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Current Research Perspectives on Pharmacological and Non-Pharmacological Treatment Options for Myopia

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Abstract: Myopia is primarily a cause of impaired vision in people under the age of 40, if left uncorrected. However, high myopia can result in uncorrectable vision loss through the development of pathological myopia, but this generally does not become a significant issue until people are aged 50 and over. Even though high prevalence of myopia is currently restricted to school-age children in the countries of East Asia, namely South Korea, Japan, China, including Hong Kong and Macau, Taiwan, and Singapore in Southeast Asia, by the year 2050, roughly half the people on the planet will be myopic. Major risk factors associated with myopia are related to environmental factors and cultural demands requiring children to undergo extensive schooling which results in reduction of time outdoors in natural light. High myopia is a significant risk factor for serious ocular conditions such as glaucoma, macular degeneration, early onset of retinal detachment and cataracts. A variety of therapeutic options are available to slow the advancement of the disease and significantly correct the condition. In recent years, several novel treatment strategies and approaches have been evaluated in clinical trials and have altered the therapeutic landscape for myopia. This review will summarize the epidemiology of this disease, cover some recent clinical advances, and existing and novel treatment options to combat myopia. Pharmacological options include muscarinic receptor antagonists, FP-class prostaglandins, and certain neurotrophic blockers including vascular endothelial growth factor (VEGF) inhibitors. The nonpharmacological treatment options include multifocal soft contact lenses, orthokeratology, and exposure to outdoor light. A brief discourse on the laboratory science related to animal models and discovery research of novel anti-myopic drugs will also be presented.

Keywords: Myopia, Myopia Treatment, Myopia Clinical Trials, Prevalence of Myopia, Quality of Life in Myopia, Myopia Progression

1. Introduction

Myopia, also known as near-sightedness, is a common ocular disorder with increasing prevalence, making it a substantial global health concern [1]. It is an eye condition in which light rays entering the eye project an image in front of the retina rather than upon the retina causing blurring of distant vision. In general, a refractive power of less than -0.5 Diopters in either eye is considered to be myopia and a refractive power of the eye that is less than -5.0 to -6.0 Diopters (D) is defined as high myopia [2]. It is predicted that by 2050 approximately 52% of the world's population will be myopic and it is a major public health concern in many East Asian countries. Myopia in these countries, affects 80% to 90% of high school graduates and 10% to 20% of these graduates have sight-threatening pathologic myopia [3]. The substantial diminution of the quality of life (QoL) of the patient, the increased medical, societal, and economic burden resulting from the myopic condition is being felt by all nations across the globe.

There are several sub-divisions of myopia on the basis of amount of refraction, age of onset, etiology and its long-term effects [4] (*Table 1*) [5]. Based on pathogenesis, myopia can alternatively be classified as primary and secondary myopia. The elongation of the visual axis of the eye in the absence of

systemic syndromes can be defined as Primary myopia. Secondary myopia is defined as visual impairment induced by cataract, drugs, diabetes mellitus or other systemic diseases [6, 7]. Once viewed as a benign condition, recent research has shown low levels of myopia can be associated with increased pre-disposition to several ocular diseases such as Glaucoma, Cataract, retinal detachment, and myopic macular degeneration, making high myopia a major cause of visual impairment and blindness if left uncorrected or untreated [8, 9].

The aim of this article is to review the literature, consolidate and critique the information, and disseminate the collated information about the disease and its mitigation involving pharmacological and other treatment modalities.

Table 1. *Classification of myopia.*

Classification basis	Types
Etiology	Axial, benign, correlational, lenticular, index, physiological, refractive, simple, syndromic
Age of onset	Congenital, childhood, juvenile onset, early adult onset, late adult onset
Progression pattern	Progressive, high progressive, high degenerative, stationary, permanently progressive, temporarily progressive
Severity of disease	Low, intermediate, high, pathological, physiological, severe, simple
Structural complications	Degenerative, malignant, pathological, pernicious, progressive, high progressive, high degenerative

1.1. Epidemiology: Prevalence and Etiology

Globally the prevalence of myopia is increasing, however, there is a discrepancy in prevalence rates across different countries due to racial and cultural differences. In the United States, its prevalence increased from 25% to 44% between 1972 and 2004 [10-12], and 41.9% of 5-19 years old children had myopia in a cross-sectional study conducted between 2008-2013 [13]. In France, prevalence rates reached similar highs at 39.1% in a cohort study on the general population [14]. In contrast, studies showed prevalence rates of 9.6%, 1.4% and 11.2% for Brazil, Paraguay, and Columbia respectively [15-17]. In Africa, Ghana and South Africa reported rates of 3.4% and 7.0% respectively [18, 19]. The highest prevalence rates were seen in China across various studies ranging from 36.9% to 65.48% [20, 21]. In neighboring parts of Asia such as South Korea and Indonesia, high prevalence rates persist at 73.0% and 32.68% respectively [22, 23]. In India, which is comparable in population to China, the prevalence rates are much lower as found by the North India Myopia (NIM) Study at 13.1% [24]. These differing rates suggest that myopia does not affect all individuals equally and that geographic location can be a significant factor.

The etiology of myopia lies in the signaling pathway that leads to an image being projected on the retina. Therefore, the signaling cascade beginning at the sensory retina, the movement of this signal across the retinal pigment epithelium and the remodeling of the sclera all play a role in the development of myopia [25]. This includes genes involved in the signaling pathway as well as environmental factors such as optical defocus induced by intense study [26]. In fact, research studies have identified 22 genetic associations with age of myopia onset [27]. On the other hand, a regression analysis of myopia prevalence from nine studies found a high correlation of myopia in medical and engineering students [28]. These studies indicate that the etiology of this condition lies in genetic, environmental and also in racial and cultural factors.

1.2. Ethnic Factors in Development of Myopia

Since myopia prevalence rates are highly varied across different countries, studies investigating ethnic factors have emerged in recent years. A study in America looked at preschool children aged 6–72 months. The r prevalence of myopia in the non-Hispanic whites was 1.2%, 3.7% in Hispanics, 3.98% in Asians, and 6.6% in African Americans [29, 30]. Children of different ethnicities and who were older showed a greater difference in the prevalence of myopia. [13, 31]. A study conducted in Southern California looked at the racial and ethnic differences in myopia in over 30,000 myopic children aged between 5–19 years. It was revealed that myopia was significantly more prevalent in Asian/Pacific Islander children than in Caucasian children, with higher prevalence in older children (17-19 years old) compared to younger children (5-7 years) [13]. Furthermore, the rate of myopia progression varies in different ethnicities, where East/Southeast Asian children progressed more rapidly than their Caucasian counterparts in any given age group [32]. While these studies were conducted on children, Varma et al investigated the prevalence of myopia among an older, adult Chinese population and found similar results [33]. Collectively, these studies emphasize that at least partially, ethnicity may be a risk factor in the development of myopia.

1.3. Geographic Factors Associated with Myopia

There have been several investigations of myopia in urban versus rural areas that have shown varying prevalence rates. In general, across various countries, rural prevalence rates are reportedly lower than urban areas [34-36] In Australia, one study showed a greater odds ratio of myopia in areas that had higher population density and, a higher prevalence of myopia among those children living in apartment complexes versus other housing arrangements [37]. A meta-analysis comparing global trends in myopia found that children living in urban areas are 2.6 times more likely to develop myopia than children living in rural areas [38]. In contrast, Morris et al. reported that myopia seen in varying geographic settings are correlated to lifestyle factors associated within those settings, suggesting that geographical factors are confounded by other variables such as low outdoor time, dim light exposures and higher population density [39, 40].

1.4. Environmental Factors Associated with Myopia

Epidemiological studies have shown that environmental

factors such as reading and extended periods of close work such as computer use play an important role in myopia development [39, 40]. There is a consensus that myopia is more prevalent in urban areas among professionals, computer users and university students [24, 43]. Studies associating myopia and near work are based on the theory of hyperopic defocus from a deficient accommodative response [44, 45]. Finland saw significant increases in myopia cases through the latter part of the 20th century, which has been attributed to the larger number of people completing secondary school in recent decades [46]. Through a meta-analysis, myopia was found to become increasingly prevalent as participants reported higher levels of education [47]. Thus, predictably, the amount and intensity of the reading required in achieving higher levels of education has also been associated with the development of myopia [48].

Early studies also hypothesized that myopic progression ended at age 18 [49]. However, this has proven to not be the case, as more students enroll more graduate courses or graduate into jobs that require over 8 hours of computer time. In a recent study that evaluated a group of college graduates with a mean age of 35, myopia was found to progress significantly in ~10% of subjects who spent a lot of time in front of the computer screen compared with subjects who did not [50]. In addition, a study by Bullimore et al. looked at 20-40 year old contact lens wearers an the study showed that that around $1/5^{th}$ progressed by at least 1 Diopter over a period of 5 years [51].

In addition to close work and reading, time spent outdoors also impacts the occurrence of myopia. A meta-analysis by Xiong et al. demonstrated that increasing the time spent outdoors for children led to a decrease in the incident of myopia [52]. In one study, myopia progression seemed to be associated with seasonal variation, where an increased rate was observed in the winter than during the summer [53]. Collectively, these findings make a strong case for the role of lifestyle and environmental factors in myopia development and progression.

1.5. Genetics and Myopia

Although environmental factors have proven to be strongly correlated with myopia, other groups have also reported that genetic factors account for 35% or greater variance in refraction [54, 55]. For instance, presence of myopia in both parents significantly increases the chances of incidence in children [56, 57]. Genome-wide association studies (GWAS) and Next-generation sequencing (NGS) have identified multiple interacting genes and chromosomal loci linked to myopia development [56, 58-60] However, the very limited success in accounting for the genetic variation suggested by the high heritability values reported in twin studies requires further investigation and adequate explanation. Likewise, the association between genetics and myopia development is not always linear since epigenetic factors may influence the overall outcome on the severity and rate of progression of myopia and requires further investigation. Complex chromosomal associations account for less than 25% of myopia cases, and not all possible associated chromosomal loci have been identified [61]. This is complicated by the fact that genetic variants associated with myopia development do not have the same effect in different families or ethnic groups.

Tkatchenko et al. have suggested that only 10% of the genes involved in variance of refractive error are known [62]. The authors studied a three-way interaction between age, time spent reading, and genetic variation at *APLP2* gene locus. This study showed that children who had the myopic version of *APLP2* gene and spent a considerable time reading vs those who read very little were 5 times more likely to develop myopia. In children who carried a normal version of *APLP2* did not develop myopia even if they spent many hours reading. The gene–environment interaction in myopia development was shown for the first time in this study and that an individuals genetic background can determine the impact of environmental factors on refractive eye development [62]. Pozarickij et al. recently reported a signature to identify gene-gene interactions or gene-environment interactions for 128 (88%) of 146 refractive error-associated variants tested [63]. Overall, it can be said that the etiology of myopia is comprised of complex interaction between genetic and environmental factors, and the underlying mechanisms remain to be elucidated.

1.6. Prevalence in Adults

Myopia has long been considered a condition primarily affecting children, however studies have shown. that the prevalence of myopia decreased progressively with age, ranging from 42.9% in adults aged 43–54 years to 14.4% among individuals aged 75 years and above [64]. Amongst African Americans of various ages a bimodal pattern was seen in the prevalence of myopia with high prevalence rates found in individuals aged 40–49 years as well as 80 years or above [65]. This bimodal pattern of myopia prevalence was also seen in adult Singaporeans aged 40–81 years [66]. This bimodal distribution is likely due to differing influences of axial myopia among younger people, and greater index myopia, due to lens nuclear sclerosis in older people [67].

1.7. Economic Cost of Myopia

The costs associated with myopia consist of the treatment expenses as well as the costs associated with reduced socioeconomic activities. In the US alone, the economic cost of eye diseases is $139 billion, with $16 billion spent on myopia correction [10, 11]. As depicted in a recent meta-analysis, the yearly global potential loss in 2015 due to vision impairment was US $244 billion from uncorrected myopia and $6 billion from myopic macular degeneration [68]. In the UK, it is estimated that partial sight and blindness in adults costs the economy around £22 billion per year, with the consumer spending for optical goods and services industry estimated at £3.1 billion [69]. High myopia also increases the risk of other eye diseases such as glaucoma, retinal detachment, and myopic macular degeneration (MMD), which leads to irreversible vision loss and also causes a

substantial cost burden to impacted individuals, their families, caregivers, and the community [70]. Thus, the economic costs of myopia are high, and are projected to increase in line with the projected increase in the prevalence of the disease over the next few decades.

1.8. Quality of Life

Quality of life is a multidimensional parameter that consists of several aspects. From this perspective, myopia affects self-perception, job/activity choices, ocular health and is one of the leading causes of blindness in the world [71]. Impaired vision leads to significant reduction in activities associated with daily living, visually intensive tasks and activities that pertain to participation in society [72]. Children with myopia have been reported to have significantly lower math scores and socio-functioning scores than their peers and suffer from low self-esteem and can succumb to depression [73, 74].

1.9. Associated Pathologic Conditions in Myopia

The major concern for those affected by myopia is the progression to high myopia, which can lead to blindness and a poor quality of life. High myopia causes irreversible vision loss by increasing the risk of other pathologic conditions such as cataracts, glaucoma, retinal detachment, and MMD [3]. It was also found that the critical range of the refractive index for retinal breaks was at -3.5 Diopters (D) to -7.5 D [75], suggesting that retinal breaks are often the predecessor of retinal detachment that requires emergency treatment. Cataracts are another complication in the progression of myopia. In a study performed in Singapore on adult patients, there was an increased prevalence of nuclear cataracts in myopes and, for high myopes particularly, there was an increased prevalence of posterior subcapsular cataracts [76].

1.10. Treatment Options

A variety of treatments are available to slow the progression of myopia and are shown in Table 2. These include spectacle lenses, contact lenses and pharmacologic agents. Surgical interventions such as refractive surgery and intraocular lens implantation in adults have gained popularity in recent times as a more 'permanent' approach dealing with myopia but lack long-term safety and efficacy studies [11].

2. Non-Pharmacological Treatments Options

2.1. Single Vision Lenses

Single vision lenses are the most common type of glasses lens that correct vision for a single distance. In one study, the hyperopic defocus in a moderately myopic (-3.25 D to -6.00 D) group of children was significantly greater than the low myopic (-0.75 D to -3.00 D) group ($p < 0.038$) [77]. In animal models, compensatory ocular growth is seen in response to lens-induced defocus [78]. These results suggest that spectacle intervention might lead to increased progression and axial elongation, but this does not happen in practice in humans.

2.2. Bifocals and Progressive Addition Lenses

Bifocal and progressive addition lenses (PALs) work on the premise of providing both near and distance vision. Bifocal lens consists of two specified areas: the upper zone of the lens for distance and the lower part for near vision. In the PALs, there are additional progressive zone between upper and lower portions that provides intermediate vision, allowing a smoother viewing transition between various distances. Bifocals and PALs have been extensively studied for slowing of myopia and have produced relatively small benefits, on the order of 0.15 D to 0.50 D over 1.5 to 3 years. However, in certain sub-groups of children these treatment effect have been larger [79, 80].

Recent advances in eyeglasses comprise of lenses made of novel materials. In a study conducted in myopic Canadian Chinese children, prismatic bifocal lenses moderately slowed the progression of myopia [81]. In the CYPRESS (Control of Myopia Using Novel Spectacle Lens Designs) Trial, 6-10 years old participants used one of three types of lenses instead of their normal glasses: control lenses or one of two proprietary test lens designs and are followed over 36 months. The study has reported promising early results in subjects using the proprietary test lenses [82]. In addition, there are now two spectacle lenses that decrease myopia advancement by at least 50% by imposing myopic defocus: 1) Stellest lens is said to incorporate H. A. L. T. (Highly Aspherical Lenslet Target) technology to control myopia progression. The H. A. L. T. technology comprises a group of aspherical lenslets on 11 rings surrounding a clear central distance correction zone that is said to produce a volume of myopic defocus signal in front of the retina [83]. 2) Defocus Incorporated Multiple Segments (DIMS) lenses, is comprised of a 9 mm central optical zone and a 33 mm annular zone that has multiple 1 mm segments containing a relative positive power of +3.50 D. A study on this lens reveals the mean myopic progression was –0.41 D in the DIMS group and –0.85 D in the control group [83]. Such technological advances are notable.

2.3. Contact Lenses

Contact lenses are ocular prosthetic devices used millions around the world. Contact lenses come in two forms – Rigid gas permeable lenses (RGP) and soft contact lenses [84]. In the CLAMP trial, slower progression was observed in RGP users compared with soft lens users, with most of the benefit appearing in the first year [85]. The LORIC study showed that overnight use of RGP lenses for 2 years slowed axial elongation and progression of myopia compared with a group wearing SVLs (0.29 mm vs 0.54 mm) [86].

2.3.1. Soft Contact Lenses

Optical lens designs have two categories. Both designs effect the central and peripheral retinal images, the first being a concentric ring design and the second a progressive power

design. The concentric ring lens design have distant viewing power in the centre of the lens and the centre is surrounded by concentric rings of near and distance powers. The progressive power lens have a gradual shift in lens power, there is no sudden image jump from one level of lens power to another. Instead, there is a gradual change in curvature. [87].

A clinical study by Sankaridurg et al [88] looked at myopia control efficacy with progressive power design silicone hydrogel contact lenses that (1) decreased both central and peripheral defocus, and (2) offered extended depth of focus with better global retinal image quality for points on, and anterior to, the retina. Furthermore it was found that with contact lenses that either caused myopic defocus at the retina or modulated retinal image quality, it lead to a significantly slower progression of myopia with greater efficacy in those who were compliant in wearing their lenses. [88]. Similarly, contact lenses designed to reduce peripheral hyperopia were shown to reduce central refractive development and the rate of myopia progression [89].

Studies have shown that using additional optical power you can influence the eye growth when myopic defocus is also presented. . These optics are typically used with concentric alternating powers in a zonal design and are commonly referred to as “dual-focus optics”, which is the basis for MiSight lenses [87]. In a 3-year double-masked randomized clinical trial, MiSight lenses significantly slowed the progression of myopia in 8–12-year-old children, mainly by slowing the change in spherical equivalent refraction and axial length [90]. MiSight lenses received FDA approval in 2019 and are now marketed as a treatment to slow myopia progression in children.

The above studies highlight the significant progress made in the contact lens therapeutics in the last decade and their superiority over conventional myopia correction methods. However, larger randomized clinical trials that follow-up on patients for a longer period of time and account for compliance in their outcome measures are needed to substantiate the safety and efficacy of these novel approaches.

2.3.2. Orthokeratology

Orthokeratology (OK) involves the wearing lenses overnight. The lenses work by flattening the centre of the cornea hence changing how the light is bent as it enters the eye. These overnight lenses are not only rigid but also gas permeable and are sturdy enough to reshape the cornea. When these lenses are removed the cornea will remain flat and the vision is corrected hence not requiring lenses or glassed during the day. [91]. Santodomingo -Rubido et al. showed in a recent seven-year follow up study that 14 the 29 orthokeratology subjects who had completed the two-year trial and were examined five years post completion of the study along with 16 of 24 control subjects, showed axial elongation in the OK group was 0.44 mm lower than the control group following 7 years of lens wear. Although orthokeratology potentially eliminates the side effects of using atropine, it does have the possibility of its own side effects which include corneal infections, an increase in higher-order corneal aberrations and a decrease in contrast sensitivity [93]. Longer-term follow-up studies are required to assess the safety and efficacy of orthokeratology, as well as myopic regression after discontinuation of treatment.

2.4. Refractive Surgery

Refractive surgery is opted for by an increasing number of myopia patients, especially adults with moderate to high myopia. Photorefractive keratectomy (PRK) and laser-assisted in situ keratomileusis (LASIK) are both laser surgery techniques used to reshape cornea tissue [94]. With PRK the top layer of the corneal epithelium is removed, and lasers reshape the other layers of the cornea and fix any irregular curvature in the eye. In more commonly performed LASIK [95], lasers are used to create a small flap to reshape the cornea. The flap is lowered back down after the surgery, and the cornea repairs itself over the next few months.

LASIK surgery has been approved as a correction procedure since 1995 [96]. With more adults opting for LASIK in recent years, procedural improvements for conventional LASIK have been studied in recent years. LASIK performed with the Wavelight Refractive suite and femtosecond-assisted LASIK (fs-LASIK) resulted in significantly better outcomes in treated subjects, in terms of visual acuity [97]. Femtosecond lenticule extraction (FLEx) refractive surgery has also been demonstrated to lead to stable outcomes in a 10-year follow-up study [98] (*Table 2*).

Table 2. *Overview of treatment options for myopia.*

Treatment	Advantages	Disadvantages
Single vision lenses	Most prescribed option Slows myopia progression	Not convenient for sports and physical activities Loss of self-esteem Risk of infection
Bi focal/ multi-focal lenses and contact lenses	Commercially available options Wide parameters for personalizing therapy	Increased cost compared to single vision lenses Need for back-up spectacles/ lenses Risk of infection
Orthokeratology	Reduces need for corrective measures during waking hours Minimal need for back-up spectacles/ contact lenses	Only corrects low to moderate myopia Variable results Consistent wear schedule is crucial
Refractive surgery / Intraocular lens implant	Reduces expenses incurred from other corrective measures Immediate, long-term effects	Cost-prohibitive Not suitable for children Not suitable for every patient

Treatment	Advantages	Disadvantages
Atropine	Demonstrated to be effective	Some side-effects reported
	Can be combined with spectacle wear	Combined cost of atropine plus spectacles/ lenses can be high
Corneal cross-linking	Advantageous for those not a candidate for surgery	Long healing time
	Can be combined with PRK, LASIK etc. for vision improvement	Does not improve vision by itself

2.5. *Exposure to Outdoor Light*

There is hypothesis that exposure to outdoor light can delay the onset of myopia as well as reduce progression in myopes. In a 1-year study in Taiwan, the light intervention group was assigned outdoor activities during school and at home while wearing of devices that measured light exposure. Both myopic shift and in axial length elongation were reduced in the intervention group versus the control group (0.35 D v. 0.47 D, (0.28 mm vs. 0.33 mm) [99]. In 2001 the National Myopia Prevention Programme in Singapore was formed. This program looked at high childhood myopia rates and the impact of outdoor activities. The program looked at messaging on good eye care habits to delay the onset of and prevent myopia among children as well as efforts on reducing screen time [100]. A country wide myopia control strategy has been implemented in China. This involves working with both the health and education sectors to bring about government policy reforms that will help in reducing behaviours that lead to myopia [101]. It is highly desirable to change the mindset of the modern parent in Asian countries that outdoor play in ambient natural light (sunlight) and exposure to the environment is just as important for health and well-being as intense schooling of children.

3. Pharmacological Treatments for Myopia

It has been postulated that near work- induced transient myopia could be a contributing factor to the progression and development of permanent myopia. This may be due to ciliary muscle's ability to contract and relax when switching from near to distant vision.

3.1. Atropine

Atropine is an old anti-cholinergic non-selective muscarinic receptor antagonist drug and its effects on slowing the progression of myopia have been extensively studied [102-104]. The randomized controlled ATOM1 study on children aged 6–12 years old, patients receiving 1% atropine showed they were significantly less myopic after 24 months (−0.40 D vs −0.86 D) compared to the placebo group. However a rebound effect was seen after treatment was stopped in the atropine treated eyes after the one year follow up. At the end of the study, atropine-treated eyes were still significantly less myopic than those that received placebo, suggesting that 1% atropine was an effective treatment to reduce myopia progression in children [102]. ATOM2 involved similar protocol to ATOM1 with the primary change being that the, children were randomly allocated to three concentrations of atropine (0.5%, 0.1% and 0.01%) for 2 years, and then similarly followed up for 1 year after discontinuation of treatment. A dose-dependent reduction in myopia progression was seen during the first 24 months, but those given a higher dose of atropine also developed myopia more quickly during the washout period. This rebound effect is related to the fact that prolonged blockage of muscarinic receptors causes a compensatory response whereby the cells treated with atropine generate new muscarinic receptors that then reverse the effects of atropine. Balancing the benefits versus regression across all the doses, 0.01% atropine was established as the most effective dose in reducing myopia progression after the third year [103].

The Low-concentration Atropine for Myopia Progression (LAMP) study, which randomized 438 myopic children ages 4 to 12 to 0.05%, 0.025% and 0.01% atropine or placebo for one year, shows mean myopia progression was –0.27 D, –0.46 D, –0.59 D and –0.81 D in the 0.05%, 0.025% and 0.01% atropine, and placebo groups, respectively, with corresponding mean axial elongation of 0.20 mm, 0.29 mm, 0.36 mm and 0.41 mm [104]. Atropine has been shown to be efficacious in slowing the progression of myopia in several studies, but with considerable side-effects [103, 105]. Cooper et al. observed that 0.2% Atropine was the highest concentration of the drug that did not display a high degree of side-effects such as mydriasis and cycloplegia [105]. Therefore, recent clinical trials have evaluated the efficacy and safety profile of a lower dose of atropine in remedying myopia progression. In a study of super-diluted atropine (0.01%), a 25% decrease in myopia progression was reported in comparison with untreated controls [106]. In addition, Chia et al. described higher and faster rates of myopic regression in patients receiving higher doses of Atropine (0.5%) versus patients receiving 0.01% of the drug [107]. These studies indicate that lower concentrations of atropine may be a viable approach to circumvent the side- effects without compromising on efficacy. Indeed, several studies assessing the efficacy of low-dose atropine (0.1%-0.01%) in decelerating myopia progression in several clinical trials across the globe, [104, 108-111]. Additionally, proprietary formulations of atropine are also being currently investigated in clinical trials for efficacy against myopia [109-111].

3.2. Pirenzepine

Pirenzepine, like atropine, is a muscarinic antagonist that has been observed to be less likely to produce mydriasis and cycloplegia, primarily due to the lower concentration used and also due to its muscarinic receptor selectivity (10-13-fold selectivity as M1 receptor antagonist relative to M3/M4 receptors). In a guinea pig model, Pirenzepine was shown to slow myopia development by regulating matrix

metalloproteinase-2 (MMP-2) and its inhibitor, TIMP-2, expression [112]. Two Pirenzepine clinical studies have taken place in in Singapore, Hong Kong, and Thailand, and the other in the United States [113, 114]. In the Singapore study, the therapeutic effect of Pirenzepine correlated with amount of usage [114]. In the U.S. study, myopia increased over one year by 0.26 D in the pirenzepine group (used once a day) and 0.53 D in the control group [113]. Although pirenzepine has been shown to have these favorable effects, there have also been reports of reduced visual acuity and induction of accommodation abnormalities [115]. Nevertheless, topical pirenzepine is not approved by the FDA and so is not currently available as a treatment option [116].

3.3. 7-Methylxanthine (7-MX)

The potential for the nonselective adenosine receptor antagonist, 7-methylxanthine (7-MX), emerged from the observation that it decreased collagen fibril diameter associated with myopic axial elongation [117]. Oral 7-MX increased the collagen-related amino acid content, and the thickness of the posterior sclera in rabbits, strengthening the sclera and reducing axial elongation [118]. In a randomized controlled trial that looked at the effect of oral 7-MX on myopia progression, children with myopia were divided into two groups. The first group was given 7-MX daily for 2 years and the second group was given placebo for the first year then 7-MX for the second year. A significant reduction in myopia progression rate was seen in patients who took 7-MX vs those who took placebo. After the second year, the myopia progression rate of both groups was significantly reduced compared with the previous year suggesting that 7-MX could effectively slow myopia progression. Moreover, there were no reported side-effects in drug-treated patients [119]. However, the sites and mechanisms of action of 7-MX are unknown, which has impeded widespread clinical study and uptake of 7-MX as a treatment strategy.

3.4. Riboflavin Cross-Linking

Keratoconus is an eye disorder where the cornea bulges out to form a cone-like shape and thins over time. These changes to the cornea cause vision problems such as astigmatism and myopia [120]. To remedy this, corneal cross-linking (CXL) is rapidly gaining popularity. CXL is a treatment where riboflavin (vitamin B2; derived from milk, meat and green food plants) drops are applied to and absorbed by the cornea. An ultraviolet light treatment is then applied to the eye, causing a reaction within the corneal stroma to create bonds called cross-links that strengthen the cornea and prevents it from thinning and weakening. The greatest patient benefit with this procedure is preventing corneal transplant surgery, thus giving patients a better quality of life.

In patients undergoing the procedure, the cornea becomes more spherical and less aberrative, resulting in a subjective improvement in visual quality [121, 122]. However, CXL alone is unable to substantially improve functional vision, but this limitation can be overcome by combining CXL with PRK [123]. PRK has been widely described to be effective in treating stable or early keratoconus, and was significantly superior when combined with CXL [124]. Presently, a novel technique referred to as 'CXL Plus', which combines CXL, with other refractive procedures such as topography-guided PRK, transepithelial topography-guided PRK, or phakic intraocular lens implantation (PIOL), either sequentially or simultaneously, is being evaluated in clinical studies [123, 125]. CXL-Plus is advantageous over typical CXL because it enhances CXL result, by improving corneal stability and by providing functional visual acuity [123].

Avedro [126, 127] is currently investigating corneal cross-linking as a refractive procedure for the non-invasive treatment of low myopia. Called the PiXL™ Procedure (Photorefractive Intrastromal Corneal Cross-Linking), Avedro announced positive safety and efficacy results and a high patient satisfaction rate [126, 127]. Additionally, clinical groups in Europe are currently using corneal cross-linking in combination with LASIK (called LASIK Xtra) through this procedure the cornea is stabilized at the same time they are receiving LASIK to help prevent the risk of ectasia [128]. In a study conducted in Greece, the application of prophylactic CXL concurrently with high-myopic LASIK improved refractive and keratometric stability, possibly by affecting corneal biomechanical properties [129]. Continued improvements are being made to the CXL procedure by using different types of riboflavin, different combinations of refractive surgery procedures etc.

3.5. Matrix Metalloproteinases (MMPs)

At the cellular level, matrix metalloproteinases (MMPs) are secreted by scleral fibroblasts and break down the extracellular matrix, which in turn assist the progression of myopia. Thus, suppression of these proteinases would potentially provide option for the prevention and treatment of myopia. In particular, micro-RNA 29a (miR-29a) was found to be effective in regulating the expression and secretion of (MMP-2) from scleral fibroblasts and retinal pigment epithelial cells (RPE) [130]. Zhang et al. found that miR-29a increased mRNA level, expression and secretion of MMP-2 in fibroblasts and RPE cells when treated with miR-29a inhibitor than with the mimic [130]. This suggests an inverse relationship between miR-29a and MMP-2 levels.

On the other hand, Chen et al. found the expression of MMP-2 increased with sonic hedgehog signaling protein and therefore, induce myopia in guinea pig model [131]. Therefore, inhibiting the sonic hedgehog signaling protein portends another form of MMP-2 regulation. Furthermore, pirenzepine has been shown to reduce the expression of MMP-2 and enhance the expression of tissue inhibitors of metalloproteinases (TIMP-2) [112].

3.6. Gamma-Aminobutyric Acid (GABA) Receptor Antagonist

The effects of GABA antagonists on axial elongation and vitreous chamber depth (VCD) elongation were studied in

guinea pigs. Myopia was induced in one eye with a diffuser and then injected with saline (control), 0.2% GABA antagonist, and 2% GABA antagonist [132]. 2% GABA antagonist significantly reduced myopia, axial length elongation, and VCD elongation.

3.7. Glyceraldehyde

Glyceraldehyde has been proposed for prevention of lens-induced axial. In a study conducted in New Zealand using spherical lens exposure in rabbits, cross-linking with glyceraldehyde was shown to be associated with shorter axial lengths [133]. The tissue subjected to the glyceraldehyde solution had a mean ultimate stress greater than those in the untreated and control groups, suggesting a stronger makeup of the tissues through cross-linking at the molecular/cellular level [133].

3.8. Vascular Endothelial Growth Factor Inhibitors

Macular choroidal neovascularization (CNV) formation is a common complications of vision impairment in patients with pathological myopia. The prognosis of myopic CNV (mCNV) is poor, with >85% of patients' visual acuity reduced to 0.1 or lower after 5-10 years of onset [134, 135]. Vascular endothelial growth factor (VEGF), a major driver of vascularization and endothelial cell recruitment and proliferation has been implicated in the pathogenesis of CNV [136]. Therefore, anti-vascular endothelial growth factor (VEGF) therapy, which inhibits vascularization, represent first-line treatment for mCNV [137]. Two anti-VEGF agents, Bevacizumab and Ranibizumab, have gained popularity in CNV therapy in recent years. Ranibizumab (Lucentis) is a recombinant humanized monoclonal immunoglobulin G1 (IgG1) κ-isotype antibody fragment that inhibits human VEGF [138, 139]. Bevacizumab (Avastin) is a bivalent full-length monoclonal IgG1 antibody with a molecular weight of 149 kD that is resistant to VEGF-A [138]. Ranibizumab (IVR) is approved for intravitreal injection for choroidal neovascularization, while Bevacizumab (IVB) has been FDA-approved for the treatment of cancer and is administered intravitreally off-label for choroidal neovascularization [139, 140]. Both drugs bind VEGF receptors to inactivate endogenous VEGF and inhibit the migration and growth of vascular endothelial cells, thereby inhibiting neovascularization [141]. Improved visual acuity and decrease in mean central retinal thickness have also been demonstrated in both drugs with 24-48 months follow-up without reports of adverse events [142, 143].

There is a need to compare the efficacy of intravitreal Bevacizumab (IVB) and intravitreal Ranibizumab (IVR) in improving the best-corrected visual acuity (BCVA) during treatment of mCNV. Most clinical studies on anti-VEGF drugs for the treatment of mCNV are uncontrolled studies and very few randomized clinical trials have been performed. As a result, conflicting information exists about the efficacy and persistence of anti-VEGF agents. A longer observation period, fully randomized and consistent trial design is required. Based on current findings, however, it can be agreed that intraocular injection of anti-VEGF drugs should be the first-line treatment of mCNV caused by pathological myopia.

3.9. Other Pharmacological Agents

Apart from Atropine, a number of pharmacological agents are currently undergoing evaluation in clinical trials for the treatment of myopia. Pharmaceutical interventions include ketorolac tromethamine (a non-steroidal anti-inflammatory drug, NSAID) for accelerating corneal healing after PRK [144, 145], oral riboflavin [146], BHVI2 (an experimental drug) [147] and tropicamide [148]. Several interventions are a combination of low-dose atropine with another drug (e.g., ketorolac tromethamine and BHVI2) and contact lenses (e.g., soft bifocal contact lenses and overnight-wear orthokeratology) [149].

3.10. Combinational Approaches

In recent years, several combinational approaches consisting of therapies detailed above have been tested to combat myopia progression. It is not surprising that almost all avenues being explored comprise of atropine as one of the therapeutic modalities. This is at least partially due to the observation that atropine is a double-edged sword displaying superior therapeutic efficacy and convenience along with significant side-effects at higher doses. Most combinational approaches aim to be able to use a lower dose of atropine to circumvent its negative effects.

A randomized controlled trial compared the effect of 0.125% atropine with a combination of 0.125% atropine and a weekly auricular acupoint stimulation in children aged 6–12 years. The combination group was significantly less myopic and had a shorter axial after the 14.7 month follow up. elongation compared to children receiving atropine alone [150]. Another auricular acupoint stimulation study divided school-age children into three groups: 0.25% atropine, 0.5% atropine, or a combination of 0.25% atropine and auricular acupoint stimulation three times daily. The study showed the combination group had a similar myopia progression as the 0.5% atropine group, but had significantly slower progression than 0.25% atropine group after the 8.3 month follow up. This suggested, that adding auricular acupoint stimulation to 0.25% atropine was as effective as 0.5% atropine alone [151]. Auricular acupoint stimulation may provide extra benefits when combined with atropine, however the treatment may not be widely accessible or preferred.

The Bi-focal and atropine (BAM) study combined 0.01% atropine and center-distance soft bifocal contact lenses in a 14-day study. While the combination was well-tolerated, no significant benefits were observed [152]. The combination of orthokeratology and 0.01% atropine was also found to be significantly beneficial in slowing the progression of myopia than orthokeratology alone [153]. While the studies have had encouraging results, larger randomized clinical trials need to be performed to confirm these results.

4. Use of FP-Receptor Prostaglandins to Treat Myopia in Guinea Pigs

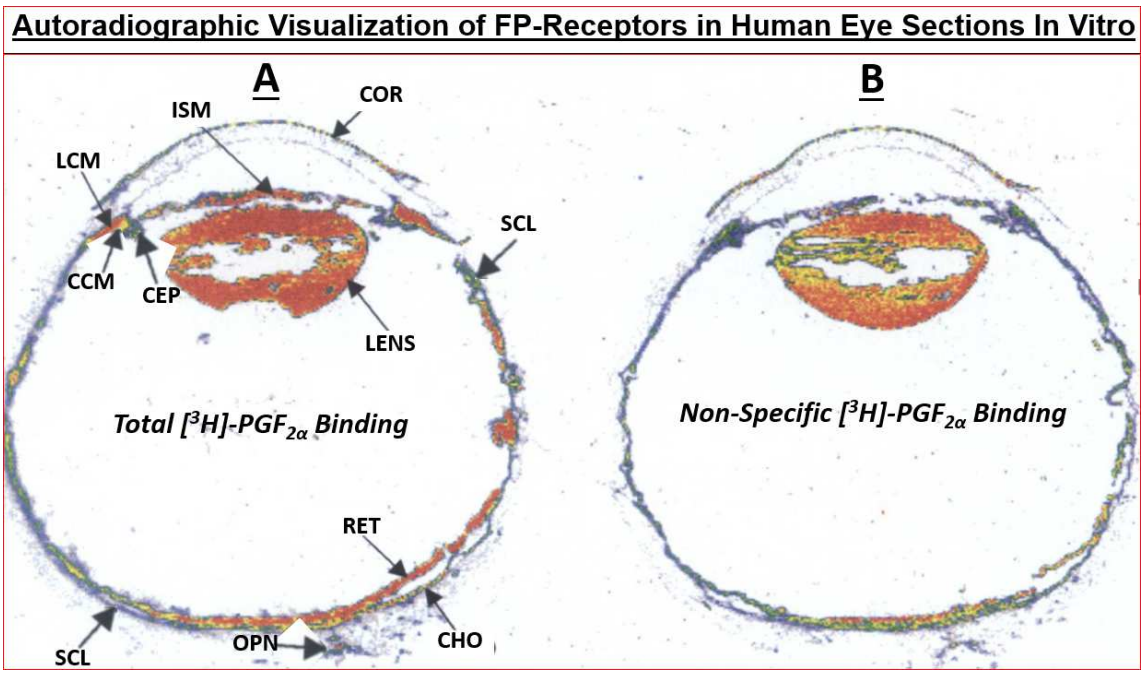

Figure 1. *Autoradiographic localization of FP-prostaglandin receptors in human eye sections.*

CCM, circular ciliary muscle; CEP, ciliary epithelial processes; CHO, choroid; ISM, iris smooth muscle; LCM, longitudinal ciliary muscle; OPN, optic nerve; SCL, sclera.

Prostaglandins (PGs) have wide-ranging biological functions in the mammalian body including inflammation, sleep, muscle contraction/relaxation, hormone release, cardiac effects directly on the atrium and via blood vessel relaxation, and in intraocular pressure (IOP) regulation [154-156]. Indeed, despite having pro-inflammatory properties, appropriate modifications of $PGF_{2\alpha}$ for instance and conversion to a pro-drug construct have resulted in the generation of potent and highly efficacious ocular hypotensive drugs to treat elevated IOP and glaucoma [155, 156]. Furthermore, an early study in form-deprivation myopia model (FDM) in chicks revealed that intravitreally injected $PGF_{2\alpha}$ significantly reduced the axial elongation stimulated by form deprivation (FD) [157]. Likewise, in a guinea pig FDM model of myopia resulted in a significant decrease in retinal arachidonic acid levels, which is a precursor for PG synthesis [158]. A more recent study showed that topical ocular delivered latanoprost, a fairly potent and selective FP-receptor agonist [155], significantly attenuated elongation of the eye and was an anti-myopic drug [159]. More detailed mechanistic investigations by another group using the same guinea pig FDM model of myopia reported that $PGF_{2\alpha}$ levels in the FDM guinea pig retinas were considerably lower than in control animals [160]. Furthermore, peribulbar injected latanoprost caused a reduction of axial length in the FDM guinea pigs, and a FP-receptor-selective antagonist, AL-8810 [161], prevented this therapeutic action of latanoprost [160]. These studies are supported by the fact that a relatively high density of FP-PG-receptors are present in human retinas and scleral tissue which now can be confidently linked to an involvement in modulating myopia and its progression (Figure 1) [162]. These intriguing pharmacological findings clearly support yet another important function of FP-class PGs in potentially lowering and controlling the deleterious effects of myopia and therefore positively impacting the QoL of patients and the socioeconomic burden associated with these diseases. How FP PG agonists drugs such as latanoprost, travoprost, and tafluprost can be deployed to treat myopia in children and adults afflicted with myopia in the future remains to be determined. However, the use of these drugs represents an excellent opportunity to reduce ocular hypertension and myopia in a concomitant manner, which not only will reduce IOP (which will help preserve vision due to protection of retinal ganglion cells) [163], but also prevent or significantly reduce axial elongation.

As discussed above, a very old non-receptor-selective drug, atropine, continues to dominate the treatment of myopia despite some significant ocular side-effects associated with its use. Due to the urgent unmet medical need for novel drugs and treatment modalities for myopia, it behooves us to develop and utilize directly translatable animal models of myopia to the human condition and disease. In this search, however, we need to be cognizant of considerable species differences in the presence, localization, density and responsiveness of receptors, and their signal transduction mechanisms, to neurotransmitters and drugs. Thus, data obtained in the animals needs to be

cautiously extrapolated to the human diseases and conditions. Accordingly, there needs to be critical attention paid to the use of suitably validated animal models of myopia in the drug discovery processes. Existing FD models of myopia have utilized avian and a variety of mammalian species, including chick, tree shrew, guinea pig, mouse, monkey and to a much lesser degree rabbit [164]. There also seems to be some progress in better understanding how some of the older generation agents that reduced myopia in these animals produce their effects. Thus, light-induced retinal dopamine has been implicated in reducing the myopia [165], but using various receptor-selective agonists and antagonist, it now seems probable that dopamine-1 receptors mediate this anti-myopic activity of dopamine [166]. In a similar vein, it appears that some of the effects of muscarinic antagonists in attenuating myopic effects of FD may be due to occupancy of and antagonism of alpha-adrenergic-2A receptors [167]. It does appear that pharmacology is leading the way in helping us grasp the drugs receptors involved in the myopia development and its mitigation. Other useful recent revelations using pharmacological tools involve the role of nitric oxide [168], vitamin D [169], PPAR-alpha agonists such as GW7647 and GW6471 [170], and various neurotrophins [171] in myopia. Lastly, novel genes and pathways [172] are being identified and characterized that would in time provide new targets to pursue from a drug discovery and development perspective addressing the myopia disease. As our knowledge grows and new treatment modalities and paradigms begin to emerge [173, 174], we must hope for good outcomes for myopia patients from all the future endeavors in this field.

5. Conclusion

The growing number of cases of myopia and severe myopia leading to permanent blindness has triggered much research in this field. In this review, we have provided an overview of the prevalence and etiology of the disease, and the standard therapeutic strategies available to counter the condition. Significant therapeutic developments have occurred over the past few years, promising to take myopia treatment to the next level and offer significant long-term relief to patients. However, more long-term, and large-scale studies need to be performed in a diverse cohort of patients in order to categorically evaluate the effectiveness of these novel therapeutic approaches.

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