Editorial

An Important Step Forward in Myopia Prevention: Low-Dose Atropine
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The article by Chia et al1 (see www.aaojournal.org/article/S0161-6420(15)00675-2/fulltext) in this issue of Ophthalmology reports 5-year follow-up from the Atropine for the Treatment of Myopia (ATOM) 2 study. ATOM2 now covers a 2-year initial phase using 0.5%, 0.1%, and 0.01% atropine, a 1-year washout period, and a further 2 years of treatment with 0.01% atropine in those who progressed more than 0.5 diopters (D) in the washout year. The article shows that 0.01% atropine produces better reduction in progression than higher doses, with marked reductions in the short-term side effects that required the use of photochromic reading glasses with higher doses and with marked reduction in the rebound effect that is observed during washout after higher doses. Longer-term follow-up is still required, but this represents an important step forward.

Control of myopia progression has become an important clinical goal because of concerns about the significantly increased risks of pathologic myopia in those with high myopia.2 It is clear there has been a major increase in the prevalence of high myopia, as well as in total myopia, in East and Southeast Asia, where the prevalence of myopia is now high (of the order of 80%–90% in those completing high school, compared with 10%–30% 50 to 60 years ago). The prevalence of high myopia has increased over the same period from a few percent to approximately 20%. Although the situation is much less extreme in other parts of the world, increasing myopia prevalence rates have been reported from the United States, Europe, Israel, and even the traditional low myopia outlier Australia. These trends foreshadow a significant increase in the burden of disease associated with high myopia, as the high levels of high myopia seen in young adults spread throughout the adult population.

ATOM2 does not have a good control group, apparently because it was anticipated that the 0.01% group would be the equivalent of a placebo control. Unexpectedly, strong effects on progression were detected, even at this low dose. The control group from ATOM1 is not precisely matched to ATOM2, but taking into account the ATOM1 trial that used 1% atropine, the latest article shows that low-dose atropine eyedrops (0.01%) were more effective than 1%, 0.5%, and 0.1% atropine eyedrops over the medium term in controlling myopia progression in Chinese children. With 0.01% atropine, the side effects of cycloplegia and mydriasis were substantially reduced, and photochromic reading glasses were requested by less than 10% of the participants.

These results consolidate a long history of the use of atropine to control myopia progression. It has been used off-license for many years to control myopia progression, with some ardent advocates, even in the West. But concerns about short- and long-term side effects have led to only limited use. In contrast, in East and Southeast Asia, where the prevalence of myopia and high myopia has been higher for longer, atropine has already been extensively used. In Taiwan, a strong system of referral of new cases of myopia by school nurses to ophthalmologists has resulted in approximately 40% to 50% of myopic children receiving atropine at some stage during childhood. In Singapore, use of atropine has been less extensive, but the results from large trials with longer follow-up have been reported. The ATOM1 and ATOM2 studies have provided convincing evidence of the efficacy of atropine in controlling myopia progression. Concerns about short-term side effects and the rebound effect now seem to have been essentially resolved with low-dose atropine.

Chia et al1 have explained the more effective prevention of progression with the lower doses in terms of what was described in ATOM1 as the rebound effect: more rapid progression in eyes treated with (1%) atropine during the washout period than in untreated eyes.3 A similar rebound was seen in the current article with 0.5% and 0.1% atropine, but little rebound was seen with 0.01%.

It is not clear what underlies the “rebound” effect. The term tends to imply a relatively transient effect, but the enhanced progression after previous treatment with 1% atropine lasts for at least 1 year and possibly even longer. This suggests that there is a need for considerable caution about using higher doses of atropine, with 0.01% atropine now the preferred option.

In this respect, one aspect of the data on 0.01% atropine raises some concerns. The rate of progression in spherical equivalent refraction (SER) in the final 2 years in those children who were treated with 0.01% atropine during that period was −0.86 D, similar to the −0.75 D change seen in the same children in the first 2 years of treatment. Given the progression tends to slow with age, a decline might have been expected, which suggests that exposure to even low-dose atropine might affect long-term regulation of eye growth. However, when looking at the changes in axial length, there is evidence of a marked decrease in progression, from a 0.58 mm increase in axial length in the first 2 years to 0.32 mm in the last 2 years. The lack of parallel between changes in SER can be explained by the reduced rate of loss of lens power with age in children, which means that a given amount of axial elongation translates into a...
larger change in SER as children get older. Thus, the data on axial length suggest that progression is in fact stabilizing, although the absence of a completely matched control group does cloud the interpretation.

Longer-term follow-up is required. It is reassuring that Chia et al report from their clinical experience that myopia does stabilize, and it also reassuring that there are no reports of major problems from Taiwan or Singapore. There should be quite a bit of data available to provide further evidence on this issue. Follow-up of the original ATOM1 cohorts would be most useful. Ophthalmologists in Taiwan, given the extensive use of atropine, should also have considerable opportunity to collect follow-up data. Most of the data will be on 1% atropine, but if 1% atropine is safe in the long-term, then a dose as low as 0.01% should be even safer. Good data on myopia stabilization will make the case for the use of atropine even stronger. But at present, clinical judgment is required to balance the need to avoid high myopia and pathologic myopia against uncertainty about stabilization.

It is unfortunate that the site and mechanism of action of atropine in slowing progression are not known. Although atropine blocks accommodation, this does not seem to be part of the pathway that leads to slowed progression, because atropine blocks axial elongation even when it does not block accommodation. Therefore, it must be acting at another site. Whether this involves reported direct effects of atropine on the sclera or effects on muscarinic receptors in the retina is currently not clear.

Obviously, clinical decisions also require a good knowledge of alternative approaches, and there are several available. Spectacles and contact lenses to slow progression are currently available commercially, but evidence of their effectiveness is both limited and somewhat out of date. They require further validation. At present, of the optical approaches, orthokeratology seems to be the best validated, on a par with low-dose atropine in terms of effect size, but with safety issues, which may limit its use in younger children, in whom the need for control of progression is the most urgent.

More information is also required on how to best target the use of atropine. The recent increasing prevalence of high myopia in East and Southeast Asia is due to incident high myopia, and ultimately pathologic myopia. There also has been considerable progress in preventing the onset of myopia through public health measures involving increased time outdoors, which could provide a less-invasive alternative. The effectiveness of this approach has been demonstrated in clinical trials, and large-scale implementation is under way in Taiwan, in combination with the use of atropine to slow progression. It is not clear whether increased time outdoors also slows progression and onset, and so far, direct longitudinal epidemiologic evidence does not support the idea. But studies on seasonal variations in progression rates, which can be marked, suggest that the possibility should not be dismissed.

There is one further issue that needs attention. Almost all recent studies on atropine have been carried out on children of Chinese origin, and it is well known that cycloplegia is more difficult in children with darker irises. Conversely, it is likely that the concentrations of atropine that are optimal in Chinese children may be too strong for use with children with light colored irises, at least in relation to the side effects. So a good trial with children of European ancestry is a significant priority.

The article by Chia et al makes the case stronger for the use of low-concentration atropine eye drops to control myopia progression. Until the questions around longer-term stabilization are resolved, use of atropine for controlling progression of myopia will require clinical judgment about the risk—benefit balance, but this article brings us one important step closer to safe control of myopia progression, high myopia, and ultimately pathologic myopia.

References


Footnotes and Financial Disclosures

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