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Is atropine an effective way to prevent myopia progression in children ?

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Is atropine an effective way to prevent myopia progression in children?

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« Je déclare sur l'honneur que ce mémoire a été écrit de ma plume, sans avoir sollicité d'aide extérieure illicite, qu'il n'est pas la reprise d'un travail présenté dans une autre institution pour évaluation, et qu'il n'a jamais été publié, en tout ou en partie. Toutes les informations (idées, phrases, graphes, cartes, tableaux...) empruntées ou faisant référence à des sources primaires ou secondaires sont référencées adéquatement selon la méthodologie universitaire en vigueur. Je déclare avoir pris connaissance et adhérer au Code de déontologie pour les étudiants en matière d'emprunts, de citations et d'exploitation de sources diverses et savoir que le plagiat constitue une faute grave. »

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Abbreviations

TABLE 1: List of abbreviations

AL	axial length
ATOM	atropine for the treatment of myopia
D	diopters
EBM	evidence based medicine
EGF-R	epidermal growth factor receptor
GWAS	genome wide association study
GABA-R	gamma aminobutyric acid receptors
ITT	intention to treat
IL-6	interleukine 6
IMI	international myopia institut
K	corneal curvature
LAMP	low-concentration atropine for myopia progression
MR3	membrane receptor 3 (of acetylcholine)
NO	nitrous monoxyde
RCT	randomized controlled trial
RPE	retinal pigmental epithelium
SER	spherical equivalent of refractive error
SE	spherical equivalent
TNF-alpha	tumor necrosis factor alpha
WHO	world health organization

I. Introduction

Myopia or nearsightedness has become a global epidemic over the past two decades. The prevalence of myopia varies by countries. Nowadays, 30 % of young adults in Europe have been registered as myopic (K. M. Williams, Verhoeven, et al., 2015) and the rate of myopia reaches 80-90% of young adults in some urban areas of East Asia. (Ang & Wong, 2020) Moreover, it tends to appear at a younger age than before and nearsightedness has been reported as one of the biggest children's eyesight issues.

FIGURE 1: Myopia global prevalence (*Myopia - Myopia Institute*, n.d.)

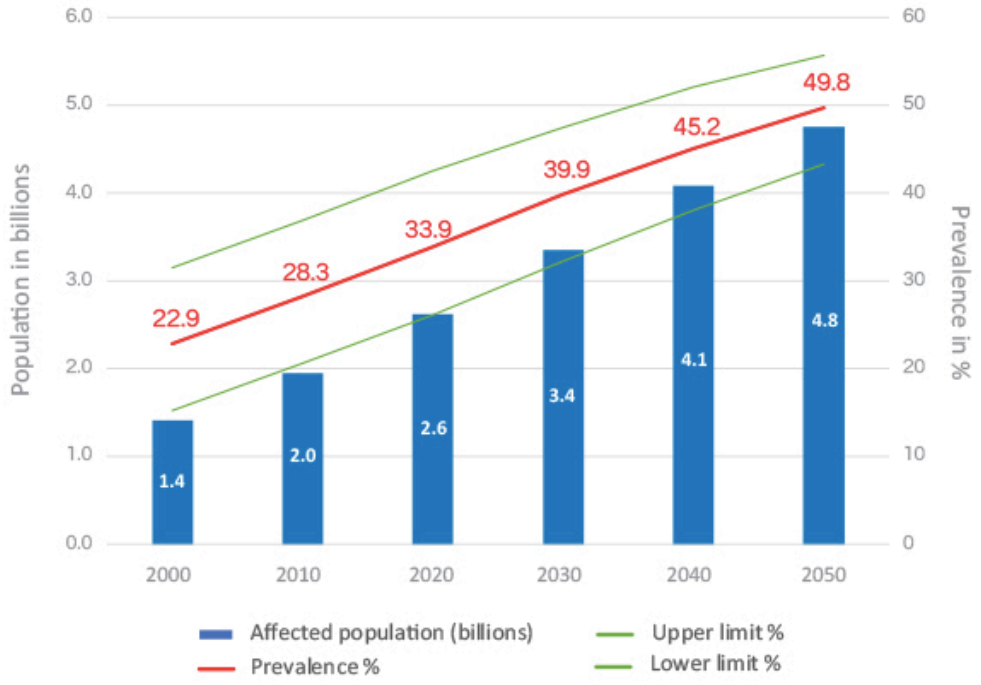
Myopia is the inability to see objects clearly at a distance can be divided in : simple myopia, high myopia and pathologic myopia. Those different types of nearsightedness could be defined by the differences of diopters (D) , a “unit of measurement of the power of a lens, used for measuring a person’s eyesight” (*Diopter*, n.d.).

Simple myopia is a myopia of -0.5 D to -4.5 D. High myopia is defined by WHO as: “ a condition in which the spherical equivalent objective refractive error is ≤ -5.00 D in either eye”(i.e S -5 or more negative).

High myopia is associated with an increased risk on becoming pathologic myopia. Pathologic myopia, or degenerative myopia, is a high myopia with secondary pathologic eye changes that can result in other pathologies like maculopathy, glaucoma, retinal detachment and cataract that ultimately may lead to blindness. (K. Williams & Hammond, 2019)

The global increasement of myopia also results in an increasing of high myopia and so in pathologic myopia. Indeed by 2050, 50% of the world population is estimated to become myopic and 1 billion to have high myopia as it is shown in the graph below. This is what makes myopia increase dangerous. (*Myopia - Myopia Institute*, n.d.)

FIGURE 2: prevalence of myopia in the world in the past and estimation in the future (*Myopia - Myopia Institute*, n.d.)



Consequently, research has been conducted to investigate the factors that play a role in myopia development. Genetic and environmental factors have emerged from the research.

Research also focused on possibilities of slowing down or preventing myopia progression in children. Those possibilities are divided in several categories: multifocal spectacles, contact lenses and pharmaceutical agents. First, multifocal spectacles or progressive

glasses, are spectacles with several prescriptions. They allow to see at all distances. Then, contact lenses include soft bifocal lenses, orthokeratology lenses and rigid gaz permeable lenses. Finally, the main pharmaceutical agents are atropine, pirenzepine and cyclopentolate. In this thesis we will focus on atropine. (Walline et al., 2020)

In the following chapters, first myopia will be discussed with the anatomy and physiology of the eye, myopia development, pathologic myopia and etiologies of myopia.
Second, atropine will also be discussed with an introduction, its mechanisms, the drug formulation and side effects. The third part will concern the most important clinical trials realized on atropine to conclude on atropine efficacy. Those trials involved Asian children because most of the research on atropine has been conducted in Asia. Indeed, as said above the myopia epidemic is much more marked in Asia than in other parts of the world. Finally, there will be a discussion and a conclusion.

II. Myopia

1. The eye

In this part, the anatomy of the eye will be quickly reminded. Then, the eye physiology will be briefly discussed.

a) Summary of the eye anatomy

The eye is a spherical globe which is hollow and its surface is composed of 3 coats.

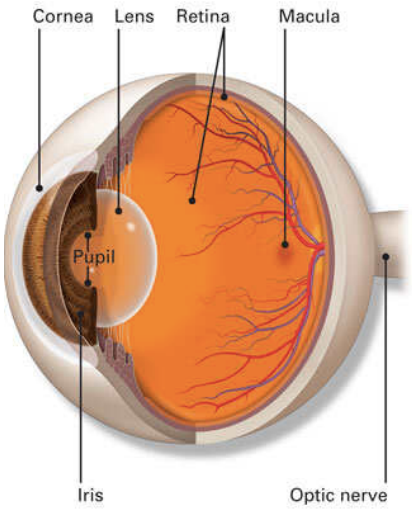
The outermost coat consists of the sclera and the cornea. The sclera is fibrous and its function is to protect the eye. The cornea is at the anterior part of the eye. It is convex and its role is to focus the light and transmit it to the retina at the posterior part of the eye.

The middle coat is vascular and includes 3 parts: the choroid, the iris and the ciliary body. The choroid use is to nurture the retina. The iris is a diaphragm regulating the amount of light entering the posterior part, also giving the eye its color. The center of the iris is the pupil. (*FMPMC-PS - Enseignement d'ophtalmologie - Niveau Deuxième Cycle*, n.d.-a)

The innermost coat is the retina. It consists of 2 different types of photoreceptors: rods and cones. The rods allow to have peripherical vision and night vision. The cones are responsible for color vision and perception of details. At the center of the retina, there is the macula which is a small surface more specially responsible for vision of details. (*Macula*, 2016)

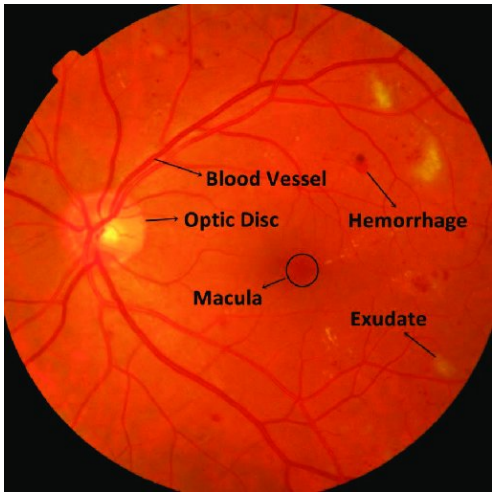
The interior of the eye is mostly filled with aqueous humor. Another medium is the crystalline lens that plays a great role in refraction and accommodation. It is attached to a muscle called the ciliary muscle. (*FMPMC-PS - Enseignement d'ophtalmologie - Niveau Deuxième Cycle*, n.d.-b)

FIGURE 3: Human eye image (*Macula*, 2016)



Besides those 3 coats, there is an important surface for ophthalmologic examination called the fundus. That includes the retina, the fovea, the optic disc, the macula and the posterior pole.(*Fundus (Eye)*, n.d.)

FIGURE 4 : Fundus image (Bharali et al., 2015)

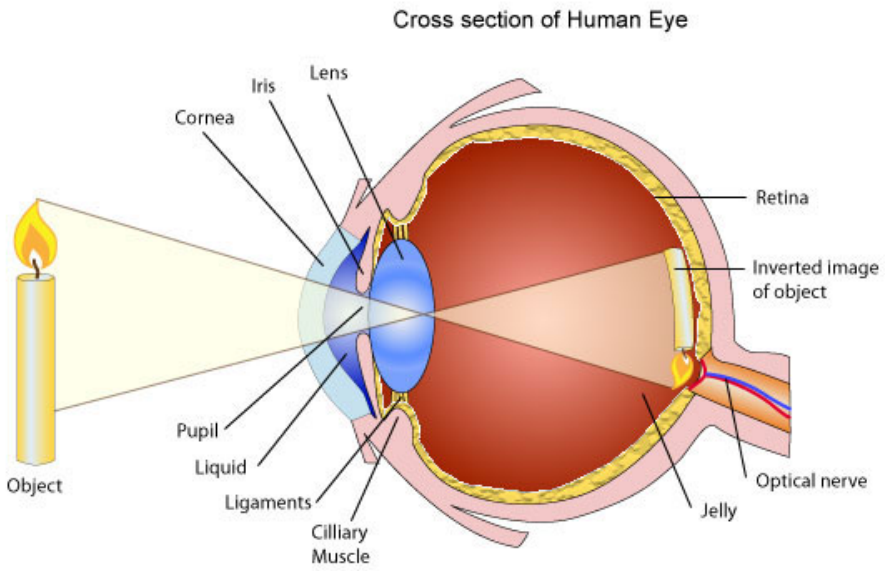


b) Eye physiology

Light path

The light goes through the cornea to the center of the retina which is called fovea. Along the way it also passes through the crystalline lens. The light is then received by the receptors of the retina and is transformed in an electric signal. That electric signal goes to the brain through the optic nerve. Then it is interpreted by the brain.

FIGURE 5 : Cross section of human eye (Lally, 2011)



Eye refraction

When light changes of medium, it is deviated at the interface of the 2 media. This phenomenon is called refraction. As light passes through different media in the eye it is refracted. This refraction principally happens in the cornea and the lens. The refraction allows to form an image of the objects on the retina.

Focus

The cornea has the highest refractive power of the eye. It is able to focus the light because of its curved shape and also because of the difference in refractive index between the media. Indeed, light goes from the air to the cornea and then from the cornea to the aqueous fluid.

Accommodation

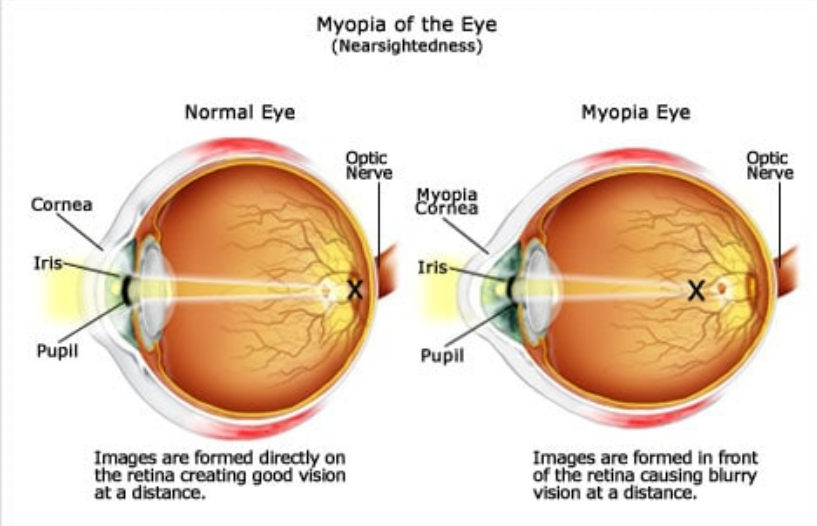
Accommodation is a type of focus that concerns near vision.

The ciliary body allows the crystalline lens to see things from far distances to short distances. In fact, when the ciliary body contracts or relaxes the form of the crystalline lens changes.
To see near objects, the ciliary body contracts and the crystalline lens becomes more curved. Loss of accommodation with age is caused by stiffening of the lens and people have more difficulty to see near objects. This is called presbyopia. (Ang & Wong, 2020)

2. Myopia development

Myopia occurs when the images of objects are not formed on the retina but in front of it. Consequently, the eye is not able to form a "correct image" of far objects but see them as blurred.

FIGURE 6 : Myopic eye (*Lens Induced Myopia (Investigative Ophthalmology) - Endmyopia® - Improve Eyesight Naturally*, n.d.)



There are 2 mains causes behind this. Myopia occurs when the axial length is too high or, when the refractive power of the cornea and lens is too high. (*Myopia - Myopia Institute*, n.d.) (The axial length is the distance between the cornea and the retina.)

The time of onset of myopia is different for every myopic person. At birth, humans are hypermetropic. That means they have to accommodate for good near and distance vision.

During its growth, the eye adapts its refractive power. This process is called emmetropization. At the age of 5 or 6, it is normally completed. When the process does not go well, refractive errors result in myopia and hypermetropia. Myopia can further progress until it stabilizes around adult age.

The biochemical mechanisms of emmetropization and myopia development are not really understood but there are several hypotheses.(Ang & Wong, 2020)

Firstly, myopia development would involve the dopaminergic pathway. Indeed, dopamine is present in multiple tissues including the retina and it would help eye development, visual signaling and refractive development. Furthermore, dopamine would be a "stop signal" in eye development. (Zhou et al., 2017) Indeed, myopia is linked with a decrease of dopamine and its metabolite. Besides, sunlight seems to act on dopamine receptors. Indeed, it was discovered in studies on animals that the synthesis of dopamine increases in the presence of sunlight. As dopamine decrease is linked with a progression of myopia, dopamine increase would produce the opposite effect and therefore slow myopia progression. So sunlight would slow myopia development. (Muralidharan et al., 2021)

Finally, chronic inflammation would also be involved in myopia development. Indeed, myopia prevalence is higher in people suffering from chronic inflammatory diseases (such as diabetes, uveitis and lupus erythematosus) than in the regular population. (Lin et al., 2016) Uveitis is an inflammation of the uvea. It can lead to a loss of vision. (*What Is Uveitis?*, 2021) Lupus erythematosus is a chronic autoimmune disease which involves multiples organs like the skin, the heart, the lungs… (Justiz Vaillant et al., 2022)

Besides, an increase of bêta transforming growth factor (TGF-ß) and matrix metalloproteinase 2 (MMP-2) has been detected in myopic subjects. Those 2 molecules are linked to inflammation: MMP-2 is involved in tissue vascularization during inflammation and TGF-ß adjusts phenomena like inflammation and cell differentiation. (Lin et al., 2016)

3. Pathologic myopia

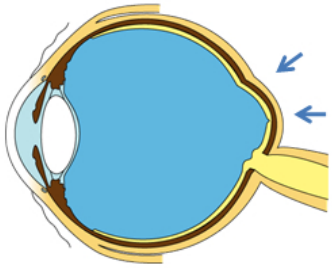
The worldwide prevalence of pathologic myopia is 3%. Its prevalence varies according to the ethnicity, with a prevalence of 1% among Europeans and 1 to 3% among Asians. The prevalence and the degree of severity also increase after the age of 40.

Pathologic myopia differs from high myopia. High myopia is characterized by a refractive error of 5.0 D or more while pathologic myopia is characterized by complications in the fundus. Pathological often follows high myopia but it is not always the case. (*IMI Pathologic Myopia*, n.d.)

There are several complications: posterior staphyloma, myopic maculopathy and high myopia-associated optic neuropathy.

First, posterior staphyloma is a protusion at the posterior part of the eye. (Ohno-Matsui & Jonas, 2019) It is very often found in pathologic myopia and it can lead to other ocular complications. (Ruiz-Medrano et al., 2019)

FIGURE 7: Posterior staphyloma (Glaucoma | Ophthalmology & Visual Science Tokyo Medical and Dental University, n.d.)



Then, myopic maculopathy is divided in 7 stages according to the META-PM classification. At stage 0, there are no lesions. At stage 1, the fundus is tessellated. At stage 2, there is a diffuse choroidal atrophy. Stage 3 is characterized by a patchy choroidal atrophy. At stage 4, there is a macular atrophy. The next stage is defined by Fuchs' spots, myopic choroidal neovascularization and lacquer cracks. Fuchs' spots are colored lesions in the macula. (*Fuchs' Spots*, n.d.) Myopic choroidal neovascularization is the formation of new

blood vessels in the choroid. It is one of the main cause of vision loss. (*Choroidal Neovascularization (CNV)*, 2021). Lacquer cracks are breaks in the inner membrane of the choroid. (*Lacquer Cracks*, n.d.) The final stage is posterior staphyloma. (*IMI Pathologic Myopia*, n.d.)

Finally, myopia-associated optic neuropathy is characterized by damages to the optic nerve. It can also lead to visual loss. (*Optic Neuropathy*, n.d.)

4. Etiologies

a) Genetic

Myopia is a pathology with a certain degree of heritability. Indeed, close to 80% of the difference (variance) of refractive error would be explained by it. (Tedja et al., 2019)

Genetic studies have been performed to understand the pathogenicity of myopia. First, mostly family studies were performed followed by population studies and the last decades these studies used GWAS for identifying genetic polymorphisms.

GWAS is the acronym for Genome Wide Associated Studies. By scanning the genome of many people having a disease and a matched number of people who don't have a disease, they make it possible to establish association between specific genes and diseases.

The GWAS permitted to identify 39 loci associated to myopia. (Tedja et al., 2019) Loci is the plural of locus that is defined as:"a specific fixed position on a chromosome where a particular gene or genetic marker is located."(*Locus (Genetics)*, n.d.)

Besides GWAS, it was also hypothesized that some ethnicities like Asians would be more susceptible to myopia due to their genetic characteristics. It is one of the elements that would explain why myopia epidemic is particularly marked in Asia.(*IMI Pathologic Myopia*, n.d.)

b) Environment influence

The modern lifestyle seems to contribute to a great part of myopia increase. There are multiple environment factors that are associated with myopia.

Firstly, according to a study computer use would moderately be associated to myopia development in children especially at a young age. However, the association between reading time and myopia seem to be stronger. It is been hypothesized that is because of a shorter distance when reading than with a computer. (Enthoven et al., 2020) Indeed, nearwork activities like reading and computing seem to favor myopia progression. (Huang et al., 2015)

Secondly, time spent outdoor is also associated with myopia. Increased outdoor exposure in childhood would give protection against myopia. In fact, light seems to act on dopamine receptors that are also involved in myopia development. Indeed, sunlight seems to give protection against myopia as explained above in myopia development. (Muralidharan et al., 2021)

Further, the level of education is also associated with increased myopia. A higher level of education is correlated to a higher rate of myopia. Level of education regroups a lot of difference parts and it is hard to determine which parts play the most important roles. It could be linked to more near-work activities, less time spent outdoors and others factors like a socioeconomic status that favors educational opportunity. (K. M. Williams, Bertelsen, et al., 2015)

During the pandemic period of covid 19, the rate of myopia increased in school age children. This rising was statistically significant linked to outdoor time and type of habitation. Reduced outdoor time compared to before the pandemic seemed to worsen myopia. On the opposite, outdoor time of minimum 2h per day gives protection against myopia progression. Furthermore, myopia development was less in children living in independent houses compared to children living in apartments. This is explained by the fact that access to the outdoor is easier in independent houses that were more likely to have a garden than in apartments. The use of electronic devices such as smartphones, computer and television however was not statistically significatively linked to myopia increase.(PubChem, n.d.)

III. Atropine

1. Introduction

The name atropine derivates from *Atropa Belladonna*. *Belladonna* means “beautiful lady”. It would refer to the women in the Middle Ages who used it to dilate their pupils and make their eyes more beautiful. As for *Atropa*, it would come from Atropos one of the three Moirai in the Greek Mythology. (Scholtz et al., 2019)

Atropine was extracted from belladonna which is a plant from the *Solanaceae* family. Belladonna is found in Europe, Western Asia and North Africa. It contains 20 alkaloids: 13 in its roots and 7 in the other parts of the plant. (Rita & Datta, 2011) Alkaloids are naturally occurring molecules containing a nitrogen atom and characterized by their basic nature. (o’connor, 2010)

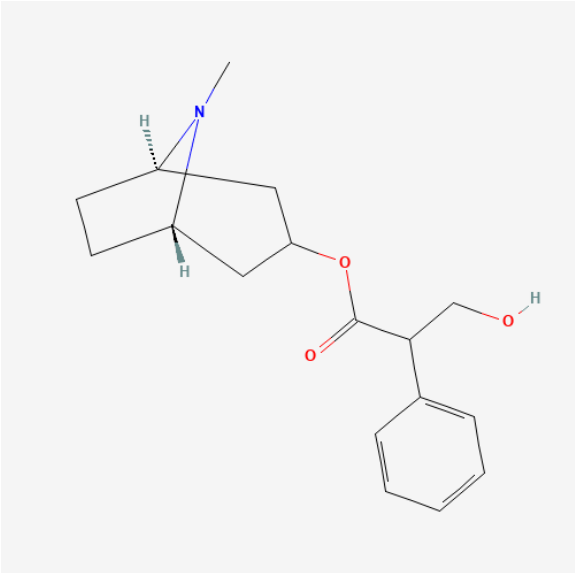
Atropine was used throughout history to treat multiple pathologies such as scarlet fever, hepatitis, skin diseases but also as a powerful poison. In 1901, Richard Willstätter synthetized atropine for the first time. Its chemical structure is a racemic mixture composed of the isomers (S)- and (L)-hyoscyamine. (Scholtz et al., 2019)

FIGURE 8 : Belladonna (‘Belladone’, 2022)

Today, atropine is still used in ophthalmology for objective refractive measurements (cycloplegia) and also in uveitis and iritis. (*CBIP | Ophtalmologie*, n.d.) Cycloplegia is a paralysis of the ciliary muscles induced by a medication. It allows to measure myopia degree. (Futura, n.d.) Furthermore, it is an antidote for nerve gases (poisonous gases that affect the nerves synthesized by humans and notably used as a weapon in World War I) (*Nerve Gases*, n.d.) and a treatment of insecticide poisoning. It's also used in bradychardia. (McLendon & Preuss, 2021) Bradychardia is a slow heart rate namely less than 60 beats per minute. (*Bradycardia | Definition of Bradycardia by Medical Dictionary*, n.d.)

As of today, atropine is prescribed in myopia by many ophthalmologists around the world. (Fang et al., 2013) The aim of the use of Atropine is to delay myopia progression and thus the risk for pathological myopia.

FIGURE 9 : Atropine chemical structure (PubChem, n.d.)



2. Mechanisms

The mechanisms of atropine are not established yet. The research is ongoing based on several hypotheses.

a) Cellular level

Atropine is classed in anticholinergic drugs and it is known since long that it is an antagonist of muscarinic acetylcholine receptors. Those receptors belong to the parasympathic system. In the eyes, their "natural" action consists in constricting the pupils. Atropine gives thus pupil dilatation.

However, in myopia its action is not yet well understood. There are several hypotheses based on animal studies. (Upadhyay & Beuerman, 2020)

Firstly, it would antagonize the membrane receptors of acetylcholine resulting in pupil dilatation. However, it also acts as an inverse agonist especially on the membrane receptor 3 of acetylcholine (MR3). Then, it would also antagonize the alpha2A-adrenergic receptors, the GABA-R and tyrosine kinase receptors such as EGF-R.

Besides, it would also be mediated by nitrous monoxide (NO). Indeed, a study focused on chicks with a form-deprivation myopia. It is a type of induced myopia. It proved that NO is necessary to atropine action. In fact, NO is involved in the eye adaptation to light. NO is produced when the amount of light increases and NO inhibitors are produced in the opposite case when the amount of light decreases. (Carr & Stell, 2016)

Finally, atropine would mediate inflammation. Indeed, atropine seems to lower IL-6 (interleukine-6) TNF-alpha (transforming necrosis factor-alpha) , c-FOS, and NFKB levels and those molecules are pro-inflammatory. (Lin et al., 2016)

b) Tissue level

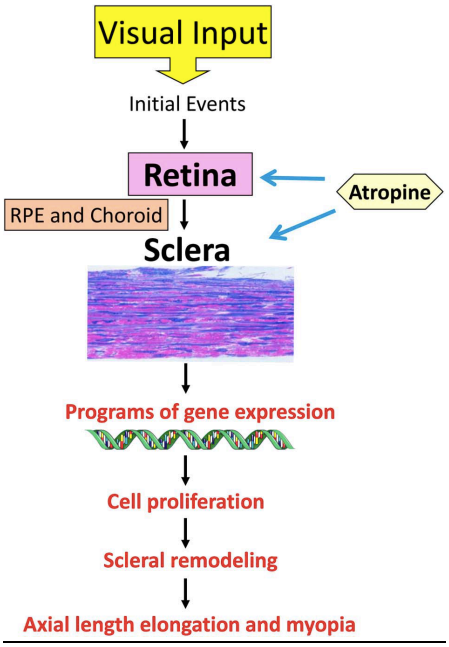
Atropine would act on 4 principal tissues: RPE and choroid, retina and sclera.

Firstly, in retina it would have an action on GABAergic transmission by decreasing GABA transporter 1 (GAT-1) protein level and also by increasing dopamine level in the eye. Indeed, dopamine would act as a “stop signal” to the eye growth. (Zhou et al., 2017).

Secondly, it would inhibit the remodeling of the sclera. In fact, in myopia the sclera becomes thinner compared to a healthy eye. This would be one of the causes of excessive axial elongation leading to refractive error in myopia. Thanks to atropine, sclera would grow thicker.

Finally, Atropine also affects the RPE and the choroid. RPE namely retinal pigmented epithelium is a coat of specials cells between the retina and the choroid. They make the link between the retina and the sclera. The choroid is partly responsible for eye development. In myopia choroids becomes thinner compared to a “normal” eye. So Atropine inhibits the thinning of the choroid. Moreover, choroid and retina both produce growth factors and atropine interfere with their activity. (Upadhyay & Beuerman, 2020)

FIGURE 10 : Signal cascade of myopia development in animal models (Upadhyay & Beuerman, 2020)



In the image above, a signal cascade of myopia development has been hypothesized in animal models. First, visual input namely visuals signals are detected by the eyes and it leads to initial events namely molecular changes in the retina. Then, those events spread to the sclera through the RPE and choroid. Afterwards, the molecular changes are transcribed and translated

to lead to new cells. Finally, they will remodel the sclera and result in axial length elongation of the eye and thus myopia development. As seen above, atropine acts in the different tissues to slow myopia. (Upadhyay & Beuerman, 2020)

It must be noted that those mechanisms are subject to caution as they are from animal studies and so it can not necessarily be extrapolated to humans. Indeed, animal studies can give a general idea of the medication mechanisms but those mechanisms can be different because of the genetic differences and the environmental interactions.

c) Accommodation

Atropine by acting on the ocular muscles inhibits accommodation. This phenomenon is called cycloplegia. (*Atropine*, n.d.) It gives a blurred vision.

d) Concentration

Clinicals trials have been led to determine which concentration of atropine would be an optimal one. It emerged from the research that the higher the concentration the more efficient it was but so were the side effects. So further studies were needed to determine an optimal concentration namely one with the best balance benefits/risks. (Chua et al., 2006)

3. Side effects

The benefits and the side effect of atropine are both dose dependent. Higher concentrations come with more side effects.

On the one hand, atropine can cause local effects. It includes ocular irritation, allergy, loss of accommodation and glare due to dilated pupils. On the other hand, atropine can induce systemic effects. Indeed, atropine causes typical anticholinergics effects namely increased heartbeat, confusion, dry mouth, constipation… (*Atropine*, n.d.)

4. Drug formulation

a) Introduction

Atropine has different formulations depending on their indication. There are injections and eye drops. In Belgium, the injections are commercialized under the name Atropine Sulfate Aguettant® and Atropine Sulfate Sterop®. They are used in the cases of intoxication to cholinesterase inhibitors or bradycardics, in bradycardia and in anesthesia.(*CBIP | Spécialités*, n.d.)

FIGURE 11 : Atropine Sulfate Sterop

(*Sterop Atropine Sulf 0,5mg 1ml 10 Amp | Apotheek Cobra*, n.d.)

FIGURE 12 : Atropine Sulfate Aguettant

(*Atropine Syringe 3g/10ml | Dental & Chiropody Products*, n.d.)

Concerning the eye drops, they are commercialized under the name Isopto-Atropine® in Belgium. They are indicated for measuring the refraction of the eye, also to heal keratitis and uveitis and finally after certain eye operations. (*CBIP | Ophtalmologie*, n.d.)

FIGURE 13: Isopto-Atropine®

(*ISOPTO ATROPINE 1,0% COLLYRE 5 ML*, n.d.)

Eye drops are the formulation of atropine in myopia prevention. As atropine does not have a market authorization for different concentrations for myopia prevention, there is not one method to prepare the formulation. Consequently, several methods have been developed those last few years. (Berton et al., 2020)

At the start, the time of conservation of eyedrops was only one month which was not convenient as atropine is a chronic treatment of myopia. Then, in a study 2 different forms were developed: one with a preservative-free device and another one with an antimicrobial conservative (cetrimide) in two distinct polyethylene multidose eyedroppers. (Berton et al., 2020)

b) Preparation method

Atropine drops were prepared via dilution. Atropine was dissolved in sodium chloride at ambient temperature and then cetrimide (in the form with preservative) and the buffer to adjust pH (consisting of Na_2HPO_4/NaH_2PO_4) were added under mild agitation. Next, the solution obtained was filtered through a 0.22 µm pore and sterilely divided in the eyedroppers. (Berton et al., 2020)

Chemical Components	Formulation (mg)	
	Without Preservative	With Preservative
Atropine sulphate (batch 18276508, exp. 31/01/2021, Inresa, France)	100	100
Natrium dihydrogenophosphate dihydrate (NaH_2PO_4) (batch 190298040, exp. 30/11/2021, Inresa, France)	7800	7800
Dinatrium monohydrogenophosphate dodecahydrate (Na_2HPO_4) (batch 18129611, exp. 30/04/2023, Inresa, France)	4480	4480
Cetrimide (batch 16F08-B01-334049, exp. 05/2020, Fagron, Netherlands)		100
Sodium chloride (NaCl) 0.9% (Versylene®; Fresenius Kabi France, Louviers, France)	q.s 1000 mL	q.s 1000 mL

TABLE 2: Composition of ophthalmic solutions (Berton et al., 2020)

c) Conservation method

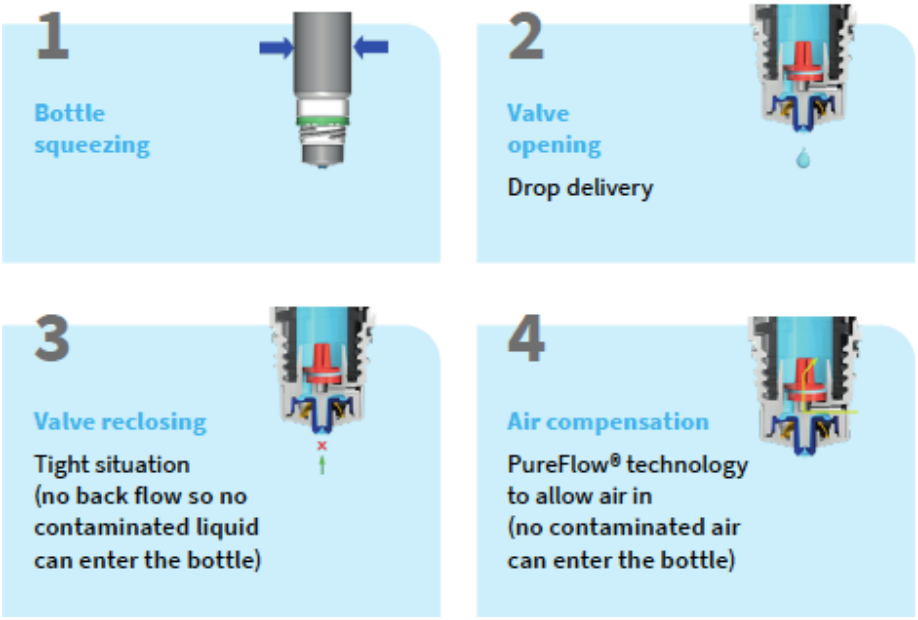
Ocular conservatives such as BAK often cause side effects like allergic reactions and can make the tear film unstable. (*CBIP | Ophtalmologie*, n.d.) The tear film is an area composed of three layers that allow to keep the eyes moist and protect them from the external environment.(*Tear Film - American Academy of Ophthalmology*, n.d.)

In the form without conservative, Novelia® caps were used to guarantee sterility. It's a new technology consisting of 2 parts: a valve and a silicone membrane.

Firstly, the valve closes after delivering a drop so it prevents contaminated liquid from coming back into the eyedropper. Moreover, there is no need to filter the liquid unlike classic eyedroppers.

Secondly, the silicone membrane to filter the air coming into the device to assure non-contaminated air. ('Developing an Efficient Ophtalmic Device Combination Product', 2020)

FIGURE 14 : Novelia® Caps functioning (*Nemera-Ophthalmic-Brochure-Digital.Pdf*, 2021)



In the image above, the functioning of the caps is explained. First, the bottle must be squeezed to allow the valve to open and deliver a drop. Then, the valve closes to prevent contaminated liquid to enter the bottle. Finally, the Pureflow technology allows the entry of clean air.

One study described the stability and the atropine concentration of those 2 forms. More precisely, it studied their stability at 25°c in an unopened state for 6 months and the atropine concentration in simulated use in 6 days. Simulated use means that one drop of atropine is extracted per day to simulate the use by the patient. (Berton et al., 2020)

The concentration of atropine measured was similar in the two forms and the level of breakdown products too.

d) Advice for use

For retarding myopia, atropine eye drops are applied once a day at night in both eyes. Before putting the eye drops, it's necessary to wash one's hands. Then, putting the child's head backwards make it easier for applying the drops. Afterwards, the dear duct must be squeezed

to limit systemic absorption. The child's cheek should also be wiped with a tissue. The children must continue to wear their glasses during the treatment. (uz, n.d.)

IV. Clinical trials

Many clinical studies on atropine use to prevent myopia in children have been performed to date. The most important ones will be summarized and discussed here to determine the effectiveness of atropine.

1. ATOM1

- Summary

ATOM1 is the Atropine for the treatment of Chilhood Myopia study 1. It was published in the journal of Ophtalmology in December 2006 by Chua et al. (Chua et al., 2006) Its goal was to determine the efficacy and safety of topical atropine in slowing myopia progression in Asian children. Indeed, before ATOM1 the only studies demonstrating efficacy of topical atropine were small studies with weak methodologies. Furthermore, the safety of atropine was not evaluated.

To have a power of 90% the study needed a minimum of 400 children. Therefore, 400 children aged from 6 to 12 were enlisted into the study. The selection criteria were myopia from -1.00 D to -6.00 D, astigmatism no more than -1.5D, anisometropia no more than 1.5D and a normal intraocular pressure. "Anisometropia characterizes a difference of refractive error between the 2 eyes." (*Anisometropia - Definition of Anisometropia by The Free Dictionary*, n.d.) For example, the left eye with -2.5 D and the right with -4.0 D.
The exclusion criteria were previous treatment of myopia, eye diseases, respiratory or cardiac diseases and allergy to atropine.

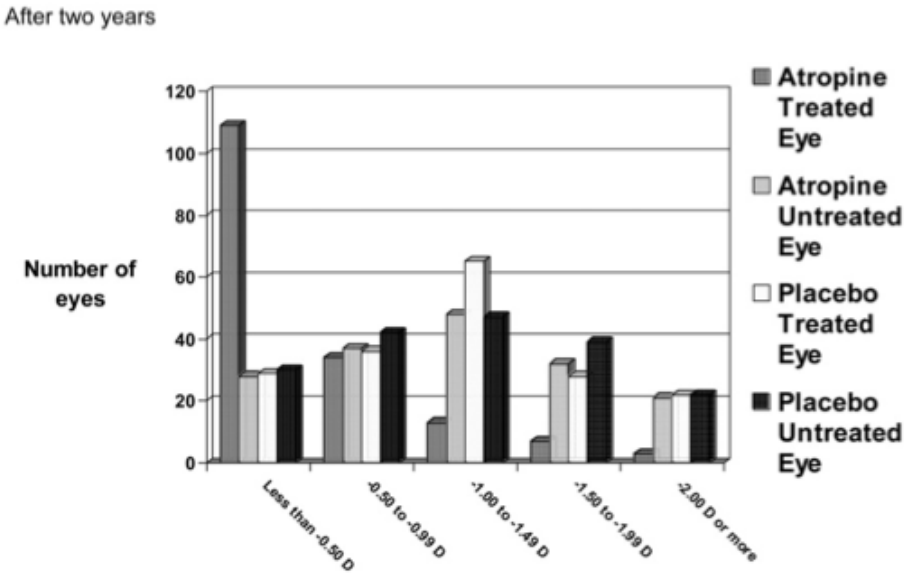
The children were randomly allocated to the Atropine and placebo groups. The concentration of atropine eye drops was 1 %. The intervention consisted of eye drops application in only one eye once a day at night. All the children were equipped with

photochromatic lenses to reduce sides effects. Photochromic lenses are spectacles lenses that darken when exposed to high frequency light such as uv-light. They allow to protect the eyes against photophobia, namely increased sensitivity to light, which is a side effect of atropine. The study was double-masked and the data was analyzed in intention to treat (ITT). ITT is a method taking in account the patients who leave the study when it is still ongoing. It allows to be closer to the medication use in real life as not all the patients take their medication in a very rigorous way.

Concerning efficacy, the primary outcome was a change in refractive error of spherical equivalent (SER). This parameter was used to measure myopia progression. The measurement of refractive error was made with cycloplegic autorefraction before the enrollment and during the study. The secondary outcome was ocular biometrics change. Concerning safety, the primary outcome was the occurrence of adverse effects.

The results of the study were a reduction of 77% in mean progression of myopia in the atropine group compared to the placebo eye. The myopia progression was -0.28 ± 0.92 D in the treatment group and -1.20 ± 0.69 D in the control group with P< 0.001. The adverse effects detected were not major. It was mainly blurred near vision, glare and allergic reactions. The side effects were minimized because it was an unilateral treatment and also thanks to the photochromatic lenses.

FIGURE 15 : progression of myopia in D after 2 years in the different groups



The main limitation was the unilateral treatment. It was chosen because adverse effects would be limited. However, over the long term it may result in anisotropia. Therefore, a second ATOM study was conducted with bilateral treatment. It means instead of only one eye the two eyes were treated in ATOM2.

- Strengths

Firstly, this clinical trial was a randomized controlled trial (RCT) which is a good point as this type of studies is very high in evidence based medicine (EBM). Indeed, their rigorous methodology allow to avoid most bias that can occur in the studies. Besides, it was double blinded. It means neither the participants nor the investigator know who received the placebo and who received the treatment.

Secondly, this study disposed of a large number of participants. This is very important as the study power precisely depends on it. It is really one of the strengths of this study because former clinical trials about atropine in myopia prevention were only small studies with a limited number of participants.

Then, another good point was the data analysis. The data was analysed in ITT which is the best method to reflect the drug "real life" unlike per protocol analysis.

Afterwards, this study has also been concerned about the safety of atropine. It was interesting to look at it as former clinical trials did not investigate it, although RCT are not the most appropriate studies to detect side effects. Observational studies are more suitable to detect them.

Finally, this study had a high retention rate as only a few patients, 44 out of the 400 children, quitted the study before its end.

- Weaknesses

Firstly, the scientists decided to treat only one eye of each of the children to limit side effects. It is true that the untreated eyes could be used as an additional control (like the placebo group). Nonetheless, it increased the risk of unblinding as children could suffer from blurred

near vision in the treated eye. Besides, even if it was to limit side effects this study is not compatible with real life practice as unilateral treatment is not used in it. It diminishes the external validity of the study.

Secondly, the photochromatic lenses even if they reduce side effects can also limit the external validity of the study. Indeed, children do not usually wear them.

- Conclusion

1% atropine eyedrops were proven to be effective in myopia prevention progression in children and side effects were not major. However, only unilateral treatment was investigated thus it was decided a second study would be conducted.

2. ATOM2

Its goal was to determine the efficacy and safety of lower concentrations of atropine namely 0.5%, 0.1% and 0.01% in a bilateral treatment. The study was divided into 2 phases: a treatment phase of 24 months and a wash-out phase of 12 months.

Phase 1

- Summary

This phase was published in 2012 in the journal of Ophtalmology by Chia et al. (Chia et al., 2012) 400 children aged from 6 to 12 years old were enrolled in this phase. Indeed, it was estimated that 400 children would give a power of 90%..

The inclusion criteria were a minimal refractive error of 2 D in both eyes, a myopia progression no less than 0.5 D in the last year and astigmatism inferior to 1.5 D. The exclusion criteria were an allergy to atropine, an ocular pathology i.e strabismus, a systemic disease and previous use of pirenzepine or atropine. Pirenzepine is a muscarinic antagonist like atropine and is also used in some studies to prevent myopia in children.

The children were allocated to the 3 treatment groups (i.e 0..5%, 0.1% and 0.01%) following a 2:2:1 ratio in 6 strata determined by age and gender. The intervention consisted of atropine eyedrops in both eyes once a day at night.

There was no control group but the authors explain that it would have not been ethical because atropine was proved to be more effective than placebo in ATOM1 study.

Moreover, the study was double blinded and the data was analysed in ITT.

The primary outcome was myopia progression over 2 years. The secondary outcomes were myopia progression at 1 year, change in AL at 1 and 2 years and side effects parameters (accommodation amplitude, pupil size).

The myopia progression over 2 years was -0.49 ± 0.60 D in the 0.01% group, -0.38 ± 0.60 D in the 0.1% group and 0.30 ± 0.63 D in 0.5% group with P=0.07. The differences were not statistically significant except between the 0.01% and 0.5% groups.

Concerning myopia progression over 1 year, there was no significant difference between the all the groups. There was just a significant difference between the 0.1% and 0.01% groups.

	Atropine (A) Dose, Mean (SD)			
	A 0.01%	*A 0.1%*	*A 0.5%*	**P Value**
Spherical equivalent (D)				
-at 1 yr	−4.9 (1.5)	−4.8 (1.4)	−4.6 (1.9)	0.26
-at 2 yrs	−5.1 (1.5)	−4.9 (1.3)	−4.7 (1.7)	0.20
-mean change over 1 yr	−0.43 (0.52)	−0.31 (0.50)	−0.17 (0.47)	<0.001*,‡
-mean change over 2 yrs	−0.49 (0.63)	−0.38 (0.60)	−0.30 (0.60)	0.07*
Axial length (mm)				
-at 1 yr	25.4 (1.0)	25.3 (0.8)	25.3 (0.9)	0.36
-at 2 yrs	25.7 (1.0)	25.4 (0.8)	25.4 (1.0)	0.08†
-mean change over 1 yr	0.24 (0.19)	0.13 (0.18)	0.11 (0.17)	<0.001*,†
-mean change over 2 yrs	0.41 (0.32)	0.28 (0.27)	0.27 (0.25)	0.002*,†

TABLE 3: results of ATOM2 phase 1 (Chia et al., 2012)

About side effects, there were rare cases of allergic conjunctivitis and dermatitis in the 0.5% and 0.1% groups.

- Strengths

This study was randomized and double-blinded. Its other strengths are the same as ATOM1 namely a large number of participants, ITT analysis and safety investigation.

- Weaknesses

On the one hand, the greatest weakness is the lack of a placebo group. Even though the efficacy of atropine drops was proven in ATOM1 it only concerned the 0.1% dose. The efficacy of the other doses have never been proven. It is completely incoherent to test other concentrations without a placebo group.

On the other hand, 1% atropine drops seem to have a dose dependent mechanism but this mechanism was not demonstrated for lower concentrations.

- Conclusion

The efficacy of the treatments was similar but fewer side effects were detected in the 001% group. 0.01% is the dose with the best balance between benefits and risks.

Phase 2

- Summary

This phase was published in 2014 in the American journal of Ophthalmology by Chia et al. (Chia et al., 2014) Its goal was to determine the residual effects of atropine after stopping the treatment. It is called the wash-out phase. A washout is defined as “the lowering of the concentration of a substance from a solution , or from the human body by withholding the substance and allowing it to be lost, metabolized or excreted”. (‘Washout’, n.d.) It means the washout of atropine is the elimination of atropine from the human body.

356 of the 400 children carried on with the study. This study was randomized and it was a prospective randomized double-blind. The data was analysed in ITT. The wash-out phase

started at the end of ATOM2 namely at 24 months and ended at 36 months. Different ocular parameters were measured at 26, 32 and 36 months. Those included the axial length, the pupil size, the accomodation and the changes in cycloplegic spherical equivalent.

	Atropine (A) Dose, Mean (SD)			
	A 0.01%	*A 0.1%*	*A 0.5%*	**P Value**
Spherical equivalent (D)				
-at 1 yr	−4.9 (1.5)	−4.8 (1.4)	−4.6 (1.9)	0.26
-at 2 yrs	−5.1 (1.5)	−4.9 (1.3)	−4.7 (1.7)	0.20
-mean change over 1 yr	−0.43 (0.52)	−0.31 (0.50)	−0.17 (0.47)	<0.001*,‡
-mean change over 2 yrs	−0.49 (0.63)	−0.38 (0.60)	−0.30 (0.60)	0.07*
Axial length (mm)				
-at 1 yr	25.4 (1.0)	25.3 (0.8)	25.3 (0.9)	0.36
-at 2 yrs	25.7 (1.0)	25.4 (0.8)	25.4 (1.0)	0.08†
-mean change over 1 yr	0.24 (0.19)	0.13 (0.18)	0.11 (0.17)	<0.001*,†
-mean change over 2 yrs	0.41 (0.32)	0.28 (0.27)	0.27 (0.25)	0.002*,†

TABLE 4: changes in spherical equivalent and axial length after 2 years Ajouter sources

Concerning the spherical equivalent, there was an increase for all the groups but it was statistically significantly less in the 0.01% (-0,72 D) group than in the 0.05% (-1,04 D) and 0.1% (-1,15 D) groups with P= 0,0002.

Regarding the axial length, there was also an increase in the all the groups but it was not statistically significantly different with P= 0,787.

- Strengths

Firstly, it was very interesting to realize a wash-out phase. Indeed, it allowed to see if atropine effect is sustainable. It is important to assess its benefit-risk balance.

Then, the study was randomized and double blind. It allowed to avoid selection bias and information bias. Besides, it was a stratified randomization which allow to diminish confounding factors (such as age and sex) between the groups.

Finally, the study had a relatively low percentage of patients loss-to-follow up namely 13%. The results of 348 children were analyzed which is still a great number.

- Weaknesses

Firstly, the duration of the trial, one year, was a bit short. It would have been better to have a study of at least 2 years.

Then, the study did not include a placebo group so the investigators used the placebo group present in ATOM1. However, the population from the placebo group was different from the one in the study. Indeed, the children were younger in the placebo group and were slightly less myopic. Besides, ATOM1 was published 8 years before the phase 2 of ATOM2.

- Conclusion

0.01% is the concentration at which the rebound effect is most limited.

3. LAMP

LAMP is the acronym for Low Concentration-Atropine for Myopia Progression. Its goal was to determine the most efficient Atropine concentration in long term treatment of myopia. It consists of 4 phases. The phase 3 and 4 are not published yet.

Phase 1

- Summary

The phase I was published in the Asia Pacific journal of Ophthalmology in September-January 2019 by Yam and al. (Yam et al., 2019) It was a randomized, double-blinded, controlled trial. 438 children aged from 4 to 12 were allocated to 4 groups. The selection criteria were a myopia of more than -1.0 D and for astigmatism not more than 2.5 D. The exclusion criteria were previous use of atropine or orthokeratology lens, systemic diseases, other ocular diseases and allergy to atropine.

The 4 groups were atropine 0.5%, atropine 0.025%, atropine 0.01% and placebo. The intervention was eye drops at the correct concentration for atropine groups and eye drops containing sodium chloride for the placebo group.

The primary outcomes was myopia progression measured by SE change over a year. The secondary outcomes were changes in axial length (AL), corneal curvature (K) and anterior chamber depth (ACD).

	Atropine (A) Dose, Mean (SD)			
	A 0.01%	*A 0.1%*	*A 0.5%*	**P Value**
Spherical equivalent (D)				
-at 1 yr	−4.9 (1.5)	−4.8 (1.4)	−4.6 (1.9)	0.26
-at 2 yrs	−5.1 (1.5)	−4.9 (1.3)	−4.7 (1.7)	0.20
-mean change over 1 yr	−0.43 (0.52)	−0.31 (0.50)	−0.17 (0.47)	<0.001*,‡
-mean change over 2 yrs	−0.49 (0.63)	−0.38 (0.60)	−0.30 (0.60)	0.07*
Axial length (mm)				
-at 1 yr	25.4 (1.0)	25.3 (0.8)	25.3 (0.9)	0.36
-at 2 yrs	25.7 (1.0)	25.4 (0.8)	25.4 (1.0)	0.08†
-mean change over 1 yr	0.24 (0.19)	0.13 (0.18)	0.11 (0.17)	<0.001*,†
-mean change over 2 yrs	0.41 (0.32)	0.28 (0.27)	0.27 (0.25)	0.002*,†

TABLE 5: changes in spherical equivalent and axial length at 1 and 2 years (Yam et al., 2019)

The SE changes were -0.27 ± 0.61 D in 0.05% group , -0.46 ± 0.45D in 0.025% group , -0.59 ± 0.61 D in 0.01 % group and -0.81 ± 0.53 D in placebo group with $P < 0.001$. AL changes between the different groups were not statistically significant with $P = 0.18$.

Concerning adverse effects, a loss of accommodation was detected but it was much smaller than in ATOM study and was not clinically significant. Besides, photophobia was detected at 2 weeks and the differences between the groups was statistically significant with $P<0.001$. However, at 1 year the difference was not statistically significant. In conclusion, the adverse effects did not have a clinical impact.

- Strengths

Firstly, unlike ATOM2 study, LAMP used a placebo group to test atropine concentrations lower than 1%.

Then, the study was a RCT conducted in double blind. It allowed to avoid bias like selection bias and information bias. Moreover, the data was analysed in ITT.

Finally, a large number of children ,438, were enrolled in the study and the attrition rate was 12,5%. It has been calculated that with 432 children the study would have a power of 90% by taking into account a 20% attrition rate. So this study had a high power.

- Weaknesses

The duration of the phase 1 was only one year which may be too short to highlight atropine effect. It is a good decision to continue in a phase 2.

- Conclusion

The results obtained after phase 1 were discordant with the results of the ATOM study. Therefore, it was decided that LAMP study would continue for one more year in a phase 2 to assess the long-term effects of atropine drops.

Phase 2

- Summary

The phase 2 was published in the journal of Ophthalmology in July 2020. (Yam et al., 2020) Out of the 438 participants in phase 1, 383 children aged from 4 to 12 years continued the study in phase 2. The groups they were randomly distributed to were the same as in phase 1 except for the children initially allocated to the placebo group. Those children were switched to the 0.05% atropine group as it was demonstrated in phase 1 that this concentration is more effective than placebo in treating myopia.

It was still a double blinded trial. So neither themselves nor the clinical investigators were aware of the group the children were in.

The primary outcomes were changes in spherical equivalent and axial length. The data were analyzed in ITT. The intervention was atropine eye drops given once a day at night. The participants were followed up at 4, 8 and 12 months.

At the end of the 2 years, spherical equivalent results were of -0.55 D with P=0.015 in the 0.05% group,-0.85 D in the 0.025% group with P< 0,001 and -1,12 D with P= 0.02 in the 0.01% group.

As for axial length, it increased of 0.39 mm with P= 0.04 in the 0.05% group, of 0.50 mm with P < 0.001 in the 0.025% group and of 0.59 mm with P = 0.10 in the 0.01% group.

Change	0.05% Atropine (n = 93)		0.025% Atropine (n = 86)		0.01% Atropine (n = 91)		Switchover Group* (n = 80)		P Values, Pairwise Comparisons (0.05% vs. 0.025%, 0.05% vs. 0.01%, 0.025% vs. 0.01% Groups)
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	
Spherical equivalent (D)									
Baseline to 24 mos	−0.55	0.86	−0.85	0.73	−1.12	0.85	−1.00	0.77	0.015†, < 0.001†, 0.02†
Baseline to 12 mos	−0.25	0.61	−0.46	0.45	−0.64	0.56	−0.82	0.49	0.004†, < 0.001†, 0.01†
12 mos to 24 mos	−0.30	0.44	−0.39	0.48	−0.48	0.44	−0.18	0.49	0.32, 0.002†, 0.14
P value‡	0.45		0.31		0.04†		< 0.001†		
Axial length (mm)									
Baseline to 24 mos	0.39	0.35	0.50	0.33	0.59	0.38	0.58	0.33	0.04†, < 0.001†, 0.10
Baseline to 12 mos	0.20	0.24	0.29	0.20	0.35	0.24	0.43	0.21	0.012†, < 0.001†, 0.049†
12 mos to 24 mos	0.18	0.16	0.22	0.18	0.25	0.18	0.15	0.18	0.32, 0.009†, 0.25
P value‡	0.57		0.02†		0.001†		< 0.001†		

TABLE 6: Changes in SE and AL over the 2 years (Yam et al., 2020)

Concerning adverse effects, there were cases of photophobia and the loss of accommodation was comparable to LAMP1. Besides, the adverse effects did not have a clinical impact. However, they were not analyzed with a statistical method.

- Strengths

Firstly, the study was a randomized trial realized in double blind. It allowed to avoid bias. Besides, the data was analyzed in ITT.

Secondly, the study included a large number of children. Indeed, 383 children continued the study and 350 reached the end of the study. The retention was therefore pretty high.

- Weaknesses

Firstly, this study did not include a placebo group. Indeed, the investigators thought it would be unethical to let some children continue in the placebo group after having proved the

efficacy of low-dose atropine. They used a predictive model to assess “natural myopia progression” but it is not comparable to a placebo group.

Then, the investigators did not realize a statistical analysis of the adverse effects. Consequently, it is not known if the number of adverse effects are statistically different between the phase 1 and the phase 2.

- Conclusion

0.05% is still the most effective dose among the doses tested at the end of the 2 years. Furthermore, the intervention is more efficient in reducing spherical equivalent change than in slowing axial length growth.

Adverse effects detected did not have a clinical impact. However, it was not known if there would be a rebound effect. A rebound effect means that after stopping the treatment the myopia would progress quickly again. Consequently, it was decided to continue the LAMP study in a phase 3. This phase is not published yet.

4. Comparative Table

In the table below, the different clinical trials selected were compared according to various criteria to determine their reliability.

	ATOM1	ATOM2		LAMP	
		Phase 1	Phase 2	Phase 1	Phase 2
Population	400 chinese children from 6 to 12 years old	400 chinese children from 6 to 12	356 chinese children from the phase 1	438 chinese children from 4 to 12 years old	383 chinese children from 4 to 12 years old
Intervention	Atropine eye drop in one eye 1x/ day at night and photochromatic lenses	Atropine eye drops in both eyes 1x/day at night	No intervention	atropine eye drops	atropine eye drops 1x/day at night
Control	Eyes untreated of treatment group, placebo group	No control group	No control group	placebo group	placebo group
Outcome	Efficacy Primary: change in SER Secondary: Ocular biometrics Safety Side effects occurrence	Primary : myopia progression over 2 years Secondary: myopia progression at 1 year, AL changes at 1 and 2 years, side effects parameters	Primary: changes in SE, AL, pupil size and accomodation	Primary changes in AL, SE, K, ACD	changes in SE and AL
Type of study	RCT	Randomized trial	Observational study	RCT	RCT
Atropine dose	1%	0.5%, 0.1%, 0.01%	No atropine	0.5%, 0.025%, 0.01%	0.01%, 0.05%, 0,025%
Duration	2 years	2 years	1 year	1 year	1 year
Publication date	2006	2012	2014	2019	2020
Blinding	Double	Double	Double	Double	Double
Statistical analyse	ITT	ITT	ITT	ITT	ITT
Results	Efficacy 0.28 ± 0.92 D in treatment group, -1,20 ± 0,69 D in control group Safety side effects not major	Myopia progression over 2 years -0.49 ± 0.60 D in the 0.01% group, -0.38 ± 0.60 D in the 0.1% group and -0.30± 0,63 D in the 0.5% group Myopia progression at 1 year no significant difference between 0.01%, 0.1% and 0.5% group just a significant difference between 0.01% and 0.1% groups Sides effects Allergic conjunctivis and dermatitis in 0.1% and 0.5 % group no cases in 0.01% group	SE changes -0.87 ± 0.52 D in 0.5 % group, -0.68 ± 0.45 D in 0.1% group and 0.28 ± 0.33 D in 0.01% group with P < 0.001 AL changes +0.35 mm in 0.5% group, -0.68 ± 0.45 D in 0.1% group and +0.19 mm in 0.01% group with P< 0.001	SE changes -0.27 ± 0.61 D in 0.05% group , -0.46 ± 0.45D in 0.025% group , -0.59 ± 0.61 D in 0.01 % group and -0.81 ± 0.53 D in placebo group with P < 0.001 AL change between the different groups was not statistically significant with P = 0.18	SE changes -0,55 D with P = 0,015 in the 0,05%, -0,85D in the 0,025% with P < 0,001 and -1,12 D with P = 0,02 in the 0,01% AL changes increase of 0,39 mm with P= 0.04 in 0,05% group, 0.50 mm with P < 0.001 in the 0.025% group and of 0.59 mm with P = 0.10 in the 0.01% group
Conclusion	Good efficacy and safety but unilateral treatment	Comparable efficacy in the different groups over the 2 years but no sides effects detected in 0.01% group	After stopping atropine, myopic rebound in all the groups but it was amplified in the 0.5% and 0.1% group compared to the 0.01% group	Discordant with ATOM study	The study confirmed the results of ATOM and 0.05% was the most optimal concentration

V. Discussion

All the clinical trials selected, except LAMP which was continued in phase 2, demonstrated atropine efficacy in slowing myopia progression in children.

Concerning methodology, the studies were pretty solid. Firstly, they were all randomized trials. This allowed to avoid selection bias. Secondly, they were all conducted in double blind which permitted to limit monitoring and evaluation bias. Thirdly, they included a large number of patients compared to the previous studies, more or less 400 patients in all the studies, which enable to increase the efficacy. Moreover, the retention rate of the studies was pretty high.

The only inconvenience was the lack of a placebo group in ATOM2 and the phase 2 of LAMP.

After analyzing the studies it can be concluded that atropine is effective in treating myopia progression in children. However, the concentration with the best risk-benefit balance is still not very clear. According to ATOM study, it would be 0.01% but according to LAMP study it would be 0.05%.

In ATOM2, the efficacy of 0.01% atropine was characterized by a mean change in SE of -0.49 D (± 0.63 D) with $P < 0.01$ over the 2 years and few adverse effects were detected. In LAMP, the efficacy of 0.05% was characterized by a mean change of -0.55 D with $P = 0.015$ over the 2 years and adverse effects detected did not have a clinical impact.

Those results would suggest that 0.01% atropine is a bit better at slowing myopia than 0.05% atropine. However, it is also necessary to consider whether or not the effect is sustained after stopping atropine. In the phase 2 of ATOM2, the effect was the most sustained in the 0.01% group with a change in SE of 0.28 D (± 0.33 D) with $P < 0.001$. In LAMP, it will be analyzed in a phase 3 which is not yet published.

VI. Conclusion

In conclusion, after analyzing the studies it can be concluded that atropine is effective in treating myopia progression in children. However, the concentration with the best risk-benefit balance is still not very clear. The phase 3 of LAMP will help to conclude which concentration between 0.01% and 0.05% is the concentration with the best risk-benefit balance.

Limits

The main limit of my thesis is that the studies only involved Asian children. Indeed, the results of those studies may not be applicable to European children because of the ethnic differences. In fact, a treatment can have different effects on people depending on their genetic heritage. The efficacy and safety of the treatment can vary from one ethnicity to another. So atropine could be less effective in European children and present more side effects than in Asian children. Unfortunately, until now few RCT were conducted on European children.

Prospects

First, the phase 3 of LAMP will soon be published to determine the concentration with the best risk-benefit balance between 0.01% and 0.05%. Then, new RCT about western children will be achieved by 2022. (Azuara-Blanco et al., 2020) (Lee et al., 2020)They will surely help to conclude whether or not atropine is effective on an European population.

In pharmacy

To prevent myopia, the pharmacist also has a role to play. He can inform the patients about the risk of developing high myopia and what it involves. He can also reinforce the importance of hygiene and dietary rules. The first important thing is to spend at least 2 hours a day outdoor. Indeed, sunlight seems to give protection against myopia progression as it has been seen in this work. Then, the second advice the pharmacist can give is to limit near-work activities like reading and computing. More specifically, time spent on continuous near-work activities must not exceed 30 minutes before taking a small break to rest the eyes. Finally, he can also recommend to have a minimum distance of 40 cm between the eyes and the visual

medium. In fact, distance seems also to play a role in myopia progression: a near-work activity with a small distance like reading is more closely associated with myopia progression than computing.

VII. Methodology

The idea of this thesis came from a report about myopia. Before that, I did not know the subject at all but I found it original and it intrigued me.

They are multiple ways to prevent myopia in children like orthokeratology, multifocal lenses, bifocal lenses but I decided to focus on the use of atropine.

I searched through several search engines such as pubmed, sciencedirect, researchgate, google scholar, nature… with the keywords “atropine myopia”.

I focused on pubmed to research the clinical trials I needed. I included the randomized controlled trials and the articles with children under the age of 18.

I also used secondary sources like the CBIP, drugbank and VIDAL and more specialized websites about myopia like the International Myopia Institut and the American Academy of Opthalmology. The International Myopia Institut was created in 2015 after a meeting between WHO and the Brian Holden Vision Institut (an institute specialized in vision) because of the increasing prevalence of myopia in the world.

For many of the definitions, I used the free medical dictionary. It is an online dictionary based on *The American Heritage® Stedman's Medical Dictionary, Second Edition* and *The Gale Encyclopedia of Medicine,Second Edition*.

VIII. Glossary

Axial length:
"The distance between the anterior and posterior poles of the eye."(*Axial Length of the Eye*, n.d.)

Cycloplegic refraction: the determination of the refractive errors of the eye and the correction with glasses. (*Cycloplegic Refraction | Definition of Cycloplegic Refraction by Medical Dictionary*, n.d.)

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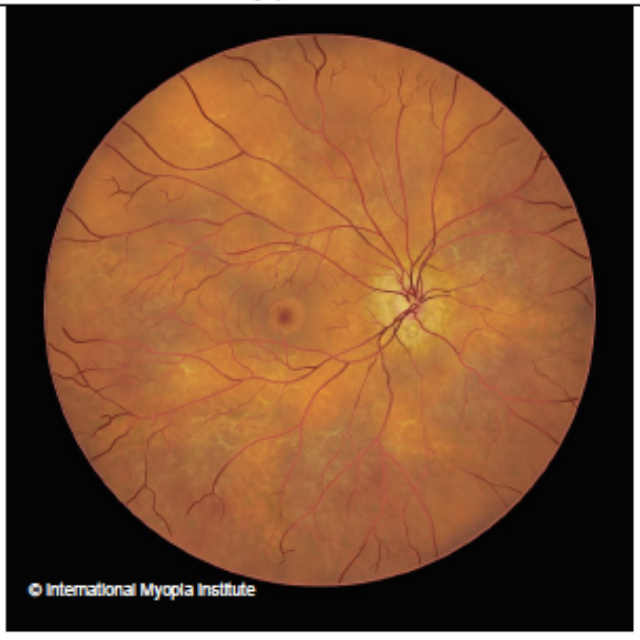
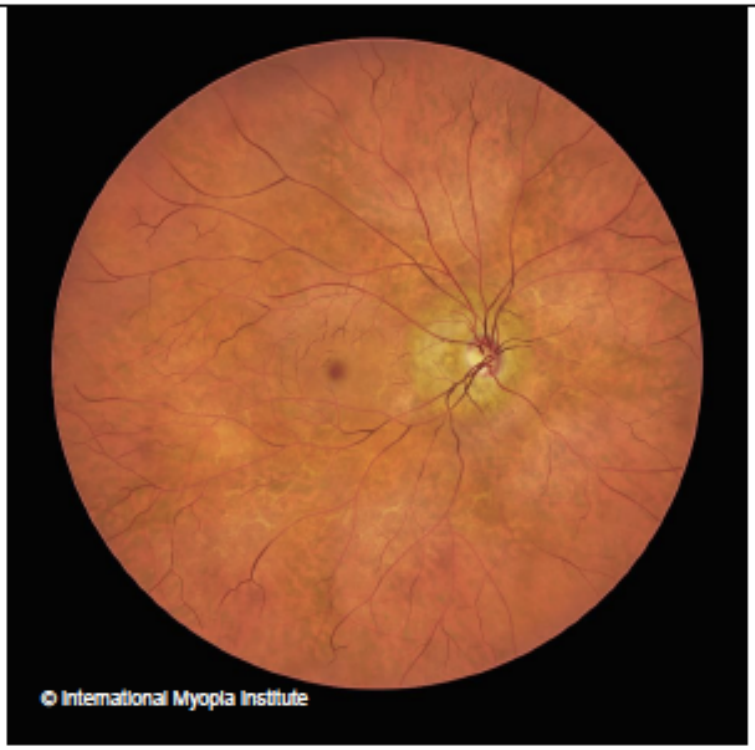
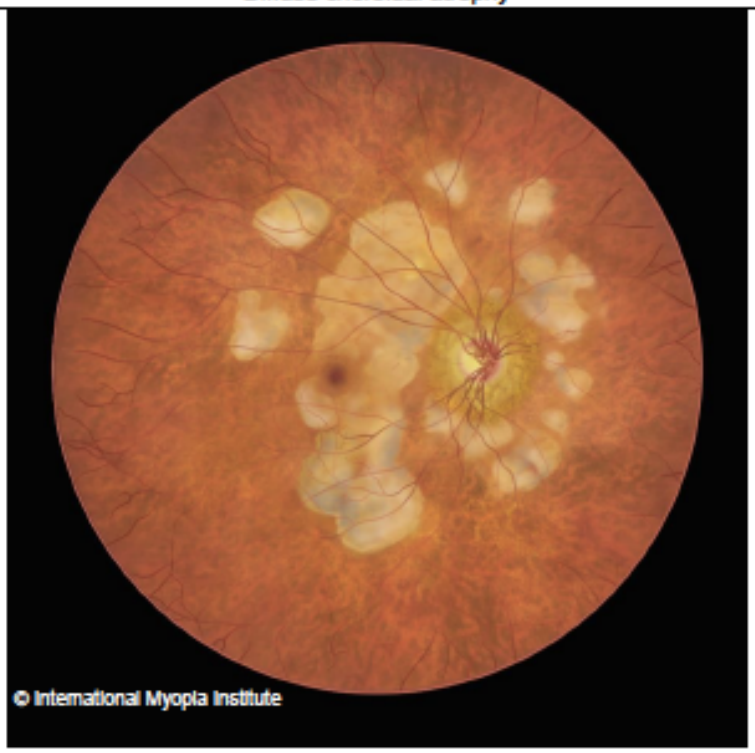
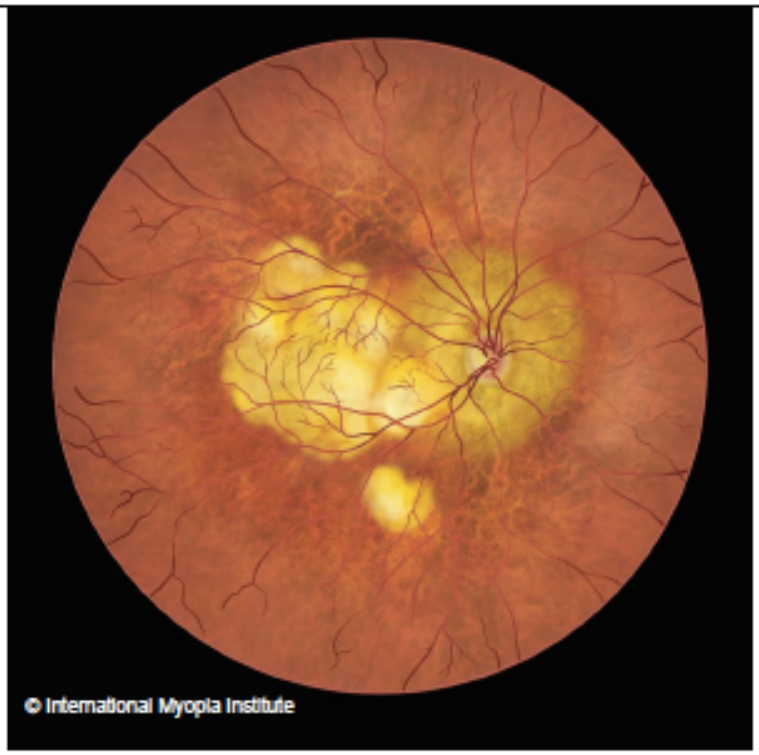
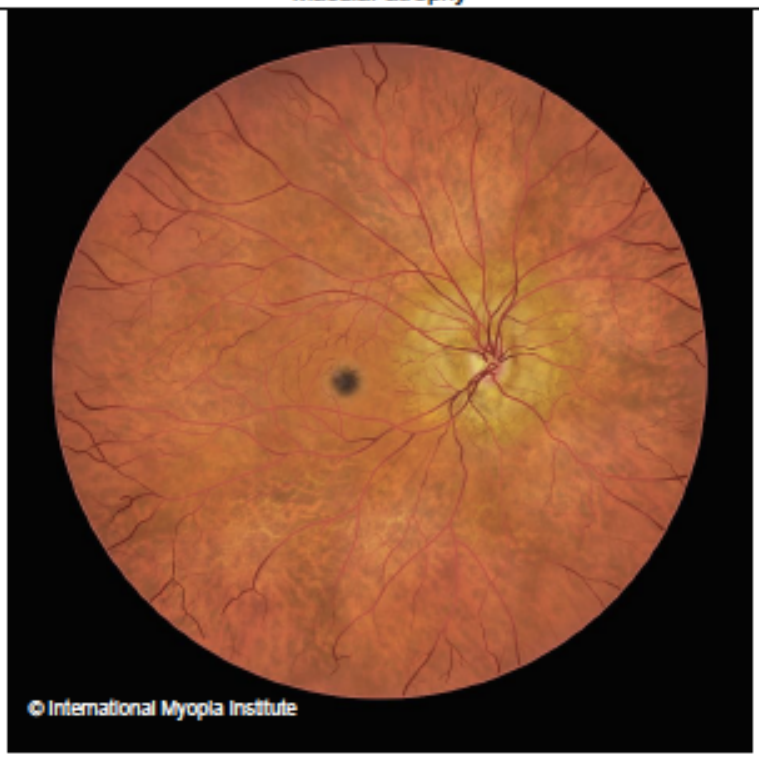
I. Appendices

Appendice 1 : META-PM classification (*IMI Pathologic Myopia*, n.d.)

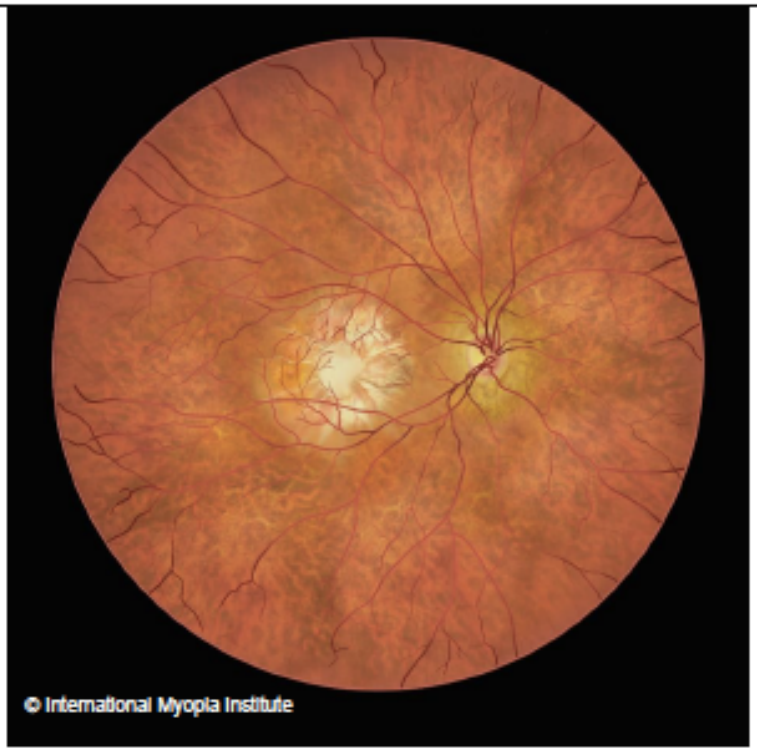
Category	Retinal Signs
0	 No myopic retinal lesions
1	 Tessellated (or tigroid) fundus

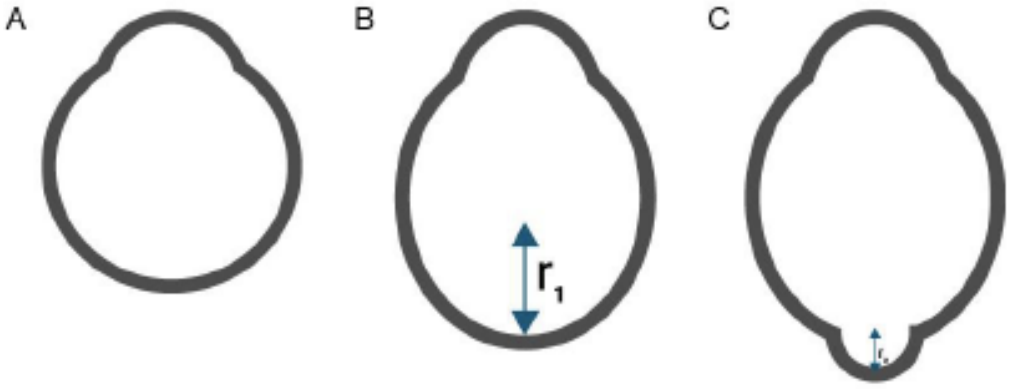
2	 Diffuse choroidal atrophy
3	 Patchy choroidal atrophy

4	 Macular atrophy
Plus Lesions	 Fuchs spot

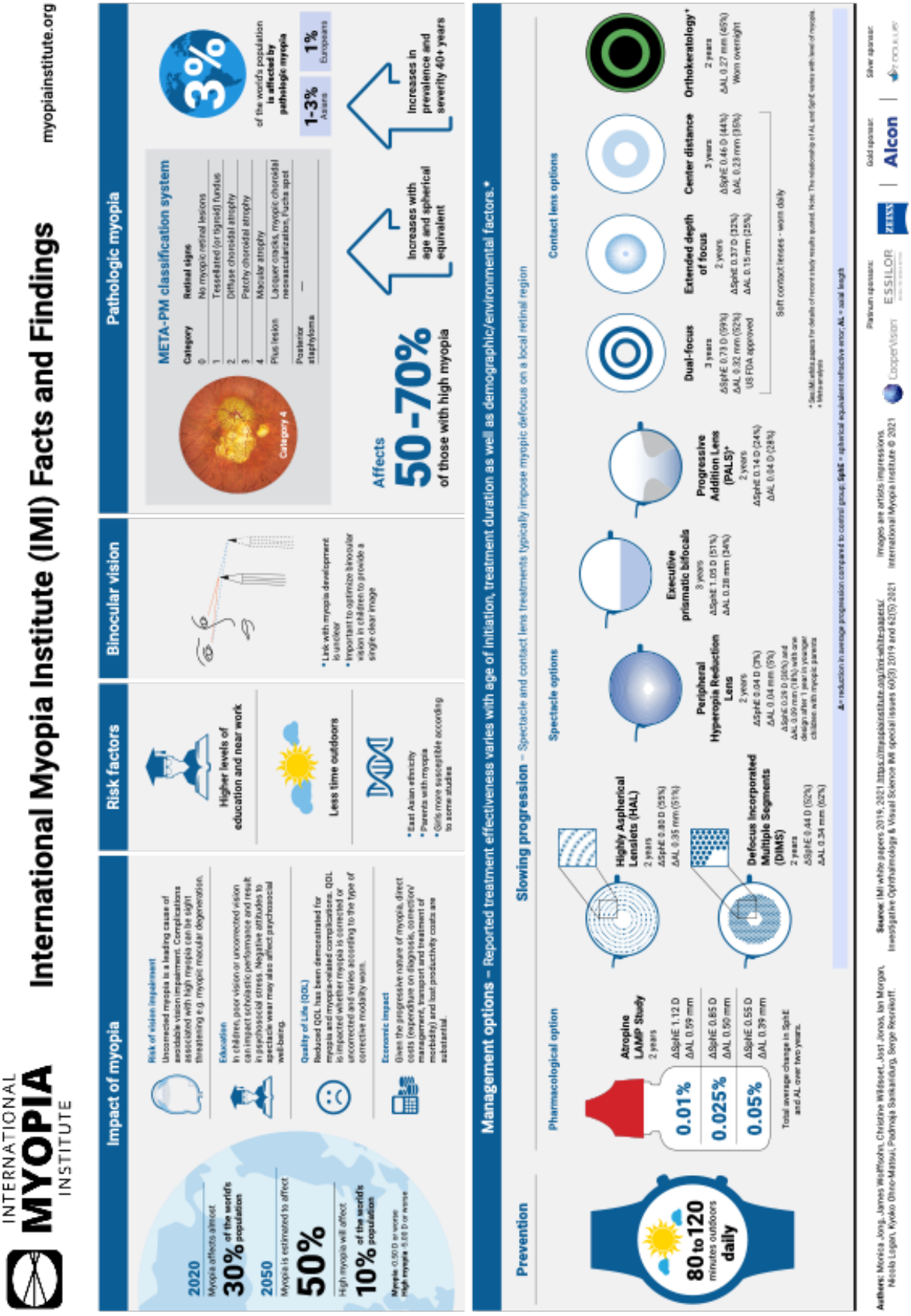
Plus Lesions	 Myopic choroidal neovascularization  Lacquer cracks

Posterior Staphyloma





Appendice 2: IMI infography (*IMI Pathologic Myopia*, n.d)



Ces 2 dernières décennies les cas de myopie ont fortement augmenté dans le monde particulièrement en Asie. Or, une simple myopie peut se transformer en haute myopie responsable de problèmes oculaires plus graves comme un glaucome, un décollement rétinien pour in fine arriver à la cécité. Différentes études ont été réalisées ces dernières pour déterminer si l'atropine pourrait ralentir la progression de la myopie chez les enfants et donc diminuer le nombre de cas de haute myopie.

Ce mémoire aborde tout d'abord la myopie, ensuite l'atropine puis différentes études cliniques sont présentées et critiquées afin de déterminer si l'atropine est efficace pour la prévention de la myopie chez les enfants.

Over the last two decades, the number of cases of myopia has risen sharply throughout the world, particularly in Asia. However, simple myopia can turn into high myopia responsible for more serious eye problems such as glaucoma, retinal detachment and ultimately blindness. Various studies have been carried out in recent years to determine whether atropine could slow the progression of myopia in children and thus reduce the number of cases of high myopia.

This thesis first discusses myopia, then atropine, and finally various clinical studies are presented and criticized to determine if atropine is efficient in the prevention of myopia prevention in children.