Editorial

What Is Next in Amblyopia Treatment?
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Occlusion of the preferred fixing eye has been a mainstay of amblyopia therapy for centuries. Credit for initially suggesting this treatment often has been given to the French polymath George Louis Leclerc, Count de Buffon (1743). However, evidence exists to suggest that attribution should go to Thabit ibn Qurra, who, although he was a Sabian and born in Harran (Turkey), was invited to join the illustrious scientific group residing in Baghdad in the second half of the 9th century. It should be emphasized that both these authors restricted their discussions to the patient with strabismus and strong fixation preference of the fellow eye. It is not clear whether their primary goal was to improve visual acuity in the deviated eye or to improve its alignment. After all, we should recall that beginning with Paul of Aegina (625–690), various forms of facial masks were devised to “force” the patients with strabismus to realign their eyes by looking through appropriately located holes in the mask. Patching may have been a logical extension of this type of approach to ocular misalignment.

In any case, occlusion (or pharmacologic penalization) of the nonamblyopic eye has proven to be an effective treatment for both anisometropic and strabismic amblyopia, although it is sometimes unnecessary in treating anisometropic amblyopia. However, there are patients who do not comply with treatment, who fail to respond to treatment, or who do not experience a complete recovery of normal vision in the amblyopic eye despite complying with the treatment. As a result, clinicians have studied numerous adjunct or alternative therapies for treating amblyopia. Some, but not all, of these therapies have been based on a reasonable understanding of the physiology of amblyopia, as it was perceived at the time, although in hindsight some seem extraordinary if not quixotic (e.g., subcutaneous strychnine).

During my career, 2 promising therapies that were enthusiastically endorsed and used widely by clinicians did not prove to be efficacious after careful study: pleoptics and the CAM visual stimulator (Clemente Clarke International, Harlow, England). Linksz first suggested that in cases of amblyopia with eccentric fixation one would encourage the anatomic fovea to resume fixation superiority if one dazzled the anatomic fovea with light while shielding the site of eccentric fixation. Pleoptic therapy was popular and widely used for 2 decades, but it is rarely used now because it did not prove to be superior to standard occlusion therapy. The use of rotating high-contrast square wave gratings to stimulate the amblyopic eye was pioneered by clinicians and scientists at the University of Cambridge. The rationale for such stimulation was based on the plausible theory that “to activate fully the entire population of visual neurons in the visual cortex a range of different spatial frequency gratings covering all orientations should be used.” Regrettably, well-controlled studies subsequently demonstrated that any visual acuity improvement that occurred in the amblyopic eye treated by this method could be accounted for by the effect of the short-term occlusion of the fixing eye during visual stimulation rather than the unique nature of the stimulation of the affected eye.

The fact that the neurotransmitter dopamine is involved in several different visual functions and that brain dopamine levels can be supplemented by a commercially available medication (levodopa) prompted some investigators in the 1990s to begin studying whether levodopa treatment for amblyopia was effective. The precise way in which levodopa therapy might improve function in the amblyopic eye has never been detailed despite its use in clinical studies of varying size and quality over the past 25 years. There is no evidence of a deficiency of dopamine in amblyopic brains. Some have suggested that levodopa treatment might enhance experience-dependent plasticity of the visual cortex. This thesis is based on animal studies that demonstrate that the N-methyl-D-aspartate receptor-1 subunit is involved in maintaining visual cortex plasticity and that activation of the dopamine receptors increases MMDRA-1 expression. However, in studies of strabismic cats, it appears that the reported changes in N-methyl-D-aspartate receptor-1 subunit expression in these animals may correlate with the experimentally induced strabismus rather than the changes in eye dominance or presence of amblyopia. The suggestion that levodopa therapy for amblyopia might be effective at the retina level rather the cortex seems highly unlikely. Although it is well established that dopamine is an important neurotransmitter in amacrine cells of the mammalian retina, there is no convincing evidence to suggest that alterations in the neural retina play a major role in the pathophysiology of amblyopia.

Currently, the decision whether to use levodopa as an adjunct therapy for amblyopia must be based on the clinical evidence of its efficacy. Unfortunately, the clinical studies of levodopa therapy for amblyopia do not provide definitive guidance: varying degrees of acuity improvement (including no improvement) have been reported. Many of the
reported studies have been small, short-term, or designed without appropriate controls. Even the studies that have reported that patching therapy augmented by levodopa results in a statistically significant improvement in visual acuity in the amblyopic eye, compared with patching therapy alone, have not shown that the effect is clinically robust. A meta-analysis of 4 randomized placebo-controlled studies found levodopa therapy to result in only a mean improvement of 1.1 logarithm of the minimum angle of resolution lines.32

Because of the uncertainty of whether adjunct therapy with levodopa provides significant clinical benefits in the management of amblyopia, the Pediatric Eye Disease Investigator Group has conducted a randomized, multiple-center, placebo-controlled trial in children aged 7 to 12 years with residual amblyopia (20/50–20/400) after patching treatment.33 A total of 139 children were randomly assigned to receive either oral levodopa 0.76 mg/kg with carbidopa 0.17 mg/kg or a placebo 3 times per day. The nonamblyopic eye was patched 2 hours per day in all participants during the 16 weeks of therapy. The results are noteworthy and require emphasis. There were no differences in mean visual acuity, adjusting for baseline visual acuity, between levodopa and placebo groups at the 4-, 10-, and 16-week interim visits. Any improvement in visual acuity in the levodopa group could be accounted for entirely by the effect of the concurrent patching treatment. This is a relatively large study that was conducted over a significant period of time. It is a well-designed placebo study strengthened by the participation of multiple centers. In reference to levodopa as an adjunct therapy for the treatment of amblyopia, it should persuade us that it is time to move on. Twenty-five years of study has not produced a convincing body of data to justify its clinical use as it has been used in amblyopia treatment.

Make no mistake, there remains plenty of work to be done to improve our treatment of amblyopia. The Pediatric Eye Disease Investigator Group is to be commended for its careful studies that have emphasized the efficacy of penalization therapy and brief periods of patching in the management of amblyopia. They have also reminded us that amblyopia therapy may be effective in certain older children who might have been considered too old to treat. Many of us have modified our protocols for treating amblyopia as the result of these studies. However, the question remains unanswered whether there are fundamentally different approaches to the treatment of amblyopia that might be more efficacious and efficient than patching or pharmacologic penalization.

Recently, a radically new theory of amblyopia has suggested that it is primarily a binocular rather than a monocular disorder.34 As a result, investigators have suggested that amblyopia might be effectively treated by promoting binocular summation by having the patient dichoptically view video games.35 Other investigators have proposed that perceptual training and transcranial random noise stimulation can improve visual acuity in amblyopia even in an adult.36,37

These suggestions deserve careful study and scrutiny. Yet, let us not forget the lessons learned from the use of pleoptics, the CAM stimulator, and levodopa therapy. Well-designed controlled studies of all new amblyopia therapies should be completed before such therapies are widely accepted into clinical practice.

It is essential that we recognize that the neural mechanisms of the various forms of amblyopia are not yet completely understood despite many enlightening anatomic and electrophysiologic studies in animal models and neuroimaging techniques in humans. Clinical studies of novel approaches to the treatment of amblyopia are welcome and should be encouraged. However, further defining the precise neural mechanisms at play in the various forms of amblyopia should be one of our highest priorities. Perhaps by doing so, sound alternatives to patching therapy will be developed that will improve our outcomes in the treatment of amblyopia.

References


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