The Role of Atropine Eye Drops in Myopia Control

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Abstract: High myopia is a major cause of uncorrectable visual impairment. It imposes major challenges and costs for refractive correction, and for the treatment of associated pathological complications. In the last 60 years, there has been a marked increase in the prevalence of high myopia in younger generations in developed countries in East and Southeast Asia, and there are signs of similar, but less pronounced increases in North America and Europe. In some parts of the world, 70-90% of children completing high schools are now myopic, and as many as 20% may be highly myopic. It is now clear that myopia results from excessive axial elongation of the eye, and this greater rate of axial elongation appears to be environmentally driven.

Experimental studies have examined the biochemical mechanisms involved in regulation of axial elongation; and, from these studies, some options have emerged for preventing the development of myopia or slowing myopia progression. Atropine eye drops have been quite extensively used in clinical practice in Asian countries. This long-lasting treatment could be beneficial, but has clear limitations and complications. Recent reports suggest that a low concentration of atropine, which has less severe side-effects, is also effective. But, a decision to use an invasive treatment such as atropine drops, even at low doses, requires careful consideration of the risk of myopia progression. A decision to use atropine in pre-myopic patients would require even more careful consideration of the risks. Here, we review the current literature relevant to the prevention of myopia progression with atropine drops.

Keywords: Myopia, progression, diluted atropine.

1. SCHOOL MYOPIA AND HIGH MYOPIA

Myopia is global public health problem with high costs associated with refractive correction and treatment of complications. Different types of myopia can be distinguished. “Congenital myopia” is a rare condition that usually has high amounts of dioptric error; as neo-nates are not usually refracted, it is generally discovered only later during the first years of life. This infantile-onset high myopia is often stationary (non progressive) [1, 2]. “Simple myopia”, usually less severe than -5 to -6 diopters (D), is the most common form. This simple myopia generally develops during the school years and is also referred to as “school myopia”. Traditionally, school myopia was regarded as developing during the late primary and early secondary school years, primarily on the basis of results obtained in Europe and North America; but in some countries of East and Southeast Asia, a majority of students are now myopic by the end of primary or elementary education, with a high prevalence of “high myopia”. Once established, myopia generally progresses during the school years, and in cases of rapid progression, it may lead on to “high myopia” – which is often defined as a refractive error that has increased beyond negative 5-6 diopters, and an axial length over 25mm [3-5]. This is a concern because, with ageing, many cases of high myopia develop “pathological myopia”, with uncorrectable vision loss produced by progressive choroidal degeneration of the posterior pole, and a range of other pathological sequelae [5-8].

The treatment for myopic refractive error could involve both clinical practice and public health approaches. From a public health perspective, any myopia is a problem requiring diagnosis and correction, as is the case for myopia in childhood. Low and moderate myopia is also associated with impaired distance vision if uncorrected or undercorrected; consequently, uncorrected myopes may be affected in their capacity for learning at school and engaging in sports activities. These complaints are seen many times in the clinic, although few studies have explored this particular issue [9]. On the other hand, progression of myopia is a major concern clinically because of the pathological issues associated with high myopia. Any treatment that can be applied to individual patients in a clinical setting, to avoid progression to high amounts of myopia, would be welcome.

2. PATHOLOGICAL ASSOCIATIONS OF MYOPIA

Simple and high myopia are both associated with ocular disorders such as cataract and glaucoma [10, 11]. On the other hand, age related macular degeneration is not associated with myopia [5]. Eyes with mild to moderate myopia (~1 D to ~5 D) show few pathological signs, but in eyes with myopia higher than ~5 or ~6 D, there is an increased prevalence of retinal pathological comorbidities [6], and degenerative myopia, which is accompanied by typical degenerative changes in the sclera, choroid, and retinal pigment epithelium that can affect visual function. The incidence and severity of pathological ailments caused by high myopia increases with age, such that changes begin to be noted in patients during the adult years [12]. For example, in his classical clinical study of 250 high myopic subjects with posterior staphyloma, Curtin found that more than 50% of the older subjects were legally blind (40-86 yrs) [6], and other recent population based studies in subjects older than 40 show that 25-50% of high myopes have myopic maculopathy and impaired vision at adult ages, with increasing pathological changes as aging continues [13-18]. Chorioretinal lesions are a consequence of excessive axial elongation, and the progressive distention of the posterior pole produces straightening of the temporal retinal vessels, development of a papillary crescent, and thinning of the sclera and choroid [7, 8, 19]. In a recent retrospective observational case series with 12 years follow up, these changes were shown to progress in about half of all eyes with myopic maculopathy [20].

Although the pathogenesis of posterior staphyloma is still under study, it is well known that the sclera is abnormal in high myopia, having low mechanical resistance. Interestingly, during induction of
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Current Pharmaceutical Design, 2015, Vol. 21, No. 32 4719

experimental myopia there is increased activity in the enzyme met-
alloproteinase – which breaks down proteoglycans and collagen –
in the sclera of birds and mammals [21, 22]. Histologically, the
sclera of human myopes is thinner than normal, with reduced di-
diameter of the collagen fibers; this echoes the histological changes
seen in the sclera of animal models of myopia. Therefore, it is
probable that this abnormal sclera is produced by direct scleral
remodeling. The choroid is also thin, with lack of vessels in some
areas. The retinal pigment epithelial cells appear flatter and broader
than usual, and in some areas are completely replaced by Müller
cells. Bruch’s membrane shows thinning, splitting and rupturing.
The the sensory retina is also thinner than normal, apparently be-
cause of loss of the ganglion cell layer in the macula [7]. These
changes are associated with a typical myopic macular degeneration
at the posterior pole. In addition, the alterations in the peripheral
retina and the vitreous can lead to retinal detachment later in life.

Our understanding of the anatomical basis of myopic pathology
has been substantially enhanced by the application of advanced
imaging techniques, such as optical coherence tomography (OCT),
and MRI. Practically all myopia (except that of keratoconus or len-
ticonus) is caused by excessive elongation of the eye, but eyes with
pathological myopia are not simply elongated, they are often also
severely deformed [20]. Pathological changes in the retina, choroid
and sclera, and visual field defects are more common in highly
deformed eyes than in less deformed eyes, and the progressive de-
velopment of these defects is the main cause of uncorrectable visual
impairment in highly myopic eyes. A range of pathological signs
have been recognized; in particular, myopic maculopathy (often
called myopic retinopathy) is characterized by the presence of one
or more of the following changes: posterior staphyloma, lacquer
cracks, myopic choroidal neovascularization, chorioretinal atrophy
in the posterior fundus, and macular retinoschisis [16] (Fig. 1).

Most of these pathological changes in the macula are irreversi-
ble, and lead to permanent vision impairment. Some promising
treatments are vitrectomy, with peeling of the internal limiting
membrane for epiretinal membranes, and intravitreal injections of
anti-angiogenics for macular neovascular membranes; but these are
invasive treatments associated with high costs and comorbidity.
Moreover, even when treatments are successful, the visual im-
provement is usually small, so their benefit is limited and the final
visual acuity remains low.

Fig. (1). Fundus photograph of degenerative myopic maculopathy in the left eye of a 54 years old woman with 20/200 best corrected visual acuity and bilateral high myopia. White plaques of chorioretinal atrophy can be seen in the fundus photo (A, black arrows). The central line represents the OCT scan seen in Figure 1B, where atrophy of the pigment epithelium, as evidenced by signal scatter, can be seen in the OCT image (the continuous arrows show the sections where the pigment epithelium is still present). The OCT image (Fig. 1B) also shows macular retinoschisis produced by an epiretinal membrane (dotted arrow).
further slow ocular growth in later years [52]. In East and South East Asia, where 80% of children in the younger generations have myopia by age 18 [33], adult onset myopia is not likely to be an issue, as most subjects are already myopic by the end of the school years. Instead, the progression of myopia during ages 20-30 in Asian myopes may increase the severity of myopia, and thereby ultimately the prevalence of high myopia. Thus, the natural history of myopia development varies according to different environments.

The final amount of myopia depends on the age of onset, the rate of progression and the uncertain age of stabilization. Onset may be rapid and clearly perceived by the patient or family members in the case of small school children, but it can also be slow and recognized many months or years after distance vision is slowly impaired, as it happens sometimes in clinical practice with adult onset myopia. Three prospective studies involving myopic children showed that myopic shifts in refraction and the rate of axial elongation accelerated immediately prior to the onset of myopia [53-55]. As said, this may not always be the case in the clinic, and this should be explored with studies involving measurement of the ocular components in myopia with onset after age 18-20. On the other hand, the rate of progression may slow down as the child ages, and it can be rapid in some cases but slow in others [44]. Among children who are found to have bilateral low myopia at an early age, some progress rapidly into high myopia at a rate of -1 diopter per year, whereas others have stable refractions during the following years [47]. In support of this, a prospective study of refractive error in children with follow-up data of progression showed that as many as 20% of those who were low myopes at baseline had stable refractions after 2½ years [56]. On the other hand, some infrequent cases discovered very early (during infancy years) with stable high myopias, probably congenital, may even develop small hyperopic shifts with growth [2]. Despite these differences, the general pattern in the urban Asian myopia epidemic, is that most children develop myopia during the school years [36].

It is clear that progression is not the same for all cases, and the age of cessation [57-59] is very difficult to assess clinically, because it can only be recognized retrospectively after one or two years of stability; and even then, some myopic subjects with stable refractions have shown progression later on in life (clinical observation). After 11 years of follow up of myopic children with school myopia in the COMET study, the authors fitted successive refractions with exponential functions to estimate the age of cessation, and concluded that myopia stabilized at a mean age of 15.61 years; however, in at least 40% of the sample the myopia progressed after that age [60, 61]. It is also frequent in clinical practice to see that progressive myopia can occur after age 18 [47], and that some high myopes continue progressing during their 20-35 adult years [62, 63]; thus, it is difficult to define a uniform age of cessation. The evidence presented here argues that the old ideas about myopia onset and stabilization are out of date [64,65]. Myopia onset in urban Asia at present is spread over a wide range of ages, with new cases arising during primary school, adolescence, and early adulthood. Similarly, the idea that the prevalence of myopia tends to stabilize at age 12 or 16 is obsolete, as it is now clear that both onset and progression can continue well into the 20s and even older.

5. RISK FACTORS IN MYOPIA DEVELOPMENT

Risk factors of myopia onset and progression are important in clinical practice when the decision has to be made whether or not to prescribe a treatment, and if so, which one to choose. Epidemiological prospective studies have helped in predicting myopia onset. It is well known that a plano cycloplegic refraction in elementary school years is a definite risk factor for myopia development during adolescence, while slightly hyperopic refractions (on the order of +0.75 diopters spherical equivalent) are predictive of low risk, at least in environments where prevalence is low [66-68]. In Taiwan, where most school children become myopic, a prospective study utilized dilute atropine treatment for pre-myopic children (plano refractions); they found that treatment with low doses of atropine significantly inhibited the onset of myopia in the experimental group, while the control group, as expected, developed myopia in short amount of time [69]. It is not known whether low hyperopia would be protective in such environments.

Near work, perhaps the most famously implicated risk factor for myopia, has been shown to have some importance - as in recent studies, which showed that myopia prevalence in children was associated with more hours spent reading, even though the association was not always strong [70] (Fig. 2) [68, 71, 72]. Although the importance of this risk factor remains controversial because the association of myopia with near work hours has not been confirmed in all studies [73], it is clear that living habits of students in law [74, 75] and engineering [76], or Jewish orthodox males [77], put them at high risk of developing myopia during study years. Recent comparison of the international records on educational performance showed that adolescents from countries with high engagement in after-school tutorials and high educational performance were the top ranking in prevalence of myopia [78].

![Fig. 2](https://via.placeholder.com/150)

Fig. (2). Data presented by Marius Tscherning, in 1882, of refractive error of 7,523 Danish military recruits; these data support the associated of myopia with near work tasks [69].

High outdoor exposure has been recently associated with lower myopia prevalence [79-81], and prospective studies in which children are exposed to additional time outdoors have shown that incident myopia can be significantly decreased by this intervention [35, 82, 83]. In Singapore, where the prevalence of myopia is very high, the government initiated a campaign asking parents to take children outdoors to play [84]. A prospective study of children originally involved in a bifocal trial in Finland provides further evidence for the protective effects of outdoors light, in that it showed that impaired myopic progression was associated with more than three daily hours of outdoor exposure [85]. If time outdoors were important in prevention of myopia, it is likely that a myopic child who spends a large amount of time indoors would be at higher risk of myopia progression. Perhaps, then, children should be encouraged to study in environments with high natural illumination. However, there is still no definitive evidence that sunlight is the predominant, much less the sole, factor responsible for the protective effect of spending time outdoors.

Parental history of myopia may represent both genetic and environmental factors, as parents share genes with their offspring, but they also tend to engage them in similar tasks and habits as those which they experienced themselves as children. Recent studies have shown increased prevalence and progression of myopia in children...
having one or two myopic parents compared to those having no parental history [71, 86-88]. In environments in which the prevalence of high myopia is low, parental history of high myopia in one or both parents is a rare and surely important finding, as it may be a definite risk factor for high myopia development in offspring. On the other hand, in Asian urban environments, where prevalence of high myopia is around 10-20 % in the younger generation, it is more likely that the new cases of myopia are environmentally driven; eventually, parental history of high myopia will not be uncommon, and therefore would not suggest a strong genetic risk.

Finally, the age of first lens prescription has been shown to be correlated with the final amount of myopia developed in adulthood, in some retrospective studies involving adult myopic subjects [47, 48, 89]. In this sense, an early onset can predict greater progression, as small children have been shown to have higher rates of progression than older ones [90] and small children have more years ahead during which their myopia can progress. Yet, as has been described before in the previous section, myopia does not progress in all children at the same rate, so an early age of onset should be considered with caution in those environments where the prevalence is low. In the case where the opposite is true, as in East Asian cities where most children have progressive myopia, an early onset is surely a concern.

6. POSSIBLE INTERVENTIONS.

There are several possible interventions to decrease the prevalence of myopia in a population, or for arresting progression in individual cases [91-96]. From an public health perspective, it does not seem possible to reduce educational pressure without major social changes, so perhaps then public health interventions are the best approach to arrest an epidemic of myopia that has arisen by environmental pressures. Current research suggests that time spent outdoors under natural light environments would be the simplest and most cost-effective intervention to attempt to decrease the prevalence of myopia in schoolchildren. As discussed above, there is significant evidence to support the protective effects of increased outdoor illumination, and these interventions could be massively applied by encouraging children to spend a certain amount of time outdoors per day, especially during school time [35, 83].

In addition to increased environmental illumination, different medical treatments have been developed and tested for arresting myopic progression on an individual bases. These include atropine eye drops, special glasses/contact lenses, and orthokeratology. The last two optical interventions are based on the establishment of myopic defocus by special multifocal lenses or by a multifocal cornea, which place a proportion of the visual images in front of the photoreceptors; it is assumed that this myopic defocus will produce a slower rate of axial elongation, and less myopic progression [97-101]. There have been several clinical observations and follow up studies in which myopic patients remained stable when fitted with orthokeratology contact lenses; the most promising, however, was a recent two year randomized clinical trial (ROMIO), which showed that orthokeratology significantly slows axial elongation, and aids in the stabilization of myopic progression [102]. Although these optical interventions are promising treatments, this review will be focussed on the clinical use of atropine for the inhibition of myopia onset and progression.

7. EARLY USE OF ATROPINE IN MYOPIA TREATMENT

In the early years of Ophthalmology, Donders [103] made two key statements about ocular hygiene in the care of myopia. First, he believed that an eye with progressive myopia was not healthy at any age, and second, that an affected eye required intervention. Donders also believed that it was convergence of the eyes, caused by prolonged and excessive near work, that may be the cause of myopia, and that myopic progression was the result of tension in the extraocular muscles. There is no evidence to support this concept, but on the basis of his observations about watchmakers, Donders concluded that use of monocular loupes dissociated the two eyes during near work, and that this dissociation could relieve muscle tension, and as a result, prevent myopia. In order to mimic the effects of the watchmaker’s loupes, Donders – and other authors during the early days of the 20th century – recommended a daily or weekly instillation of a 1% solution of atropine in one eye only. The daily use of atropine for a prolonged period was also advocated in 1923 by Parsons [104], although only in cases where myopic progression was apparent. Whether myopia was progressive, and thus suitable for atropine treatment sparked controversy between Parsons, and another doctor named Jackson; Jackson [105] believed that “all cases of myopia are progressive”, while Parson held to the belief that “it is impossible, clinically and experimentally, to draw a distinct line of demarcation between progressive and non-progressive myopia”. In response to this controversy, Smith and Schweinitz noted, that it was necessary “to suspect every myope, and especially every youthful myope, of a tendency to increase” [106], while Sorsby [107] claimed that 30% of myopic children were stable during the times he reviewed all treatment options for progressive myopia. It is clear that these early clinical driven speculations and suggestions were controversial, and that we still face the problem of making clear in the clinic, at first visit, which children are rapid or slow progressors.

The first case of atropine use in clinical literature was about a practical application of monocular cycloplegia to physician’s daughter [108]. When first examined, the 9 year old girl showed a simple myopia in both eyes, fully corrected by −0.50 D, and 20/15 visual acuity in each eye. Five years later, acuity was only 16/120 in each eye (uncorrected), and with full correction (−5.0 D) was 16/15, so she was prescribed −4.5 D lenses for each eye. However, even with full corrected of −4.5D spectacles, her vision continued to get progressively worse; thus, monocular cycloplegia by the instillation of 1% atropine solution was begun, and a few days later, vision had returned to 16/15 each eye. Instillation of atropine was continued in the right eye only at intervals of three or four days for a month. After almost 12 years of examination and periodic atropine installation, the required spectacle correction was −5.50 D of spherical equivalent for the right eye and −5.375 D for the left eye [108].

In a similar case, another girl was under observation for ten years (1924-1934). In that period, six increases in her correction were observed, especially during periods of intense near work; application of monocular cycloplegia by atropine reduced this increase in myopia. In another case, a 34 year old woman with high myopia (−17.0 D and −20.0 D), best visual acuity 20/200 and 20/100 in right and left eyes respectively, with annoying “flickering” as a possible prodromal symptom of retinal detachment, used 1% atropine solution each eye weekly for seven months. After another six months of cycloplegia, vision and refraction remained unchanged and the flickering abated [108].

8. THE FIRST CASE SERIES

After Donders' report of monocular cycloplegia as a method to prevent the increase of myopia [103], this topic still met with skepticism. However, Luedde [108] in 1932 reported the use of atropine monocularly to control myopia, and in the 1960’s, Bedrossian conducted a study of 90 children treated with atropine in one eye for one year this first controlled study was reported at the XX International Congress of Ophthalmology in Munich in 1966 [109]. In Bedrossian's study [109], guidelines for selection of patients were: evidence of myopia increasing more than 0.5 diopter per year, ages of 8 to 13 years, parents and children with motivation, and economic and geographic stability for a regular follow-up. Patients instilled 1% atropine in the test eye at bedtime every night. The following year, the eye used as a control became the test eye and the original test eye was the control eye. The refraction was
measured one month after eye switching, then the test eye was examined under atropine, and the control eye under tropicamide every three to four months. After this time, final refraction was obtained. Sixty-two children were followed for two years and 28 for four years. Myopia increased more than -0.38 D in only 12 treated eyes, no change occurred in 152 treated eyes, and myopia decreased in 72 treated eyes. Thirty-three patients were examined between 12 and 36 months, and 24 patients between 37 and 75 months after cessation of atropine (Table 1). In both groups, the average annualized increase of myopia was 0.06 D, which suggested a long-term effect of the treatment. The myopia in the treated eyes did not increase during treatment periods; this is consistent with the results of the recent ATOM studies, as will be discussed later.

Boyd [110] had used atropine in both eyes for the management of school myopia since 1967. His patients were between 6 and 14 years of age, with less than -1.0 D of myopia at the beginning of the treatment; upon the completion of the study, reversal in some cases was reported. Gimbel [110] conducted his study from 1968 to 1973 on the use of 1% atropine for the control of myopia in 279 patients between 5 and 15 years of age, who had recently-developed or increasing myopia. Patients used one drop of atropine in each eye every night, but this was increased at times to twice daily to get a better effect. Treatment was reduced when reading difficulties occurred, and again increased when myopia started to progress. First refraction was done after one month of treatment, and then in three-month, or six to twelve month intervals. One hundred and seventeen patients were checked after one year, 72 were checked after two years, and 22 were followed for three years (Table 1). The optimum dosage was one drop every night, but some patients with reading difficulties used one drop of atropine on one eye one day, and into the other eye the next day. In all, 4% of the test subjects developed an allergy to atropine, and 30% reported other side effects. After one year of treatment, there was a significant decrease in myopia comparing to the control group; this effect, however, was not present in the second and third year of treatment (Table 1).

Kelly, in 1975, reported a one-year study on 77 children, aged 11 and younger, and 69 children, 12 years or older, treated with atropine and phenylephrine [111]. The progression of myopia was much greater in the control group (phenylephrine) than in atropine group after 1 year (85% vs 29%) (p<0.01) and after 2 years (95% vs 43%) (p<0.01). In 1978, Dyer presented data on 86 out of 265 clinical patients who received atropine for 2 years or longer [112]. He reported no progression in 47% of the atropine group but in only 2% of the control group. Progression of 1.0 or more diopters of myopia occurred in only 19% of atropine-treated eyes but in 84% of control eyes. (p<0.01). Sampson, also in 1978, reported on 100 patients who had received atropine, but there was no control group [113]. His conclusion was that atropine is effective while it is used, because rapid progression occurred in some patients after cessation. Gruber in 1979 examined 100 children treated with atropine from a few days up to 7.5 years (mostly 1.5 years) and 100 children of a control group [114]. He reported a progression of myopia of –0.28 D per year in the control group and –0.11 D in the atropine group during the time atropine was used, increasing to –0.46 D after discontinuation of treatment.

In 1984, Brodstein reported on 435 patients who received atropine for 2.8 years and 146 controls followed for a median of 6.6 years [115]. One hundred and eighty two patients (42%) were subsequently excluded from the atropine group because of noncompliance or inconsistent use of atropine (165) or allergy to atropine (17). The mean progression of myopia was –0.12 D per year in the atropine group and –0.34 diopter per year in the control group (p<0.001). Yen (1989) [116], conducted a one-year clinical trial in Taiwan to compare atropine treatment with cyclopentolate and saline. Final examination after 15 months included 96 patients (32 in each of the three groups). Progression of myopia was –0.22 diopters in atropine group, –0.58 diopters in cyclopentolate group, and –0.91 diopters in saline group (p<0.01). In 1995, Kennedy reported on 118 girls and 96 boys (median age 11 years) who received atropine between 1967 and 1974 [117]. The duration of treatment ranged from 18 weeks to 11.5 years. The mean rate of myopia progression was 0.05 diopters per year in the atropine group, and significantly greater in the control group (0.36 diopters per year) (p<0.001). Final refractions standardized to the age of 20 years showed that myopia was less in the atropine group (2.79 diopters) than in the control group (3.78 diopters) (p<0.001). Recently, Romano [118] who has long been advocating 1% atropine use (with bifocals) for arresting myopia progression, has made a great emphasis on the clinical application of this treatment, and Shih et al. [2] tested atropine vs. multifocals in a randomized controlled study, and showed that atropine arrested progression during 18 months of follow-up.

It is clear then, that the evidence for the effectiveness of atropine has been around for a long time, but there has been very little generalization of its use. Atropine is low cost and has no patent, so it provides a cheap, readily available treatment to aid the prevention of myopia. However, the medical industry has never proposed the randomized clinical trials necessary for its approval for use in this fashion, and therefore, its use is not supported by the public health authorities in any country. Therefore, because it is not approved for

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<td>control eye</td>
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<td>p=0.03</td>
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| ** not statistically significant

Legend:
↓ decrease of myopia
↑ increase of myopia
* statistical data not given
use in myopia prevention the use of atropine to prevent myopia by eye-care practitioners has been strictly off-label; which can cause significant ethical concerns for clinicians who may not be willing to use daily 1% atropine for long periods in children, because of possible toxic or other side-effects. This situation has been unfortunate, but attitudes towards atropine have been gradually changing; mostly due to more rigorous investigation of the effects of atropine through the use of animal models, which have led to more well-designed and impactful human clinical trials.

9. ANIMAL MODELS OF MYOPIA.

In the 1970’s, when atropine was being tested in humans by Bedrossian [109], a model of animal myopia was being developed in parallel. Two scientists, Hubel and Wiesel, who were studying the development of visual pathways in monkeys by depriving one eye of its vision by lid suture during early growth, made the incidental discovery that the occluded eye became larger and myopic [120,121]. Their experiments on visual pathways finally led them to win the Nobel Prize, but Wiesel also paid attention to the induction of myopia by eye occlusion, and presented with Raviola an ARVO abstract showing this model in 1975 [120,121]. A few years later, Josh Wallman extended the occlusion model to the chicken eye with a simple experiment, using diffuser goggles instead of lid-suture, Wallman was able to show that the occluded chicken eye developed 15 dioptries myopia in the matter of a few days; thus the animal model of experimentally-induced form-deprivation myopia was conceived [122]. Ten years later, it was discovered that experimentally-induced myopia could also be induced by placing negative lenses in front of the growing eye [123]. Also in a few days, chick eyes compensated for the imposed defocus by increasing the rate of axial elongation and developing myopia. These experiments showed that the plane of image formation with respect to the photoreceptors could modulate the growth of the eye. Images that are focussed behind the photoreceptors at the back of the retina (hyperopic defocus) tend to make developing eyes grow more rapidly, and in contrast – images focussed in front of the photoreceptors slow down axial elongation in growing eyes. Experiments about eye growth and myopia development use these two experimentally-induced models of myopia, named form-deprivation myopia (occlusion of vision by lid suture in the past, and now by translucent diffusers) and lens-induced myopia (application of negative lenses). These models have been tested and developed in a variety of mammals including rhesus monkeys, marmosets, tree shrews, mice and guinea pigs, and even in bird (chicks, pigeons) and fish eyes, demonstrating that the regulation of eye growth by quality and level of image focus in the eye is almost universal [124-130].

Soon after the discovery of form deprivation myopia, it was learned that atropine also arrested myopia development in these experimental models [131]. In 1985, Raviola and Wiesel showed that atropine instillation prevented experimental myopia in the monkey model of lid suture. At that time, thinking among clinical opthalmologists was that myopia onset and progression involved accommodation for near-work. Thus, Raviola and Wiesel thought that accommodation was involved in myopia development, and that atropine blocked myopia by preventing this accommodation. But, in 1993, atropine was shown to arrest experimental myopia development via a non-accommodative mechanism, as it stopped the development of myopia in chickens - animals in which accommodation is mediated by striated muscle fibers and nicotinic receptors, and hence are not influenced by atropine, which affects muscarinic receptors [132, 133].

Where might atropine act to prevent myopia? From animal studies it is well known that the rate of scleral expansion is regulated locally, within the eye, by mechanisms that involve visual processing and signaling in retinal circuits, relays via the retinal pigment epithelium and choroid, and changes in matrix proteoglycan turnover in the sclera [21, 134, 135]. The site of atropine’s anti-myopia action, therefore, should then be somewhere in the cascade of events that go from image formation in the retina up to the modulation of scleral growth. The three layers of the eye-wall (retina, choroid and sclera) act together as an organ capable of regulating the rate of axial elongation according to environmental exposures. In animal models, imposed defocus of images put at the back of the retina by negative lenses produce changes in several retinal mediators (like dopamine, glucagon, acetylcholine or fibroblast growth factor) [134] that induce scleral proteoglycan remodeling, leading to greater fibrous tissue distensibility in mammals [21, 22]. Furthermore, atropine has been shown to prevent the development of myopia in animal models both at the retinal and scleral levels; [136-138] but it is still not clear where the principal action takes place [139].

10. RECENT CLINICAL STUDIES ON ATROPINE USE IN HUMAN MYOPIA IN SINGAPORE AND TAIWAN

To date, the most important study about atropine for myopia progression prevention was the ATOM 1 (Atropine in the Treatment Of Myopia), in which Chua et al. in Singapore [119] performed the first randomized double blind study with 400 children, who received 1% atropine drops or placebo daily over 2 years. In this study, myopia progression was reduced 77% (progression of -0.28D vs -1.20D in two years). Axial length increased 0.39 ± 0.48 mm in the placebo group and had no significant change in the atropine treated group. However, the study reported also some important side effects of 1% atropine use, such as cycloplegia and mydriasis, which in some cases lead to discontinuation of its use. This provoked some later studies comparing efficiency and visual side effects of lower doses of atropine. This was analyzed in a retrospective, case-control study enrolling myopic school-aged 21 children from Taiwan, who received 0.05% atropine eye drops every evening, compared with a control group of 36 untreated children [140]. Mean myopia progression for the treated group was -0.28±0.26 D annually, whereas that of the control group was significantly higher at -0.75±0.35 D per year. Also, Shih et al. [141] had tested concentrations of 0.5%, 0.25% and 0.1% atropine, and found that all three concentrations were effective in arresting myopia progression in a controlled study with two years follow up.

In another single-center, double-masked, randomized study (ATOM 2), the safety and efficacy of 0.5%, 0.1% and 0.01% atropine solutions were studied in Singapore. Participants were 400 children, aged 6-12 years with myopia at least -2.0 D and astigmatism -1.5 D or less. Diluted 0.5%, 0.1% and 0.01 % atropine was administrated once a day at bedtime to both eyes for 2 years [142]. No control group was included in this study, and the data of ATOM 1 were used for comparison. Mean myopia progression and increase in axial length were greater in the 0.01% group (Table 2), but the differences in myopia progression and axial length change between groups were clinically insignificant. Atropine 0.01% had minimal effects on accommodation and pupil size, and no significant effect on visual acuity. Allergic skin and conjunctival reactions occurred in 6 cases in the 0.1% and 0.05% atropine groups, but in no cases in the 0.01% group. In conclusion, atropine 0.01% had minimal side effects and similar efficacy in controlling myopia progression when compared with other dilutions [142].

In a very recent follow up of the ATOM 2 study, 356 children (89%) were reviewed at 26, 32 and 36 months after drug administration was discontinued, and spherical equivalent, axial length, visual acuity, pupil size and accommodation were measured [143]. Myopia progression, increase in axial length and spherical equivalent change in refraction were measured (Table 2 and Fig. 3). Those findings indicated that there was a myopic recurrence in the 0.5% and 0.1% eyes. In the 0.01% eyes, the atropine effect on progression was moderate, but sustained with no rebound effect; however, there was no control group in this study. To study a possible reduction of retinal sensitivity over time in atropine-treated myopic chil-
preferences, 50 children enrolled in ATOM 2 study [144], 35 of whom consented to have fERG (full-field electrotretinogram) recordings at baseline, 24 months (end of treatment) and 32 months (8 months after cessation of atropine). Twenty nine children had good quality fERG on all 3 visits; their mean age was 9.5±0.8 years and mean spherical equivalent was –5.0±1.6 D. There was no significant correlation of axial length with any fERG measures (saturated amplitude, scotopic and photopic fERG amplitude, implicit time). Multivariate analysis showed that a change in 30 Hz flicker response amplitude was associated with increased axial length, but there was no evidence that changes in other responses were associated with age, axial length or atropine doses. The conclusion was that the gradual decline in cone function over time was not influenced by atropine treatment [145].

A nationwide study in Taiwan revealed a trend towards increased rate of prescribing atropine eye drops for myopic children, and a shift to prescribing lower atropine concentrations during the years 2000 to 2007 [145]. A recent review and meta-analysis of the literature about atropine use for arresting myopia progression showed that atropine in different concentrations was really effective for this purpose [146]. This study included four randomized control trials and seven cohort studies, which showed statistically significant mean differences in myopic progression between treated and controls groups. The mean differences in myopia progression under atropine were greater for Asians than for Caucasians in this meta-analysis, which concluded that atropine could be more useful in Asians. However, it is well known that Asians have greater rates of progression than Caucasians. For example, the myopic Caucasian children in the Orinda study had a change in axial length of 2mm in 9 years (a 0.22mm change per year) and a -0.33 diopter per year change in spherical equivalent [41], while the persistently myopic Asian children in the Singapore SCORM study had a rate of axial length change of 0.28mm per year and a -0.58 diopter per year change in spherical equivalent refractive error [43]. If, instead of looking at differences in myopia progression under atropine treatment, the meta-analysis had considered the percentage reduction in spherical equivalent (calculated as the percentage difference in progression between treated and controls) the values would be 71.08% reduction for the Asian randomized control studies, 74.09% reduction in the Asian cohort studies, and 77.24% reduction in the Caucasian cohort studies, thus, showing that atropine is similarly useful in Asian and Caucasian populations.

**Table 2. Ocular parameters in the different concentrations of atropine.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Atropine doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5%</td>
</tr>
<tr>
<td>Myopic progression after 2 years (D) *</td>
<td>-0.30±0.6</td>
</tr>
<tr>
<td>Axial length change after 2 years (mm) *</td>
<td>0.27±0.25</td>
</tr>
<tr>
<td>Myopic progression during washout phase (D) **</td>
<td>-0.87±0.52</td>
</tr>
<tr>
<td>Axial length change during the year of washout (mm)**</td>
<td>0.35±0.2</td>
</tr>
<tr>
<td>Overall change Spherical equivalent after 3 years (D)**</td>
<td>-1.15±0.81</td>
</tr>
</tbody>
</table>

* ATOM 2 - Ophthalmology 2012
** ATOM 2 - Am J Ophthalmol 2013

**Fig. (3).** Mean spherical equivalent change (and 95% confidence intervals) for the four atropine dilutions and the control group in the ATOM studies. Phase 1 is the 24 months treatment period and phase two is the one year follow up after treatment with the drug was interrupted. With 0.01% atropine there was no rebound effect in the spherical equivalent refractive error, and that even with a high dilution of atropine, there was still a significant difference in inhibition of myopia progression when compared with the placebo group at follow up.
Table 3. Adverse events in ATOM studies

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Atropine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.01% (n=84)*</td>
</tr>
<tr>
<td>Allergic conjunctivitis</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Allergy-related dermatitis of the eyelids</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Irritation</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Blur</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Glare</td>
<td></td>
</tr>
<tr>
<td>Loss of distant BCVA &gt; 1 line</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>Accomodation amplitude (D)</td>
<td>11.3 diopters</td>
</tr>
<tr>
<td>Mesopic pupil size increase (mm)</td>
<td>1.3 mm</td>
</tr>
<tr>
<td>Photopic pupil size increase (mm)</td>
<td>1.1 mm</td>
</tr>
</tbody>
</table>

* ATOM 2  
** ATOM 1

11. COMPLIANCE AND SIDE-EFFECTS OF ATROPINE USE

In the ATOM 1 study, photophobia and near vision complaints were frequent adverse effects (4.5% and 1% respectively), and photochromatic multifocals had to be prescribed; however, there were no adverse systemic effects. When treatment was stopped after two years, a rebound effect was seen in treated children, but even at three years follow up the treated group had significantly less myopia than the control group [147]. In the ATOM 2 study, dilute 0.01% atropine had minimal effects upon accommodation and pupil diameter, and did not affect near visual acuity. Allergic conjunctivitis and dermatitis were present in 13 cases (4.1%) included in the 0.5% or 0.1% atropine treatment groups combined, and none in the 0.01% atropine group (Table 3); thus, 0.01% atropine seems to be an effective treatment for arresting myopia progression with negligible side effects.

Although there were no reports of cataract or retinal disorders in the short term in the atropine 1% or lower dilution studies [148], whether there were any long lasting effects on the retina or the lens during adult years is unknown. Compliance with a prolonged topical treatment in children is an important issue, as has been shown with glaucoma and uveitis treatment in pediatric ophthalmology [149, 150]. In order to encourage compliance with treatment programs, some important measures can be taken. First, diluted atropine drops are more tolerable than those with higher concentrations, as they do not burn. Second, establishing a habit with nightly treatment could be possible, by ensuring that drops are instilled at the same time each night, after tooth brushing, for example. Frequent appointments with the child and his parents would also help in maintaining interest in treatment; perhaps a schedule of two or three visits a year could be adequate, not for measuring refraction, but for checking whether any adverse effects have developed, and for prescribing the drops, and to maintain a presence to help encourage children and parents to continue atropine therapy. One important issue in this therapy is the high expectation of patients and parents regarding the outcome of this treatment. It should be clearly explained that atropine is unlikely to reduce the level of myopia, and thus the child will not be able to give up using spectacles, but that it is possible that the patient will have to make fewer changes in the prescription as time passes by. The goal that one should set for this treatment is stability in refraction at a time when myopia usually increases.

If the treatment if followed with good compliance, and myopia can be arrested, becoming stable or progressing slowly [151], one should come to the point at which stopping the treatment must be discussed. There is clinical evidence that myopia can begin between ages 20-30 [47,48]; and when this is the case, in many cases progression continues until university studies are ended. Also, high myopia can continue progressing between ages 30-35 in some cases (clinical observation [62 ]). For this reason, it is difficult to define a convenient age at which the treatment should be stopped, purely on the basis of age. The age of cessation is also important when planning refractive surgery for myopia, and to our knowledge, there is no definite age at which myopia can be considered stable for that purpose. Instead, a retrospective clinical evaluation showing stable refractions for some years in each individual case is generally accepted as a safe condition for the surgery. In the case of atropine treatment, in order to avoid the rebound effects that have been described in the ATOM I study [119], a regimen of 3 days per week could be prescribed instead of daily application, or the concentration could be reduced even further. This is a promising research area.

12. LONG-TERM CONCERNS

As children have long life expectancy, concerns of possible long term effects during adulthood have to be considered. For example, a long lasting treatment with eye-drops might cause early onset cataracts as a result of toxic actions. High myopes are prone to cataracts at an early age, so atropine treatment may complicate the hypothetical problem, and parents have to be informed. As it is practically impossible to perform a trial long enough to investigate the effects of late-life complications, especially when the problem of increasing myopia is so relevant in urban environments, it is easy to understand why a the long-term effects of a treatment such as atropine may be overlooked, simply because it is a welcome alternative to current therapies. In the short term, no toxic adverse effects have been reported, and that should be enough evidence. Nevertheless, patients under treatment should be monitored closely, and informed consent of both parents and the child is of utmost importance.

Atropine use could have long-term cognitive effects too, as it is well known that oral anticholinergic use is associated with transient and reversible deficits in working memory as revealed by several cognitive tests [152, 153]. Recently, the use of oral anticholinergic
medications has been associated with prevalence and incidence of dementia in the elderly population [154, 155]. The oral doses of anticholinergics used for systemic treatment, however, are thousands of times higher than those used in the case of atropine eye drops, so this may not be a concern for this ophthalmological treatment in children. However, it would be interesting to undertake cognitive testing in children under atropine treatment for myopia, because depression has been long been associated with some ocular treatments with drops (such as timolol 0.5% for glaucoma in adults).

13. REGULATORY ISSUES

One of the problems with atropine use is that until it is commercially approved and available, even at low concentrations, clinicians would have to use it off-label and prescribe it to be prepared in compounding pharmacies. Many eye care practitioners are not familiar with these practices, and they may be concerned about this mode of prescription. However, the preparation of atropine is easy and non-expensive: only 2 drops of 1% atropine (commercially available) in 10ml of artificial tears (also commercially available) in a sterile background gives 0.01% atropine drops, and many medications are used off-label or compounded in this way all over the world [156-158]. In addition, off-label treatment is legal and widely used. It is estimated that in some disciplines, including Pediatrics and Oncology, off-label prescriptions are high as 70-90% of all prescriptions, whereas the average off-label frequency in medicine was shown to be about 20% [156, 157]. Off-label treatment should, however, be used only when sufficient basis of experimental support is available. In view of this considerations, it is clear that the amount of literature available on the use of atropine justifies its use as an off-label intervention. The more problematic issue is the use of a compounded drug, since it needs the collaboration with compounding pharmacies [159]. In many countries, however, they are easily available [154].

14. CAN ATROPINE BE USED TO PREVENT THE ONSET OF MYOPIA?

It is clear from the ATOM studies that low concentration atropine decreases the rate of axial elongation and myopia progression in myopic children. Low concentrations of atropine might also decrease the rate of axial elongation in emmetropic children, as was shown in a study that enrolled pre-myopic children in Taiwan [69]. Ocular growth in emmetropic children is very slow during school-years (about 1mm in 10 years). For example, in the Singapore SCORM study, children who remained emmetropic had a mean axial elongation rate of 0.10 mm per year, while children who developed myopia had a mean rate of 0.28mm per year [43]. If the rate of axial elongation can be reduced in emmetropic children, then it could be used for preventing myopia onset. It is also clear that the effective concentration of drug reaching the posterior pole is very low during treatment with 0.01% atropine drops, but yet it is still useful in retarding ocular elongation in myopic children. This treatment is important in the long run, because it might be effective if maintained during many years. If the required amount of drug is so small, perhaps the posology of eye drops to prevent myopia onset in pre-myopic children could be twice or three times a week; research in this area is promising, especially with respect to compliance with such a treatment. In addition, the concentration could be varied seasonally during the year. Several studies showed that myopia progression was faster during the winter season than during the summer times [97, 160-162], and a prospective study in Taiwan already has explored using lower atropine concentrations during summer in myopic children with good results [163].

CONCLUSION

Myopia prevalence is increasing in younger generations of highly developed urban environments, with dramatic increase in high myopia prevalence. This poses a great burden of medical, social, and economic cost that will increase as the population ages because of myopic maculopathy [164]. Any treatment that could arrest myopic progression would be welcome, and many innovative therapies are midway between research and established clinical practice. The main purpose of innovative therapies is to benefit the individual patient; thus, when we have to make a decision to begin a long-lasting treatment with diluted atropine drops we should evaluate the risk factors in an individual patient (Table 4), and look for the commitment of the patient and immediate family when treating a child. For example, evaluation of cycloplegic refractive error is the gold standard to avoid treating accommodative spasms that may simulate myopia in children, and the rare progressive keratoconus cases should be detected before onset of treatment, to avoid confusing them with axial myopia. Risk factors that need to be considered include: high prevalence of myopia in the environment, early age of onset, parental history of high myopia, rapid rate of progression (1 diopter or more per year), low outdoor exposure to ambient light, and high exposure to near work, including reading books and playing hand held electronic devices. In environments with high prevalence of myopia, such as many Asian cities, children could be treated as soon as they are found to have known risk factors for myopia development – such as low myopia, or refractions that have become plano.

Table 4. Risk factors of myopia.

<table>
<thead>
<tr>
<th>Prevalence of myopia in the environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early age of onset</td>
</tr>
<tr>
<td>Parental history of high myopia</td>
</tr>
<tr>
<td>A plano cycloplegic refraction in elementary school years</td>
</tr>
<tr>
<td>A confirmed rapid progression (1 dioptor or more per year)</td>
</tr>
<tr>
<td>Low outdoor exposure to ambient light</td>
</tr>
<tr>
<td>High exposure to near work</td>
</tr>
</tbody>
</table>

As 0.01% atropine seems to be safe and non-toxic at such a dilution, it could also be used daily in progressive myopic university students who have to use near vision for many hours, such as lawyers [75] or engineers [46]. Other innovative treatments such as dual focus or multifocal contact lenses which are beginning to show some effect in slowing myopia progression [165] could be used alternatively or in conjunction with topical treatments. We believe that in environments with high prevalence of myopia and high myopia, such as East and South East Asian countries, public health programs can be of great help in changing refractive prescription patterns (via special lenses and atropine drops) and modifying population habits (increasing outdoor exposure). In this last sense, changing light exposure during classroom time with special architectonic designs is also a promising area of research and treatment [166,167].

Other promising areas of research include comparison of the outcomes with all options and their combinations (special multifocal spectacles or contact lenses, orthokeratology, diluted atropine or outdoor exposure). For example, a recent retrospective study compared orthokeratology and 0.125% atropine showing that both were similarly effective in arresting axial and refractive components of myopia development in Taiwanese children [168]. It would be also interesting to test whether different treatments have additive effects.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.
ACKNOWLEDGEMENTS

Authors thank Prof. Audrey Chia, the Singapore National Eye Center, Singapore for her consent to use the Fig. (3).

METHOD OF LITERATURE SEARCH

We included all available studies on atropine use in myopia treatment, based in PubMed, internet and library search, but analyzed in detail the recent prospective and randomized studies after 2000.

REFERENCES


The Role of Atropine Eye Drops in Myopia Control

Current Pharmaceutical Design, 2015, Vol. 21, No. 32 4729

[100] Smith EL 3rd, Campbell MC, Irving E. Does peripheral retinal input explain the promising myopia control effects of corneal re-shaping therapy (CRT or ortho-K) & multifocal soft contact lenses? Ophthalmic Physiol Opt 2013; 33: 379-84.


[106] Schweinitz G. Diseases of the eye. USA: W. B. Saunders, 1924, ed


