Current and emerging pharmaceutical interventions for myopia

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ABSTRACT

Myopia is a major cause of visual impairment. Its prevalence is growing steadily, especially in East Asia. Despite the immense disease and economic burden, there are currently no Food and Drug Administration-approved drugs for myopia. This review aims to summarise pharmaceutical interventions of myopia at clinical and preclinical stages in the last decade and discuss challenges for preclinical myopia drugs to progress to clinical trials. Atropine and oral 7-methylxanthine are shown to reduce myopia progression in human studies. The former has been extensively studied and is arguably the most successful medication. However, it has side effects and trials on low-dose atropine are ongoing. Other pharmaceutical agents being investigated at a clinical trial level include ketorolac tromethamine, oral riboflavin and BHVI2 (an experimental drug). Since the pathophysiology of myopia is not fully elucidated, numerous drugs have been tested at the preclinical stage and can be broadly categorised based on the proposed mechanisms of myopisation, namely antimuscarinic, dopaminergic, anti-inflammatory and more. However, several agents were injected intravitreally or subconjunctivally, hindering their progress to human trials. Furthermore, with atropine being the most successful medication available, future preclinical interventions should be studied in combination with atropine to optimise the treatment of myopia.

INTRODUCTION

Uncorrected refractive error accounts for over 52% of moderate and severe vision impairment globally.[1] There is a considerable variation in prevalence of myopia between ethnicities and geographies. For instance, 5.8% of schoolchildren in rural Mongolia are myopic compared with approximately 80% in urban Taiwan.[2 3] Furthermore, a study has concluded that the global economic burden of uncorrected refractive error, which is predominantly due to myopia, could be as much as US$200 billion or more annually.[4] Despite the urgent need and economic argument for effective myopia treatments, there are currently no Food and Drug Administration-approved drugs for myopia. Therefore, this review aims to summarise the current and emerging pharmaceutical interventions for myopia and discuss challenges for preclinical myopia drugs to progress to clinical trials.

DRUGS AT CLINICAL TRIAL LEVEL

A search on ClinicalTrials.gov using the keyword 'myopia' yielded 489 interventional trials. The vast majority were related to choroidal neovascularisation, laser eye surgery or lens-based therapy. Twenty trials specifically examined the effect of drugs on myopia progression (table 1). Of these 20, there were 13 active trials, 5 completed trials and 2 with unknown status. Among the five completed trials, four have published their results.

The Atropine in the Treatment of Myopia 1 (ATOM1) study [5] was a randomised controlled trial (n=400) that observed the effect of 1% atropine on children aged 6–12 years old for 2 years, after which the medication was stopped, and the children were monitored for another year. The study showed that eyes that received 1% atropine were significantly less myopic after 24 months (−0.40 D vs −0.86 D, p<0.001) and this change was predominantly due to the slower growth of vitreous chamber and axial length. Interestingly, after atropine was stopped, atropine-treated eyes showed a greater degree of myopia progression after 1 year of follow-up (−0.35 D vs −0.15 D, p<0.001). Nonetheless, at the end of the study, atropine-treated eyes were still significantly less myopic than those that received placebo (−1.35 D vs −1.55 D, p=0.028), suggesting that 1% atropine was an effective treatment to reduce myopia progression in children.

Rebound effect is common after a prolonged period of antagonism and is believed to arise from receptor upregulation.[6] However, it raises several questions that need to be addressed. For instance: Would the treated eyes eventually reach the same degree of myopia, rendering the treatment ineffective after a certain time period? If so, could patients be on a long-term regime? What are the safety considerations (eg, reduced accommodative function)? When is the optimal time to stop treatment, considering that myopia progression slows with age?[7] During the 1-year washout period, myopia progression was significantly more pronounced in the first 6 months of atropine-treated eyes (−1.51±1.40 vs −0.40±0.65 D/year, p<0.0001), suggesting that the rebound effect might be, to some extent, attributed to a short-term reversible action. One possibility is that atropine has an acute effect on accommodation since there were significant differences in spherical equivalence and near corrected visual acuity between atropine and placebo-treated eyes 2 weeks after treatment but not axial length. However, a subsequent multivariate analysis has shown that the myopic rebound is also associated with an increase in vitreous chamber depth and axial length.[5] This may indicate that atropine suppresses axial growth, primarily in the vitreous chamber, and a sudden cessation activates the rebound effect.

Table 1 Summary of clinical trials that examined the effect of pharmaceutical intervention on myopia progression

NCT No	Title	Phase	Status	Interventions	Characteristics	Population, n (age)	Location
NCT00457717	Myopia control by combining auricular acupoint and atropine eyedrops	1	Completed	► 0.25% and 0.5% atropine ► Combination of 0.25% atropine and acupuncture	► Intervention model: parallel assignment ► Masking: single	60 (6–15)	Taiwan
NCT00263471	Myopia progression and the effect of 7-methylxanthine	2	Completed	► 7-methylxanthine	► Intervention model: parallel assignment ► Masking: double	90 (8–13)	Denmark
NCT00371124	ATOM: safety and efficacy study of 0.5%, 0.1%–0.01% atropine treatment to both eyes In treatment of myopia In children	2/3	Completed	► 0.01%, 0.1% and 0.5% atropine	► Intervention model: parallel assignment ► Masking: double	400 (6–12)	Singapore
NCT02130167	Low concentration atropine for myopia progression in school children	NA	Completed	► 0.01% and 0.05% atropine	► Intervention model: parallel assignment ► Masking: triple (participant, care provider, investigator)	60 (6–12)	Taiwan
NCT02055378	The effect of low-concentration atropine combined with auricular acupoint stimulation in myopia control	NA	Completed	► 0.125% atropine ► Combination of 0.125% atropine and acupuncture	► Intervention model: parallel assignment ► Masking: single (care provider)	73 (6–12)	Taiwan
NCT03329638	APPLE: a study assessing the efficacy and safety of DE-127 ophthalmic solution in subjects with mild or moderate myopia	2	Active—not recruiting	► DE-127 (atropine by Santen) low, medium and high doses	► Intervention model: parallel assignment ► Masking: double (participant, investigator)	100 (6–11)	Singapore
NCT03312257	BAM: bifocal & atropine in myopia (BAM) study	NA	Active—not recruiting	► Combination of +2.50 D and soft bifocal contact lenses and 0.01% atropine	► Intervention model: single group assignment ► Masking: none (open label)	49 (7–11)	USA
NCT03690414	Evaluation of short term use of experimental eye drops BHVI2, 0.02% atropine and BHVI2 plus 0.02% atropine eye drops	1	Active—not yet recruiting	► BHVI2 (experimental drug) ► 0.02% atropine ► Combination of BHVI2 and 0.02% atropine	► Intervention model: parallel assignment ► Masking: quadruple	60 (6–13)	NA
NCT03690089	Low-dose atropine eye drops to reduce progression of myopia in children in the United Kingdom	2	Active—not yet recruiting	► 0.01% atropine	► Intervention model: parallel assignment ► Masking: quadruple	289 (6–12)	UK
NCT03508817	Atropine 0.01% eye drops in myopia study	1	Active—recruiting	► 0.01% atropine	► Intervention model: parallel assignment ► Masking: none (open label)	150 (6–15)	Oman
NCT03552016	Evaluation of progression of myopia in children treated with vitamin B2 and outdoor sunlight exposure	2	Active—recruiting	► 200 and 400 mg oral riboflavin	► Intervention model: single group assignment ► Masking: triple (participant, care provider, investigator)	100 (6–12)	USA
NCT03350620	CHAMP: study of NVK-002 in children with myopia	3	Active—recruiting	► NVK-002 (atropine) concentrations 1 and 2	► Intervention model: cross-over assignment ► Masking: double (participant, investigator)	483 (3–17)	USA
NCT03334253	MTS1: low-dose atropine for treatment of myopia	3	Active—recruiting	► 0.01% atropine	► Intervention model: parallel assignment ► Masking: single (outcomes assessor)	186 (5–12)	USA
NCT03140358	ATOM3: the use of atropine 0.01% in the prevention and control of myopia	3	Active—recruiting	► 0.01% atropine	► Intervention model: parallel assignment ► Masking: quadruple	570 (5–9)	Singapore
NCT03402100	Eye drops study for myopia control in schoolchildren	NA	Active—recruiting	► 0.01% and 0.05% atropine ► 0.25% ketorolac tromethamine ► Combination of 0.25% ketorolac tromethamine and 0.01% or 0.05% atropine	► Intervention model: parallel assignment ► Masking: quadruple	150 (6–12)	Taiwan
NCT03374306	Topical application of low-concentration (0.01%) atropine on the human eye with fast and slow myopia progression rate	NA	Active—recruiting	► 0.01% atropine	► Intervention model: parallel assignment ► Masking: double (participant, investigator)	80 (7–10)	Hong Kong

Continued

Table 1 Continued

NCT No	Title	Phase	Status	Interventions	Characteristics	Population, n (age)	Location
NCT03097198	Effect of plum-blossom needle vs tropicamide eye drops on juvenile myopia	NA	Active—recruiting	► Plum-blossom needle acupuncture ► 0.5% tropicamide	► Intervention model: cross-over assignment ► Masking: double (investigator, outcomes assessor)	98 (8–20)	China
NCT02955927	Combined atropine with orthokeratology in childhood myopia control (AOK)—a randomized controlled trial	NA	Active—recruiting	► 0.01% atropine • Combination of 0.01% atropine with overnight-wear orthokeratology	► Intervention model: parallel assignment ► Masking: single (outcomes assessor)	60 (6–11)	Hong Kong
NCT00541177	Study of myopia prevention in children with low concentration of atropine	4	Unknown—estimated completion in 2008	► 0.25% atropine ► 0.5% tropicamide	► Intervention model: parallel assignment ► Masking: single (outcomes assessor)	60 (7–12)	Taiwan
NCT02544529	Echothiophate iodide for the prevention of progression of myopia	4	Unknown—estimated completion in 2015	► 0.03% echothiophate iodide	► Intervention model: single group assignment ► Masking: triple (participant, care provider, investigator)	33 (9–15)	USA

ATOM, Atropine in the Treatment Of Myopia; CHAMP, study of NVK-002 in Children With Myopia; NA, not applicable.

To explore the long-term effectiveness of atropine in lower concentrations, ATOM2[8] (n=400) was conducted. Children were allocated three concentrations of atropine (0.5%, 0.1% and 0.01%) for 2 years, and then similarly stopped for 1 year. However, those with myopia progression of more than −0.5 D after the washout period were restarted on 0.01% atropine for 2 years. As anticipated, there was a dose-dependent reduction in myopia progression during the first 24 months. However, as with ATOM1, those that were given a higher dose of atropine developed myopia more quickly during the washout period, resulting in 0.01% atropine being the most effective dose in reducing myopia progression after the third year. This outcome persisted with overall myopia progression at the end of fifth year being lowest in the 0.01% group (−1.38 D) compared with the 0.1% (−1.83 D, p=0.003) and 0.5% (−1.98 D, p<0.001) groups. Similarly, children in 0.01% group had the smallest axial elongation, but this was not statistically significant. This finding was similar to a recent trial on the effect of low-concentration atropine over 1 year.[9] However, in this study, significant reduction in axial length was seen in 0.025% and 0.05% atropine after a year of treatment in a dose–response relationship.

ATOM2 gives more insight into the optimal concentration of atropine and when should the treatment be stopped and restarted. Even though 0.01% atropine did not slow down myopia progression as much as the higher concentrations, it has a significantly milder rebound effect, resulting in a better outcome after the washout period. Consequently, fewer children in the 0.01% required retreatment (24% vs 59% and 68%) and they tended to be younger across all three groups. As expected, restarting 0.01% atropine reduced myopia progression among those who progressed >0.5 D during the washout year, suggesting that retreatment is effective. Among those who were initially randomised to 0.01% atropine, the mean myopia progression after 5 years was −1.38 D, which was similar to −1.40 D seen in those who received placebo at two-and-a-half years, implying that 0.01% atropine slowed myopia progression by 50%. Thus, the authors recommended that children with >0.5 D myopia progression should receive 0.01% atropine for 2 years. The treatment should be continued until there is a good response (eg, progression <0.25 D/year) and they are older since they are less likely to suffer from rebound effect. This can be restarted if an increase in myopia occurs. On the other hand, even though myopia progression tends to slow down with age, it can continue into adulthood especially among those with higher education.[10] As such, patients, especially those with existing high myopia, might consider continuing with atropine for a longer period of time even after their progression has slowed down.

Because of the encouraging result from ATOM2, ATOM3 (NCT03140358), which looked into 0.01% atropine with a larger sample size, was started in 2017 and expected to complete in 2023.

Another randomised controlled trial[11] (n=110) 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. After a mean follow-up of 14.7 months, the combination group was significantly less myopic (−0.41 D vs −0.66 D, p<0.001), had a shorter axial elongation (0.24 mm/year vs 0.32 mm/year, p=0.0004) and a greater reduction in intraocular pressure (IOP) (−1.01 mm Hg/year vs −0.13 mm Hg/year, p=0.006). However, only 20 patients in the combination group completed at least 6 months of follow-up (37.0%) compared with 53 patients who received atropine only (94.6%). The most common reason for this poor compliance was inability to attend weekly acupoint stimulation (22/34, 64.7%), followed by pain (7/34, 20.6%). Thus, a weekly auricular acupoint stimulation might not be a feasible option especially for schoolchildren.

Interestingly, another trial on auricular acupoint stimulation[12] (n=71) divided school-age children into three groups: 0.25% atropine, 0.5% atropine, or a combination of 0.25% atropine and auricular acupoint stimulation thrice daily. After a mean follow-up of 8.3 months, the combination group had a similar myopia progression as the 0.5% atropine group (0.15 D/year vs 0.21 D/year, p=1.00). However, its progression was significantly slower than 0.25% atropine group (0.21 D/year vs 0.38 D/year, p<0.05), suggesting that addition of auricular acupoint stimulation to 0.25% atropine was as effective as 0.5% atropine alone. Despite having acupoint stimulation thrice daily, only three patients dropped out from the combination group compared with one and two in the 0.25% and 0.5% atropine groups, respectively. This might be due to a shorter follow-up period compared with the above trial (8.3 vs 14.7 months). Furthermore, even though auricular acupoint stimulation may

appear to provide extra benefits when given with atropine, the treatment is arguably not widely accessible, so this might not be a feasible option for the general public.

The last published study was a randomised controlled trial[13] (n=77) that observed the effect of oral 7-methylxanthine, an adenosine receptor antagonist, on myopia progression and axial length. Myopic children were divided into two groups: the first group received daily 7-methylxanthine for 2 years while the second group received a placebo for the first year then 7-methylxanthine for the second year. After which, the treatment was stopped for both groups and the participants were followed up for another year. Furthermore, patients were stratified into a moderate or high baseline axial growth rate based on the axial length taken 6 months prior to the study's initiation. After a year, there was a significant reduction in myopia progression rate compared with baseline among those who took 7-methylxanthine ($p<0.0005$) as opposed to placebo ($p=0.098$). After the second year where both groups took 7-methylxanthine, the myopia progression rate of both groups was significantly reduced compared with the previous year ($p=0.013$ and $p=0.01$ for first and second groups, respectively), suggesting that 7-methylxanthine could effectively reduce myopia progression. Finally, there was a reduction in axial growth among those with moderate baseline who took 7-methylxanthine compared with placebo after 24 months (0.329 vs 0.427 mm, $p=0.048$). More importantly, there was no report of side effects, indicating that oral 7-methylxanthine was a safe and effective treatment for myopic children.

Among the 13 currently active trials, pharmaceutical interventions include low doses of atropine (0.01%–0.05%), ketorolac tromethamine (a non-steroidal anti-inflammatory drug, NSAID), oral riboflavin, BHVI2 (an experimental drug) and tropicamide. Several interventions are a combination of low-dose atropine with another drug (eg, ketorolac tromethamine and BHVI2) and contact lenses (eg, soft bifocal contact lenses and overnight-wear orthokeratology)

Mechanisms of drugs used in clinical trials

The process of myopisation is still not fully elucidated. Wallman and Winawer[14] wrote a comprehensive review on eye growth and the processes implicated in myopia. In animal models where hyperopic defocus is induced through negative lens, there are choroidal thinning and axial elongation associated with scleral remodelling, particularly at the posterior pole.[15 16] Interestingly, this process is preserved even after the optic nerve is severed,[17] suggesting that there is a local control of the eye shape. It seems, then, reasonable to posit that there is a signal cascade from the retina that effects change in the choroid and sclera. This section will outline possible targets in this cascade and suggest how drugs used in the clinical trials may act to reduce myopia progression.

Atropine

Muscarinic acetylcholine receptors (mAChR) are G-protein coupled receptors that can be categorised into two groups based on their respective G-proteins.[18] M_1, M_3 and M_5 are linked to G_q protein that activates phospholipase C, while M_2 and M_4 are coupled to G_i, which inhibits adenylyl cyclase and reduces cAMP level. Atropine—a non-selective mAChR antagonist—has been shown to significantly reduce myopia progression in ATOM trials,[5 8] suggesting that mAChRs may be involved in the signalling cascade. Furthermore, since atropine also reduces myopia in chick eyes, where the ciliary muscles contain nicotinic receptors rather than mAChR,[19] atropine is likely to act at the retina itself and not through the accommodation system.

On the other hand, atropine-mediated inhibition of myopia may not involve mAChR. For instance, several mAChR antagonists, such as 3-quinuclidinyl benzilate, dicyclomine and methoctramine, are ineffective or partially effective at a high concentration at preventing myopia in a chick model.[20] Furthermore, ablation of amacrine cells, which provide an important source of acetylcholine, does not impact the progression and atropine-mediated inhibition of myopia in chicks.[21] Finally, numerous mAChR antagonists also inhibit α2A-adrenoceptor and their relative potencies at this receptor significantly correlates with the antagonists' abilities to inhibit form-deprived myopia in chicks.[22] Interestingly, there is no significant correlation between potencies at M_4 receptor and myopia suppression, supporting the notion of non-muscarinic mechanisms of atropine.

One possibility is that atropine binds to mAChRs on retinal amacrine cells, which release dopamine and may have inhibitory effect on eye growth.[23] This is consistent with findings from animal models, which show that retinal dopamine synthesis, storage and metabolism are significantly decreased in myopic monkeys[24] and chicks.[25] Interestingly, reserpine and 6-hydroxydopamine, which deplete dopamine store, reduce myopia progression in chicks.[26 27] On the other hand, dopamine receptor agonists such as quinpirole and SKF38393 also reduce myopia progression in tree shrews[28] and guinea pigs,[29] suggesting that it is the release of dopamine that modulates myopia progression. Additionally, Pendrak *et al* had shown that while axial elongation abruptly dropped after form-deprived eyes had their diffusers removed, it took 1 week for retinal dopamine storage to recover.[30] This lag time further suggests that it is dopamine release rather than storage that reduces myopia progression. However, the effect of dopamine release is not straightforward. Even though agonism of D2-like family receptors, such as D_2, D_3 and D_4, reduces myopia in tree shrews[28] and chicks,[31] it promotes myopia in guinea pigs,[29] indicating that the mechanisms may be species specific. (See review by Zhou *et al*[32] for more information on dopamine signalling and myopia.)

Additionally, atropine may act on the sclera and reduce its remodelling and elongation directly. Using form-deprived chicks, researchers showed that there was an increase in DNA synthesis and glycosaminoglycan production at the posterior sclera of eyes with experimental myopia.[33] These levels were then decreased by administration of mAChR antagonists with atropine being the most effective followed by pirenzepine, a selective $M_{1/4}$ antagonist.[34]

Finally, atropine may inhibit myopia by reducing inflammation. Lin *et al*[35] showed that myopia was more common among children with chronic inflammatory conditions (eg, uveitis, systemic lupus erythematosus, and so on) and postulated that atropine might have anti-inflammatory effects. Using form-deprived hamsters, they demonstrated that form deprivation increased major inflammatory markers such as nuclear factor-κB, interleukin-6 and tumour necrosis factor-α, and administration of atropine significantly reduced their levels and degree of myopia. Thus, the anti-inflammatory effect of atropine might also be responsible for halting myopia progression.

Other mAChR antagonists

Pirenzepine is a selective $M_{1/4}$ receptor antagonist. Studies in chicks and tree shrews have shown that it is an effective treatment for myopia.[36 37] Additionally, two randomised controlled trials in Asia and the USA demonstrated that administration

of 2% pirenzepine ophthalmic gel twice daily was effective and well tolerated.[38 39] However, there are no further trials on pirenzepine, presumably because it is not as effective as atropine and requires a twice-daily administration. However, a recent bioengineering approach attempts to increase its bioavailability by pairing pirenzepine with sorbic acid and encapsulating the complexes into micelles. This increases the absorption in rabbits by 1.5 times, potentially eliminating the requirement of twice-daily dosage in the future.[40] On the other hand, clinical trials in 1960s suggested that tropicamide and hyoscine might be effective at reducing myopia progression.[41 42] However, they were not randomised and have not been replicated since.

7-Methylxanthine

7-Methylxanthine, an adenosine receptor antagonist, is a metabolite of caffeine that can be taken orally.[40 41] It is suggested that adenosine activates adenosine A2 receptor on the retinal pigment epithelium (RPE) and enhances the standing potential.[43] Since children with high ametropia tend to present with retinal electrophysiological abnormalities, administration of 7-methylxanthine may mitigate this.[44] Additionally, a study on rabbits shows that 7-methylxanthine increases the thickness, collagen concentration and diameter of collagen fibrils at the posterior sclera.[45]

Ketorolac tromethamine

Ketorolac tromethamine is an NSAID, which may hinder myopia progression according to the chronic inflammation hypothesis. It can be used as eye-drops to relieve itching in allergic conjunctivitis. Interestingly, a cohort study[46] shows that children with allergic conjunctivitis have a higher incidence and risk of developing myopia compared with those without (HR 2.35, 95% CI 2.29 to 2.40). Furthermore, a study using lens-induced myopia (LIM) in chicks demonstrates that ketorolac tromethamine could reduce myopia progression via reduction in axial elongation.[47]

Riboflavin

Another hypothesis for myopisation posits that abnormal elongation is secondary to scleral defect.[48] One method to enhance scleral strength is via collagen cross-linking using ultraviolet A (UVA) and riboflavin.[49] Using LIM model in guinea pigs, Li *et al*[50] showed that oral riboflavin and whole-body UVA irradiation could significantly reduce myopia progression, axial elongation and scleral matrix metalloproteinase-2 (MMP-2) while increasing scleral thickness. In the currently active randomised controlled trial on oral riboflavin (NCT03552016), participants are encouraged to play outside for 30 min daily to increase UV light exposure.

IOP-lowering drugs

A cross-sectional study of Israeli adults aged 40 and above suggests that there are significantly more myopes among individuals with IOP of more than 20 mm Hg.[51] This is supported by another study on children in the USA.[52] However, a prospective cohort study in China[53] on children aged 7–9 years who received yearly inspection shows that there are no significant differences in the IOP among myopes and non-myopes prior to the onset of myopia. In fact, myopic children present with raised IOP after the onset, suggesting that raised IOP is a consequence of myopia rather than the cause. Additionally, a trial on 159 myopic children using timolol maleate shows that it has no impact on myopia progression after 2 years despite a decrease in IOP by 3 mm Hg.[54] However, animal studies have shown that brimonidine and latanoprost, an alpha-adrenergic agonist and prostaglandin analogue, respectively, could mitigate myopia progression in guinea pigs.[55–57] This will be discussed in further detail at a preclinical trial section.

DRUGS AT PRECLINICAL LEVEL

Methods to induce myopia

To better understand the effect of pharmaceutical interventions at the preclinical stage, a background knowledge in animal models of myopia is crucial. Two methods are widely used to induce myopia in animals: form deprivation and lens induced. Form-deprivation myopia (FDM) is based on the work of Wiesel and Raviola who reported that lid-sutured macaque monkeys developed myopia secondary to axial elongation.[58] Crucially, monkeys reared in the dark did not develop this feature,[59] suggesting that reduction in spatial contrast through the translucent eyelid was necessary. Furthermore, these animals had reduced posterior scleral thickness, which is similar to human myopic eyes. Apart from lid suturing, FDM can be achieved by placing a frosted diffuser over the animal's eye. This technique has also been successfully applied to other animals such as guinea pigs,[60] rabbits,[61] chicks,[62] tree shrews,[63] mice[64] and rats.[65]

LIM was developed after the discovery that chicks with imposed optical defocus could compensate by adjusting their eye growth.[66] Wearing negative lenses causes hyperopic defocus and increases the rate of eye growth, resulting in axial elongation and subsequent myopia. Apart from chicks, LIM can be similarly achieved in tree shrew,[67] guinea pig[68] and rhesus monkey.[69]

LIM is regarded as a closed loop condition while FDM is an open loop system because the former has a definite endpoint when the eyes become fully compensated for the hyperopic defocus. Although these two methods can induce myopia, there is evidence to suggest that the underlying mechanisms are different based on their differing responses to various duration, types and intensity of lights.[70 71] Nonetheless, both approaches lower retinal dopamine level due to, at least in part, a reduced rate of dopamine release.[72] Additionally, LIM and FDM appear to be mediated by the expression of ZENK, a transcriptional factor with zinc-finger DNA-binding domains.[73]

Animal models of myopia

FDM and LIM can be applied to several animal models. However, guinea pigs and chicks are the most commonly used models in pharmaceutical experiments in the past decade. Guinea pigs are born with a well-developed visual system and can distinguish between different objects and line orientations.[74] Its retina is avascular and dominated by rods (83%–92%).[75] Furthermore, it has dichromatic vision and lacks a fovea.[76] Nonetheless, the animal is easy to keep and maintain, and has reasonably large pupils and eyes (axial length 8.0 mm), making refraction measurement relatively convenient.

Similarly, chick's retina is avascular and lacks a fovea.[77] However, it contains a region called area centralis that contains a higher concentration of photoreceptor, which resembles a macula in human.[78] This rod-free area is circular (approximately 3 mm in diameter) and possess the highest concentration of cone cells (15 000–36 000 cells/mm^2) compared with the peripheral region (8000 cells/mm^2). Furthermore, chick eyes contain pectin—a comb-like structure of blood vessels that is thought to provide nutrients and oxygen to the retina. More importantly, unlike mammals, chick sclera is bilayer and contains an inner cartilaginous layer in addition to the fibrous layer.[79] Since scleral remodelling is an important feature of myopia, chicks might not

be able to replicate this change adequately. Nonetheless, similar to guinea pigs, chicks are relatively easy to handle.

Apart from the relatively low cost of maintaining these animals, both models could develop substantial myopia in a short period of time. Wildsoet and Schmid[80] have shown that FDM chicks using diffuser can develop −9 D myopia in 5 days while LIM guinea pigs with −4 D lens could develop statistically significant axial elongation and refractive error after 10 days.[81]

Tree shrews are not used as much as chicks or guinea pigs in myopia studies. However, similar to humans, they have a single-layered sclera and their scleral fibroblasts contain α-smooth muscle actin,[82] suggesting that the animal might be able to capture scleral changes better than chicks. However, it lacks a fovea and there is no clear indication of accommodation.[83] Furthermore, it requires more complex handling and breeding.

Despite being relatively easy to handle, hamsters are not used as much, and our understanding of their ocular anatomy is not as extensive. The animal lacks a fovea and contains a non-collagenous cribrosa unlike humans.[84] However, it appears that hamsters possess structures necessary for accommodation even though rodents in general do not accommodate.[85]

It is important to acknowledge that most children develop myopia without strong stimuli like lid suturing and diffuser. Thus, these animal models may not reproduce the same disease as childhood myopia and human studies are still necessary to evaluate the effectiveness of treatments. However, they are still vital in identifying new molecular targets and increasing our understanding of myopisation.

Pharmaceutical experiments on animals

A search on Embase database for the keywords 'myopia', 'drug therapy' and 'animal experiment' yielded 60 results. After excluding irrelevant studies and duplicates, 30 pharmaceutical interventions that successfully reduced myopia progression in animals from 2008 to 2018 were identified and classified into six categories (table 2). (See review by Ganesan and Wildsoet[86] for earlier drugs.)

Dopaminergic drugs

There are two families of dopamine receptors based on their primary action on a second messenger.[87] Stimulation of D1-like family (D1R), such as D_1 and D_5, activates adenylyl cyclase, while D2-like family (D2R), such as D_2, D_3 and D_4, activation inhibits this enzyme. All dopamine receptor (DR) subtypes are expressed in the retina except D_3 receptor subtype.[88] Studies have shown that retinal dopamine storage is significantly reduced in FDM monkeys[24] and chicks.[25] Thus, it seems plausible that reversing this process would reduce myopia progression, which has been demonstrated by several studies using guinea pigs, tree shrews and chicks in table 2. Interestingly, even though agonism of D2R inhibits FDM in tree shrews[28] and LIM in chicks,[31] it promotes FDM in guinea pigs,[29] suggesting that mechanisms are complex and may be species specific.

Anti-inflammatory drugs

The basis for anti-inflammatory drugs stems from a finding that myopia is more common in chronic inflammatory conditions.[35] The study shows that key inflammatory markers are upregulated in form-deprived eyes of hamsters. These markers are further upregulated in the presence of inflammatory stimulators (eg, lipopolysaccharide and peptidoglycan). Conversely, administration of cyclosporine A, an immunosuppressant, reduces their levels. Crucially, atropine has a similar effect, suggesting that anti-inflammatory is one of the mechanisms in which the drug reduces myopia progression. Furthermore, ketorolac tromethamine, an NSAID, is shown to inhibit LIM in chicks.[47]

Antimuscarinic drugs

Due to the effectiveness of atropine—a non-selective muscarinic receptor antagonist—in mitigating myopia progression, several other antimuscarinic agents with higher selectivity for muscarinic receptor subtypes have been investigated. Pirenzepine, a selective $M_{1/4}$ antagonist, inhibits LIM in chicks and increases glycosaminoglycan synthesis in the posterior sclera.[89] Even though it appears to have fewer side effects than atropine, clinical trials have shown that it is effective as a twice-daily ophthalmic gel, making it less convenient for patients.[38 39] On the other hand, selective M_1 and M_4 antagonists have been shown to reduce myopia in FDM tree shrews,[90] suggesting that the drug might work on a common pathway downstream. However, Nickla *et al*[91] reported that while administration of muscarinic toxin 3, a selective M_4 antagonist, reduced myopia in FDM chicks, it had no significant effect on LIM chicks. This further adds to the evidence that the mechanisms underlying myopia formation in form-deprivation and lens-induced methods might be different and a thorough investigation should be conducted.

IOP-lowering drugs

Even though a human trial on timolol maleate showed that it was ineffective at reducing myopia, studies in guinea pigs demonstrated that brimonidine and latanoprost, an alpha-adrenergic agonist and prostaglandin analogue, respectively, could reduce myopia progression.[55–57] One explanation is that raised IOP is a part of accommodation-induced myopia. It is shown that continuous near work induces a transient shift towards myopia.[92] Furthermore, IOP is significantly raised with accommodation in progressing myopes, but not in emmetropes.[93] Thus, IOP-lowering medications could be effective in slowing myopia.

Miscellaneous drugs

Several agents in this category target specific molecules that are raised or lowered in myopic eyes. For instance, insulin-like growth factor-2 (IGF-2) antisense oligonucleotide reduces IGF-2 level in FDM guinea pigs[94] while 8-Br-cAMP increases retinal apolipoprotein A1 expression in LIM chicks.[95] Both drugs reduce myopia progression in the respective animals, suggesting that these molecules play a role in myopisation. However, it is unclear exactly how they contribute to myopia development and progression.

In contrast, three candidates provide further evidence to the current theories of myopia formation. Astaxanthin, an antioxidant, is shown to inhibit LIM in guinea pigs and improve collagen fracture and fibre arrangement.[96] This suggests that lowering oxidative stress, potentially secondary to chronic inflammation, may reduce myopia progression. On the other hand, to strengthen the structural integrity of sclera, Garcia *et al*[97] injected a hydrogel, synthesised from hyaluronic acid, into the sub-Tenon's capsule of FDM guinea pigs. This reduces axial elongation and myopia progression without causing noticeable adverse events, lending support to the scleral defect theory. Furthermore, DL-alpha-aminoadipic acid reduces the level of transforming growth factor-β_2 (TGFβ_2),[98] which induces matrix metalloproteinases to degrade scleral extracellular matrix (ECM) components.[99]

Table 2 Summary of drugs are shown to effectively reduce myopia progression in myopia animals from 2008 to 2018

Drug	Description	Observation	Reference
Dopaminergic			
SKF38393	D1R agonist	Inhibits FDM in guinea pigs	29
Quinpirole	D2R agonist	Inhibits FDM in tree shrews; inhibits LIM in chicks with transient choroidal thickening initially; enhances FDM in guinea pigs	28 29 31
Sulpiride	D2R antagonist	Inhibits FDM in guinea pigs	29
Spiperone	D2R antagonist	Inhibits FDM in tree shrews	28
PD168077	Selective D_4 receptor subtype agonist	Inhibits FDM in tree shrews	28
Levodopa	Dopamine precursor	Inhibits FDM in guinea pigs	116
Citicoline*	Increase DA level	Inhibits FDM in guinea pigs	117
Apomorphine	Non-selective DA receptor agonist	Inhibits FDM but not LIM in guinea pigs; inhibits LIM in chicks	31 118
Anti-inflammatory			
Cyclosporine A†	Immunosuppressant	Inhibits FDM in hamster. Reduces c-Fos, NF-kappaB, IL-6 and TNF-alpha	35
Lipopolysaccharide and peptidoglycan	Inflammatory stimulator	Enhances FDM in hamster. Increases c-Fos, NF-kappaB, IL-6 and TNF-alpha	35
Ketorolac tromethamine†	NSAID	Inhibits LIM in chicks	47
Antimuscarinic			
Atropine†	Non-selective muscarinic antagonist	Inhibits FDM and LIM in several animals	19 23 35 36
Muscarinic toxin 3 (MT3)	Selective M_4 antagonist	Inhibits FDM but not LIM in chicks; inhibits FDM in tree shrews	90 91
Muscarinic toxin 7 (MT7)	Selective M_1 antagonist	Inhibits FDM and LIM in tree shrews	90
Pirenzepine	Selective $M_{1/4}$ antagonist	Inhibits LIM in chicks	89
IOP lowering			
Brimonidine†	Alpha-adrenergic agonist	Inhibits LIM in guinea pigs	55
Latanoprost†	Prostaglandin analogue	Inhibits FDM in guinea pigs	56 57
Miscellaneous			
Bevacizumab	Anti-VEGF antibody	Inhibits FDM in chicks, reduces choroidal thickening during recovery after form deprivation	100
Cyclopamine	Sonic hedgehog neutralising antibody to reduce MMP-2 activity	Inhibits FDM in guinea pigs	101
Amphiregulin antibody	Antibodies against amphiregulin, a member of the epidermal growth factor family	Inhibits LIM in guinea pigs	102
Insulin-like growth factor-2 (IGF-2) antisense oligonucleotides	Downregulates IGF-2 expression	Inhibits FDM in guinea pigs	94
DL-alpha-aminoadipic acid	Selectively damage retinal Müller cells	Inhibits FDM in guinea pigs, reduces retinal transforming growth factor-β_2 (TGFβ_2) level	98
7-Methylxanthine	Adenosine receptor antagonist	Inhibits FDM in guinea pigs and prevents thinning of sclera and collagen fibril; inhibits LIM in rhesus monkey	119 120
CGP46381	$GABA_B$ receptor antagonist	Inhibits FDM in guinea pigs	121
Astaxanthin*	Ketocarotenoid (antioxidant)	Inhibits LIM in guinea pigs, improves collagen fracture and fibre arrangement	96
8-Br-cAMP	Increases retinal apolipoprotein A1 (ApoA1) expression	Inhibits LIM in chicks with transient choroidal thickening initially	95
Hydrogel	Synthesised from acrylated hyaluronic acid with a conjugated cell-binding peptide and enzymatically degradable cross-linker	Inhibits FDM in guinea pigs with no adverse reaction	97
Chinese medicine and natural extracts			
Difrarel*	Bilberry extract	Inhibits FDM in guinea pigs, reduces upregulation of MMP-2 and degradation of collagen I in sclera	106
Bu Jing Yi Shi*	Traditional Chinese medicine tablets	Inhibits FDM in guinea pigs, increases scleral fibroblasts, and TGFβ_1 and Smad3 levels	107
Blackcurrant extract* and anthocyanins		Inhibits LIM in chicks	108

*Indicates oral administration.
†Indicates ophthalmic solution. All other drugs are administered via injection (intravitreal, subconjunctival, peribulbar, sub-Tenon's capsule).
DA, dopamine; FDM, form-deprivation myopia; GABA, gamma-aminobutyric acid; IL-6, interleukin 6; IOP, intraocular pressure; LIM, lens-induced myopia; MMP-2, matrix metalloproteinase-2; NF, nuclear factor; NSAID, non-steroidal anti-inflammatory drug; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

Additionally, three antibodies, bevacizumab, cyclopamine and amphiregulin, are shown to be effective at reducing myopia progression in animal models of experimental myopia.[100–102] Bevacizumab is an anti-vascular endothelial growth factor that is already used to treat neovascular age-related macular degeneration and choroidal neovascularisation.[103 104] Cyclopamine is a sonic hedgehog (Shh) neutralising antibody. Chen *et al* demonstrated that cyclopamine reduced both refractive error

and MMP-2 level in a dose-dependent manner in FDM guinea pigs with the highest dose (200 µg/mL) almost completely eliminating myopic development.[101] This suggests that Shh signalling pathway contributes to refractive shift, possible by inhibiting the transdifferentiation of RPE[105] or reducing MMP-2 level that degrades scleral ECM. Amphiregulin is an epidermal growth factor that may stimulate the RPE to produce Bruch's membrane. Since administration of amphiregulin antibody reduces axial elongation in LIM guinea pigs, it may be one of the essential molecular factors involved in myopisation.

However, it is important to acknowledge that apart from astaxanthin, all the drugs in this category are administered via an injection, which could hinder their progression to clinical trials.

Chinese medicine and natural extracts

Difrarel, a bilberry extract, and Bu Jing Yi Shi, a combination of six herbal extracts, reduce FDM in guinea pigs[106 107] by lowering scleral ECM degradation. The former is shown to reduce the upregulation of MMP-2 and degradation of collagen I, while the latter increases scleral fibroblasts and $TGF\beta_1$ that regulates the remodelling of scleral ECM. Additionally, blackcurrant extract reduces myopia and axial elongation in LIM chicks in a dose-dependent manner.[108] The authors postulate that anthocyanin, an active component in blackcurrant, regenerates rhodopsin and possibly decreases the level of retinal retinoic acid, which is upregulated in form-deprived eyes.[109 110]

Considerations for progression from preclinical to clinical stage

Clinical trials are an integral part of drug development. However, it is also a costly process. In 2014, the US Department of Health and Human Services reported that the average cost of bringing one drug from phase 1 to phase 4 in ophthalmology was $69.4 million, the fourth highest therapeutic area behind respiratory, pain and anaesthesia, and oncology.[111] Thus, even though these drugs have been shown to effectively reduce myopia progression in animals, a careful consideration must be taken before advancing them onto the clinical trial stage.

Atropine is the most common and effective treatment available currently. Based on the success of low-dose combination therapies in oncology and hypertension control where synergistic drugs are more effective and produce fewer adverse reactions,[112 113] it seems beneficial that future drugs should complement atropine and work in a synergistic manner. However, it is challenging to theoretically deduce suitable candidates since ideally, they should work on different pathways, and the mechanisms of atropine in the context of myopia are still not fully understood. Although atropine reduces inflammatory markers in form-deprived eyes,[35] more research is still needed to elucidate its mechanisms and the processes of myopisation.

Another important consideration is drug administration. Several compounds tested in animals require an injection, which may prevent patients from taking them especially in children and teenagers where the prevalence of needle phobia is up to 22%.[114] In contrast, ophthalmic solution (eg, anti-inflammatory and IOP-reducing agents) and oral tablets (eg, citicoline, astaxanthin and natural extracts) are much better tolerated. However, they require daily, if not frequent, administration that can impact compliance. For instance, 70% of participants using 1% atropine were compliant,[115] compared with 89% who took a daily tablet of 7-methylxanthine.[13] However, this could be due to the lack of significant side effects in the latter.

Finally, unlike glaucoma or age-related macular degeneration, myopia is predominantly a childhood condition. Novel treatments should be assessed for long-term safety and effectiveness even after the cessation of drugs to ensure that there is minimal or no risk to normal development.

CONCLUSION

We have summarised the current and emerging pharmaceutical interventions in myopia treatment. Presently, only atropine, pirenzepine and 7-methylxanthine are shown to reduce myopia progression in human trials. Drugs such as ketorolac tromethamine, oral riboflavin and an experimental drug are being tested in clinical trials. In the past decade, there have been several promising pharmaceutical agents that successfully suppress myopia in animal models. However, they are predominantly administered via an injection, making their progression towards clinical trials unlikely. Nonetheless, these results still add to our knowledge of the pathophysiology of myopia, which is vital to the overall process of drug development. Finally, based on the successes of low-dose combination therapy in other fields of medicine, this approach should be considered in the future treatment of myopia. However, since there is already substantial evidence to support the effectiveness of low-dose atropine as a monotherapy to control myopia, it seems appropriate for countries with lower income and a high prevalence of myopia to consider its usage while more research is conducted.

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