Myopia prevention: Newton is still right

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"What we know is a drop; what we don't know is an ocean."
—Isaac Newton

Myopia is a significant global public health issue. Nearly 100 million children and 1.5 billion people worldwide are myopic, with a prevalence rate approaching 70%-80% in parts of Asia. Although decreasing the likelihood of glaucoma, retinal detachment, and myopic retinopathy in adulthood are important goals of myopia prevention, quality of life, convenience issues, and long-term costs are also important factors for patients as well.

In the previous issue of the *Journal of AAPOS*, Yi and colleagues[1] report that daily instillation of atropine 1% to both eyes in children with −0.5 D to −2.0 D of myopia is effective in preventing myopic progression and axial elongation, and improving unaided visual acuity. Given the large body of work on atropine for myopia prevention, their results are not surprising. Although there are several limitations to their study, the general conclusion are consistent with what one would expect from the existing literature on the topic. It would have been ideal to ensure that both eyes of each subject were fully cyclopleged prior to measurement of uncorrected acuity. Formal measurement of compliance via chip-embedded bottle caps is a more accurate method. Uncontrolled or as needed bifocal use is not advised in pharmacologic myopia prevention trials to avoid any confounding influences. Formal standardized assessment of adverse effects using a validated instrument would have been ideal. Finally, rather than reporting only mean refractive data, results could have been analyzed via criterion progression, that is, reporting how many subjects in each group progressed by more than −0.5 D, −1.0 D, or −1.5 D over the study period.

Presumably all of the subjects in this study had dark irides. Side effects of topical atropine 1%, a nonselective muscarinic antagonist, become much more bothersome in blue-eyed children. This is one of the major reasons why other methods of myopia prevention, both pharmacologic and nonpharmacologic, have been pursued. Unfortunately, though in some cases *statistically* significant, results of trials with bifocals, progressive addition lenses, contact lenses, and topical timolol have not yielded consistently *clinically* meaningful or generalizable results.[2] Thus, the most notable pharmacologic trials over the past decade have focused on lower concentrations of atropine and more selective M1-receptor antagonists, both of which should produce less cycloplegia and mydriasis than atropine 1%.

Chia and colleagues[3] demonstrated effectiveness of 0.5% and 0.1% atropine in retarding myopic progression. They included an atropine 0.01% arm as well, which was originally intended as a control group, but to their surprise, was found to be nearly as effective as the higher concentrations (myopic progression of −0.49 D vs −0.30 and −0.38 D); in addition, this dose was associated with a smaller rebound effect after treatment was discontinued.[4] As expected, near visual acuity was not significantly impaired at this dose. Pirenzepine is a fairly selective M1 receptor antagonist which similarly produces less cycloplegia and mydriasis than atropine 1%. Although Yi and colleauges[1] state otherwise, this has been studied in two randomized controlled clinical trials in the US and Singapore.[5,6] In the US study, myopic progression was reduced to −0.25 D after 1 year compared to −0.53 D in the control group, with only 4% dropout due to excessive antimuscarinic effects in a population of approximately 40% light-eyed individuals. There was a two- to threefold increase in the percentage of subjects progressing more than −0.50 D or −0.75 D after 1 year in the treated group and almost a tenfold difference for those progressing more than −1.0 D. The Singapore study showed a 1-year progression rate of −0.47 D versus −0.94 D in the placebo group.

Other potential future treatments might target dopamine, which has been shown to inhibit axial elongation in form-deprivation myopia in animals,[7] and all-*trans* retinoic acid, which affects the relationship between choroidal thickness and refractive state and thus could modify the signaling processes in ocular growth.[8] Sub-Tenon's injection of agents to promote collagen polymerization and scleral reinforcement may show future promise as well.[9,10] Recently, increased time outdoors has also been shown to decrease the likelihood of developing myopia.[11,12]

So why is myopia prevention pursued so rarely by the majority of doctors who care for children's vision? Newton's words ring true—our knowledge base remains woefully inadequate, for two primary reasons. The first of these reflects the inherent difficulties in conducting clinical trials for myopia prevention. Due to the temporal profile of the condition, to truly expand our knowledge, trials must be very long—5 years or more—and designed with drug holidays to examine rebound effects. Hence they are plagued by difficulties with patient recruitment, retention, and compliance. The financial impact of such trials is enormous, and, for new drugs, further complicated by patent expirations just when regulatory approval and marketing would begin. Furthermore, the additional safety

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mechanisms in place for pediatric trials also affect recruitment and trial conduct, as well as cost. This obviously makes new drug development less enticing, but even if we assume that atropine 0.01% is the best agent, we remain ignorant about many factors important for clinical use: At what age, refractive error, or family history should intervention begin? What is the best dosing frequency and duration? Should it be given as a drop, a gel, or via a sustained-release device periocularly or via contact lens? When does rebound progression cease to become a factor after drug discontinuation? What factors are important in minimizing long-term ocular complications in adulthood?

Newton's words also apply for another, more fundamental, reason. Truth be told, we really don't know that much about the biochemical, cellular, and molecular processes responsible for progressive myopia. For example, for years prolonged accommodation was felt to be the likely etiologic culprit. But the fact that a selective muscarinic antagonist like pirenzepine, which relatively spares accommodation, was effective places this theory in doubt, as do a number of epidemiologic studies. Atropine is clearly effective, but we don't know whether the primary site of action is the sclera, the retina, the choroid, or all three. Is the effect of time outdoors related to peripheral retinal focus, less accommodation, or light-mediated dopamine release? What part of the electromagnetic spectrum is most related to myopic progression? How much can environmental factors override both known and as yet unknown genetic causes?

If it seems as though there is a long way to go before prevention of myopia becomes clinically commonplace, we can remember this: in the mid-17th century, we had no laws of classical mechanics, no concept of universal gravitation, no binomials or calculus, and no practical reflecting telescopes. Most scientists did not believe that light was comprised of particles, and some were still convinced that the universe was geocentric. By the end of the century, Isaac Newton had changed all of that. Let us hope that we are on the verge of another such revolution in the myopia world.

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