Biological mechanisms of atropine in myopia control (Review)

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Received May 4, 2026; Accepted July 22, 2026

DOI: 10.3892/mmr.2026.13993

Abstract. Myopia is now recognized as a progressive, potentially sight-threatening disease rather than just a refractive error, with its prevalence rising rapidly worldwide due to its high occurrence, major vision losses and huge public health cost. The World Health Organization estimates that 2.6 billion individuals in the world were myopic in 2020 this figure is projected to increase to 3.364 billion by 2030. Although myopia may be better controlled in its early stages, it may not be completely reversed at this time. Of all of the methods for controlling myopia, atropine, a muscarinic receptor antagonist, remains an effective pharmacological option for slowing myopia progression in children. However, the mechanisms of action of atropine remain to be fully elucidated. This review provided a systematic review for myopia epidemiology, pathogenesis, the effects and side effects, as well as up-to-date possible mechanisms, in the hope of facilitating that researchers in this field elucidate its underlying mechanisms so that clinical ophthalmologists may be able to better control this disease.

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Key words: atropine, myopia, axial length, spherical equivalent, rebound

1. Introduction

Global burden of myopia. Myopia has evolved into one of the most pressing global public health crises of the 21st century, with its prevalence reaching epidemic proportions across all age groups, particularly affecting children and adolescents. The World Health Organization (WHO) estimates that ~2.6 billion people worldwide were myopic in 2020 (1), which are projected to increase to 3.36 billion by 2030 as per the 2025 WHO report (2). In addition, high myopia prevalence is about 2.7%, projected to ~1 billion individuals by 2050 (3). This significant escalation in prevalence is relatively alarming in East Asian countries, where myopia rates among school-aged children exceeded 80% in certain regions, with high myopia (defined as refractive error ≤-6.00 D) affecting >20% of the population (4). The highest rates are in East and Southeast Asia (for example, South Korea, Taiwan, Singapore, China and Japan), where up to 90% of urban teenagers and young adults are myopic (5), but the prevalence rate is only ~30% in the US and other Western nations, and <10% in studied African populations (<10%) (6). Other factors also affect myopia onset and progression. For example, age of onset usually starts at 6-18 years; however, adult-onset and progression into the 30s are common due to prolonged near-work (7). Genetic factor research suggests that children with myopic parents have a higher risk of developing myopia compared to those without (8). Environmental factor study shows higher near-distance work and lower educational levels are associated with increased myopia (9). Gender and demographic factors suggest that females generally have a slightly higher prevalence and progression of myopia compared to males, and urban

living is associated with higher rates than rural living (10). Complications and disease burden also show that uncorrected myopia is the leading cause of distance vision impairment globally and high myopia significantly increases the lifetime risk for diseases such as myopic macular degeneration, retinal detachment, glaucoma and early-onset cataracts (11). A summary of the epidemiology of myopia is provided in Table I.

The clinical significance of myopia extends beyond simple refractive error correction. High myopia is associated with severe ocular complications that can lead to irreversible visual impairment and blindness, including retinal detachment, myopic maculopathy, glaucoma and cataract formation (12). These complications are directly correlated with the degree of myopia, with each additional diopter of myopia increasing the risk of sight-threatening complications by ~20% (1). The economic burden of myopia is also substantial, including costs associated with corrective lenses, frequent eye examinations and treatment of associated complications, placing a significant strain on healthcare systems globally (13).

The pathogenesis of myopia involves a complex interplay between genetic and environmental factors. While genetic predisposition plays an important role, recent evidence suggests that environmental factors, such as outdoor exposure, increased near-work activities and urbanization, have contributed significantly to the rapid rise in myopia prevalence (14). The COVID-19 pandemic has further exacerbated this trend with lockdown measures, leading to decreased outdoor time and increased screen time, resulting in accelerated myopia progression among children (15).

Overview of atropine in myopia control. Among the various therapeutic approaches developed for myopia control, atropine has emerged as an effective pharmacological intervention, with a clinical history spanning over six decades (16). Atropine is a naturally occurring antimuscarinic alkaloid derived from the belladonna plant (*Atropa belladonna*) and other Solanaceae species. It functions as a non-selective competitive antagonist of all five muscarinic (M) acetylcholine receptor subtypes (M1-M5), which are widely distributed throughout ocular tissues, including the cornea, iris, ciliary body, retina, retinal pigment epithelium (RPE), choroid and sclera (17). The evolution of atropine use in myopia control has been marked by significant advances in the understanding of its optimal dosing strategies. Early studies utilized high concentrations of 0.5 to 1%, atropine, which demonstrated that the efficacy in slowing myopia progression was up to 80-95%, associated with side effects including photophobia, blurred near vision and significant rebound phenomenon upon discontinuation (12). The development of low-concentration formulations, for example, 0.01%, has supported its clinical application by providing effective myopia control with mild side effects and reduced rebound (18). The 3-year Low-Concentration Atropine for Myopia Progression (LAMP) study further confirmed the sustained efficacy of continued treatment, with the 0.05% concentration maintaining control of both refractive error progression and axial length elongation (19). However, despite its clinical success, the precise biological mechanisms underlying atropine's anti-myopic effects remain elusive and continue to be the subject of intense research. Traditional theories have focused on atropine's cycloplegic effects and inhibition of excessive accommodation (17). Nevertheless, emerging evidence suggests that its mechanisms of action are more complex and multifaceted, involving interactions with multiple ocular tissues and signaling pathways (20), each of which is discussed below.

2. Review design

Review type. This is a systematic review. To design this systematic review on atropine's mechanism in myopia control, major biomedical databases were searched for peer-reviewed pharmacological and ophthalmological literature. The databases included PubMed (https://pubmed.ncbi.nlm.nih.gov), Web of Science (www.webofscience.com), Scopus (www.scopus.com) and Google Scholar (www.scholar.google.com), as well as Clinical Trial Registries (www.isrctn.com) and ClinicalTrials.gov (www.ClinicalTrials.gov) to identify its ongoing mechanisms.

Search terms. The search terms included Combined Medical Subject Headings (Emtree) and free-text keywords; interventions such as atropine, muscarinic antagonists and anticholinergics; conditions such as myopia, short-sightedness, refractive error, axial elongation and scleral remodeling; and mechanistic information such as mechanism of action, pharmacodynamics, pharmacokinetics, receptors, choroidal thickness (ChT), fibroblasts and signal transduction.

Inclusion and exclusion criteria. The inclusion criteria were studies exploring the pathways of atropine (e.g., non-selective M receptor antagonism), scleral remodeling, choroidal thickening, *in-vivo* animal models, *in-vitro* cell studies or human clinical trials analyzing the biomechanism (e.g., changes in accommodation or retinal signaling). Exclusion criteria were studies failing to define the dose/concentration, articles solely focusing on general myopia epidemiology without evaluating atropine pathways or non-peer-reviewed commentaries without original data.

Screening approach. The screening approach included deduplication screening such as importing all search results into reference management software (e.g., EndNote) to remove duplicates. Title and abstract screening was performed based on relevance to atropine's biological or clinical effects. The full text of retained articles was screened against the rigid inclusion and exclusion criteria. Any disagreements were resolved via consensus or consultation within the authors and online data searches.

Selecting mechanistic vs. clinical evidence. The selection of mechanistic vs. clinical evidence included mechanistic evidence: Extracted from *in-vitro* studies (e.g., scleral fibroblasts) and animal experiments (e.g., chick or guinea pig models). This evidence was selected based on its ability to pinpoint cellular pathways, such as how atropine regulated extracellular matrix (ECM) remodeling, inhibited scleral hypoxia or modulated growth factors like transforming growth factor-β (TGF-β); clinical evidence was extracted from randomized controlled trials (RCTs) and cohort studies [such as the Atropine for the Treatment of Childhood Myopia

Table I. Summary of myopia epidemiology.

Epidemiological category	Characteristics and statistics
Global prevalence (2)	Approximately 30% of the global population; projected to increase to 50% (~3.364 billion individuals) by 2030.
High myopia prevalence (3)	Affects ~2.7% of the global population; projected to 9.8% (~1 billion individuals) by 2050.
Regional differences (5)	Highest rates in East and Southeast Asia (for example, South Korea, Taiwan, Singapore, China and Japan), where up to 90% of urban teenagers and young adults are myopic.
Western/other populations (6)	About 30% prevalence in the US and other Western nations, steadily increasing. Lower rates in studied African populations (<10%).
Age of onset (7)	Typically starts at school age (6-18 years), but adult-onset and progression into 30s are increasingly common because of prolonged near-work (any activity that requires your eyes to focus on close objects within arm's reach, primarily reading, writing, and screen use).
Risk factors (genetic) (8)	Children with myopic parents have a ~2 times higher risk of developing myopia compared to those without.
Risk factors (environmental) (9)	Higher near-distance work and lower educational levels are associated with increased myopia. By contrast, increased time spent outdoors is a good protective factor.
Gender and demographics (10)	Females generally show a slightly higher prevalence and progression of myopia compared to males (20% greater risk). Urban living is associated with higher rates than rural living.
Complications and disease burden (11)	Uncorrected myopia is the leading cause of distance vision impairment globally. High myopia significantly increases the lifetime risk for irreversible conditions such as myopic macular degeneration, retinal detachment, glaucoma and early-onset cataracts.

(ATOM) and LAMP studies]. This evidence was used to validate the biological mechanisms observed in labs translated to humans, specifically measuring outcomes like axial length elongation and spherical equivalent (SE) refraction over time.

3. M receptor-mediated mechanisms

Distribution of M receptors in ocular tissues. M receptors are ubiquitously distributed throughout the eye, playing a significant role in both neuronal and non-neuronal functions that regulate ocular growth and refractive development (21). These G protein-coupled receptors are found in virtually every ocular tissue, including the cornea, iris, ciliary body and ciliary muscles, epithelium of the crystalline lens, retina (particularly in amacrine cells), RPE, choroid and sclera (specifically in scleral fibroblasts) (17).

The ciliary muscle represents the innervated ocular tissues with M receptors, primarily expressing the M3 subtype. These receptors mediate accommodation by controlling ciliary muscle contraction, which in turn affects the shape of the lens and the eye's refractive power (22). However, the role of ciliary muscle M receptors in myopia control extends beyond simple accommodation regulation. A recent study has demonstrated that atropine causes structural changes in the ciliary muscle, including thickening and posterior displacement, rather than simple relaxation, suggesting that its effects on this tissue are more complex than previously understood (23).

In the retina, M receptors are predominantly localized in amacrine cells, where they modulate neurotransmitter release and retinal processing of visual information. The retina contains multiple M receptor subtypes, with M1, M3 and M4 receptors being more prominently expressed. These receptors are involved in regulating dopamine release, which is a well-known neurotransmitter in myopia development (24). The RPE, which forms an interface between the neural retina and the vascular choroid, also expresses muscarinic receptors that are involved in relaying growth regulatory signals from the retina to the sclera (17).

The choroid and sclera represent important sites of M receptor action in myopia control. In the choroid, these receptors regulate vascular tone and blood flow, critical for maintaining adequate oxygen and nutrient supply to the outer retina and sclera (25). The scleral fibroblasts express all five M receptor subtypes, with M1, M3 and M4 receptors being upregulated and M2 and M5 receptors being downregulated in response to myopic stimuli (17). This differential expression pattern suggests that specific receptor subtypes may play distinct roles in scleral remodeling during myopia development.

Re-evaluation of the cholinergic hyperactivity hypothesis. The traditional understanding of atropine's anti-myopic mechanism is rooted in the cholinergic hyperactivity hypothesis that excessive cholinergic activity promotes myopic eye growth, and that atropine blocks this hyperactivity (25). However, recent research has challenged this paradigm, revealing a more complex relationship between cholinergic signaling and myopia development (26).

Studies examining the relationship between atropine and dopamine release have revealed additional complexities. While early research suggested that atropine stimulates dopamine release as part of its anti-myopic mechanism, more recent investigations have shown that atropine only affects the levels of dopamine and its metabolite DOPAC at the highest doses tested, and that dopamine antagonists do not alter atropine's anti-myopic effects (27). These findings suggest that the relationship between cholinergic signaling and myopia is

more nuanced than previously understood and that atropine's mechanisms of action likely involve multiple pathways rather than simple cholinergic antagonism (27).

The re-evaluation of the cholinergic hyperactivity hypothesis has important implications for understanding atropine's mechanism of action and developing more targeted therapeutic approaches. It suggests that atropine's efficacy may result from its ability to modulate multiple receptor systems and signaling pathways rather than simply blocking excessive cholinergic activity (28). This 'shotgun approach' to myopia treatment, as described by Upadhyay and Beuerman, involves atropine interacting with various biological receptors, including α2A-adrenergic receptors, gamma-aminobutyric acid (GABA) receptors, and receptor tyrosine kinases in addition to muscarinic receptors (17).

Non-selective blockade and synergistic effects of M receptors. Atropine's broad-spectrum antagonism of all five M (M1-M5) receptor subtypes likely contributes significantly to its superior efficacy compared to selective muscarinic antagonists. This non-selective blockade enables atropine to simultaneously target multiple pathways involved in ocular growth regulation, creating a synergistic effect that is greater than the sum of its individual receptor interactions (17).

The differential expression and function of M receptor subtypes in various ocular tissues suggest that each subtype plays distinct roles in myopia development. For instance, M1 receptors in the sclera are involved in regulating fibroblast proliferation and collagen synthesis, while M3 receptors in the ciliary body and choroid modulate smooth muscle contraction and vascular tone. The M4 receptors in the retina are implicated in dopamine release regulation, and M2 and M5 receptors may have more specialized functions in specific ocular tissues (17).

Recent evidence indicates that atropine can act as an inverse agonist at M3 receptors and potentially all other M receptor subtypes, as it reduces basal receptor activity in a concentration-dependent manner *in-vitro* (29). This inverse agonistic property may be important in tissues where M receptors exhibit constitutive activity, allowing atropine to not only block agonist-induced effects but also reduce baseline receptor signaling.

The concept of receptor cross-talk and synergistic effects is further supported by studies showing that atropine can interact with non-M receptors including α2A-adrenergic receptors, GABA receptors and receptor tyrosine kinases such as the epidermal growth factor receptor (EGFR) (17). These off-target interactions may contribute to atropine's efficacy by modulating additional signaling pathways involved in ocular growth and development. For example, atropine has been shown to reduce EGFR activity in mouse primary scleral fibroblasts in a dose-dependent manner, suggesting that it can modulate cellular proliferation and ECM remodeling through non-cholinergic mechanisms (17) and via transglutaminase (TGase) (30).

4. Mechanisms targeting choroidal function

Improvement of choroidal microcirculation. The choroid, a highly vascularized tissue that provides essential oxygen and nutrient supply to the outer retina, plays a significant role in myopia development and progression. Recent research has highlighted the importance of choroidal blood flow and thickness in regulating ocular growth, with myopic eyes typically exhibiting choroidal thinning and reduced blood flow. Atropine has been shown to significantly improve choroidal function through multiple mechanisms, representing a key component of its anti-myopic effects (26).

A comprehensive study using C57BL/6 mice with form-deprivation myopia demonstrated that atropine treatment restored both choroidal and scleral thickness while increasing the choroidal vascular index, indicating improved microcirculation (26). The restoration of ChT is significant as it has been identified as a potential biomarker for myopia progression, with each diopter increase in myopia associated with a 13.62 μm reduction in ChT (31).

The mechanisms underlying atropine's effects on choroidal circulation involve multiple pathways. Atropine has been shown to increase retinal dopamine release, which in turn stimulates choroidal thickening (32,33). Studies in chicken models revealed that higher retinal dopamine levels or release correlate with thicker choroid, and that atropine's effects on ChT can be partially blocked by dopamine antagonists (34). This suggests that the retinal-dopamine-choroid axis represents an important pathway through which atropine exerts its anti-myopic effects.

Atropine alters eye structure to slow myopia progression primarily by inducing dose-dependent and transient increases in ChT. A thicker choroid helps protect the sclera from hypoxia and regulates eye elongation. Key findings from human choroidal imaging and intervention studies are summarized in Table II; for example, the WA-ATOM study with 0.01% atropine over 3 years suggested that 68.3% of atropine's structural effect acted directly on the choroid, and waning effects were noted after 18 months (35), and the LAMP study with 0.05, 0.025, 0.01% atropine over 2 years indicated that ~18.5% of the anti-myopia effect was mediated by choroidal thickening and 0.05% was the most optimal dose for early and sustained structural response (36). A recent meta-analysis with various doses of atropine supported that high-dose atropine thickened the choroid via the total choroidal area and changes in stromal area may predict post-rebound efficacy (37).

Furthermore, atropine's ability to improve choroidal microcirculation may involve direct effects on choroidal blood vessels (26). The choroid contains a rich network of blood vessels innervated by both cholinergic and adrenergic fibers, and atropine's blockade of M receptors may lead to vasodilation and increased blood flow. This is supported by studies showing that atropine can prevent the diurnal thinning of the choroid that occurs under normal conditions (38), suggesting that it maintains choroidal vascular tone and perfusion.

The clinical significance of improved choroidal circulation extends beyond simple thickness measurements. Enhanced choroidal blood flow provides better oxygen and nutrient supply to the outer retina and RPE, which is important in myopic eyes where these tissues may be compromised due to mechanical stretching and reduced perfusion. Improved choroidal function may also contribute to better retinal function and reduced risk of myopic complications such as choroidal neovascularization and macular degeneration (25). The mechanisms of action of atropine on choroidal function are summarized in Table III; for example, atropine's mechanisms in choroidal

Table II. Summary of key findings from human choroidal imaging and intervention studies.

Study and dosage	Duration	Effect on ChT	Key mechanisms and findings
WA-ATOM study 0.01% atropine (35)	3 years	Minimal choroidal thickness (ChT) response (ChT remained stable compared to untreated thinning)	68.3% of atropine's structural effect acts directly on the choroid. Waning effects were noted after 18 months.
LAMP study 0.05, 0.025, 0.01% (36)	2 years	0.05%: Significant, sustained thickening; 0.01%: Mild to no significant thickening	Up to 18.5% of the anti-myopia effect is mediated by choroidal thickening. 0.05% is the most optimal dose for early and sustained structural response.
Clinical trial (NCT03949101) 1 vs. 0.01% (33)	6 months	1%: Significant thickening; 0.01%: Little to no choroidal response	High-dose atropine thickens the choroid via the total choroidal area, and changes in stromal area predict post-rebound efficacy.
Recent meta-analysis various doses (37)	Information not available (N/A)	0.05%: Average +25.7 μm; 0.025%: Average +10.7 μm; 0.01%: Clinically insignificant changes	Confirms a concentration-dependent choroidal thickening response to atropine, with ChT serving as a reliable biomarker for treatment response.

Table III. Summary of atropine mechanisms in choroidal function.

Mechanism category	Specific action	Effect on choroid of eye
Vascular (31)	Promotes choroidal vascularity index and blood flow	Increases sub-foveal choroidal thickness through relaxing vascular smooth muscle
	Reverses choroidal thinning by hyperopic defocus	Maintains a thicker, more stable choroid in near-work
Muscarinic (39)	Inhibits cholinergic-nitrergic receptors (M2, M4)	Decreases contraction of non-vascular smooth muscle in the choroid
Molecular (40)	Reduces TGF-β1, promotes basic growth factor 2 activity	Decreases collagen synthesis in the sclera
Cellular (41)	Inhibits hypoxia-inducible factor-1α signaling pathway	Decreases scleral hypoxia and ocular axial growth
Structural (26)	Restores tight junctions	Protects tissue against hypoxia-induced damage

function might be via increase of sub-foveal choroidal thickness through relaxing vascular smooth muscle, via reversal of choroidal thinning by hyperopic defocus, thus maintaining a thicker, more stable choroid in near-work (31); it might also be through muscular receptors to decrease contraction of non-vascular smooth muscle in the choroid (39), via growth factors such as reducing TGF-β1 to promote basic growth factor 2 activity, thus decreasing collagen synthesis in the sclera (40), and via inhibiting the hypoxia-inducible factor-1α (HIF-1α) signaling pathway, thus decreasing scleral hypoxia and ocular axial growth (41).

Mediation of retina-sclera signal transmission. The RPE and choroid play significant roles in relaying growth regulatory signals from the retina to the sclera, representing an important pathway in ocular growth control (42). This retina-RPE-choroid-sclera axis has emerged as an important mechanism in myopia development, and atropine's effects on this pathway are essential for understanding its anti-myopic mechanisms (42).

Research has demonstrated that the RPE acts as an intermediary in transmitting visual signals from the retina to the sclera. Studies using chick models showed that co-culturing RPE from lens-induced myopic eyes with primary scleral fibroblasts increased fibroblast proliferation and decreased glycosaminoglycan content, while co-culturing retina alone with fibroblasts had no effect (17). This finding suggests that the growth regulatory signals initiated by visual defocus are processed and transmitted by the RPE rather than the retina directly.

Atropine's effects on this signaling pathway are multifaceted. The drug has been shown to modulate the expression and activity of various growth factors in the RPE and choroid, including TGF-β and basic fibroblast growth factor (bFGF) (17,43). Specifically, atropine inhibits the expression and secretion of TGF-β2 by blocking M receptors in RPE cells, while decreasing TGF-β1 activity and increasing bFGF2 activity in primary mouse scleral fibroblasts in a dose-dependent manner (17). These growth factors play important roles in regulating ECM remodeling in the sclera, with

TGF-β promoting collagen synthesis and bFGF stimulating fibroblast proliferation.

The choroid's role in signal transmission is also important. The choroid not only provides vascular support but also secretes various factors that influence scleral growth. Studies have shown that the choroid can mechanically influence scleral thickness and volume through its own volume changes, and that it may secrete growth factors that either stimulate or inhibit scleral growth independently of its thickness (44). Atropine's ability to increase ChT and blood flow may enhance its capacity to transmit growth-inhibiting signals to the sclera.

Recent evidence has also highlighted the role of the choroid in regulating scleral hypoxia. Choroidal blood flow is the primary source of oxygen and nutrient supply to the sclera, and reduced choroidal perfusion leads to scleral hypoxia and subsequent ECM remodeling (45). Atropine-associated improvement of choroidal circulation may therefore reduce scleral hypoxia and inhibit the hypoxia-induced signaling pathways that promote myopic eye growth.

5. Mechanisms targeting scleral remodeling

Regulation of scleral fibroblast activity. The sclera, as the outermost fibrous layer of the eye, serves as the primary mechanical barrier that resists intraocular pressure and maintains ocular shape. Scleral fibroblasts are the cellular components responsible for synthesizing and remodeling ECM, making them important targets for myopia control interventions (46,47). Atropine has been shown to exert profound effects on scleral fibroblast biology, influencing their proliferation, survival and synthetic capacity (48).

The p53 pathway represents an important regulator of cellular responses to stress, including hypoxia. Under normal conditions, p53 is maintained at low levels through ubiquitination. However, cellular stress leads to p53 stabilization and activation, resulting in cell cycle arrest, senescence, inflammation (49), apoptosis (50), remodeling and decidualization (51), and a marker of cancer (52). Atropine's modulation of the p53 pathway may prevent excessive fibroblast apoptosis in hypoxic conditions, thereby maintaining the population of cells capable of synthesizing ECM components (53).

The β-catenin pathway is also important in scleral fibroblast function, in regulating cell proliferation and ECM synthesis. β-catenin can function as a transcriptional co-activator when it accumulates in the nucleus, leading to the expression of genes involved in cell cycle progression and matrix synthesis (54). Atropine's effects on β-catenin signaling may promote scleral fibroblast proliferation and enhance their capacity to synthesize collagen and other ECM components, counteracting the degradative processes associated with myopia development (26).

Inhibition of ECM remodeling. The ECM of the sclera undergoes significant remodeling during myopia development, characterized by decreased collagen synthesis, increased collagen degradation and altered composition of proteoglycans. This remodeling results in scleral thinning, reduced mechanical strength and increased susceptibility to expansion under intraocular pressure. Atropine's ability to inhibit these pathological changes represents a mechanism of its anti-myopic action (41).

The effects of atropine on specific ECM components are also important. The drug has been shown to increase the expression of fibronectin (Fn) and collagen type I (Col1a1) and to upregulation of regulator of G-protein signaling 2 in the sclera of form deprivation myopia (FDM) mice (48,55). An immunofluorescence study revealed that FDM induces significant decreases in the expression of these proteins, but atropine treatment substantially reverses these changes (26). Quantitative PCR analysis further confirmed that atropine increases the mRNA levels of Fn while decreasing the expression of HIF-1α, a regulator of the hypoxic response in the sclera (26).

The role of hypoxia in scleral ECM remodeling has emerged as a theme in myopia research. Recent single-cell RNA sequencing studies have shown that hypoxia signaling (HIF-1α) is a major mechanism leading to scleral ECM remodeling (41). In myopic eyes, reduced choroidal blood flow leads to scleral hypoxia, which activates HIF-1α and downstream pathways that promote ECM degradation and myofibroblast differentiation (41). Atropine's ability to improve choroidal circulation and reduce HIF-1α expression represents a mechanism for inhibiting hypoxic damage to the sclera.

Furthermore, atropine's effects on scleral fibroblasts extend to their differentiation state. Hypoxia promotes the transdifferentiation of scleral fibroblasts into myofibroblasts, which are characterized by increased expression of α-smooth muscle actin (α-SMA) and enhanced contractile properties (26). Atropine treatment inhibits this transdifferentiation process, as evidenced by reduced α-SMA expression and maintained expression of fibroblast markers (26). This anti-fibrotic effect may be important in preventing the irreversible changes associated with advanced myopia.

Thickening of the scleral fibrous layer. A clinically significant effect of atropine treatment is its ability to increase scleral thickness in the posterior pole where myopic changes are most pronounced (26). This thickening represents a direct counteraction to the scleral thinning that characterizes myopia development and provides mechanical resistance to further ocular expansion (46).

The mechanisms underlying scleral thickening involve both increased collagen synthesis and decreased collagen degradation (46). Atropine treatment has been shown to increase the production of collagen fibers and improve their organization, leading to a more structurally sound sclera. The drug also affects the glycosaminoglycan (GAG) content of the sclera, which is important for maintaining hydration and mechanical properties (46). Studies in chick models demonstrated that atropine reduces GAG synthesis in form-deprived eyes, which may help maintain the proper balance between hydration and mechanical strength (17).

The clinical implications of scleral thickening are substantial. A thicker sclera provides greater mechanical resistance to the expansion forces generated by intraocular pressure, potentially slowing or halting axial elongation (56). This mechanical benefit is important in high myopia, where scleral thinning can lead to posterior staphyloma formation and associated complications (57). Furthermore, increased scleral thickness

Table IV. Summary of atropine mechanisms in scleral remodeling.

Target level	Mechanism	Specific effect
Cellular in fibroblasts (45)	Inhibiting proliferation	Decreases active fibroblasts in the sclera, reducing tissue remodeling
Molecular in collagen (40)	Increasing type I collagen	Promotes scleral stiffness and tensile strength, preventing further stretching
Molecular in ECM (46)	Reducing TGF-β1/glycosaminoglycans synthesis	Mediates ECM synthesis, inhibiting abnormal remodeling
Enzymatic (30)	Inhibiting TGase	Inhibits TGase activity, which is typically increased in the remodeling process
Signal (55)	Inhibiting regulator of g-protein signaling 2	Mediates signaling in ocular growth
	Activating peroxisome proliferator-activated receptor gamma coactivator 1-α/nuclear factor erythroid 2-related factor 2/heme oxygenase-1	Inhibits mitochondrial dysfunction and ECM degradation
Vascular and metabolic (45)	Reducing hypoxia (hypoxia-inducible factor-1α)	Promotes choroidal blood flow, inhibiting hypoxia-induced scleral remodeling

ECM, extracelluar matrix; TGase, transglutaminase.

may also improve the eye's ability to maintain its shape during accommodative efforts, reducing the accommodative dysfunction that is often associated with myopia (46). The mechanisms of atropine action on scleral remodeling are summarized in Table IV, for example, the main atropine mechanisms in scleral remodeling included cellular mechanisms in fibroblasts by inhibiting proliferation, decreasing active fibroblasts in the sclera, thus reducing tissue remodeling (45), molecular mechanisms by increasing type I collagen to promote scleral stiffness and tensile strength, thus preventing further stretching (40) by reducing TGF-β1/glycosaminoglycans (GAG) synthesis, thus mediating ECM synthesis, inhibiting abnormal remodeling (46).

6. Regulation of neurotransmitter and neurogenic pathways

The dopamine system: A re-evaluated role. The dopamine system has long been considered an important player in myopia development and control, with dopamine serving as a key neurotransmitter that inhibits ocular growth. However, recent research has significantly complicated our understanding of how dopamine interacts with atropine and contributes to myopia control mechanisms.

Early studies suggested that atropine's anti-myopic effects were mediated through the stimulation of retinal dopamine release (58). Atropine may stimulate retinal activity markers ZENK (an immediate early gene that has been employed as a surrogate marker to map neuronal activity in the brain) and c-Fos (an immediate-early transcription factor that is rapidly activated in response to external cellular stimuli, such as growth factors, stress, or neuronal activity) in cells of the inner nuclear layer, indicating increased neuronal activity (24).

However, subsequent research has challenged the notion that dopamine is the primary mediator of atropine's anti-myopic effects. A comprehensive study by Thomson *et al* (27) found that atropine only affected dopamine and DOPAC levels at their highest dose tested (360 nmol), and that dopamine antagonists did not alter atropine's anti-myopic effects. This finding suggests that while dopamine may play a role in atropine's mechanism of action, it is not the sole or even the primary pathway through which the drug exerts its effects.

The complexity of the dopamine system in myopia control is further illustrated by studies examining the interaction between dopamine and other neurotransmitter systems. Research has revealed that dopamine D1 receptors are involved in transmitting signals from GABA-C receptors, with D1 receptor antagonists like SCH-23390 antagonizing the actions of GABA-C receptor antagonists (59). This crosstalk between neurotransmitter systems suggests that the regulation of ocular growth involves a complex network of interactions rather than simple linear pathways.

Recent proteomic studies have provided additional insights into the relationship between atropine, dopamine and myopia control. Analysis of retinal proteins in form-deprived myopic guinea pigs treated with 1% atropine revealed alterations in eukaryotic initiation factor 2 (EIF2) signaling, glycolysis and dopamine secretion pathways (60). Specifically, atropine treatment was associated with changes in proteins involved in dopamine synthesis and release, including alpha-synuclein (SNCA), which was localized to the inner margin of the inner nuclear layer and spread throughout the inner plexiform layer of the retina (60).

The role of dopamine in choroidal function adds another layer of complexity to its relationship with atropine. Studies have shown that retinal dopamine levels are positively correlated with ChT, and that atropine's effects on choroidal thickening are at least partially mediated through dopamine release (34,61). However, the precise mechanisms by which dopamine influences choroidal function remain elusive and may involve direct effects on choroidal blood vessels, modulation of growth factor release or other indirect pathways.

GABAergic system modulation. The GABAergic system represents another component of the neurotransmitter network involved in myopia control, with GABA serving as the primary inhibitory neurotransmitter in the retina. Previous research has revealed complex interactions between the GABAergic and other neurotransmitter systems that are relevant to understanding atropine's mechanisms of action (62).

The relationship between GABA and atropine is interesting given that atropine has been shown to interact with GABA receptors in addition to M receptors. Atropine has been identified as having potential off-target effects at GABA receptors in different ocular tissues (17). While the significance of these interactions is not fully understood, they may contribute to the broad-spectrum effects that make atropine such an effective myopia control agent.

Research on GABA transporters has provided additional insights into the role of the GABAergic system in myopia. Since GABA transporters terminate GABAergic transmission by facilitating reuptake into presynaptic neurons and surrounding glial cells, the reduction in transporter levels could lead to increased extracellular GABA concentrations and enhanced GABAergic signaling (63). This mechanism may contribute to the inhibitory effects on ocular growth that are characteristic of atropine treatment.

The GABAergic system's involvement in retinal processing of visual information is relevant to myopia development. GABAergic amacrine cells are involved in processing contrast and spatial information, and their dysfunction has been implicated in the development of form-deprivation myopia [reviewed in (64)]. Atropine's effects on GABAergic signaling may therefore influence how the retina processes visual information, potentially affecting the growth regulatory signals that are transmitted to other ocular tissues (62).

Serotonergic and other neurotransmitter systems. While the cholinergic, dopaminergic and GABAergic systems have received much attention in myopia research, emerging evidence suggests that other neurotransmitter systems, for example, the serotonergic system, may also play important roles in ocular growth regulation and atropine's mechanisms of action.

Serotonin is synthesized from tryptophan and serves as a neurotransmitter with diverse functions in the retina, including the regulation of circadian rhythms, photoreceptor function and neural processing [reviewed in (65)]. A recent study has implicated serotonin in the control of ocular growth, with some evidence suggesting that serotonin may promote myopic eye growth (66). However, the relationship between serotonin and atropine is complex and not well understood.

The interaction between different neurotransmitter systems adds another layer of complexity to understanding atropine's mechanisms. A study has suggested that 5-hydroxytryptamine receptors may play a role in modulating signaling from GABA receptors to dopaminergic receptors in the retina (67). This crosstalk between neurotransmitter systems suggests that the regulation of ocular growth involves an integrated network rather than independent pathways.

Recent advances in understanding the role of the nervous system in myopia development have been highlighted by genome-wide association studies (GWAS) (68). A comprehensive GWAS in Asian populations identified nine loci associated with high myopia, with gene ontology analysis revealing a significant role of the nervous system in pathogenesis, related to 'synaptic signaling', 'neuronal development' and 'Ras/Rho signaling' (68). These findings suggest that the neural mechanisms underlying myopia are more extensive than previously appreciated and may involve multiple neurotransmitter systems working in concert.

The concept of neurotransmitter systems working synergistically is supported by studies examining the effects of environmental factors on ocular growth (9). Outdoor activity and bright light exposure are known to inhibit myopia development, and these effects are thought to involve the stimulation of dopamine release (69). However, research suggests that multiple neurotransmitter systems may be involved in mediating the protective effects of outdoor activity, including serotonin, norepinephrine and possibly others (70). Atropine's broad-spectrum effects on multiple receptor systems may therefore allow it to mimic or enhance some of these protective mechanisms.

7. Signal transduction pathways

TGF-β/bone morphogenetic protein (BMP) pathway regulation. The TGF-β/BMP signaling pathway represents an important regulatory network in ocular growth and scleral remodeling (71,72). This pathway is involved in several cellular processes, including cell proliferation, differentiation, apoptosis and ECM synthesis, making it an important target for understanding atropine's mechanisms of action in myopia control (73).

TGF-β exists in three isoforms (TGF-β1, TGF-β2 and TGF-β3) in mammals, each with distinct but overlapping functions in ocular tissues. Studies in mammalian models of myopia have demonstrated that all three TGF-β isoforms are expressed in scleral tissue and scleral fibroblasts, and their expression is differentially regulated during myopia development (71,74). Remarkably, downregulation of each isoform occurs within just one day of myopia induction (TGF-β1, -32%; TGF-β2, -27%; TGF-β3, -42%), with TGF-β2 showing a significant decrease by day 5 (-50%) (74).

The BMP pathway, which is closely related to the TGF-β pathway, also plays important roles in ocular growth regulation (72). BMPs are a subgroup of the TGF-β superfamily and are involved in bone and cartilage development, as well as tissue remodeling. While the specific roles of BMPs in scleral remodeling during myopia are not as well characterized as those of TGF-β, recent studies have suggested that BMP signaling may be involved in regulating scleral fibroblast activity and ECM synthesis (75).

The concept of signaling cross-talk between TGF-β/BMP pathways and other signaling networks adds another layer of complexity to understanding atropine's mechanisms. Research has shown that TGF-β/BMP signaling extensively communicates with other pathways, including mitogen-activated protein kinase, phosphatidylinositol-3 kinase/Akt, Wnt, Hedgehog, Notch and cytokine pathways (73). This cross-talk creates a complex regulatory network where atropine's effects on one pathway can have cascading effects on multiple others, potentially explaining the drug's broad-spectrum efficacy in myopia control (76).

Wnt/β-catenin signaling cascade. The Wnt/β-catenin signaling pathway has emerged as a crucial regulator of ocular growth and myopia development, with recent research revealing that dysregulation of this pathway is a characteristic feature of myopia (77). The canonical Wnt pathway, which is mediated through β-catenin, plays important roles in cellular proliferation, differentiation and tissue remodeling, making it a significant target for understanding atropine's mechanisms of action (78).

A comprehensive study by Liu *et al* (77) demonstrated that the canonical Wnt signaling pathway is progressively activated during myopia development in mice. Importantly, inhibition of this pathway using the small molecule inhibitor niclosamide markedly reduced lens thickness, vitreous chamber depth and axial length elongation, resulting in significant myopia inhibition (77). This finding suggests that targeting Wnt signaling pathways has potential as a therapeutic strategy for myopia control.

The clinical relevance of Wnt pathway dysregulation in myopia is supported by studies showing that plasma levels of the Wnt inhibitor dickkopf Wnt signaling pathway inhibitor 1 (DKK-1) are markedly decreased in patients with myopia (77). DKK-1 is a secreted protein that binds to Wnt receptors and inhibits canonical Wnt signaling (79). The decrease in DKK-1 levels suggests that reduced inhibition of Wnt signaling may contribute to the excessive ocular growth seen in myopia.

The relationship between Wnt signaling and other pathways involved in myopia development adds another layer of complexity to understanding atropine's mechanisms. Research has shown that Wnt signaling can interact with TGF-β/BMP pathways, creating a network of regulatory interactions that control scleral remodeling (80). Additionally, the Wnt pathway has been implicated in the regulation of matrix metalloproteinases (MMPs), including MMP-2, MMP-3, MMP-7 and MMP-9, some of which are involved in myopia through regulation of scleral collagen metabolism (72).

Studies have also highlighted the role of Wnt signaling in the retina during myopia development. Research in form-deprived myopic mice showed increased expression of Wnt2b, Fzd5 (a Wnt receptor) and β-catenin in the retina (81). The Wnt agonist Norrin had opposite effects, suggesting that the Wnt pathway may be involved in retinal processing of visual signals that regulate eye growth. Atropine's effects on retinal Wnt signaling may therefore contribute to its overall anti-myopic efficacy (82).

Growth factor networks

Vascular endothelial growth factor (VEGF). The VEGF pathway represents a component of the ocular growth regulatory network, in relation to choroidal function and scleral hypoxia (83). VEGF is a dimeric glycoprotein responsible for angiogenesis and vascular permeability, and its role in myopia development has become increasingly recognized (83).

Studies in human subjects have revealed significant differences in VEGF expression and choroidal characteristics among emmetropic, non-high myopic and high myopic groups (84,85). The myopic groups showed thinner ChT, reduced choriocapillaris vessel density and lower VEGF content in tears compared to emmetropic subjects (84). Importantly, VEGF content in tears showed a progressive decrease from emmetropic to non-high myopic to high myopic groups (86), suggesting that reduced VEGF signaling may contribute to the choroidal abnormalities seen in myopia.

The relationship between VEGF and atropine is complex and multifaceted. Atropine has been shown to increase retinal dopamine release, which in turn stimulates choroidal thickening (32). Since dopamine and VEGF are both involved in regulating choroidal blood flow and ChT, there may be interactions between these pathways. Additionally, atropine's effects on choroidal circulation may influence VEGF expression and activity through improved oxygen and nutrient supply to the choroid (87).

Basic fibroblast growth factor (bFGF). The broader growth factor network involves multiple other factors that interact with VEGF in complex ways. bFGF, also known as FGF-2, is another key player in ocular growth regulation (88). bFGF is a potent mitogen and inhibitor of collagen synthesis, and its regulation by atropine may help balance the effects of other growth factors like TGF-β, which promotes collagen synthesis (89).

HIF-1α. The HIF-1α pathway has emerged as an important mechanism in myopia development, through its role in mediating scleral hypoxia and subsequent ECM remodeling (41). This pathway represents a link between reduced choroidal blood flow, scleral hypoxia and the pathological changes that characterize myopic eye growth (41).

Recent single-cell RNA sequencing studies have provided compelling evidence that hypoxia signaling, specifically HIF-1α, is a major mechanism leading to scleral ECM remodeling (41). Using protein-protein interaction networks, researchers found interactions between human myopia risk genes and genes involved in hypoxia, suggesting that genetic susceptibility to myopia may be partly mediated through hypoxia-related pathways [reviewed in (45)].

The clinical significance of HIF-1α in human myopia is supported by gene set enrichment analysis of genome-wide association study data from 593 patients with high myopia (≤-6 D) (90). This analysis revealed that the HIF-1α signaling pathway was significantly enriched in patients with high myopia (≤-10 D), suggesting that HIF-1α signaling contributes to human myopia by mediating interactions between genetic and environmental factors (90).

The HIF-1α pathway regulates multiple downstream targets that are relevant to scleral remodeling. Under hypoxic conditions, HIF-1α activates genes involved in glycolysis, angiogenesis and ECM remodeling (91). One important target is VEGF, which is upregulated by HIF-1α and promotes angiogenesis and vascular permeability (92). Atropine's effects on HIF-1α may therefore influence VEGF expression and contribute to the drug's effects on choroidal circulation (93).

Gene expression regulation and epigenetic mechanisms. The regulation of gene expression in ocular tissues represents a mechanism through which atropine exerts its anti-myopic effects. Recent advances in molecular biology techniques, such as next-generation sequencing and proteomics, have provided significant insights into the complex transcriptional and post-transcriptional networks that are modulated by atropine treatment (94).

Bioinformatics analysis of these regulated proteins revealed involvement of three major pathways: EIF2 signaling, glycolysis and dopamine secretion (60). The most significantly regulated proteins were found to be closely connected to SNCA, which was localized to the inner margin of the inner nuclear layer and spread throughout the inner plexiform layer of the retina (60).

The EIF2 signaling pathway is interesting, as it regulates the initiation of protein synthesis in response to cellular stress (95). The finding that atropine modulates EIF2 signaling suggests that the drug may influence the overall protein synthesis machinery in retinal cells, potentially affecting the production of growth factors, receptors and other proteins involved in ocular growth regulation (60).

Epigenetic mechanisms, including DNA methylation, histone modifications and non-coding RNA regulation, represent additional layers of gene expression control that may be relevant to myopia development and atropine's effects (96). Studies have shown that hypoxic glycolytic reprogramming and histone lactylation in the sclera contribute to the transdifferentiation of scleral fibroblasts into myofibroblasts (97). Specifically, increased lactate production during hypoxia induces H3K18 lactylation, which promotes Notch1 expression and subsequently induces fibroblast-to-myofibroblast transdifferentiation (45).

The relationship between epigenetic modifications and atropine treatment is beginning to be explored. While direct evidence of atropine's effects on histone modifications is limited, the drug's ability to reduce scleral hypoxia may indirectly influence epigenetic modifications by reducing the metabolic changes (such as increased lactate production) that lead to histone lactylation (98). Additionally, atropine's effects on growth factor signaling may influence DNA methylation patterns and histone modifications through changes in transcriptional activity (99).

MicroRNAs (miRNAs) represent another important class of molecules involved in gene expression regulation. A study has identified specific miRNA-mRNA interactions involved in atropine-treated corneal epithelial cells, including hsa-miR-651-3p-EPHA7, hsa-miR-3148-TMEM108 and hsa-miR-874-5p-TBX6 (94). While these studies focused on corneal cells rather than the tissues directly involved in myopia, they suggest that atropine may exert its effects through miRNA-mediated regulation of gene expression (94).

Nuclear receptors. Peroxisome proliferator-activated receptors (PPARs) in the nuclear hormone receptor superfamily belong to the ligand-initiated transcription factors. Among the PPAR isoforms, PPARγ has been shown to be inhibited by hypoxic stress during adipocyte differentiation (100). A study has found that PPARγ activation and antagonism can affect the regulation of scleral hypoxia and collagen expression levels (101). The inverse relationship between PPARγ and HIF-1α expression levels regulates collagen expression and controls the development of FDM, providing a new intervention method for treating myopia by targeting scleral hypoxia (101).

The relationship between PPARγ and atropine is interesting given the drug's effects on choroidal circulation and scleral hypoxia (26). By improving choroidal blood flow and reducing scleral hypoxia, atropine may prevent the inhibition of PPARγ that occurs under hypoxic conditions (26). This could lead to increased PPARγ activity and subsequent regulation of genes involved in lipid metabolism, inflammation and ECM remodeling (102).

Other nuclear receptors and transcription factors that may be relevant to atropine's mechanisms include retinoic acid receptors and retinoid X receptors, which are involved in visual transduction and ocular development (103). Additionally, the cAMP response element-binding protein and nuclear factor κB are transcription factors that are activated by various signaling pathways and may be influenced by atropine treatment (104).

8. *In-vitro*, animal models and proteomics studies

In-vitro studies. *In-vitro* studies demonstrate that atropine exerts anti-myopic effects directly on scleral fibroblast ECM biosynthesis and downregulating hypoxia or inflammation. It works by increasing collagen production, altering gene expression and preventing cell damage, proving its direct role in stabilizing and thickening the sclera. For example, *in-vitro* studies using mouse scleral fibroblasts (MSFs) have demonstrated that atropine protects these cells from hypoxia-induced damage (26). When MSFs are exposed to chemical hypoxia induced by $Na_2S_2O_4$, they experience cytoskeletal disruption and impaired proliferative capacity (105). However, atropine treatment preserves cytoskeletal integrity and maintains normal cellular functions through the modulation of several signaling pathways, including p53 and β-catenin (26). Recent research has also highlighted the role of scleral fibroblasts in mediating atropine's effects on scleral thickness (48). *In-vitro* studies have shown that atropine can directly affect the synthetic activity of scleral fibroblasts, increasing their production of collagen and other ECM components (48). The drug achieves this through the modulation of various signaling pathways, including the TGF-β pathway, which is an important regulator of collagen synthesis. Atropine treatment has been shown to decrease TGF-β1 activity in a dose-dependent manner, which may help maintain optimal collagen synthesis without excessive fibrosis (17). The functional significance of TGF-β isoform regulation is highlighted by *in-vitro* studies showing that all three isoforms can increase collagen production in primary scleral fibroblasts in a dose-dependent manner (74). Changes in TGF-β levels that mimic those observed during myopia induction cause a ~15% reduction in collagen synthesis, which is similar to changes reported *in vivo* (74). This finding suggests that the early alterations in TGF-β expression may reflect a role for these cytokines in mediating the retinoscleral signal that controls myopic eye growth (74,106). Atropine's effects on the TGF-β pathway are complex and multifaceted. The drug has been shown to inhibit the expression and secretion of TGF-β2 by blocking M receptors in RPE cells (17). Additionally, atropine decreases TGF-β1 activity levels and increases bFGF2 activity levels in primary mouse scleral fibroblasts in a dose-dependent manner (17). These changes in growth factor activity may help maintain the balance between ECM synthesis and degradation, preventing the excessive matrix remodeling that characterizes myopia development (46). Major *in-vitro* studies are summarized in Table V; for example, the main *in-vitro* studies indicated that atropine significantly upregulated type I collagen and

Table V. Summary of major *in-vitro* studies.

Study/focus	Cell model	Key findings and mechanism of action	Link and support
Extracellular matrix biosynthesis modulation (48)	Human scleral fibroblasts	Atropine significantly upregulated type I collagen and fibronectin biosynthesis, thickening the sclera and reducing its elasticity/tendency to elongate.	Supported by clinical and experimental evidence.
Transcriptomic and gene analysis (26)	Scleral fibroblasts	Atropine induced differentially expression of genes (e.g., anti-remodeling pathways). Concentration-dependent changes, with low doses mitigating potential cytotoxicity.	Aligned with clinical data and current myopia management protocols.
Hypoxia and cytoskeletal integrity (107)	Mouse scleral fibroblasts	Atropine protected fibroblasts from hypoxia-induced damage, preserved cytoskeletal integrity, modulated P53/β-catenin pathways and reduced hypoxia-inducible factor-1α hypoxia markers.	This mechanism is supported by animal studies and clinical evidence.

fibronectin biosynthesis, thickening the sclera and reducing its elasticity/tendency to elongate in human scleral fibroblasts (48), that atropine induced differentially expression of genes (e.g., anti-remodeling pathways), which were concentration-dependent, with low doses mitigating potential cytotoxicity in scleral fibroblasts (26), and that atropine protected fibroblasts from hypoxia-induced damage, preserved cytoskeletal integrity, modulated P53/β-catenin pathways and reduced HIF-1α hypoxia markers in mouse scleral fibroblasts (107).

Animal models. Animal models are foundational for studying the complex, vision-driven mechanisms of myopia and validating pharmacological interventions like atropine. Research generally focuses on FDM, lens-induced defocus LIM and genetic models to evaluate axial elongation and scleral remodeling. For example, in a pivotal study by Thomson *et al* (27), various cholinergic agonists, including muscarinic agonists (muscarine, pilocarpine), nicotinic agonists (nicotine) and non-specific cholinergic agonists (oxotremorine, carbachol), were administered to chicks with FDM. Paradoxically, all these agonists were found to inhibit rather than to activate FDM development, in contrast to no effect on normal ocular development. This finding directly contradicts the cholinergic hyperactivity hypothesis, as increased cholinergic stimulation should theoretically worsen myopia if high cholinergic activity is the underlying cause (27). Comprehensive studies using FDM mouse models have demonstrated that atropine treatment significantly reduces axial elongation and ECM remodeling, as indicated by a decrease in collagen volume fraction (26). The drug achieves this through multiple mechanisms, including the modulation of MMPs and their tissue inhibitors (TIMPs). MMPs, particularly MMP-2 and MMP-9, are important enzymes responsible for collagen degradation in the sclera (26). Atropine treatment has been shown to downregulate the expression and activity of these MMPs while upregulating TIMPs, thereby shifting the balance toward ECM preservation rather than degradation (17).

In FDM mice, atropine restored scleral thickness in the central, intermediate and peripheral regions, effectively counteracting the thinning effects induced by form deprivation (26). This restoration of scleral thickness is important in the posterior sclera, where the mechanical stresses are great and where pathological changes associated with high myopia are severe (108). Intravitreal injection of atropine in chicken eyes was found to increase vitreal dopamine levels, with a peak difference between treated and control eyes occurring after 2 h (24). This effect was enhanced by bright light exposure, suggesting a synergistic relationship between atropine and environmental factors known to influence dopamine release. Studies in FDM mouse models have shown that atropine treatment can modulate β-catenin expression and activity in the sclera (26). Specifically, atropine treatment was associated with increased expression of p53 and zona occludens 1 (a tight junction protein), suggesting that the drug may influence multiple signaling pathways that converge on β-catenin regulation (26).

Atropine's effects on the HIF-1α pathway are significant given its role in improving choroidal circulation. Studies in FDM mouse models have shown that atropine treatment reduces the expression of HIF-1α in both scleral and choroidal tissues (26). This reduction in HIF-1α expression is associated with improved ChT and vascular index, suggesting that atropine's ability to improve choroidal microcirculation reduces scleral hypoxia and inhibits hypoxia-induced pathological changes (26). Research has also revealed the role of HIF-2α in scleral remodeling. A study showed that scleral HIF-2α knockdown significantly delays myopia development in FDM mice, with inhibition of scleral MMP-2 upregulation and COL1α1 reduction (107). This finding suggests that targeting both HIF-1α and HIF-2α may be important for effective myopia control.

Experimental studies in animal models have provided additional insights into VEGF's role in myopia. In a guinea pig model of form-deprivation myopia, researchers observed reduced choroidal vasculature along with significant downregulation of choroidal VEGF expression (87).

The insulin-like growth factor 1 (IGF-1) pathway represents another important component of the growth factor network. Research has shown that the combination of IGF-1 and FGF-2 can induce excessive ocular growth and severe myopia in chick models (109). This finding suggests that the balance between different growth factors is crucial for normal ocular development, and that perturbations in this balance can lead to pathological eye growth. Atropine's effects on

Table VI. A breakdown of the primary animal models utilized in atropine-control myopia research.

Animal model	Common induction methods	Key ocular advantages and relevance	Primary anti-myopia findings
Chick (110)	FDM (diffusers), LIM (minus lenses)	Relatively large eyes (8-14 mm), rapid eye growth (100 μm/day), highly sensitive to optical defocus.	Atropine significantly protects against axial elongation, decreases scleral cell proliferation and boosts dopamine release. Supported by clinical evidence such as ATOM studies.
Mouse (111)	FDM, LIM, genetically modified/knock-outs (e.g., Cathepsin H, alkB homolog 5, RNA demethylase)	Amenable to genetic manipulation, fully mapped, high photopic visual input required.	Atropine effectively reduces axial length growth, regulates scleral extracellular matrix (fibronectin/ collagen) remodeling and alters electroretinogram responses. Supported by clinical evidence such as ATOM studies.
Guinea pig (112)	FDM, LIM	Excellent visual acuity, very similar biochemical markers and scleral responses to humans.	Validates that atropine inhibits axial elongation independent of its accommodative (pupil-dilating) effect, targeting non-accommodative pathways. Supported by clinical evidence such as ATOM and LAMP studies.
Tree shrew (113)	FDM, LIM	Diurnal animals with highly developed visual pathways and accommodative dynamics similar to primates.	Demonstrates that M receptors (specifically M1 and M4) play a role in inhibiting ocular growth pathways. Supported by clinical evidence.

FDM, form deprivation myopia; LIM, lens-induced myopia; ATOM, atropine for the treatment of myopia; LAMP, low-concentration atropine for myopia progression.

multiple growth factor pathways may therefore represent an important mechanism for maintaining the proper balance of growth signals (26). The major animal models for atropine to control myopia are summarized in Table VI; for example, the main breakdown of the primary animal models utilized in atropine-control myopia research included that atropine significantly protects against axial elongation, decreases scleral cell proliferation and boosts dopamine release in a chick model (110), that atropine effectively reduces axial length growth, regulates scleral extracellular matrix (fibronectin/collagen) remodeling and alters electroretinogram responses in a mouse model (111), that atropine inhibits axial elongation independent of its accommodative (pupil-dilating) effect, targeting non-accommodative pathways in a guinea pig model (112), and that M receptors (specifically M1 and M4) play a role in inhibiting ocular growth pathways in a tree shrew model (113).

Proteomics studies. Proteomics studies on myopia control reveal that atropine works by regulating scleral extracellular ECM remodeling, modulating amino acid metabolism, and altering key metabolic and visual signaling pathways in the retina. Studies in chick models have demonstrated that GABA-A/C receptor agonists can modulate the efficacy of dopamine receptor agonists. Specifically, the GABA-A/C receptor agonist muscimol negates the efficacy of dopamine D_1 (D1) receptor agonist SKF-38393 but does not affect the activity of D2/4 receptor agonist quinpirole (114). This selective interaction suggests that the GABAergic system may differentially regulate different aspects of dopamine signaling, potentially providing a mechanism for fine-tuning ocular growth responses. A study found that atropine reduced protein levels of GABA transporter-1 (GAT-1) and, to a lesser extent, GAT-3, in mouse retinas with lens-induced myopia (17). The molecular evidence by next-generation proteomics revealed that retinal EIF2 signaling is associated with glycolysis and dopamine secretion via SNCA in atropine treatment of myopia in the FDM-induced guinea pig model (60). Recent proteomic analysis in humans and mice suggests that the innate immune system in myopia was mediated via granzyme A and the S100 family (115). Inhibiting such inflammatory pathways might suppress abnormal immune responses and scleral remodeling associated with axial elongation. However, this approach remains debated. In addition, atropine, a muscarinic antagonist, may inhibit myopia progression through retarding thinning of the sclera and choroid in mice and chick models, via blocking M receptors in RPE cells, which mediates TGF-β1, reducing scleral hypoxia and ECM degradation (39,44). Major proteomics studies are summarized in Table VII; for example, the main proteomics studies on myopia control included that atropine reduces retinal GABA levels, restoring balanced axial growth signals in the eye in a mouse model (62), that

Table VII. Summary of proteomics studies on myopia control.

Study focus	Animal/human model	Key protein/pathway alterations	Anti-myopic mechanism summary
GABAergic signaling (62)	Mice	Elevated GABA transporter 1 in myopic eyes is significantly reduced by atropine.	Atropine reduces retinal GABA levels, restoring balanced axial growth signals in the eye. While there are no direct, non-invasive measurements of human retinal GABA levels, this mechanism heavily aligns with the established clinical efficacy of atropine in human patients.
Metabolic pathways (60)	Guinea pigs	Downregulation of eukaryotic initiation factor 2 signaling and glycolysis proteins; upregulation of dopamine secretion.	Suppresses abnormal retinal energy use (glycolysis) and promotes dopamine release, which inhibits excessive eye elongation. Remained experimental or hypothesis-generating, no direct clinical evidence.
Inflammatory pathways (115)	Mice and humans	Reversal of inflammatory signaling activity (granzyme A and S100 family signaling).	Suppresses abnormal inflammatory and innate immune responses commonly seen in developing myopia. The concept linking inflammatory signaling to myopia development is supported by emerging proteomic and epidemiological evidence. However, it is still an area of active translational research rather than established clinical therapy.
Choroidal and scleral remodeling (39,44)	Mice and chicks	Modulation of TGF-β1, reduction in scleral hypoxia and decreased extracellular matrix remodeling.	Prevents the thinning of the choroid and sclera by blocking muscular receptors on retinal pigment epithelium cells. These animal and *in-vitro* findings are well supported by clinical evidence, which forms the scientific foundation for modern myopia control using muscarinic antagonists like atropine.

GABA, gamma-aminobutyric acid.

myopia might be controlled by atropine by downregulating eukaryotic initiation factor 2 (EIF2) signaling and glycolysis proteins and upregulating dopamine secretion, thus inhibiting excessive eye elongation in a guinea pig model (60), and that atropine modulated TGF-β1, reduction in scleral hypoxia and decreased ECM remodeling, thus preventing the thinning of the choroid and sclera by blocking muscular (M) receptors on retinal pigment epithelium (RPE) cells in mouse and chick models (39,44). The mechanisms of atropine in controlling myopia are summarized in Fig. 1.

9. Clinical evidence and efficacy

Low-concentration atropine trials: ATOM, LAMP and Childhood Atropine for Myopia Progression (CHAMP). In ATOM1, 400 children aged 6 to 12 years were treated with 1.0% atropine vs. placebo for 2 years. The key findings and efficacy outcomes were that 1.0% atropine eye drops significantly slowed the progression of myopia. However, patients in the 1.0% group experienced clinically challenging side effects, including significant pupil dilation (mydriasis) and loss of accommodation (near-vision blur) (116). The ATOM2 study was performed in 400 children aged 6 to 12 years, who received 0.5, 0.1 or 0.01% atropine, or placebo for 5 years in total (2 years active treatment, 1 year washout, and up to 2 years of re-treatment for progressing patients) (117). The key findings and efficacy outcomes were that there was a dose-dependent response, showing that higher doses (0.5 and 0.1%) slightly controlled myopia progression more than 0.01%, but were associated with pupil dilation and blurry near-vision. After stopping the drops, the 0.01% dose had the lowest rate of rebound myopia, suggesting that 0.01% might serve as a globally recognized standard for low-dose myopia control. In the ATOM3 trial, 207 children aged 5 to 9 years were treated with 0.01% atropine vs. placebo for 2 to 2.5 years (followed by a 1-year washout) (118). The key findings were that while 0.01% atropine was well-tolerated, which slowed myopia progression and axial elongation, the treatment effect compared to placebo was modest.

The LAMP study series represent comprehensive investigations into the efficacy and safety of low-concentration atropine for myopia control (119,120). These landmark trials have changed clinical practice by establishing evidence-based guidelines for atropine use in children with myopia (119).

The LAMP Phase 1 study, published in 2019, was a randomized, double-blind, placebo-controlled trial involving 438 children aged 4 to 12 years with myopia of at least-1.0 diopter (119). Participants were randomized to receive 0.05,

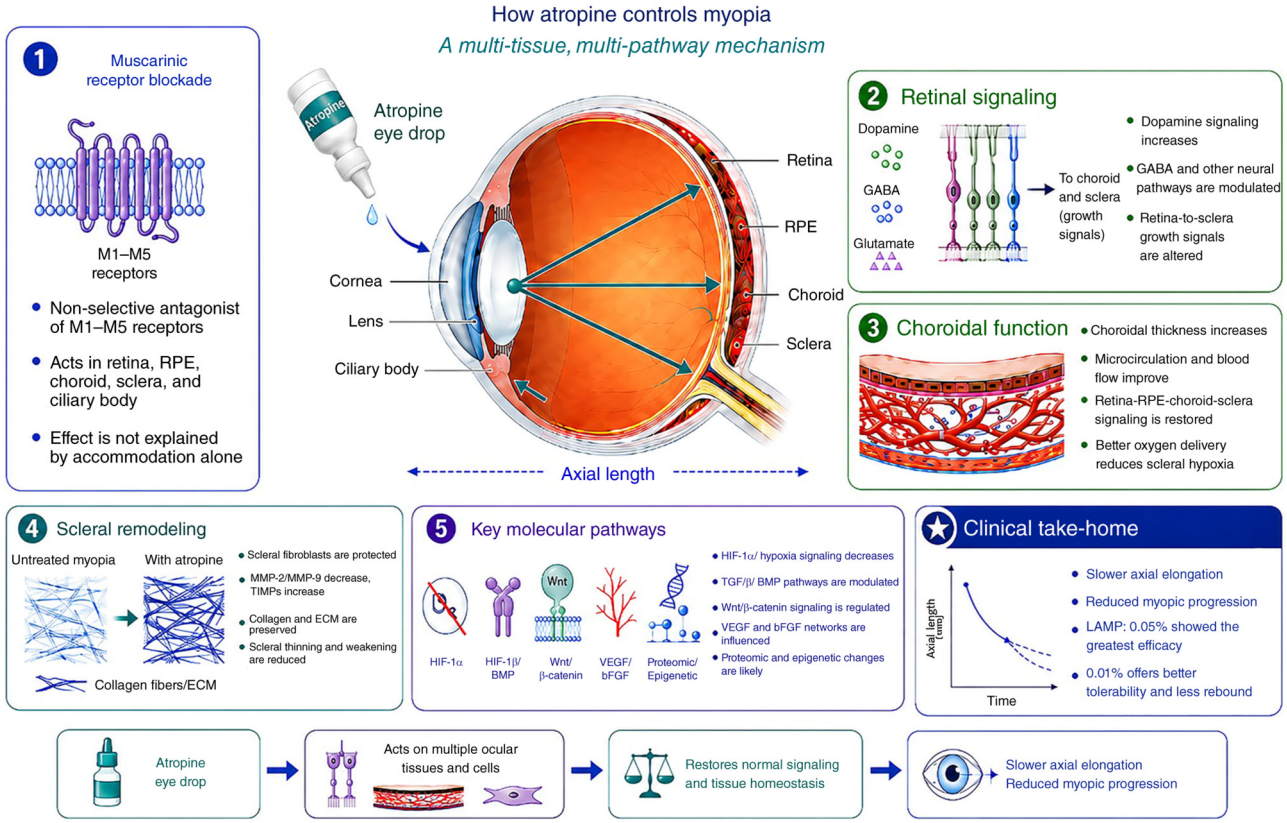

Figure 1. How atropine controls myopia. Atropine controls myopia by acting as a muscarinic antagonist that triggers retinal and scleral signaling, increases dopamine and choroidal thickness, and suppresses scleral hypoxia and ECM breakdown, including i) Neurotransmitter and vascular changes: A) dopamine: Atropine increases retinal dopamine and its metabolite DOPAC (3,4-dihydroxyphenylacetic acid) is a major breakdown product created when the brain breaks down the chemical messenger dopamine, suppressing growth signals that drive eye elongation. B) GABA: Atropine alters GABAergic transmission by reducing GAT such as GAT-1 and GAT-3 transporter levels in the retina. C) Choroidal thickness and oxygen delivery: Atropine rapidly thickens the choroid, boosts the CVI, improves microcirculation and enhances oxygen delivery to counter tissue stress. ii) ECM and scleral structural remodeling: A) Scleral thinning: Myopia causes the back of the eye (sclera) to thin and stretch; atropine restores and protects scleral thickness. B) ECM, MMPs and TIMPs: Atropine regulates ECM by balancing MMPs and TIMPs, preventing the breakdown of collagen type I needed to keep the sclera strong. iii) Retinal signaling pathways: A) HIF-1α & VEGF: Atropine reduces the hypoxia marker HIF-1α and VEGF to normalize blood supply. B) TGF-β, BMP, Wnt and bFGF: Atropine influences growth factors and signaling cascades, including TGF-β, BMP, Wnt/β-catenin pathways and bFGF to inhibit the structural cascades causing axial elongation. M1-M5, muscarinic receptor subtype 1-5; CVI, choroidal vascular index; RPE, retinal pigment epithelium; GABA, gamma-aminobutyric acid; Gat, GABA transporters; MMP, matrix metalloproteinase; TIMPs, tissue inhibitors of metalloproteinases; ECM, extracellular matrix; HIF, hypoxia-inducible factor; TGF, transforming growth factor; BMP, bone morphological protein; Wnt, wingless-related integration site; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; LAMP, low-concentration atropine for myopia progression.

0.025 or 0.01% atropine, or placebo eye drops once nightly for 1 year. The results demonstrated a concentration-dependent effect, with mean SE changes of -0.27±0.61, -0.46±0.45, -0.59±0.61 and -0.81±0.53 D in the 0.05, 0.025, 0.01% and placebo groups, respectively (P<0.001). Axial length changes showed similar trends, with respective mean increases of 0.20±0.25, 0.29±0.20, 0.36±0.29 and 0.41±0.22 mm, respectively (P<0.001) (119).

The two-year follow-up (LAMP Phase 2) in 474 children aged 4 to 9 years confirmed the sustained efficacy of continued treatment (119). Over the 2-year period, mean SE progression was 0.55±0.86, 0.85±0.73 and 1.12±0.85 D in the 0.05, 0.025 and 0.01% atropine groups, respectively (P=0.015, <0.001 and 0.02 for pairwise comparisons) (119). Importantly, the efficacy of 0.05 and 0.025% atropine remained similar between years one and two, while the 0.01% group showed mild improvement in the second year (P=0.04) (121).

The three-year results (LAMP Phase 3) in 438 children aged 4 to 12 years provided crucial insights into the long-term efficacy and rebound phenomenon (19). During the third year, children were randomized to either continue or discontinue treatment (washout). The washout subgroups showed significantly faster progression than the continued treatment groups across all concentrations: -0.68±0.49 vs. -0.28±0.42 D (P<0.001) and 0.33±0.17 vs. 0.17±0.14 mm (P<0.001) for 0.05% atropine; -0.57±0.38 vs. -0.35±0.37 D (P=0.004) and 0.29±0.14 vs. 0.20±0.15 mm (P=0.04) for 0.025%; and -0.56±0.40 vs. -0.38±0.49 D (P=0.04) and 0.29±0.15 vs. 0.24±0.18 mm (P=0.13) for 0.01% atropine (19).

Beyond the LAMP studies, other clinical trials have provided additional evidence for low-concentration atropine efficacy. The CHAMP study, conducted in a predominantly non-Asian population, demonstrated that 0.01% atropine significantly reduced myopic SE progression at 36 months (122). This is important as it demonstrates the efficacy of atropine across different ethnic groups, though the magnitude of effect may vary.

The clinical significance of these findings extends beyond simple refractive error measurements. The LAMP studies also assessed quality of life outcomes and found that all

concentrations of atropine tested were well tolerated without adverse effects on vision-related quality of life (119). This is important for pediatric patients, where compliance and quality of life considerations are crucial for long-term treatment success.

The LAMP studies in 576, 573 and 576 children, aged 3 to 17, 3 to 16 and 2 to 16 years, respectively, significantly advanced myopia management, establishing the clinical viability of low-dose atropine. However, critical appraisal reveals key methodological constraints, demographic limitations and nuances regarding long-term efficacy and rebound effects (119). The details are discussed below.

Critical appraisal categories. a) Trial design: LAMP utilized a rigorous randomized, double-masked, placebo-controlled design. However, the crossover design-where placebo patients were switched to 0.05% atropine in year 2-eliminated the long-term control group, complicating the evaluation of multi-year absolute efficacy compared to a non-treated cohort. b) Ethnicity: The original cohort consisted entirely of East Asian children in Hong Kong. Because myopia progression and eye growth dynamics vary significantly across different demographics, extrapolating these exact outcomes to multi-ethnic populations requires caution. c) Age range: The studies heavily focused on children aged 4 to 12 years. While this captures the primary window of myopia onset and rapid progression, data on younger toddlers or older adolescents is sparse, which limits age-specific dosing protocols. d) Baseline refractive error: Participants predominantly presented with moderate to high myopia (e.g., at least-1.0 D). Generalizability to low myopes (e.g., -0.50 to -0.75 D) remains a clinical assumption, as the progression rates in this cohort may not mirror those with a smaller baseline refractive error. e) Axial length outcomes: While 0.05% atropine successfully retarded axial elongation, the biological growth of the eye does not stop completely. Axial elongation was still present, meaning the treatment slows but does not halt the physical growth of the eye. f) Concentration-dependent efficacy: The LAMP trials uniquely demonstrated a clear concentration-dependent response, with 0.05% emerging as the optimal balance for controlling both spherical equivalent and axial elongation over 3 years. Conversely, 0.01% was found to be minimally effective in suppressing axial elongation compared to placebo. g) Adverse effects: Low concentrations (0.01 to 0.05% atropine) demonstrated minimal to no impact on accommodation, pupil size or vision-related quality of life. This represents a major safety improvement over the historically high adverse event profiles of 1.0% atropine. h) Rebound after cessation: Upon treatment cessation in year three, accelerated myopia progression (rebound) was observed across all concentrations. While this effect was more pronounced in younger children and higher concentrations, multi-year follow-ups indicate that final axial length outcomes in formerly treated eyes remained largely superior to those of untreated eyes. i) Limitations of generalizability: Generalizability is limited by the strict adherence of a highly compliant, institution-based cohort and the lack of broad ethnic and environmental diversity (e.g., varying levels of ambient outdoor light exposure across different regions).

The CHAMP trials are the largest and longest placebo-controlled study of low-dose atropine in a majority non-Asian population. It demonstrated that preservative-free 0.01% atropine safely slows myopia progression, though the magnitude of efficacy varies compared to studies in Asian populations (123).

The CHAMP trial design and dataset. a) The study: The CHAMP phase 3 trial evaluated preservative-free low-dose atropine (NVK002) at 0.01 and 0.02% against a placebo across 26 North American sites and five European centers, involving children aged 3 to 17 years. b) Efficacy: While both concentrations meaningfully slowed axial elongation compared to placebo, the 0.01% concentration demonstrated more consistent efficacy in slowing the overall spherical equivalent refractive error (SER) progression. c) Duration and safety: The trial included a washout and extended 4-year continuous study periods. The results showed no meaningful myopia rebound effect after cessation and a low incidence of adverse effects such as dry eye.

Discrepancies across populations and trials. The magnitude of atropine's effect (particularly at 0.01% concentration) appears to differ among datasets, which can be attributed to the following: a) Iris pigmentation and drug absorption: Many early, highly successful low-dose atropine trials (like the landmark ATOM and LAMP studies) were conducted in East and Southeast Asian populations. Because atropine binds to melanin, children with lighter irides (more common in non-Asian/Caucasian datasets) may experience altered pharmacokinetics, potentially requiring different concentrations for optimal efficacy. b) Baseline progression rates: Non-Asian cohorts often present with distinct baseline refractive errors and slower natural myopia progression rates than their East Asian counterparts. This baseline variance can make the absolute magnitude of the treatment effect appear less dramatic in Western datasets. c) Concentration variations: While Asian studies (such as the LAMP-2 trial) have noted a stronger therapeutic trade-off using 0.05% atropine, the CHAMP trial demonstrated that the 0.01% preservative-free formulation provided the ideal safety and efficacy balance for North American and European children.

Other notable non-Asian datasets. To address the lack of generalizability from Asian-centric data, several localized trials have evaluated low-dose atropine in Western and mixed populations:

CHAMP-UK trial (NCT03690089). A multicenter study evaluating 0.01% atropine in British children that highlighted the importance of establishing independent, regional safety and mechanism-of-action data (124).

Study of atropine to reduce myopia progression (STAR) study (NCT03918915): Investigated atropine at 0.01 and 0.03% in diverse cohorts, yielding data that subsequently supported the European Medicines Agency's marketing authorization for low-dose atropine to slow pediatric myopia (125).

Low-dose atropine for the prevention of myopia progression (APP) study (Danish) (NCT03911271). The study evaluated 0.01% atropine and 0.1% loading doses in European Caucasian children, noting slightly reduced overall effect magnitudes compared to Asian populations, which researchers attributed to lighter iris pigmentation and differences in baseline ocular concentrations (126).

RCTs confirm that low-dose atropine eye drops are an effective, evidence-based pharmacological treatment to slow childhood myopia progression. Key studies like the ATOM, LAMP and CHAMP trials highlight 0.01 and 0.05% concentrations as the best balance between efficacy and safety. The core parameters, dosages and key findings of the major multi-year RCTs for atropine-controlled myopia are summarized in Table VIII, for example, of the core parameters, dosages and key findings of the major multi-year randomized controlled trials for atropine-controlled myopia included that 1.0% atropine significantly slowed myopic progression but induced considerable pupil dilation and blurred near vision (116), 0.01 and 0.02% atropine proved to be optimal, significantly suppressing progression with minimal visual side effects, and showed less 'rebound' effect upon cessation (117,118,127-129), and 0.05% atropine was the most effective control over progression (19,117,119,121).

Ethnic differences and global efficacy variations. The efficacy of atropine in myopia control exhibits significant variations across different ethnic populations, highlighting the importance of considering genetic and environmental factors in treatment planning (16). These differences have important implications for global implementation of atropine therapy and may reflect underlying differences in the pathophysiology of myopia across populations (130).

The CHAMP study, conducted across 26 clinical sites in North America and 5 countries in Europe, involved 576 children of various ethnicities (57% white, 16% Asian, 17% black, 29% Hispanic/Latino) who used placebo, NVK002, 0.01% atropine or 0.02% atropine topically over 3 years (129). This study was important as it represented the largest and longest placebo-controlled clinical trial of low-dose atropine conducted in a majority non-Asian, ethnically diverse population.

The CHAMP study results revealed important ethnic differences in treatment response. The study featured fewer Asian children (expected to have faster progression rates) and more black children (thought to have slower progression rates) compared to Asian-centric studies (131). These demographic differences likely contributed to the overall efficacy outcomes observed in the study.

The LAMP studies, conducted primarily in Asian populations, demonstrated better efficacy compared to non-Asian studies (119). The 0.05% concentration in LAMP showed a ~67% reduction in myopia progression after 1 year, while similar concentrations in non-Asian populations showed more modest effects (119). These differences may reflect genetic variations in M receptor expression or function, as well as differences in baseline progression rates across ethnic groups (132,133).

Environmental factors also play a role in treatment response variations. It has been shown that children from East Asian countries, where myopia prevalence is highest, may have different underlying mechanisms of myopia development compared to children from other regions (134). The higher baseline progression rates in Asian populations may make them more responsive to intervention, though this hypothesis requires further investigation (135).

The implications of these ethnic differences for clinical practice are significant. Healthcare providers should consider the patient's ethnic background when selecting the atropine concentration and monitoring treatment response. Additionally, future research should focus on understanding the biological basis for these differences, which may lead to personalized treatment approaches based on genetic and environmental factors.

Safety profile and side effect management. The safety profile of atropine has been extensively evaluated across multiple clinical trials, with low-concentration formulations demonstrating excellent tolerability compared to higher concentrations (136). Understanding the safety profile and managing potential side effects is crucial for successful long-term treatment of children with myopia.

The most common side effects associated with atropine treatment include mydriasis (pupil dilation) and cycloplegia (loss of accommodation), which can cause photophobia and blurred near vision (17). The LAMP studies systematically evaluated these effects and found that the magnitude of these side effects was concentration-dependent (119). The 0.05% group showed the most significant effects, with mean increases in photopic and mesopic pupil diameter of 1.03±1.02 and 0.58±0.63 mm, respectively. The 0.025% group showed intermediate effects (0.76±0.90 and 0.43±0.61 mm), while the 0.01% group showed minimal effects (0.49±0.80 and 0.23±0.46 mm) (119).

The accommodation amplitude was also affected in a concentration-dependent manner, with reductions of 1.98±2.82, 1.61±2.61 and 0.26±3.04 D in the 0.05, 0.025 and 0.01% atropine groups, respectively (119). Importantly, the 0.01% concentration showed a minimal effect on accommodation, which is important for school-aged children who require good near vision for reading and other close work activities (137).

Long-term safety data from the LAMP 3-year study showed that accommodation loss and pupil size changes remained consistent over time and were well tolerated (119). Visual acuity and vision-related quality of life remained unaffected across all concentration groups, supporting the safety of long-term treatment (121).

Systemic side effects from topical atropine are rare but can occur with higher concentrations or in children with sensitive systems. These may include flushing, dry mouth, tachycardia and behavioral changes (138). However, with low-concentration formulations and proper administration techniques (such as punctal occlusion), systemic absorption is minimized, and these side effects are rare (136).

The management of side effects involves several strategies. For patients experiencing photophobia, tinted lenses or sunglasses can provide relief (139). For accommodation difficulties, near vision aids or temporary cessation of near work during peak drug effect (typically 2-4 h after instillation) may be helpful (140). In certain cases, reducing the concentration or frequency of administration may provide an acceptable balance between efficacy and side effects (141).

Importantly, the LAMP studies found that visual acuity and vision-related quality of life were not affected by atropine treatment, suggesting that the benefits of myopia control outweigh the minor inconveniences associated with the side effects (119). This finding is important in establishing low-concentration atropine as a safe and effective treatment option for children with myopia.

Table VIII. Summary of the core parameters, dosages and key findings of the major multi-year randomized controlled trials for atropine-controlled myopia.

Study name	Duration, years	Patient age, years	Atropine dosages tested	Key findings and efficacy outcomes	(Refs.)
ATOM 1	2	6-12	1.0% vs. placebo	1.0% atropine significantly slowed myopic progression but induced considerable pupil dilation and blurred near vision.	(116)
ATOM 2	5	6-12	0.5, 0.1, 0.01%	0.01% proved to be optimal, significantly suppressing progression with minimal visual side effects, and showed less 'rebound' effect upon cessation.	(117)
ATOM 3	2; washout period, 1	5-9	Nightly drop of 0.01% atropine vs. placebo	Atropine 0.01% slowed myopia progression, but the difference compared to the placebo group did not reach statistical significance. The rate of new-onset myopia was similar between the atropine and placebo groups. A modest trend toward reduced myopia progression and onset was observed, suggesting potential benefit, though researchers noted the study may have been underpowered to detect small differences.	(118)
LAMP phase 1	Up to 2+	4-12	0.05, 0.025 and 0.01%, placebo	Showed a clear concentration-dependent response; 0.05% demonstrated the most effective control over progression, while 0.01% also provided a 27% reduction in progression.	(119)
LAMP phase 2	2	4-12	0.05, 0.025 and 0.01%, placebo	0.05% atropine was most effective in controlling myopia progression (spherical equivalent) and slowing axial elongation. Efficacy was dose-dependent. 0.05% performed significantly better than 0.025%, which in turn outperformed 0.01%. All tested doses were well-tolerated with minimal impact on vision-related quality of life, pupil diameter or accommodation.	(121)
LAMP phase 3	3	4-12	0.05, 0.025 and 0.01%	Continued atropine treatment significantly slowed myopia progression and axial elongation better than stopping treatment. 0.05% atropine remained the most effective concentration over the trial period. A faster increase in myopia progression occurred when treatment stopped, which was linked to younger age and higher concentrations. However, from a clinical perspective, the rebound differences among the 3 concentrations were small.	(19)
CHAMP phase 1	3; follow-up, 1	3-16	0.02, 0.01% vs. placebo	The 0.01% dose showed a statistically significant reduction in myopia progression and axial elongation compared to the placebo, with a higher proportion of responding patients. The 0.02% dose did not show a statistically significant difference in the primary responder proportion over the 3-year period compared to placebo, though it did show a certain reduction in axial elongation. Both concentrations maintained excellent safety profiles. Additionally, long-term findings showed that 0.01% atropine had a negligible rebound effect after treatment cessation.	(127)
CHAMP phase 2	3	3-16	0.02, 0.01% vs. placebo	0.01% atropine had statistical significance compared to placebo across all primary outcome measures. It demonstrated the best balance of clinical efficacy and safety, significantly slowing both SER progression and axial (eye) elongation. The responder proportion (those whose vision progressed <0.5 diopters)was notably higher in the 0.01% group. 0.02% atropine slowed axial elongation in children compared to placebo at 36 months, and the overall responder analysis and spherical equivalent refractive error progression did not reach statistical significance against the placebo group. Both concentrations were well-tolerated with an excellent safety profile, negligible impact on pupillary dilation and no significant loss of focusing ability (accommodation)	(128)

Table VIII. Continued.

Study name	Duration, years	Patient age, years	Atropine dosages tested	Key findings and efficacy outcomes	(Refs.)
CHAMP phase 3	3	3-16	0.02, 0.01% (preservative-free NVK002) vs. placebo	0.01% meaningfully slowed myopia progression and axial elongation compared to the placebo group, with excellent safety profiles (128).	(129)

CHAMP, childhood atropine for myopia progression; ATOM, atropine for the treatment of myopia; LAMP, low-concentration atropine for myopia progression.

10. Atropine rebound

Atropine rebound is a temporary acceleration of myopia progression and axial elongation that often occurs after atropine eye drops are discontinued (142). The severity of the rebound varies significantly based on dosage, treatment duration and patient age, though its precise biological mechanisms are still being researched (142).

High- vs. low-concentration rebound. High concentration (e.g., 0.5-1.0%): Cessation of high-dose atropine generally causes a significant and clinically measurable rebound effect, often leading to rapid myopic shifts and axial elongation that offset some of the gains made during the treatment period (143). Low concentration (e.g., 0.01-0.05%): Lower concentrations have a drastically reduced- and in numerous cases, clinically negligible-rebound effect (144). Studies like the landmark LAMP study have shown that 0.01 and 0.05% atropine yield steady, modulated myopia control with minimal adverse effects upon cessation (119).

Biological mechanisms and factors. The exact biological reasons behind atropine rebound are complex and interconnected. Receptor regulation (rebound super-sensitivity): Atropine is a non-selective M receptor antagonist (primarily blocking all M receptors in the retina and sclera) (28). Long-term blockade may lead to an upregulation or hypersensitization of these receptors (76). When the atropine is suddenly removed, the sudden abundance of available receptors can trigger an accelerated response to endogenous signaling, driving rapid eye growth (142).

Concentration and duration. Rebound is concentration-dependent. Higher concentrations lead to more robust receptor blockage, meaning the eventual release of that blockage upon cessation is more intense (144). Similarly, longer durations of therapy may increase dependency and result in a more pronounced rebound (142).

Age at cessation. Age is a critical determinant. Younger children, whose eyes are biologically programmed for faster growth, show the most significant rebound effects (145). Younger patient age is associated with a higher risk of stopping the drops resulting in rapid progression (145). Clinicians often recommend tapering off or continuing therapy until a patient is in their mid-teens to avoid rebound (142).

Baseline progression rate. Patients who have a high baseline rate of progression or severe refractive errors tend to experience more marked rebound effects (146).

Accommodation recovery. At higher concentrations, atropine paralyzes the ciliary muscle, causing accommodation impairment (blurred near vision) (147). When the drops are stopped, the sudden recovery and resumption of normal accommodation, or 'catch-up' focusing, could hypothetically play a role in temporary refractive changes, though it is usually a short-lived phenomenon (142).

Choroidal changes. Atropine therapy has been shown to induce temporary thickening of the choroid, which is associated with

a retardation in axial length growth (144). Upon cessation, the choroid can thin back out, which may correspond with a rapid resumption of axial elongation (148).

Clinical management. Because sudden cessation can cause myopic jumps, many experts advocate for a tapering strategy-gradually reducing dosing frequency (e.g., from every night to a few times a week) over several months (149). This allows the ocular structures and receptor populations to adapt slowly rather than experiencing sudden physiological shock, significantly reducing or eliminating the risk of rebound (142).

11. Limitations

Current atropine myopia control faces limitations due to an 'impossible triangle' of dose-dependent trade-offs. While widely used, challenges remain with efficacy variances across demographics (such as in US populations), bothersome side effects (like photophobia at higher strengths), the risk of myopia rebound upon cessation and an ongoing need for long-term safety data (144).

Inconsistent efficacy and dose-dependent dilemmas. There is a clinical paradox between concentration, efficacy and side effects in atropine therapy: a) High concentration (0.5-1.0%): Highly effective at halting eye elongation, but causes significant side effects, including severe light sensitivity, blurred near vision and a significant rebound effect upon discontinuation (150). b) Low concentration (0.01-0.05%): The most common standard, it limits side effects but varies significantly in how well it works (151). The landmark LAMP studies found that 0.05% atropine was the optimal balance, but its effectiveness still varies from child to child (119). c) Demographic variance: Landmark trials like the pediatric eye disease investigator group (PEDIG) study by the American Academy of Ophthalmology concluded that 0.01% atropine did not slow myopia progression or axial elongation significantly compared to a placebo in US-based cohorts (131), suggesting it may not work universally for all populations.

Ocular and systemic side effects. Atropine is a muscarinic antagonist that dilates pupils and temporarily reduces the eye's focusing ability. Side effects depend heavily on the dosage used: a) Photophobia and glare: Dilated pupils allow too much light into the eye, making outdoor environments uncomfortable and potentially exposing children to higher levels of ultraviolet light. Patients often require prescription of photochromatic lenses or sunglasses (152). b) Near-vision blur: Impaired focusing can make prolonged reading and close-up screen work difficult for some (153). c) Systemic issues: Rare but possible systemic reactions include a dry mouth, rapid heartbeat (tachycardia) and facial flushing (76).

The rebound effect. Once atropine treatment is stopped-typically during the mid-teens when eye growth naturally stabilizes-many children experience accelerated myopia progression and rapid eye growth (150). This rebound effect is more pronounced with higher concentrations, though it can still occur even with low-dose therapies. To counter this, eye doctors must often slowly wean children off the drops over several months instead of abruptly stopping (142).

Limited efficacy in older teenagers and adults. Atropine works to halt the eye's focusing strain, but evidence primarily supports its use in children and adolescents (typically ages 4 to 16 years) (150). There is little to no clinical proof that atropine eye drops are an effective treatment to slow worsening myopia in older teenagers and adults whose eyes are already fully developed.

Unresolved long-term safety concerns. Because childhood myopia is treated continuously for several years, there remain questions about the long-term impacts of exposing developing eyes to continuous M receptor blockade. Recent studies have raised the need for continuous monitoring, as longer-term administration may correlate with an increased risk of specific ocular complications if not managed appropriately (144,154).

12. Future perspectives and emerging mechanisms

Novel targets and combination therapies. The future of myopia control with atropine is likely to involve the development of combination therapies that target multiple pathways simultaneously, achieving greater efficacy than monotherapy while minimizing side effects (155). Recent research has identified several promising targets and therapeutic combinations that warrant further investigation (156).

One promising approach is the combination of atropine with optical interventions. The Atropine and Spectacle Lens Combination Treatment study evaluated the efficacy of 0.025% atropine combined with Defocus Incorporated Multiple Segments (DIMS) spectacle lenses vs. 0.025% atropine with single-vision lenses (157). The results demonstrated significantly better control with the combination treatment, with 39.6% of children in the DIMS group showing no axial elongation over 12 months compared to 12.2% in the single-vision group (P=0.002) (157).

The combination of atropine with orthokeratology represents another promising approach. A retrospective study of 33 patients showed significant reduction in axial length growth with combined 0.01% atropine and orthokeratology treatment, without notable changes in uncorrected visual acuity and intraocular pressure (158). Age was identified as a key factor affecting outcomes, with younger patients showing better responses to the combined treatment (159).

Emerging evidence suggests that the timing and frequency of atropine administration may also be optimized. A randomized controlled trial comparing twice-daily vs. once-nightly administration of 0.01% atropine found that twice-daily dosing resulted in significantly better control of axial elongation (0.21±0.18 vs. 0.32±0.14 mm, P=0.002) and SE progression (-0.31±0.50 vs. -0.06±0.37 D, P<0.001) (160). This represents a 34% reduction in axial elongation and 53% improvement in SE progression with twice-daily dosing.

Novel drug targets are also emerging from the increasing understanding of myopia pathophysiology. The Wnt signaling pathway has shown promise, with studies demonstrating that inhibition of canonical Wnt signaling using niclosamide significantly reduces myopia development in animal models (77). The identification of DKK-1 as a potential biomarker and therapeutic target is interesting, as plasma levels of this Wnt inhibitor are decreased in myopic patients (77).

The HIF-1α pathway represents another important target for future therapeutic development. Given the central role of scleral hypoxia in myopia development, drugs that can reduce scleral hypoxia or inhibit HIF-1α signaling may provide additional benefits when combined with atropine (41). Several compounds have already shown promise in preclinical studies, including ω-3 polyunsaturated fatty acids, PPARγ agonists and various herbal compounds (161).

Safety and clinical implications. Recommended dose of atropine: Low-dose atropine is a highly effective, off-label intervention for slowing childhood myopia progression and axial elongation (150). The optimal balance of efficacy, side effects and rebound risk guides concentration selection, with current clinical evidence favoring 0.05% as the ideal starting point for many patients (154). More studies are needed for establishing a standard method for treatment of myopia in the near future, starting from information summarized in Table IX; for example, the atropine concentration profile suggested that 0.01% atropine was the best for older children, those with pre-existing light sensitivity or as a maintenance taper (122), that 0.025% atropine was often considered a 'middle-ground' for older teens or when 0.05% atropine causes side effects (130), that 0.05% atropine is recommended as first-line for rapidly progressing myopia in children aged <12 years (162), and that 0.1% atropine is used if lower concentrations fail to halt progression but require careful adaptation (136), that 0.5% atropine is rarely used for myopia control due to high symptom burden and severe rebound risk (163), and that 1% atropine is reserved primarily for severe conditions or amblyopia penalization therapy (164,165).

Recommended practical management and clinical implementation. Patient selection and indications treatment are typically initiated in children aged 4 to 12 years who show >-0.50 D of myopia and a documented progression rate of >0.50 D over 6 months (120). Younger children (under age 10) are the most critical candidates because they are at a higher risk of rapid myopia progression (8).

Recommended treatment duration and monitoring. a) Duration: Treatment is typically maintained for at least 2 to 3 years. Therapy may continue until the child reaches their mid-teens when eye growth naturally slows down (166). b) Axial length monitoring: Refractive error alone is not enough to gauge treatment success; axial length should be monitored every 6 to 12 months with ocular biometry to ensure it remains <0.10 to 0.20 mm of growth per year (167).

Recommended cessation strategy and rebound management. Stopping atropine abruptly can lead to 'rebound' myopia progression, particularly with higher concentrations (165). To avoid this, clinicians generally implement a tapering phase over 6 to 12 months (e.g., reducing the frequency from nightly to every other night, then twice a week) before total cessation (165). If rapid progression or axial elongation resumes post-treatment, retreatment should be initiated immediately.

Recommended combination with optical interventions. To combat both pharmacological side effects and structural eye lengthening, atropine is often combined with optical corrections: a) Progressive addition lenses or executive bifocals: Prescribed for children who experience near-blur on higher

Table IX. Summary of atropine concentration profile.

Concentration, %	Efficacy	Photophobia and pupil dilation	Near blur and accommodation loss	Rebound risk	Clinical implementation notes
0.01%	Minimal slowing of axial length; ~40% slowing in spherical equivalent	Virtually none; pupil size remains near normal	Barely noticeable; no reading glasses required	Minimal	Best for older children, those with pre-existing light sensitivity, or as a maintenance taper (122)
0.025%	Moderate	Mild; occasional need for sunglasses outdoors	Slight, usually tolerated well	Low to moderate	Often considered a 'middle-ground' for older teens or when 0.05% causes side effects (130)
0.05%	Optimal balance: Highest efficacy-to-side-effect ratio	Moderate; sunglasses may be required in bright sunlight	Mild; rarely requires additional reading correction	Low to moderate	Recommended first-line for rapidly progressing myopia in children aged <12 years (162)
0.1%	High	Significant; requires consistent UV-blocking sunglasses	Noticeable; may require progressive or bifocal near additions	High	Used if lower concentrations fail to halt progression but require careful adaptation (136)
0.5%	Very high	Severe; constant use of photochromic lenses or sunglasses needed	Severe; mostly intolerable without bifocal/progressive spectacle correction	Very high	Rarely used for myopia control due to high symptom burden and severe rebound risk (163)
1.0%	Maximum efficacy (reduces progression by >70%)	Severe; ciliary muscle paralysis, extreme light sensitivity	Severe near vision blur	Extreme	Reserved primarily for severe conditions or amblyopia penalization therapy (164,165)

concentrations or who require accommodative relief (168). b) Multifocal contact lenses or orthokeratology: Can be prescribed concurrently for patients requiring both clear vision correction and myopia control (169). c) Photochromic lenses: Highly recommended for all atropine patients to manage the associated photophobia outdoors (170). d) Mechanistic insights into drug development. The ongoing investigation of atropine's mechanisms of action continues to provide valuable insights that can inform the development of next-generation myopia control therapies (144). These insights are important as we move toward developing more targeted and effective treatments that address the root causes of myopia rather than simply managing its symptoms.

One important insight from recent research is the recognition that atropine's efficacy results from its broad-spectrum effects on multiple ocular tissues and signaling pathways. This 'shotgun approach' (17) may be more effective than targeting single pathways, but it also contributes to side effects. Future drug development efforts should focus on identifying compounds that can achieve similar broad-spectrum effects while having more selective action on specific tissues or pathways.

The role of scleral hypoxia in myopia development has opened new avenues for therapeutic development. Drugs that can improve choroidal circulation, reduce scleral hypoxia or inhibit hypoxia-induced signaling pathways may provide benefits either as monotherapy or in combination with atropine (31,41). Several compounds have already shown promise in preclinical studies, including *Ginkgo biloba* extract, crocetin and various vasodilators (171,172).

The discovery of an epigenetic mechanism in myopia development, histone lactylation, represents a novel therapeutic target (45). The finding that lactate-induced H3K18 lactylation promotes myofibroblast transdifferentiation suggests that drugs targeting this pathway may be effective in preventing scleral remodeling (97). This represents a new approach to myopia treatment that could potentially be more effective than current methods.

The interaction between different signaling pathways provides another area for therapeutic innovation. The extensive crosstalk between TGF-β/BMP, Wnt and other pathways suggests that drugs that can modulate multiple pathways simultaneously may be more effective than single-target approaches (77). Understanding these pathway interactions may also help identify optimal combination strategies.

The development of drug delivery systems that can achieve sustained release of therapeutic compounds in ocular tissues represents another important advancement (28). Current topical atropine requires daily administration, which can lead to compliance issues, particularly in children. Long-acting formulations or implantable devices that can provide sustained drug release over months or years may improve treatment outcomes and reduce side effects.

Finally, the integration of artificial intelligence (AI) and machine learning approaches may help identify new therapeutic targets and predict treatment responses. By analyzing large datasets of patient outcomes, genetic information and molecular markers, these approaches may reveal patterns and relationships that are not apparent through traditional research methods.

13. Conclusions

This comprehensive review has explored the multifaceted biological mechanisms through which atropine exerts its remarkable efficacy in controlling myopia progression. The evidence presented demonstrates that atropine's anti-myopic effects are not mediated through a single pathway but rather through a complex interplay of mechanisms involving multiple ocular tissues, neurotransmitter systems, signaling pathways and molecular targets.

The M receptor-mediated mechanisms represent a direct and well-characterized pathway through which atropine acts. The drug's non-selective blockade of all five M receptor subtypes (M1-M5) enables it to simultaneously target multiple tissues and functions, from ciliary muscle relaxation to modulation of retinal processing and scleral remodeling. However, the re-evaluation of the cholinergic hyperactivity hypothesis has revealed that atropine's effects are not simply due to blocking excessive cholinergic activity but rather involve complex interactions with multiple receptor systems.

The mechanisms targeting choroidal function are important, with atropine's ability to improve choroidal microcirculation and restore ChT representing key components of its anti-myopic effects. These actions are mediated through multiple pathways, including increased retinal dopamine release, direct effects on choroidal blood vessels, and modulation of growth factor expression in the RPE and choroid. The restoration of normal choroidal function not only improves retinal health but also reduces scleral hypoxia, thereby inhibiting the pathological remodeling processes that drive myopia progression.

The effects on scleral remodeling represent clinically significant mechanisms of atropine's action. Through its regulation of scleral fibroblast activity, inhibition of ECM degradation and promotion of collagen synthesis, atropine is able to restore the mechanical integrity of the sclera and prevent further axial elongation. The drug's ability to modulate key signaling pathways such as TGF-β/BMP, Wnt/β-catenin and HIF-1α provides multiple mechanisms for achieving these effects.

The regulation of neurotransmitter and neurogenic pathways adds another layer of complexity to atropine's mechanisms. While the dopamine system has received significant attention, recent research has revealed that atropine's effects involve multiple neurotransmitter systems working in concert. The drug's ability to modulate GABAergic, serotonergic and other systems suggests that it may influence how the retina processes visual information and transmits growth regulatory signals to other ocular tissues.

The signal transduction pathways regulated by atropine are diverse and interconnected. The TGF-β/BMP pathway, Wnt/β-catenin pathway and VEGF signaling network all play roles in ocular growth regulation, and atropine's effects on these pathways are likely to be synergistic. The involvement of HIF-1α and hypoxia-mediated pathways has emerged as an important mechanism, highlighting the role of scleral hypoxia in myopia development and the potential for anti-hypoxia strategies for treatment.

The molecular and genetic mechanisms underlying atropine's effects are increasingly well understood, with recent

advances in proteomics and genomics revealing the complex transcriptional and post-transcriptional networks that are modulated by the drug. The identification of specific proteins and pathways involved in atropine's action, including EIF2 signaling, glycolysis and dopamine secretion, provides new targets for therapeutic development.

The clinical evidence supporting atropine's efficacy is compelling, with large-scale, long-term studies demonstrating consistent benefits across different populations. The LAMP study series has established the efficacy and safety of low-concentration atropine, with 0.05% showing the greatest efficacy while 0.01% provides an excellent balance between efficacy and tolerability. The recognition of ethnic differences in treatment response highlights the need for personalized approaches, while the excellent safety profile supports long-term use in children.

Looking toward the future, the development of combination therapies and personalized medicine approaches offers significant potential for improving outcomes beyond what is achievable with atropine monotherapy. The identification of novel targets, such as the Wnt pathway, HIF-1α signaling and epigenetic mechanisms, provides new opportunities for therapeutic innovation. The integration of genetic information, biomarker development and advanced drug delivery systems promises to revolutionize myopia treatment in the coming years.

In conclusion, while the exact mechanisms of atropine's anti-myopic effects remain incompletely understood, the evidence clearly demonstrates that this remarkable drug acts through multiple pathways to achieve its therapeutic effects. The comprehensive understanding of these mechanisms provided by this review serves as a foundation for optimizing current treatment strategies and developing the next generation of myopia control therapies. As we continue to unravel the complexities of ocular growth regulation and myopia pathogenesis, the insights gained from studying atropine's mechanisms will continue to inform and guide our efforts to combat this global health crisis.

Acknowledgements

Not applicable.

Funding

This work was supported by the Basic Research Fund for Science and Technology Department of Yunnan Province and Kunming Medical University, China (grant no. 202401AY070001-289 to QZ).

Availability of data and materials

Not applicable.

Authors' contributions

QZ and YiZ designed and conceptualized this study. QZ, GZ and LW equally contributed to reference search, content organization and manuscript drafting. XL, ZH, JY, JZ, YuZ and XZ contributed to data/reference collection and organization of part of the draft. AW, YiZ and LX contributed to organization and paper editing and finalization. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools, including ChatGPT (GPT-5.6 Luna) by OpenAI (http://openai.com/index/gpt-5-6/), Claude (Opus 5) by Anthropic (http://www.anthropic.com/claude/opus) and Google Gemini (Gemini 3.6 Flash) by Google (http://ai.google.dev/gemini-api/docs/models/gemini-3.6-flash), were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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