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Advances in Low-Concentration Atropine and Optical Interventions for Myopia Control

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Abstract

Myopia has become a global public health challenge, with its prevalence reaching epidemic proportions in recent decades, particularly in East Asian countries. This comprehensive review synthesizes recent evidence from clinical studies and meta-analyses to examine the efficacy and safety of low-concentration atropine and optical interventions for controlling myopia progression in children and adolescents. We show that low-concentration atropine (specifically 0.01%, 0.025%, and 0.05%) effectively slows myopia progression with a favorable safety profile. Furthermore, we evaluate optical interventions including orthokeratology (Ortho-K), Defocus Incorporated Multiple Segments (DIMS) spectacles, and peripheral progressive addition lenses. Emerging evidence suggests that combination therapy, integrating low-concentration atropine with an optical intervention, may yield superior effects compared to either modality alone. This review also discusses key issues such as treatment personalization, long-term adherence, and future research directions, providing evidence-based insights for clinicians managing childhood myopia.

Keywords: Myopia Control; Low-Concentration Atropine; Orthokeratology; Defocus Incorporated Multiple Segments (DIMS); Combination Therapy

1. Introduction

The global prevalence of myopia has increased at an alarming rate, with projections indicating that nearly half the world's population will be affected by 2050 (Holden et al., 2016). This trend poses a significant public health challenge, as higher levels of myopia substantially increase the

lifetime risk of sight-threatening ocular pathologies such as myopic maculopathy, retinal detachment, glaucoma, and cataract (Flitcroft, 2012). The economic and social burdens associated with managing myopia and its complications are considerable, driving intense research into effective methods to control its progression, especially during childhood.

Current understanding attributes the myopia epidemic to complex gene-environment interactions, with prolonged near work and limited time outdoors identified as key modifiable risk factors (Holden et al., 2016). This has prompted the development of interventional strategies aiming to slow axial elongation, the primary anatomical correlate of myopia progression. Among these, pharmacological intervention with low-concentration atropine eye drops and optical interventions using specially designed contact lenses or spectacles have emerged as the most extensively studied and clinically adopted approaches (Yam et al., 2019; Lam et al., 2020).

The purpose of this review is to synthesize the current evidence regarding the use of low-concentration atropine and various optical interventions for myopia control in children and adolescents. We evaluate their respective efficacy, safety profiles, and proposed mechanisms of action. Furthermore, we explore the growing evidence base for combination therapy, which integrates these modalities. Finally, we highlight prevailing challenges, gaps in knowledge, and future directions for research and clinical practice in this rapidly evolving field.

2. Main Content

2.1. Low-Concentration Atropine

2.1.1. Efficacy of Different Concentrations

The concentration-dependent efficacy of atropine is well-established. Landmark studies like ATOM1 and ATOM2 demonstrated that while 1% atropine was highly effective, it caused significant side effects like photophobia and near blur; lower concentrations, particularly 0.01%, offered a better risk-benefit balance (Chia et al., 2016; Chua et al., 2006). The subsequent LAMP study provided a clearer hierarchy: 0.05% atropine was most effective in reducing spherical equivalent (SE) progression and axial elongation over three years, followed by 0.025% and 0.01%, all superior to placebo (Yam et al., 2019; Yam et al., 2022; Yam et al., 2020). Emerging evidence suggests dosing frequency matters; twice-daily administration of 0.01% atropine may enhance efficacy compared to once-daily, especially in younger children (Xu et al., 2025).

Table 1. Efficacy of Different Atropine Concentrations in Key Clinical Trials

Concentration	Study	Follow-up	SE Progression (D), Mean ± SD	Axial Elongation (mm), Mean ± SD	Side Effect Grade
1%	ATOM1 (Chua et al., 2006)	2 years	-0.28 ± 0.92	0.02 ± 0.35	Significant

0.5%	ATOM2 (Chia et al., 2016)	2 years	-0.30 ± 0.60	0.27 ± 0.25	Moderate
0.1%	ATOM2 (Chia et al., 2016)	2 years	-0.38 ± 0.60	0.28 ± 0.28	Moderate
0.05%	LAMP Year 1(Yam et al., 2019)	1 year	-0.27 ± 0.61	0.20 ± 0.25	Mild
	LAMP Year2(Yam et al., 2020)	2 years	-0.55 ± 0.85	0.35 ± 0.33	Mild
	LAMP Year3 (Yam et al., 2022)	3 years	-0.78 ± 1.05	0.50 ± 0.43	Mild
0.025%	LAMP Year1(Yam et al., 2019)	1 year	-0.46 ± 0.63	0.29 ± 0.32	Mild
	LAMP Year2(Yam et al., 2020)	2 years	-0.85 ± 0.90	0.48 ± 0.38	Mild
	LAMP Year 3 (Yam et al., 2022)	3 years	-1.10 ± 1.12	0.68 ± 0.48	Mild
0.01%	ATOM2 (Chia et al., 2016)	2 years	-0.49 ± 0.63	0.41 ± 0.32	Very Mild
	LAMP Year1(Yam et al., 2019)	1 year	-0.59 ± 0.67	0.35 ± 0.29	Very Mild
	LAMP Year2(Yam et al., 2020)	2 years	-1.04 ± 0.97	0.59 ± 0.38	Very Mild
	LAMP Year3 (Yam et al., 2020)	3 years	-1.19 ± 1.15	0.75 ± 0.51	Very Mild
Placebo	LAMP Year1-3 (Yam et al., 2019; Yam et al., 2022; Yam et al., 2020)	1-3 years	-0.81 ~ -1.57*	0.41 ~ 0.82*	-

*Data approximated from the original study for comparison.

2.1.2. Mechanisms and Safety

The exact mechanism remains unclear but is believed to be primarily non-accommodative, involving direct action on muscarinic receptors (e.g., M1/M4) in the retina and sclera, influencing pathways like TGF-β and matrix metalloproteinases to inhibit scleral remodeling (Arumugam and

McBrien, 2012). Choroidal thickening and modulation of retinal dopamine signaling are also hypothesized contributors (Wu et al., 2019; Zhang and Wildsoet, 2015).

Safety is significantly improved at low concentrations. Common side effects like mild, transient photophobia and near vision blur are dose-dependent and generally well-tolerated at 0.01% (Chia et al., 2016). Allergic reactions are possible but uncommon. Systemic effects are rare. Rebound progression after cessation is a consideration but appears less pronounced with lower concentrations such as 0.01% and 0.05% (Lee et al., 2024).

2.2. Optical Interventions

2.2.1. Main Modalities and Efficacy

Optical interventions work by manipulating peripheral retinal defocus to provide a signal that slows eye growth.

(1) Orthokeratology (Ortho-K): Overnight wear of rigid gas-permeable lenses that temporarily reshape the cornea, providing clear daytime vision and a myopic defocus ring in the periphery. Meta-analyses show it slows axial elongation by approximately 45% on average (Sun et al., 2015a; Sun et al., 2015b).

(2) Defocus Incorporated Multiple Segments (DIMS) Spectacles: Spectacle lenses with a central correction zone surrounded by multiple micro-lenses creating constant peripheral myopic defocus. A 2-year randomized controlled trial (RCT) showed a 52% reduction in axial elongation compared to single-vision lenses (Lam et al., 2020).

(3) Peripheral Progressive Addition Lenses: Spectacles with added plus power in the lower/near segment to reduce accommodative lag. Evidence for efficacy is less consistent and generally suggests a more modest effect compared to Ortho-K or DIMS (Perea-Romero et al., 2025).

Table 2. Comparison of Major Optical Interventions for Myopia Control

Intervention	Primary Mechanism	Average Efficacy	Key Advantages	Key Limitations/Risks
Orthokeratology	Corneal reshaping, inducing peripheral myopic defocus	Approximately 45% reduction in axial elongation (Sun et al., 2015b)	No daytime optical device; high efficacy	Risk of microbial keratitis; requires expert fitting/compliance
DIMS Spectacles	Continuous peripheral myopic defocus via embedded lenslets	Approximately 52% reduction in axial elongation (Lam et al., 2020)	Non-invasive; excellent safety; easy wear	Potential minor peripheral visual disturbance; cost
Peripheral Progressive Lenses	Reduction of accommodative lag & peripheral defocus modulation	Variable, typically less than above (Perea-Romero et al., 2025)	Non-invasive; suitable for non-contact lens wearers	Weaker evidence base; need adaptation to progressive design

2.2.2. Limitations

Ortho-K carries a risk of microbial keratitis, emphasizing the critical need for strict hygiene and professional supervision (Bullimore and Brennan, 2019). Its efficacy and suitability can be influenced by corneal topography and patient age. Spectacle-based interventions, while very safe, depend heavily on consistent wear time for optimal effect, and their higher cost can be a barrier.

2.3. Combination Therapy

2.3.1. Rationale and Evidence

Combining low-concentration atropine (acting via biochemical pathways) with an optical intervention (acting via physical defocus signals) offers a multi-targeted approach, potentially yielding additive or synergistic effects (Tan et al., 2019; Zheng and Tan, 2022). Clinical studies support this: a randomized trial found Ortho-K combined with 0.01% atropine resulted in significantly less axial elongation at one month than either treatment alone (Tan et al., 2019). Similarly, combining atropine with DIMS spectacles showed enhanced efficacy, particularly in children with rapid baseline progression (Yam et al., 2025).

In addition to the synergistic clinical effects, emerging evidence suggests that the combination of low-concentration atropine and optical interventions may involve complementary molecular mechanisms. Atropine is believed to act on muscarinic receptors (particularly M1 and M4) in the retina and sclera, modulating downstream signaling pathways such as TGF-β and matrix metalloproteinases (MMPs), which are critical for scleral remodeling and axial elongation (Arumugam and McBrien, 2012). Optical interventions, such as DIMS and Ortho-K, induce peripheral myopic defocus, which may influence retinal dopamine release and choroidal thickness, both implicated in eye growth regulation (Zhang and Wildsoet, 2015). The convergence of pharmacological and optical signals may act on shared pathways—such as retinal pigment epithelium-derived signaling—or target distinct but complementary processes, leading to additive inhibition of myopia progression.

2.3.2. Clinical Considerations

Combination therapy is particularly suited for rapid progressors or those inadequately controlled on monotherapy. A pragmatic approach is to initiate one intervention (often optical) and add low-concentration atropine (typically starting with 0.01%) if progression remains concerning after 6-12 months. Individualized decision-making based on progression rate, age, ocular parameters, and adherence is paramount.

2.4. Comparison Between Low-Concentration Atropine and Repeated Low-Level Red-Light Therapy

Repeated low-level red-light (RLRL) therapy has recently emerged as a novel non-pharmacological intervention for myopia control. A multicenter randomized controlled trial by Jiang et al. (2022) demonstrated that RLRL therapy significantly reduced axial elongation and spherical equivalent progression over 12 months, with an efficacy comparable to 0.05% atropine. Unlike atropine, which requires daily eye drops and may cause photophobia or allergic reactions,

RLRL is administered in clinic-based sessions and has shown a favorable safety profile with no reported systemic adverse events.

However, the two interventions differ in mechanism, patient acceptability, and applicability. Atropine acts via biochemical modulation of scleral and retinal pathways, while RLRL is thought to stimulate choroidal thickening and retinal dopamine release through photobiomodulation. In terms of patient selection, atropine may be more suitable for children with good adherence to daily medication, whereas RLRL may benefit those who prefer non-pharmacological, clinic-supervised treatments. Combination of both modalities has not yet been systematically studied, but may offer additive effects in rapid progressors. Future studies should evaluate the safety and efficacy of combining RLRL with atropine or optical devices in pediatric populations. Future research should explore head-to-head comparisons in diverse ethnic groups and age ranges to refine treatment algorithms.

3. Discussion

The evidence synthesized confirms that both low-concentration atropine and specific optical interventions are effective for slowing childhood myopia progression. The choice between them, or the decision to combine them, hinges on a nuanced risk-benefit analysis tailored to the individual patient. Atropine offers a non-optical, systemic-acting approach but requires daily instillation and long-term commitment. Optical interventions like Ortho-K and DIMS provide an immediate visual correction benefit and act locally but have specific contra-indications (Ortho-K) or adherence dependencies (spectacles).

The promising results for combination therapy align with the multi-factorial nature of myopia pathogenesis, suggesting that concurrently targeting different physiological pathways (biochemical and optical) can be more effective. However, most combination studies have relatively short follow-up periods. Longer-term data are needed to confirm sustained efficacy, understand any interactive effects on safety (e.g., corneal health under Ortho-K with concurrent atropine), and establish optimal protocols for initiation and cessation.

A significant challenge remains the inability to reliably predict an individual's response to a given therapy. Future integration of genetic markers (Tedja et al., 2018), biometric data (e.g., baseline choroidal thickness), and environmental factors into predictive models is crucial for advancing personalized myopia management. Furthermore, most evidence derives from Asian populations; more research in other ethnic groups is warranted to ensure global applicability. Emerging therapies, such as repeated low-level red-light therapy which has shown significant efficacy in recent RCTs (Jiang et al., 2022), also warrant further long-term safety and efficacy evaluation.

The emergence of RLRL therapy adds a new dimension to myopia management. Its efficacy, combined with its non-invasive and non-pharmacological nature, makes it an attractive option for children who cannot tolerate atropine or fail to adhere to daily eye drop regimens. However, long-term safety data beyond one year remain limited, and its availability is currently restricted to specialized centers. Therefore, treatment selection should be guided by patient age, progression

rate, compliance potential, and access to follow-up care. Integrating RLRL with existing optical or pharmacological interventions may represent a future direction for personalized myopia control.

4. Conclusions

Low-concentration atropine and advanced optical interventions are cornerstone evidence-based strategies for controlling myopia progression in children. Their distinct mechanisms provide a rationale for combination therapy, which emerges as a potent option for managing rapid progression. Successful implementation requires individualized treatment plans, careful monitoring, and strong patient/parent education regarding adherence and safety. Future research should focus on long-term outcomes, predictive analytics, and refining combination protocols to optimize efficacy and safety, ultimately mitigating the future burden of high myopia. Personalized treatment strategies integrating genetic, biometric, and behavioral factors will be key to optimizing outcomes.

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