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A Comprehensive Review of Myopia

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Abstract

Myopia is a prevalent refractive error affecting millions worldwide, with a significant increase in incidence expected in the coming years, particularly in areas experiencing rapid urbanization. Uncorrected myopia as low as -1.50 diopters is considered to cause moderate visual impairment, and regular monitoring by healthcare professionals is crucial for effective management. High myopia poses a greater risk for sight-threatening complications such as myopic maculopathy, glaucoma, and cataracts. The onset and progression of myopia are influenced by both genetic and environmental factors, with the latter playing a more prominent role. Significant efforts have been made to slow myopia progression through optical, environmental, and pharmaceutical interventions. Genes involved in circadian rhythm regulation, pigmentation, and collagen metabolism have been associated with myopia development. Environmental factors such as near work, lack of outdoor activity, improper lighting, and socioeconomic conditions contribute to the rising prevalence of myopia. Optical approaches for myopia control include bifocals, progressive addition spectacles, and contact lenses incorporating peripheral defocus management. Pharmaceutical strategies explored include atropine, pirenzepine, tropicamide, 7-methylxanthine, and certain intraocular pressure-lowering agents. Long-term efficacy data

for these interventions are limited, and concerns exist regarding the potential rebound effect upon treatment discontinuation. A multifaceted approach addressing both genetic predisposition and environmental modifications is necessary to control the growing global burden of myopia effectively.

Keywords: Myopia, genetic risk factors, environmental risk factors.

Introduction

It is estimated that millions of children and adults worldwide are affected by myopia, resulting in significant burdens on individuals, their families, and society (Holden et al., 2016). In addition to the already high prevalence in many East Asian countries, the incidence is expected to rise substantially in the coming years in other regions. A significant portion of this increase is anticipated to occur in areas experiencing rapid urbanization, such as South Asia. According to a report from the World Health Organization, uncorrected myopia as low as -1.50 diopters (D) is considered to cause moderate visual impairment. Effective management of this condition requires regular monitoring by healthcare professionals to assess the progression of myopia and ensure the correction of any vision loss while maintaining ocular health. While any degree of myopia poses a risk for vision impairment and sight-threatening complications, eyes with high myopia, particularly in older individuals, face a greater likelihood of developing complications such as myopic maculopathy, glaucoma, and cataracts. With the increasing prevalence of myopia and the aging population, the risk of future occurrences of myopic maculopathy, retinal detachment, cataracts, retinal breaks, and glaucoma is expected to rise.

The onset and progression of myopia are influenced by both genetic and environmental factors, with the latter playing a more prominent role. Evidence from animal models demonstrates the modulation of eye growth by visual feedback, while human observational studies have shown an association between myopia and urban living, higher socioeconomic status, increased near work, and reduced outdoor activity. Moreover, genetic changes have been too gradual to account for the rapid rise in myopia prevalence observed in many East Asian and Southeast Asian countries (Morgan et al., 2018).

In recent decades, significant efforts have been made to slow the progression of myopia through optical, environmental, and pharmaceutical interventions. These efforts have increased substantially over the past 20 years, as supported by numerous peer-reviewed studies and meta-analyses. While the translation of research findings into mainstream clinical practice is gaining momentum, progress is hindered in many countries due to the lack of long-term efficacy data, concerns about rebound effects following discontinuation of treatment, practitioners' perceptions of myopia control, limited access to myopia control products, and regulatory barriers. This review aims to summarize the evidence for the efficacy of optical and pharmaceutical strategies for myopia control, as well as to discuss challenges related to obtaining long-term data and the rebound effects upon discontinuation of treatment.

Risk factors

1. Genes Related to Myopia

Genetic factors play a critical role in the onset and progression of high myopia. Numerous studies have highlighted the significant contribution of genetic factors in myopia development (Cai et al., 2019). Specifically, genes involved in circadian rhythm regulation and pigmentation have been associated with myopia and ametropia. Research has confirmed that MTOR and PDGFRA are linked to the severity of myopia, with a gene-gene interaction observed between them (X. Li et al., 2022). Variations in GJD2 genotypes have been found to influence the development of myopia in different ways. Additionally, PDE4B has been proposed as a potential novel gene for susceptibility to high myopia and may play a crucial role in its

development. Flitcroft DI and colleagues identified 21 new candidate genes related to myopia, including ADAMTS18, ADAMTS2, ADAMTSL4, AGK, ALDH18A1, ASXL1, COL4A1, COL9A2, ERBB3, FBN1, GJA1, GNPTG, IFIH1, KIF11, LTBP2, OCA2, POLR3B, POMT1, PTPN11, TFAP2A, and ZNF469 (Flitcroft et al., 2018). Furthermore, FLRT3/SLC35E2B and MYP2 have been suggested as candidate genes associated with high myopia (H.M.), influencing its pathogenesis. Simpson CL and colleagues discovered that WISP1 and SSPO could be potential pathogenic genes in Ashkenazi Jewish families. Meguro A and colleagues identified HIVEP3, NFASC/CNTN2, CNTN4/CNTN6, FRMD4B, LINC02418, and AKAP13 as being linked to high myopia (Flitcroft et al., 2018). In European populations, genes such as FAM150B-ACP1, LINC00340, FBN1, DIS3L-MAP2K1, ARID2-SNAT1, and SLC14A2 have been associated with refractive error. In studies conducted in chicks, PIK3CG and PRKAR2B have been significantly correlated with myopia susceptibility (Huang et al., 2019), suggesting a potential genetic locus related to the risk of myopia in the population.

Research has also revealed that mutations in specific genes contribute to early-onset high myopia. Heterozygous loss-of-function (LoF) mutations in CPSF1, ARR3, and NDUFAF7 have been linked to early-onset high myopia. In a study of Chinese cohorts with high myopia, seven heterozygous mutations were identified, including p.Pro287Leu, p.Arg319Thr, and p.Arg84Trp from SLC39A5, as well as p.Lys661Arg, p.Ala528Thr, p.Phe44Leu from LEPREL1, and p.Arg321 from LRPAP1. Among these, p.Pro287Leu, p.Arg319Thr, and p.Lys661Arg were noted as potential pathogenic mutations (Feng et al., 2017). Mutation in TNFRSF21 has been found to result in nonsyndromic high myopia in Chinese populations. Additionally, Zheng, Y. H. and colleagues identified a mutation in AGRN, providing further evidence for AGRN's role in the inheritance of high myopia. Moreover, mutations in P4HA2 may lead to axial elongation of the myopic eye (Napolitano et al., 2018). These findings significantly expand the current understanding of the genetic spectrum associated with high myopia.

Recently, Simpson, C. L. and colleagues identified significant genetic linkage peaks for myopia at 7p15.2 and 7p14.2 in African American families. Similarly, Musolf AM et al. reported a genetic linkage peak for myopia at 10q26.13 in Chinese Han patients. Additionally, myopia has been associated with loci at 1p36.12, 8q24, 7q36.1, and 11p15.1 in Ashkenazi Jewish families, indicating a genetic connection to the occurrence of myopia.

a. Single Nucleotide Polymorphism and Myopia

Several studies have shown that specific single nucleotide polymorphisms (SNPs) are associated with severe myopia (both moderate and extreme forms). These include PAX6 rs644242, ZC3H11B rs4373767, and BICC1 rs7084402, as well as VIPR2 rs885863 and rs6979985 (Zhao et al., 2022). Other SNPs, such as ZMAT4 rs7829127, TNKS rs4840437 and rs6989782, PDGFRA rs2114039, SOX2 rs4575941, FGF10 rs339501, rs2973644, and rs79002828, have also been found to correlate with severe myopia. RSPO1 SNP rs12144790 and WNT7B rs10453441 are associated with the visual axis length in children. Additionally, SNPs such as ZFHX1B rs13382811, PTPN5 rs1550870, and RASGRF1 rs6495367, as well as TGF receptor one rs10760673 and TGF receptor 2-AS1 rs7550232, are linked to myopia in children. MMP-9 rs2236416 has also been found to be interrelated to myopia, suggesting the potential role of the MMP-9 gene locus in myopia development (Y. Li et al., 2022). Moreover, variations in 4q25 rs10034228, 15q14 rs524952, and MIPEP rs9318086 have been shown to increase susceptibility to myopia and its severity in southern Chinese populations, amplifying the risk of high myopia by tenfold (Liu et al., 2021).

b. DNA Methylation and Myopia

DNA methylation has been recognized as a crucial factor in the occurrence and progression of myopia. Studies have demonstrated the involvement of IGF-1 gene methylation in the pathogenesis of form deprivation myopia (FDM) in guinea pigs. Furthermore, LINE-1

hypermethylation has been associated with high myopia in both humans and mice (Hsi et al., 2019). It has also been shown that reduced DNA methylation levels are a risk factor for early-onset myopia in children (Swierkowska et al., 2022), highlighting the importance of DNA methylation in myopia development. These findings open up new possibilities for intervening in myopia through methylation-related strategies.

c. Non-Coding RNA and Myopia

Non-coding RNAs, which include microRNAs (miRNAs), repetitive RNAs, intronic RNAs, and long non-coding RNAs (lncRNAs), play a significant role in regulating gene expression and have a broad potential for controlling various biological processes (Matsui & Corey, 2017). Several microRNAs, such as mmu-mir-1936, mmu-mir-338-5p, mmu-mir-673-3p, miR-328, miR-708a, and miR-148, have been implicated in myopia and may serve as biomarkers for the condition. MicroRNA-29a has been shown to influence myopia development by regulating type I collagen synthesis (Zhu et al., 2022). Additionally, hsa-miR-142-3p in the aqueous humor has been positively correlated with visual axis length (Q. Li et al., 2022). Interventions targeting choroidal vascular dysfunction by adjusting circRNA-FoxO1 levels have been proposed as potential strategies for preventing and treating myopia. Moreover, studies have indicated that collagen metabolism impacts the mechanical properties and remodeling of the sclera, thereby affecting scleral growth, axial elongation, and the development of myopia (Ouyang et al., 2019). In myopic eyes, scleral expression of miR-29a, miR-29b, miR-29c, and MMP2 has been significantly increased, while the expression of COL1A1 has been notably reduced. Treatment with 1% genipin has been shown to reverse these effects in the sclera and may provide a therapeutic avenue for myopia management (Wang et al., 2020). Guo D et al. identified 27 differentially expressed microRNAs in the sclera of guinea pigs with lens-induced myopia, with 10 being up-regulated and 17 down-regulated. Among these, miR-19b-3p plays a role in myopia development by regulating metabolic processes. Numerous studies have enriched the expression profiles of miRNAs and lncRNAs, which may offer new insights into the pathogenesis and biology of myopia.

2. Environment and Myopia

a. Near Work

Near work has been shown to significantly reduce choroidal blood perfusion (ChBP), a phenomenon that may lead to scleral hypoxia and the development of myopia (Zhao et al., 2020). The reduction in ChBP contributes to scleral hypoxia and the transdifferentiation of scleral myofibroblasts, with increased expression of α-Smooth muscle actin, which ultimately facilitates the progression of myopia. On the other hand, increased ChBP can alleviate scleral hypoxia, thus inhibiting myopia development. Recent studies, including our own, have demonstrated that electroacupuncture can enhance choroidal vascular density, potentially improving scleral hypoxia and inhibiting scleral growth in myopia-induced guinea pigs (Yu et al., 2022).

Near work typically refers to activities that involve working distances of less than 30 cm (Sherwin et al., 2012). Modern activities such as reading and engaging with digital screens (e.g., computers, video games, and the internet) are now considered forms of near work. Sun JT et al. reported that sustained close work for over 30 minutes without a 5-minute break increases the likelihood of myopia development. Saxena R et al. showed that reading or writing for more than 6 hours per day and playing video games for over 4 hours per week are significant risk factors for myopia. Interestingly, video games appear to have a stronger association with myopia than reading, possibly due to the small size and high resolution of modern smart devices, which require a closer viewing distance to enlarge retinal images and capture fine

details (Medina, 2022). This suggests that preventing myopia progression could be achieved by increasing the size of smart devices, thereby enhancing the viewing distance.

b. Outdoor Activities

Numerous studies have indicated that a lack of outdoor activity is a risk factor for myopia, while increased outdoor exposure provides a protective effect (Saxena et al., 2017). Outdoor activities lasting more than 2 hours per day have been shown to offer protective benefits against myopia. Enthoven CA et al. suggested that outdoor exposure exceeding 7 hours per week is required to counterbalance low-intensity near work, while more than 14 hours per week is necessary to mitigate moderate to high-intensity near work. However, this protective effect appears to be limited to the onset of myopia and does not necessarily prevent the progression of the condition once it has been diagnosed (Xiong et al., 2017). Interestingly, a study on the offspring of rural children in Handan City indicated that outdoor activities had a weaker protective effect on myopia in these children. Additionally, research has suggested that puberty may play a regulatory role in the relationship between outdoor time and refractive development among Chinese children and adolescents, offering insights into potential mechanisms and intervention strategies. Exposure to green spaces has been linked to a reduced risk of developing myopia, suggesting an additional avenue for intervention (Dadvand et al., 2017). These findings emphasize the importance of outdoor activities in controlling myopia, highlighting that increased outdoor exposure could potentially prevent the condition.

c. Light

Dopamine, an essential neurotransmitter in the retina, plays a critical role in retinal development, visual signal transmission, and refractive development. Bright light (2500–5000 lx) has been shown to inhibit the development of form deprivation myopia (FDM) by activating dopamine D1 receptor signaling in the retinal ON pathway. The dopamine D1 receptor has been identified as key in the apomorphine-induced inhibition of FDM in mice. Researchers have found that 120 minutes of outdoor lighting per day in schools can be beneficial in slowing myopia progression, whereas a lack of sunlight may exacerbate myopia. Exposure to brighter light (400–40000 lx) has been linked to a reduced risk of myopia, while lower ambient light levels (~50 lx) may diminish the effectiveness of the visually dependent mechanism regulating refractive development. Additionally, the use of LED lights for tasks and dim lighting are potential risk factors for myopia. Hu YZ et al. found that low correlated color temperature (CCT) light (2700–3000 K) was effective in slowing axial growth in young monkeys compared to high color temperature lights (4000–5000 K) (Hu et al., 2022). This study suggests that creating environments with low CCT lighting in classrooms could help mitigate axial hyperelongation and myopia in children. Furthermore, recent research has indicated that purple light may also inhibit myopia, presenting a potential preventive strategy for myopia development (Jiang et al., 2018). Studies on color cues have shown that narrowband, long-wavelength illumination could prevent axial elongation, a condition typically induced by form deprivation or hyperopic defocusing, by generating directional signals associated with myopia defocusing (Hung et al., 2018).

d. Classroom Environment

Zhang XY et al. found that compliance with school environmental monitoring standards can protect against the occurrence and development of myopia in students (Zhang et al., 2023). For instance, factors such as a per capita area of 1.36 m^2, uniformity of desk arrangement (0.40–0.59), blackboard reflection ratios (0.15–0.19), and appropriate blackboard illumination (150–500 lx) were identified as protective factors for axial length. A uniformity ratio of 0.40–0.59 for the blackboard was considered a risk factor for axial length, while illumination levels of 150–500 lx on desks were found to be protective for the diopter. The pilot study by Zhou Z et al. suggested that replacing traditional classrooms with bright classrooms could play a role in preventing and controlling myopia (Zhou et al., 2017).

e. Education and Economy

The prevalence of myopia has been linked to the level of economic development, with studies showing that children in rural and suburban areas experience significantly lower rates of myopia than their peers in urban areas with higher socioeconomic status. Economic development is often accompanied by a greater focus on wealth acquisition, where many individuals turn to education as a means of achieving economic success. This leads to heavier educational burdens, extended education years, longer working hours, and reduced outdoor activity, ultimately increasing the prevalence of myopia. Conversely, higher levels of education may further exacerbate myopia rates, as they often correlate with higher socioeconomic status. Furthermore, the increase in educational pressures has been associated with the acceleration of myopia development, with longer years of education linked to a higher prevalence of myopia. In the United States, a similar relationship has been found between myopia and higher education levels. These findings underscore the complex relationship between economic development, education, and the development of myopia.

f. Population Density

Zhang XY et al. observed that a per capita area of 1.36 m^2 was a protective factor for axial length, suggesting that smaller living spaces are linked to the development of refractive errors. High population density and reduced family sizes were found to be associated with shorter axial lengths and refractive errors in children. Smaller living spaces, particularly in urban environments, could serve as potential risk factors for myopia development. Additionally, the defocusing profile in the family environment, especially in the central near vision field, was identified as a possible risk factor for childhood refractive errors and myopia development. Evidence suggests that urban and indoor environments may resemble spatial frequency components known to induce form deprivation myopia in animal models, further supporting the idea that such environments may increase the risk of myopia (Flitcroft et al., 2020).

In conclusion, various environmental factors—including near work, outdoor activities, light exposure, classroom environments, educational and economic factors, and population density—play a significant role in the onset and progression of myopia.

Candidates for Myopia Control

As certain individuals are at a higher risk of developing high myopia, it is crucial to identify these at-risk groups to ensure better outcomes in terms of ocular health and vision. Myopia typically manifests in school-age children between the ages of 6 and 12 and progresses before stabilizing during adolescence. However, in some cases, progression continues beyond the teenage years and into adulthood. A progression model based on a meta-analysis of studies reporting annual myopia progression in children of Asian and European descent using single-vision spectacles found that younger children and those of Asian ethnicity exhibit faster progression. Those with faster-than-average progression or those in the progression phase for a longer period are at an increased risk of developing high myopia and should be considered candidates for myopia control treatment. Recent evidence also indicates a decrease in the age of onset, contributing to a longer progression period and an elevated risk of becoming highly myopic. Additionally, factors such as female sex, relative peripheral hyperopia and asymmetry, near esophoria, esofixation disparity, high accommodative convergence/accommodation ratio, lag of accommodation, and reduced outdoor time are thought to influence myopia progression, though their roles are not entirely clear. For example, some studies have not found a correlation between accommodative lag and myopia progression. While increased outdoor time may delay the onset of myopia, it does not appear to significantly slow progression in individuals who are already myopic (Xiong et al., 2017).

Strategies for Myopia Control

Over the past two decades, there has been a significant increase in strategies aimed at slowing the progression of axial myopia, utilizing optical, pharmaceutical, and environmental approaches. As a myopic eye already has an axial length longer than the optical focal length, an ideal myopia control strategy would prevent further axial growth to reduce the progression of myopia and the associated risk of sight-threatening conditions such as glaucoma and myopic maculopathy. Models predict that a strategy capable of slowing myopia progression by 30% to 40%, when instituted early, substantially reduces the risk of developing high myopia and its related complications (Brennan, 2012). While studies using 1% atropine suggest that it may be effective in halting eye growth, the observed rebound of myopia following the discontinuation of atropine and orthokeratology indicate that the mechanisms regulating eye growth remain poorly understood. Therefore, once a myopia control treatment is initiated, it may be necessary to continue the treatment beyond the period of progression, extending into adolescence and early adulthood.

OPTICAL APPROACHES FOR MYOPIA CONTROL

Progression of myopia with myopia control treatments has typically been compared with progression observed using single-vision spectacles or single-vision soft contact lenses. Although no significant differences in progression were found between single-vision spectacles and contact lenses, there is limited data, and it remains unclear whether factors such as peripheral retinal defocus, influenced by the contact lens power profile or pantoscopic tilt of spectacle lenses, could affect progression.

In experimental models, relative hyperopic defocus at the retina was shown to induce axial elongation, while relative myopic defocus inhibited or slowed eye growth. Insufficient accommodative responses for near tasks lead to retinal hyperopic defocus at the central retina, triggering axial elongation. Indeed, accommodative lag has been observed in myopic eyes. More recent studies on animal models have suggested that the peripheral retina plays a dominant role in driving emmetropization and that hyperopic defocus at the peripheral retina can lead to axial elongation. Furthermore, myopic eyes have been found to experience relative peripheral hyperopia, although it is not fully established whether there is a direct association between peripheral hyperopia and the onset or progression of myopia.

The spectacle and contact lens designs for myopia control aim to reduce hyperopic defocus and induce myopic defocus at the central retina during near work, or at the peripheral retina for all viewing distances. These lenses typically feature (1) one or more regions designed to correct the myopic refractive error and restore vision, and (2) one or more regions that are relatively more positive than the region used for correcting myopia. The positive power region (plus power) is intended to reduce hyperopic defocus and/or induce myopic defocus (Ruiz-Pomeda et al., 2018). The position of this region on the lens can vary. For example, to reduce accommodative lag, the plus power region is positioned to ensure the wearer looks through it while viewing near distances. Alternatively, to reduce peripheral hyperopic defocus, the plus power region is positioned toward the periphery on the optical zone of the lens, generating myopic defocus at the peripheral retina while simultaneously providing clear vision at the fovea. In addition to spectacles and soft contact lenses, rigid contact lenses used in orthokeratology, initially developed for myopia correction, also offer a beneficial side effect of myopia control. Orthokeratology works by flattening the central corneal curvature and steepening the midperipheral corneal area, creating a retinal image profile that reduces hyperopic defocus at the peripheral retina (Kang & Swarbrick, 2016).

Spectacle-based myopia control approaches include bifocals (with or without prism), progressive addition spectacles, and lenses incorporating peripheral defocus management. Data from well-conducted clinical trials (most with durations of 1-2 years) have provided insights into the overall reduction in progression with myopia control lenses compared to standard

lenses, evaluating changes in spherical equivalent and axial length. These studies reveal that while spectacle-based approaches slow myopia progression, the difference in progression compared to standard single-vision spectacles is generally small to moderate (usually 20% or less). There are exceptions, where greater efficacy is observed in a 3-year trial with bifocals (with and without prism), as well as in subgroups such as those with esophoria or young children with myopic parents. In comparison to spectacles, contact lens and orthokeratology-based methods demonstrate higher efficacy. The reduced efficacy of spectacles compared to contact lenses or orthokeratology may stem from peripheral or off-axis gazing that disrupts retinal signals, insufficient power to reduce hyperopic defocus, or noncompliance with using specific lens portions for specific tasks (Kanda et al., 2018). Moreover, a lack of understanding regarding the exact causes of myopia limits the development of more effective interventions.

Contact lenses used for myopia control are typically multifocal or specially designed multifocal-like lenses, with a central optical zone that corrects the distance refractive error, alongside one or more peripheral portions featuring positive power (plus power). The goal of the plus power is to reduce peripheral defocus or induce myopic defocus, often incorporated as rings, steps, or gradual increases in power. An exception is the extended-depth-of-focus (EDOF) contact lens, which has a non-monotonic power profile that incorporates both relatively positive and negative zones designed to degrade image quality for points behind the retina, preventing axial elongation. The treatment effect of contact lenses for myopia control has been shown to range from 20% to 70% for spherical equivalent and 27% to 79% for axial length. In one study considering lens wear compliance, efficacy was greater in those wearing lenses for 5 or more hours daily, with progression reduced by 25% to 46% (Lam et al., 2014).

In orthokeratology, rigid contact lenses are worn overnight, and their optical zone incorporates a flatter central zone than the cornea's flattest curvature, along with a steeper midperipheral reverse curve. This leads to flattening of the central cornea and steepening of the midperiphery, creating a retinal image profile that corrects distance refractive error at the fovea, with myopic defocus at the periphery. The treatment efficacy of orthokeratology lenses has been found to range from 30% to 56%. For all optical approaches, the overall efficacy represents the mean reduction seen across various eyes in comparison with a control, meaning some eyes may benefit more than others.

PHARMACEUTICAL STRATEGIES FOR MYOPIA CONTROL

Pharmaceutical compounds explored for myopia control in human trials include atropine, pirenzepine, tropicamide, 7-methylxanthine, and certain intraocular pressure-lowering agents, such as timolol. Among these, selective muscarinic receptor antagonists like pirenzepine and mydriatic agents such as tropicamide showed early promising results. However, for unknown reasons, there were no further clinical developments or approved products for these compounds. It is believed that rhythmic variations in intraocular pressure may exert force on the sclera, promoting excessive growth, although a causal relationship has not yet been conclusively demonstrated. In one trial, the application of 0.25% timolol twice daily did not influence myopia progression.

Atropine

The initial use of atropine was based on its presumed action on the accommodative mechanism, with prolonged accommodation thought to exert force on the choroid and sclera. However, studies on chicks showed that atropine worked via nicotinic receptors rather than muscarinic ones in the ciliary muscle. Subsequent research has explored atropine's effects on retinal neurotransmitters, the choroid, retinal pigment epithelium, and the sclera, but its precise mechanism remains unclear, with possible action through antimuscarinic activity on the M1-M5 receptors, direct tissue effects, or other receptor pathways.

Atropine 1% was used in early studies, showing effectiveness in slowing eye growth, but also causing significant adverse effects, such as photophobia and blurred near vision, which required management with bifocal and photochromic spectacles. Concerns were also raised about potential long-term retinal toxicity or photic damage due to the drug's accumulation, although studies have shown that retinal function remained unaffected. Due to the severe side effects associated with higher concentrations, lower concentrations of atropine, such as 0.01%, have been trialed. The efficacy of 0.01% atropine in reducing myopia progression has been significant in terms of spherical equivalent change, although there has been no corresponding significant effect on axial length compared to controls. Despite showing efficacy in slowing myopia, the use of 0.01% atropine requires further examination. Additionally, even at lower concentrations, significant effects have been observed on pupil size and accommodation, despite being associated with fewer adverse effects compared to higher concentrations (Cooper et al., 2013).

7-Methylxanthine

7-methylxanthine, a nonselective adenosine receptor antagonist, has been shown to reduce axial myopia induced by hyperopic defocus in a primate model. A pilot human clinical trial involving 68 myopic children demonstrated that after 12 months, the change in axial length was less in the treatment group (0.35 ± 0.15 mm) compared to the placebo group (0.38 ± 0.17 mm), although this difference was not statistically significant ($P = 0.567$). Additionally, 7-methylxanthine was found to increase both the diameter and content of collagen fibrils in the posterior sclera, as well as to increase the thickness of the posterior sclera. It is proposed that 7-methylxanthine exerts its effects by strengthening the sclera, though the exact mechanism remains unclear.

Long-Term Efficacy of Optical and Pharmaceutical Approaches

It is well-established that myopia progression can be slowed to clinically meaningful levels through one or more optical and pharmaceutical interventions. However, long-term data are limited. With the exception of a few trials lasting 3 years or more, most trials evaluating optical or pharmaceutical myopia control strategies have been of shorter duration (1 to 2 years). There is also concern that the magnitude of control may decrease over time, with greater effects observed in the first year of lens wear, followed by a reduction thereafter. Some studies reported consistent effects year after year, while others noted a slight decrease in efficacy over time. Consequently, it is not entirely clear whether the control magnitude decreases with prolonged use. Furthermore, as eye growth slows with age, it may become increasingly difficult to detect significant differences between treatment and control groups in terms of axial elongation. Additional factors, such as patient dropouts and noncompliance, may also influence the results. For instance, myopic individuals who progress more rapidly during the trial may perceive no benefit and be more likely to drop out and seek alternative treatments. Higher dropout rates from the control or placebo group, which may remove patients who are experiencing insufficient efficacy, could lead to biased estimates of treatment effects, as has been observed in other medical fields. Furthermore, longer trial durations increase the risk of noncompliance, which could result in an apparent reduction in overall efficacy. In fact, compliance was found to be a critical factor in achieving greater myopia control, with more significant slowing of myopia in eyes with high compliance. Noncompliance is more likely to occur when the benefits of the intervention are not immediately apparent, as is often the case with pharmaceutical treatments such as atropine. These considerations must be carefully accounted for when evaluating the long-term efficacy of myopia control strategies.

Rebound of Myopia

The "rebound effect" refers to the reappearance or acceleration of a condition after the abrupt cessation of treatment. This effect has been observed with several pharmaceutical agents, where it is thought to result from the body's return to its baseline state after discontinuing the drug, or

from withdrawal symptoms following treatment cessation. In the context of myopia progression, rebound refers to an increase in the rate of myopia progression after the cessation of treatment, compared to the progression rate either in a control group or during the treatment phase. A faster rate of myopia progression following the discontinuation of atropine treatment, compared to the rate during treatment, was observed. After one year of non-treatment, net myopia was lower in the eye that experienced rebound compared to the control eye; however, it remains unclear whether the final level of myopia would have been similar to the control eye had the follow-up period been extended beyond one year. When data were analyzed in 6-month intervals, eyes that discontinued atropine showed greater progression during both the first and second 6-month periods. However, less progression was noted in the second 6-month period, indicating that much of the rebound effect occurred soon after discontinuation. Although the precise mechanism remains unknown, substantial evidence from both systemic and ocular drug use suggests that gradually tapering the drug dosage, rather than an abrupt withdrawal, generally mitigates the rebound effect. Rebound after atropine discontinuation appears to be dose-dependent, with minimal rebound seen with lower concentrations. However, to date, no studies have explored the efficacy of tapered doses in reducing rebound effects.

While rebound is commonly associated with the abrupt discontinuation of medications, there is concern about whether optical strategies for myopia control might also be susceptible to rebound effects. When eyes treated with progressive addition spectacles were switched to single-vision lenses, the rate of myopia progression was not greater than expected, suggesting no rebound effect. In a subsequent study, when orthokeratology and rigid gas permeable lenses were alternated between eyes after 6 months of treatment, eyes that switched from orthokeratology to rigid gas permeable lenses exhibited greater axial length change compared to those that continued wearing rigid gas permeable lenses. Another study found that discontinuation of orthokeratology in children younger than 14 years led to a rapid increase in axial length. Although further research is needed to better understand rebound effects associated with myopia control strategies, these studies highlight the inherent difficulty of exploring this phenomenon, as they require the removal of effective treatment, raising ethical concerns. It may be more appropriate to continue myopia control treatments until myopia has stabilized, indicated by no significant change in spherical equivalent refractive error or axial length for several years, at which point eye growth would be considered complete. In such cases, tapering the treatment could be considered should discontinuation be necessary.

Conclusion

The development and progression of myopia are influenced by a complex interplay of genetic and environmental factors. Genetic predisposition plays a key role in the susceptibility to myopia, with numerous genes identified as contributing to its onset and severity. However, environmental factors such as near work, outdoor activity, light exposure, and socioeconomic conditions are also critical in shaping the prevalence and progression of myopia. Increased near work, limited outdoor exposure, and improper lighting in classrooms contribute to the rising rates of myopia, while outdoor activities, exposure to bright light, and optimal classroom environments provide protective effects. Moreover, the economic development of a region, as well as population density and family living conditions, have been identified as distal factors influencing myopia prevalence.

Interventions aimed at reducing myopia risk must focus on addressing both genetic and environmental components. Encouraging outdoor activities, improving lighting in educational environments, and minimizing excessive near work are practical strategies that can help mitigate myopia's impact. Additionally, public health efforts should consider the role of economic development and educational pressures in exacerbating myopia prevalence. Further

research is needed to better understand the mechanisms through which these factors interact and to refine prevention strategies. Ultimately, a multifaceted approach that combines genetic awareness with environmental modifications holds promise for controlling the growing global burden of myopia.

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