was attained for longer axial lengths but was less consistent for refractive significance, helping define regulatory pathways. Regarding this study, independent reporting pointed out the investigational status in the USA, concerning fillers with compounded eye drops and the importance of shelf-stable GMP products [14, 15, 16].

Dose-Response, Age Effects, and Comparative Efficacy

Across trials, efficacy increases with concentration in the range of low doses, with 0.05% generally producing the largest effect on axial length and spherical equivalent, followed by 0.025% and 0.01%. LAMP subgroup analyses demonstrate younger children respond less favorably at any one low dose, confirming earlier initiation and use of higher concentrations of low doses in rapid progressors or younger ages. Meta-analytic syntheses and comparison studies validate superior axial control with 0.05% vs 0.01%, further substantiating 0.05% as an extremely effective low-dose modality in clinical practice [17, 11, 18, 19].

Safety, Tolerability, and Quality of Life

Low-dose atropine is typically well tolerated, with dose-related minimal pupil enlargement and mild reduction of accommodation that rarely impairs distance or near function at 0.01-0.05%. Randomized information among children with intermittent exotropia indicates 0.01% preserves binocular vision measures, with constant stereoacuity and little effect on clinical exotropia control, and reduces myopia progression. The most reported side effects in low-dose studies are photophobia and allergic conjunctivitis, but in meta-analyses of both pre-myopic and myopic groups, incidence is low and can be controlled [20, 21, 18, 9].

Rebound and Treatment Duration: Discontinuation can induce rebound advancement that is proportional to earlier concentration and younger age at stop, with meta-analysis suggesting greater initial rebound and decreasing effect at 12 months after stop. LAMP phase 3 demonstrated sustained treatment superior to washout in year three and that stopping at increased ages or following lower concentrations is accompanied by less rebound and favors multi-year treatment with individualized tapering over sudden stop in rapid progressors. Five-year follow-ups are still sparse, although ATOM-associated cohort monitoring confirms the relevance of ongoing surveillance during peak progression years [22, 23, 13, 5].

Comparative and Combination Strategies

- **Ortho-k plus atropine:** Randomized and prospective studies demonstrate additive early decrease in axial elongation when atropine 0.01% is combined with orthokeratology versus ortho-k monotherapy, with greatest differential during the first few months and a persistent net advantage over one to two years [24, 25].
- **Options for spectacle/contact lenses:** Consensus statements place atropine alongside very effective optical modalities; combined or sequential management can be constructed to suit age, rate of progression, and tolerance, in line with a multi-modal, longitudinal model of care [4].
- **Soft multifocals with atropine:** Retrospective data suggest that combinations with peripheral defocus soft contact lenses are feasible, but more high-quality prospective trials are needed to determine best-practice protocols and dosing synergy [26].

Logistics Relating to Regulations, Access, and Practice

In some areas, low-dose atropine continues to be off-label and custom-made with different concentrations and formulations, increasing the desire for stable, GMP-grade products, which are currently under review. As of late 2023-2024 reporting, a proprietary 0.01% formulation completed a phase 3 trial and an application for review with an expectation for a regulatory decision; however, the clinical practice for most continues to be low-dose compounded atropine. In some jurisdictions (for example, Singapore) 0.01% atropine has local licensing, which illustrates the heterogeneous global access and underscores the need for region-specific guidance and informed consent [8, 15, 16, 14].

Clinical Guidance

- **Whom to treat:** Children with documented progression, early onset, family history of high myopia, or rapid axial elongation are the ones most likely to benefit from pharmacologic control, which is typically started in the early school years and maintained until the peak progression [4].
- **What dose to start:** Many clinicians consider starting at 0.05% for the fast progressors or the younger children due to the greater control of axial myopia, while 0.01-0.025% may be reasonable for milder progression or in the case of tolerability concerns, which can be adjusted for the response and side effects [11, 19, 4].
- **How to Monitor:** Six- to twelve-month assessments with cycloplegic refraction and axial length are routine, observing for threshold progression that triggers dose increase, adding optical, or optimization of adherence [4].

- **When to stop:** Taper after two to three years of stable therapy and at older ages to prevent rebounding, with readiness to restart in the event of clinically significant relapse recurrence, in accordance with LAMP and meta-analytic guidelines [13, 22].

Controversies and Nuances

There is still debate surrounding the isolated 0.01% efficacy, with later dose-ranging results and observations that support higher low-dose concentrations for biometry control casting doubt on the early interpretation of ATOM2. Western population trials have indicated heterogeneity of 0.01% outcomes but remain to show clinically relevant benefits with standard formulation in phase 3 results and in pooled analyses, with a focus on formulation homogeneity and study design in highlighting results. Mechanistic research still reduces understanding of choroidal and scleral targets, with the potential to inform dose-selection and combination strategies to optimize long-term structural outcomes in the future [7, 23, 8, 11, 14].

Future Directions

Long-term safety and efficacy lasting beyond five years, standardized tapering protocols to reduce rebound, and head-to-head comparisons in diverse populations concerning low-dose concentrations and combination regimens remain primary objectives. Improvements in formulation and subsequent approvals may make stable, preservative-free products more accessible, decreasing variability in compounded offerings and allowing equitable application of myopia control pharmacology [15, 23, 16].

Table 1: Low-Dose Atropine-Dose, Efficacy, and Tolerability

Concentration	Refractive/Axial Efficacy	Notable Side Effects
0.01%	Small refractive benefit; limited or inconsistent axial effect across studies; positive in CHAMP for axial and refraction with proprietary formulation [8, 11, 14].	Minimal mydriasis (~0.8 mm) and mild accommodation loss (2-3 D) in ATOM2; low AE rates [9].
0.025%	Moderate axial and refractive control; dose-ordered between 0.01% and 0.05% in LAMP [11].	Slightly greater photophobia/near blur than 0.01% but generally mild [11].
0.05%	Strongest low-dose control of axial length and refraction; durable across up to five years in LAMP [11, 12].	Mild dose-related increases in pupil size and reduced accommodation; usually well tolerated [11].
≥0.1%	Short-term efficacy also has more of these: photophobia, near blur, and higher rebound on cessation [9, 4].	More frequent visual symptoms, and taper recommended to mitigate rebound [4].

Conclusion

Totality of evidence on minimized side effects, and well-tolerated therapeutic levels in pediatric myopia has been achieved in 0.05% mydriatics versus higher concentrations. Refractive and axial benefits of myopia control, as well as myopia progression, were significantly greater in the continuation versus the early-threshold washout groups. Individualized, multi-modal care has been shown in the literature to maximize outcomes across childhood. Presbyopia and myopia complications will trump lifetime risk in the myopia epidemic. The desired optical length control will need integration with currently relied-upon optical strategies to control myopia progression. Further advances in mechanism, clinical care and regulation will clarify optimal dose, duration of control, and therapeutic integration.

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