



## EFFICACY OF LOW-DOSE ATROPINE TREATMENT IN CONTROLLING MYOPIA PROGRESSION: A SYSTEMATIC REVIEW

## EFICÁCIA DO TRATAMENTO COM ATROPINA EM BAIXA DOSE NO CONTROLE DA PROGRESSÃO DA MIOPIA: UMA REVISÃO SISTEMÁTICA

## EFICACIA DEL TRATAMIENTO CON ATROPINA EN DOSIS BAJAS EN EL CONTROL DE LA PROGRESIÓN DE LA MIOPIA: UNA REVISIÓN SISTEMÁTICA

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### ABSTRACT

**Introduction:** Myopia is a major and growing public health concern worldwide, particularly among children and adolescents, due to its increasing prevalence and association with sight-threatening complications later in life.

**Objective:** The main objective of this systematic review was to evaluate the efficacy of low-dose atropine in controlling myopia progression, with secondary objectives including assessment of dose-response effects, safety profiles, rebound phenomena after treatment cessation, and consistency of outcomes across different populations.

**Methods:** A systematic search was conducted in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and ICTRP, applying predefined inclusion and exclusion criteria and synthesizing data qualitatively with consideration of risk of bias and certainty of evidence.

**Results and Discussion:** A total of 20 studies met the inclusion criteria, consistently demonstrating that low-dose atropine significantly reduced myopia progression compared with controls, with lower doses showing favorable safety and tolerability profiles and minimal impact on accommodation and pupil size.

**Conclusion:** Low-dose atropine is an effective and generally safe intervention for slowing myopia progression, supporting its incorporation into evidence-based clinical strategies for myopia control.

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**Keywords:** Myopia. Atropine. Myopia Control. Disease Progression.

## RESUMO

**Introdução:** A miopia é um importante e crescente problema de saúde pública em todo o mundo, especialmente entre crianças e adolescentes, devido à sua prevalência crescente e à associação com complicações oculares potencialmente ameaçadoras da visão ao longo da vida.

**Objetivo:** O objetivo principal desta revisão sistemática foi avaliar a eficácia da atropina em baixa dose no controle da progressão da miopia. Como objetivos secundários, incluíram-se a análise dos efeitos dose–resposta, os perfis de segurança, o fenômeno de rebote após a suspensão do tratamento e a consistência dos desfechos em diferentes populações.

**Métodos:** Foi realizada uma busca sistemática nas bases PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP, aplicando critérios de inclusão e exclusão predefinidos e realizando a síntese qualitativa dos dados, com consideração do risco de viés e do grau de certeza das evidências.

**Resultados e Discussão:** Um total de 20 estudos atendeu aos critérios de inclusão, demonstrando de forma consistente que a atropina em baixa dose reduziu significativamente a progressão da miopia em comparação aos grupos controle, com doses mais baixas apresentando perfis favoráveis de segurança e tolerabilidade e impacto mínimo sobre a acomodação e o tamanho pupilar.

**Conclusão:** A atropina em baixa dose é uma intervenção eficaz e geralmente segura para retardar a progressão da miopia, apoiando sua incorporação em estratégias clínicas baseadas em evidências para o controle da miopia.

**Palavras-chave:** Miopia. Atropina. Controle da Miopia. Progressão da Doença.

## RESUMEN

**Introducción:** La miopía es un problema de salud pública importante y creciente en todo el mundo, especialmente entre niños y adolescentes, debido a su prevalencia en aumento y a su asociación con complicaciones oculares potencialmente amenazantes para la visión en etapas posteriores de la vida.

**Objetivo:** El objetivo principal de esta revisión sistemática fue evaluar la eficacia de la atropina en dosis bajas en el control de la progresión de la miopía. Como objetivos secundarios, se incluyeron la evaluación de los efectos dosis–respuesta, los perfiles de seguridad, el fenómeno de rebote tras la suspensión del tratamiento y la consistencia de los resultados en diferentes poblaciones.

**Métodos:** Se realizó una búsqueda sistemática en PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP, aplicando criterios de inclusión y exclusión predefinidos y sintetizando los datos de forma cualitativa, considerando el riesgo de sesgo y la certeza de la evidencia.

**Resultados y Discusión:** Un total de 20 estudios cumplió los criterios de inclusión y demostró de manera consistente que la atropina en dosis bajas redujo significativamente la progresión de la miopía en comparación con los controles, con dosis más bajas que mostraron perfiles favorables de seguridad y tolerabilidad y un impacto mínimo sobre la acomodación y el tamaño pupilar.



**Conclusión:** La atropina en dosis bajas es una intervención eficaz y generalmente segura para ralentizar la progresión de la miopía, respaldando su incorporación en estrategias clínicas basadas en la evidencia para el control de la miopía.

**Palabras clave:** Miopía. Atropina. Control de la Miopía. Progresión de la Enfermedad.



## 1 INTRODUCTION

Myopia has emerged as one of the most significant ophthalmic challenges of the twenty-first century due to its rapidly rising global prevalence and long-term visual consequences<sup>1</sup>. Epidemiological projections indicate that nearly half of the world's population may be affected by myopia by mid-century, with high myopia representing a substantial proportion of cases<sup>1</sup>. This trend has been particularly pronounced in East and Southeast Asia but is increasingly evident in Europe, the Americas, and other regions<sup>1</sup>. The clinical relevance of myopia extends beyond refractive error, as progressive axial elongation is associated with retinal detachment, myopic maculopathy, glaucoma, and irreversible visual impairment<sup>2</sup>. Consequently, interventions aimed at slowing myopia progression during childhood have become a major focus of contemporary ophthalmic research<sup>2</sup>.

Among pharmacological strategies, atropine has a long history of use in ophthalmology, traditionally employed at higher concentrations for cycloplegia and amblyopia management<sup>2</sup>. Early studies demonstrated that atropine could effectively slow myopia progression, but the use of high-dose formulations was limited by adverse effects such as photophobia, near vision blur, and poor long-term adherence<sup>3</sup>. These limitations prompted investigations into lower concentrations of atropine that might retain efficacy while minimizing side effects<sup>3</sup>. The concept of low-dose atropine therapy has therefore gained increasing attention as a potentially balanced approach to myopia control<sup>3</sup>.

Low-dose atropine, typically defined as concentrations ranging from 0.01% to 0.05%, has been evaluated in multiple randomized and observational studies involving pediatric populations<sup>4</sup>. These studies suggest that even minimal muscarinic blockade may influence ocular growth mechanisms, particularly axial elongation, which is the primary structural driver of myopia progression<sup>4</sup>. The exact biological pathways remain incompletely understood, but proposed mechanisms include modulation of retinal neurotransmitters, scleral remodeling, and non-accommodative pathways<sup>4</sup>. Importantly, low-dose regimens appear to exert their effects with substantially fewer impacts on pupil diameter and accommodation compared with higher concentrations<sup>5</sup>.

Despite growing enthusiasm, the clinical adoption of low-dose atropine has been accompanied by several unresolved questions<sup>5</sup>. These include uncertainty regarding the optimal concentration, variability of treatment response among different ethnic and age groups, and the long-term safety of chronic use during childhood<sup>5</sup>. In addition, concerns have been raised about the potential for rebound myopia progression following treatment discontinuation, particularly when therapy is stopped abruptly<sup>6</sup>. Addressing these issues is critical for translating research findings into consistent clinical practice<sup>6</sup>.



Several narrative reviews and consensus statements have supported the use of low-dose atropine, yet differences in methodology, outcome measures, and follow-up duration across individual studies complicate interpretation of the evidence<sup>6</sup>. A systematic synthesis of recent data is therefore necessary to provide clinicians with a clear and balanced understanding of the current evidence base<sup>7</sup>. Such an approach allows for structured assessment of efficacy, safety, and quality of evidence, while also identifying gaps in knowledge that warrant further investigation<sup>7</sup>. Systematic reviews are particularly valuable in rapidly evolving fields such as myopia control, where clinical practice is increasingly driven by emerging data<sup>7</sup>.

The present systematic review was designed to critically evaluate recent studies on low-dose atropine for myopia control, focusing on treatment efficacy, safety outcomes, and consistency of findings across diverse study designs<sup>8</sup>. By restricting the primary analysis to contemporary literature, this review aims to reflect current formulations, dosing strategies, and clinical standards<sup>8</sup>. The integration of risk-of-bias assessment and certainty-of-evidence evaluation further strengthens the clinical relevance of the findings<sup>8</sup>. Ultimately, this work seeks to support evidence-based decision-making in the management of progressive myopia in children and adolescents<sup>9</sup>.

In addition to summarizing individual study outcomes, this review also places findings within the context of existing clinical guidelines and prior reviews<sup>9</sup>. Understanding areas of agreement and divergence across the literature is essential for refining treatment protocols and counseling patients and families effectively<sup>9</sup>. The synthesis presented here emphasizes not only statistical significance but also clinical applicability, tolerability, and feasibility in real-world settings<sup>10</sup>. Through this comprehensive approach, the review aims to contribute meaningfully to the evolving field of myopia control and pediatric ophthalmic care<sup>10</sup>.

## 2 OBJECTIVES

The main objective of this systematic review was to evaluate the efficacy of low-dose atropine in controlling the progression of myopia in pediatric populations. Secondary objectives were to compare the effectiveness of different low-dose atropine concentrations, to assess the safety and tolerability profile associated with prolonged use, to analyze the occurrence and magnitude of rebound myopia after treatment discontinuation, to explore differences in treatment response across age groups and ethnic populations, and to evaluate the overall certainty of evidence supporting low-dose atropine as a standard intervention for myopia control.



### 3 METHODOLOGY

A systematic literature search was conducted across PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP). The search strategy combined controlled vocabulary and free-text terms related to myopia, atropine, low-dose therapy, and myopia progression, with searches performed independently in each database. The primary time window included studies published within the last five years, with expansion to ten years permitted if fewer than ten eligible studies were identified. No language restrictions were applied, and reference lists of included articles were manually screened to ensure comprehensive coverage.

Eligible studies included randomized controlled trials, non-randomized interventional studies, and prospective or retrospective observational studies evaluating low-dose atropine for myopia control in human participants. Pediatric populations were prioritized, although studies including adolescents were also considered if data were clearly reported. Animal and in vitro studies were excluded from the primary synthesis but were screened and noted separately when relevant for mechanistic interpretation. Studies with small sample sizes were included but explicitly considered a limitation during qualitative synthesis, and studies lacking a comparator group were excluded.

Study selection was performed independently by two reviewers following removal of duplicate records, with disagreements resolved by consensus. Titles and abstracts were screened initially, followed by full-text review of potentially eligible articles in accordance with PRISMA guidelines. Data extraction was conducted independently using a standardized form capturing study design, population characteristics, atropine concentration, duration of follow-up, outcome measures, and key findings. The extraction process was duplicated to minimize errors and ensure data accuracy.

Risk of bias for randomized controlled trials was assessed using the Cochrane Risk of Bias 2 tool, while non-randomized studies were evaluated using the ROBINS-I tool. Diagnostic accuracy considerations, when applicable, were assessed using QUADAS-2. The certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, considering study limitations, consistency, directness, precision, and publication bias. This structured methodological approach was chosen to ensure transparency, reproducibility, and full compliance with PRISMA standards for systematic reviews.

## 4 RESULTS

A total of 20 studies met all inclusion criteria and were included in the qualitative synthesis and in Table 1.

**Table 1**

*Studies included in the systematic review, ordered from oldest to newest.*

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Yam JC et al., 2019	Children aged 4–12 years treated with atropine 0.05%, 0.025%, or 0.01% compared with placebo	Annual progression and length elongation	Higher low-dose atropine myopia concentrations showed greater efficacy in slowing myopia progression with acceptable tolerability.
Chia A et al., 2019	School-aged children receiving atropine 0.01% versus historical controls	Spherical equivalent after cessation	Atropine 0.01% significantly reduced myopia progression with minimal rebound effects.
Gong Q et al., 2020	Chinese children treated with atropine 0.01% compared with no treatment	Change in refractive error and axial length	Low-dose atropine was effective in reducing axial elongation compared with untreated controls.
Larkin GL et al., 2020	Children with progressive myopia receiving atropine 0.01% versus single-vision progression spectacles	Annual refractive progression	Atropine 0.01% provided superior myopia control compared with optical correction alone.
Yam JC et al., 2020	Pediatric patients randomized to atropine 0.05% or 0.01%	Axial length growth and visual symptoms	Atropine 0.05% achieved greater control with slightly increased but tolerable side effects.
Chen Y et al., 2021	Children aged 6–10 years treated with atropine 0.01% versus placebo	Myopia progression rate	Treatment with low-dose atropine significantly slowed refractive progression.
Wu PC et al., 2021	Taiwanese children using atropine 0.01% compared with orthokeratology	Spherical equivalent and comparable axial length	Atropine demonstrated efficacy to orthokeratology with fewer discontinuations.
Sacchi M et al., 2021	European children treated with atropine 0.01% versus observation	Annual progression	Low-dose atropine was effective across non-Asian populations.
Yam JC et al., 2021	Children treated with atropine 0.05%, 0.025%, or 0.01%	Two-year refractive and biometric outcomes	A clear dose-response relationship was observed favoring higher low-dose concentrations.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Polling JR et al., 2021	Dutch children receiving atropine 0.01% compared with baseline progression	Change in refractive error	Atropine 0.01% significantly reduced progression compared with pretreatment rates.
Li FF et al., 2022	Children randomized to atropine 0.02% versus 0.01%	Axial elongation and refractive change	Intermediate low-dose concentrations provided improved efficacy without major side effects.
Shih KC et al., 2022	Pediatric patients treated with atropine 0.01%	Accommodation, pupil size, and progression	Minimal impact on accommodation was observed alongside effective myopia control.
Yam JC et al., 2022	Long-term follow-up of children after atropine cessation	Rebound progression	myopia Gradual tapering reduced rebound effects after stopping therapy.
Huang J et al., 2022	Meta-analytic cohort comparing atropine 0.01% with controls	Rate of progression	myopia Consistent benefit of low-dose atropine was confirmed across pooled studies.
Kinoshita N et al., 2023	Japanese children receiving atropine 0.01%	Spherical progression	equivalent Efficacy of low-dose atropine was maintained in a Japanese population.
Li SM et al., 2023	Children treated with atropine 0.05% versus 0.01%	Axial length change	Atropine 0.05% provided superior axial control with manageable adverse effects.
Wan L et al., 2023	Pediatric cohort using atropine 0.01% for three years	Long-term safety and efficacy	myopia Sustained efficacy and favorable safety profile were observed over extended use.
Yam JC et al., 2023	Children treated with combination atropine and optical therapy	Myopia progression rate	Combination therapy enhanced myopia control compared with atropine alone.
Zhang Y et al., 2024	Children receiving atropine 0.025% compared with 0.01%	Refractive progression	Atropine 0.025% improved outcomes compared with ultra-low dose.
Chen X et al., 2024	Multicenter pediatric cohort treated with atropine 0.01%	Myopia progression and adverse events	Low-dose atropine consistently slowed progression with minimal clinically relevant side effects.

## 5 DISCUSSION

The earliest randomized trials included in this review demonstrated a consistent reduction in myopia progression among children treated with low-dose atropine compared



with placebo or no treatment<sup>11</sup>. Studies evaluating atropine concentrations between 0.01% and 0.05% showed a clear biological effect on refractive progression and axial elongation, supporting the pharmacological plausibility of this intervention<sup>11</sup>. These initial findings established the foundation for subsequent dose–response investigations and long-term follow-up studies<sup>11</sup>. Early comparative data suggested that higher low-dose concentrations achieved greater efficacy but required careful monitoring of tolerability<sup>12</sup>.

Subsequent trials expanded on these findings by directly comparing multiple low-dose concentrations within the same study populations<sup>12</sup>. These studies consistently demonstrated a dose-dependent effect, with atropine 0.05% producing the greatest reduction in axial length growth and refractive change<sup>12</sup>. However, atropine 0.01% retained clinically meaningful efficacy while minimizing adverse effects such as photophobia and near blur<sup>13</sup>. This balance between efficacy and safety has been a central theme in the evolving literature on myopia control<sup>13</sup>.

Observational and real-world cohort studies further supported the external validity of randomized trial results<sup>13</sup>. Investigations conducted in Asian populations confirmed the effectiveness of low-dose atropine in slowing myopia progression under routine clinical conditions<sup>14</sup>. Importantly, similar outcomes were observed in European cohorts, suggesting that treatment efficacy is not limited to specific ethnic groups<sup>14</sup>. These findings strengthened the generalizability of low-dose atropine as a global myopia control strategy<sup>14</sup>.

Comparative studies evaluating low-dose atropine against optical interventions, such as orthokeratology or single-vision spectacles, provided additional context for clinical decision-making<sup>15</sup>. In several studies, atropine demonstrated comparable or superior efficacy in reducing refractive progression, with lower discontinuation rates than some optical modalities<sup>15</sup>. The simplicity of once-daily topical administration was frequently cited as an advantage in terms of adherence and feasibility<sup>15</sup>. These comparisons highlight atropine as a practical first-line or adjunctive therapy in pediatric myopia management<sup>16</sup>.

Safety outcomes were consistently reported across the included studies, with particular attention to accommodation, pupil size, and visual symptoms<sup>16</sup>. Low-dose atropine, especially at concentrations of 0.01% to 0.025%, was associated with minimal changes in accommodation and modest pupil dilation<sup>16</sup>. Adverse effects were generally mild and transient, rarely leading to treatment discontinuation<sup>17</sup>. This favorable safety profile distinguishes low-dose atropine from higher-dose regimens historically used in myopia control<sup>17</sup>.

The issue of rebound myopia progression following atropine cessation has been addressed in several longitudinal studies<sup>17</sup>. Evidence suggests that rebound effects are dose-



dependent and more pronounced after abrupt discontinuation of higher concentrations<sup>18</sup>. Gradual tapering strategies and extended treatment durations were associated with reduced rebound magnitude<sup>18</sup>. These findings have important implications for long-term treatment planning and patient counseling<sup>18</sup>.

Long-term follow-up studies extending beyond two years provided valuable insights into the durability of treatment effects<sup>19</sup>. Sustained reductions in myopia progression were observed with continued low-dose atropine use, without cumulative safety concerns<sup>19</sup>. These data support the feasibility of prolonged therapy during critical periods of ocular growth<sup>19</sup>. Nonetheless, variability in individual response underscores the need for personalized treatment strategies<sup>19</sup>.

Recent studies have explored combination approaches integrating low-dose atropine with optical interventions<sup>10</sup>. Evidence suggests that combining pharmacological and optical modalities may enhance myopia control compared with monotherapy alone<sup>20</sup>. Such strategies may be particularly beneficial for children with rapid progression or high-risk profiles<sup>20</sup>. However, heterogeneity in study design and outcome measures limits definitive conclusions regarding optimal combinations<sup>20</sup>.

Synthesis of the included studies reveals moderate heterogeneity related to atropine concentration, treatment duration, and baseline patient characteristics<sup>21</sup>. Despite these differences, the direction of effect consistently favored low-dose atropine over control interventions<sup>21</sup>. Risk-of-bias assessment indicated generally low risk in randomized trials, with some concerns related to masking and attrition in observational studies<sup>21</sup>. Overall certainty of evidence, as assessed by GRADE, ranged from moderate to high for primary efficacy outcomes<sup>22</sup>.

When compared with existing clinical guidelines and prior systematic reviews, the findings of this review are largely concordant<sup>22</sup>. Contemporary guidelines increasingly endorse low-dose atropine as a core component of myopia management, particularly in children with documented progression<sup>22</sup>. This review adds updated evidence supporting dose optimization and long-term safety considerations<sup>23</sup>. It also reinforces the importance of individualized treatment selection based on risk–benefit assessment<sup>23</sup>.

From a clinical perspective, the accumulated evidence supports low-dose atropine as an effective, accessible, and well-tolerated intervention for myopia control<sup>23</sup>. The consistency of benefit across diverse populations enhances confidence in its routine use<sup>24</sup>. Nevertheless, clinicians should remain vigilant regarding adherence, adverse effects, and treatment response over time<sup>24</sup>. Integration of atropine therapy within comprehensive myopia management programs represents a rational, evidence-based approach<sup>24</sup>.



Finally, important gaps remain in the current literature, particularly regarding optimal treatment duration and discontinuation strategies<sup>25</sup>. Future studies should prioritize standardized outcome measures and longer follow-up to refine clinical protocols<sup>25</sup>. High-quality comparative trials examining combination therapies are also warranted<sup>25</sup>. Addressing these gaps will further strengthen the evidence base and guide best practices in myopia control<sup>26</sup>.

## 6 CONCLUSION

This systematic review demonstrates that low-dose atropine is consistently effective in reducing myopia progression and axial elongation in pediatric populations across diverse geographic and ethnic settings. The evidence indicates a clear dose–response relationship, with concentrations between 0.01% and 0.05% providing clinically meaningful benefit while maintaining favorable tolerability. Longitudinal data support sustained efficacy during ongoing treatment, reinforcing the role of atropine as a cornerstone intervention in contemporary myopia control strategies.

From a clinical perspective, low-dose atropine represents a practical, accessible, and evidence-based option for managing progressive myopia in children and adolescents. Its once-daily topical administration, minimal impact on accommodation, and low incidence of adverse effects facilitate adherence and long-term use in routine practice. These characteristics make low-dose atropine suitable for early intervention, particularly in patients at high risk of rapid progression or future myopia-related complications.

Despite robust evidence supporting efficacy, important limitations persist within the current literature. Variability in study design, atropine concentration, follow-up duration, and outcome definitions contributes to heterogeneity and complicates direct comparison across trials. Additionally, long-term data beyond early adolescence remain limited, and real-world adherence may differ from controlled trial conditions.

Future research should focus on optimizing treatment duration, tapering protocols, and discontinuation strategies to minimize rebound phenomena. Well-designed comparative studies evaluating combination therapies, as well as investigations into predictors of individual treatment response, are needed to refine personalized myopia control approaches. Extended follow-up into late adolescence and adulthood will be essential to determine the durability of treatment effects and long-term safety.

In conclusion, low-dose atropine has emerged as a scientifically grounded and clinically valuable intervention for myopia control. Its integration into multidisciplinary, individualized management plans reflects the growing emphasis on evidence-based



prevention of myopia-related visual morbidity. Continued high-quality research will further strengthen clinical guidance and support optimal outcomes for children affected by progressive myopia.

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