Updates in Amblyopia Treatment

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Introduction

Amblyopia is a common visual disorder that affects 2-4% of the population. It is the leading cause of visual impairment in children, with as many as 800,000 preschoolers at risk in the United States alone. As many as half of these children are estimated to escape detection before reaching school age. Patients with amblyopia are at greater risk of losing vision in their better-seeing eye: three times that of a non-amblyopic adult, and 17 times that of a non-amblyopic child. If amblyogenic factors are diagnosed and treated early, it can be prevented and thus potentially lessen amblyopia from being a public health issue.

What is Amblyopia?

Amblyopia is defined as the reduction of best-corrected visual acuity associated with an early history of abnormal visual experience. This abnormal visual experience may arise from amblyogenic factors such as unilateral strabismus, image degradation via anisometropia or high refractive error, or form deprivation, such as from a cataract. Strabismus and anisometropia are the most common causes of amblyopia. If left untreated, these amblyogenic factors hinder normal visual development in the primary visual cortex (V1) and extra-striate areas during a susceptible, or critical, period of maturation. Therefore, development of amblyopia usually occurs when a patient is young. It is far less likely to develop when a patient is of adult age.

While there are amblyogenic risk factors, realize that there is no definitive clinical test for amblyopia. Amblyopia is a diagnosis of exclusion. The reduction in vision cannot be attributed to pathology in the eye or visual pathway. However, amblyopia may coexist with ocular disease, such as with optic nerve hypoplasia or congenital cataracts.

How is Amblyopia Currently Treated?

Monocular deprivation, using occlusion therapy, e.g., patching or use of filters, or pharmacological penalization, has been the mainstay of amblyopia treatment for many years. The primary goal of monocular deprivation is to force the use of the amblyopic eye by obstructing the vision in the fellow, better-seeing eye. Over the past few decades, the
Pediatric Eye Disease Investigator Group (PEDIG) has carried out a series of clinical trials - many of which are randomized, the Amblyopia Treatment Studies (ATS), to evaluate the management of amblyopia.\(^9\)

Based on the findings over several ATS, a staged approach is recommended for treating amblyopia:

1. Prescribe optical correction only, with the optimal prescription.
2. If amblyopia persists after the patient has worn optical correction for approximately ten weeks, start occlusion therapy – two hours daily for mild to moderate amblyopia, and six hours daily for severe amblyopia.
3. If amblyopia persists after the patient has undergone occlusion therapy for ten weeks, increase the amount of occlusion to six hours daily.
4. Once the maximum visual acuity has been achieved in the amblyopic eye, monitor the patient for recurrence – approximately once every six to eight weeks.

**What to Prescribe?**

No set guidelines exist for prescribing for patients with amblyopia. However, it is recommended that patients with amblyopia undergo both objective and subjective procedures under non-cycloplegic and cycloplegic conditions to determine their refractive errors.\(^7\)

Clinicians may choose from several diagnostic cycloplegic agents available. However, for the purpose of determining an accurate refractive error in patients with amblyopia, 1% cyclopentolate is often the drug of choice. Cyclopentolate ophthalmic solution offers a similar cycloplegic effect to atropine, but has a faster onset and shorter duration of action. It also achieves a longer clinically-effective cycloplegic effect than 1% tropicamide, and may reveal more latent hyperopia since it results in less residual accommodation.\(^10\)

If the amblyopia is due to myopia or high astigmatism, these patients will likely benefit from wearing their full refractive correction.\(^7\) This is particularly true for patients with oblique astigmatism, as this may place these individuals at elevated risk for amblyopia.\(^11\) A symmetrically reduced prescription may be considered for patients with amblyopia due to high isometropic hyperopia.\(^11\) Though it may be prudent to limit the amount of undercorrection of the hyperopic refractive error to two diopters or less; cutting the hyperopic correction by greater than that may induce an esodeviation. On the other hand, if these patients also exhibit an eso-ocular posture, it may be beneficial to prescribe the full amount of hyperopia. Moreover, a near-addition may be considered for patients found to have high accommodative convergence to accommodation ratio (AC/A). In patients with anisometropia, it is advisable to correct the full difference in spherical and cylindrical refractive errors, and to correct the amount of myopia or hyperopia according to age.\(^11\)

**How Much Improvement Can be Expected with Optical Correction Alone?**

In one randomized clinical trial by PEDIG involving 84 children between the ages of 3 to less than 7-years-old who had severe untreated anisometropic amblyopia, 77% of the patients showed improvement in visual acuity of at least two lines with the use of optical correction and no patching. In addition, amblyopia was determined to have resolved in approximately one-third of the patients. About 30 weeks were required for stabilization criteria to be met. This criteria consisted of lack of improvement in acuity measured across two visits spaced five weeks apart.\(^12,13\)

These results were also reported in a multi-center cohort study by PEDIG consisting of patients of similar age, who had untreated strabismic or strabismic-anisometropic amblyopia. These patients were also treated with optical correction alone. Similarly, approximately three-fourths of the patients showed improvement in visual acuity of at least two lines. Furthermore, amblyopia was considered resolved also in one-third of the patients.\(^14\)

A subsequent study by PEDIG investigating binocular visual acuity improvement in children 3 to 10 years of age with bilateral amblyopia showed approximately a four-line improvement in binocular visual acuity after one year...
with the use of optical correction alone. In addition, three-fourths of these patients had a binocular visual acuity of at least 20/25 within the one year.

Taken together, these findings suggest that approximately three-fourths of patients experience at least a two-line improvement in acuity with the use of optical correction alone.\(^{15}\)

**When Should Occlusion Therapy be Initiated?**

If improvement in acuity appears to stall and a crowding effect remains, suggesting that additional improvement can be made, one can start occlusion therapy. According to PEDIG's protocol, improvement in visual acuity may be considered to have plateaued if there is no change measured over two visits spaced five weeks apart.

**How Many Hours Should a Patient Perform Patching?**

In all, evidence suggests that patients with mild and moderate amblyopia patch for two hours a day. Patching for this amount of time yielded similar outcomes in visual acuity for patients with these severities of amblyopia, compared to patching for six hours a day. Mild amblyopia is defined as visual acuity of the amblyopic eye better than 20/40, and moderate amblyopia is defined as visual acuity between 20/40 and 20/100.\(^{2,16}\) For patients with severe amblyopia - visual acuity worse than 20/100 - patching for six hours per day is recommended. Results from PEDIG showed this amount to be equivalent to full-time patching \(^{\text{Table 2}}\).\(^{17}\)

**How Does Patching Compare to Atropine, or the use of a Bangerter Filter?**

The use of 1% atropine was found to yield similar improvements in visual acuity as patching when comparing treatment outcomes in children both 3 to 7 years old and ages 7 to 12 years old with moderate amblyopia.\(^{18}\) Improvement appeared to be maintained at two years after the six-month treatment had been discontinued, although residual amblyopia of a two-line interocular acuity difference was common (average amblyopic eye acuity \(\sim\)20/32).\(^{19}\) The use of atropine on the weekends only appeared to have an equivalent treatment effect as compared to its use every day.\(^{20}\) Like atropine, the use of a Bangerter filter – a transparent filter that degrades the visual acuity in the fellow eye – appeared to be equivalent to patching in treatment of moderate amblyopia in children.\(^{21}\)

In comparing ease of treatment between patching, atropine and use of a Bangerter filter, the burden of treatment was evaluated by PEDIG using the Parent and Child Amblyopia Treatment Index (ATI) survey. This 20-item questionnaire was used to compare adverse effects, compliance and social stigma of treatment.\(^{22}\) Treatment compliance seemed to be higher with both atropine and Bangerter filter use as compared to patching, and there were less perceived adverse effects and social stigma.\(^{21,23}\) Anecdotally, atropine may also be more appealing since it is relatively inconspicuous, and there is no concern of its removal, sensitivity to adhesive, or peeking around it as there is with use of a patch. For more comparison of the pros and cons of atropine versus patching, please see \(!Table 3\).\(^{3}\)

**What if Patching for Two Hours a Day is Insufficient?**

For residual amblyopia that remains after patching for two hours a day, increasing the duration of patching to six hours a day may yield additional improvement. PEDIG conducted a randomized trial involving 169 children with residual strabismic or anisometropia amblyopia. Pre-randomization, these patients performed two hours of daily patching for 12 weeks. However, they showed no improvement in visual acuity between two visits at least six weeks apart. Some of these children then continued to patch for two hours daily, others were randomly assigned to increase their patching to six hours a day. After ten weeks, increasing the duration to six hours daily yielded
approximately another one-to-two-lines of improvement. In the six-hour group, 40% showed two or more lines of improvement, as compared to less than 20% in the two-hour group.

**What About Regression?**

Fortunately, the majority of patients undergoing amblyopia treatment will maintain their improved visual acuity. Assessment of visual acuity stability over one year in 80 children with moderate or severe amblyopia reveals that 82% were able to maintain improvement in acuity of two or more lines. Only 7% showed regression of acuity of two or more lines. However, subsequent investigations have shown recurrence of amblyopia to be closer to 25%. There are a number of factors that may place a patient at risk of experiencing regression after discontinuing treatment, including:

- Older age when starting treatment
- Greater magnitude of visual acuity improvement, i.e., better acuity at the end of treatment
- Prior history of recurrence
- Initial refractive error: moderate to high hyperopia, or initial anisometropia
- Early-onset esotropia

The latter two factors, moderate to high hyperopia and early-onset esotropia, suggest that amblyopic patients with infantile esotropia syndrome or accommodative esotropia are more likely to experience recurrence.

Surprisingly, PEDIG investigations show little impact between ocular posture, stereoacuity and age, and recurrence of amblyopia. That is, patients who were heterotropic, microtropic and orthotropic (phoric) were just as likely to experience a return in their amblyopia. Excellent stereoacuity also was found to offer no protection against recurrence. And, recurrence rate was similar amongst children of different age groups. In other words, younger children appeared to experience recurrence of amblyopia at a similar rate to older patients. This speaks against clinical dogma that after a certain age, amblyopia treatment can be safely discontinued with minimal risk of recurrence.

**Older Children and Adults May Benefit From Amblyopia Treatment, Too.**

Conventionally, amblyopia treatment has been reserved for children. However, in more recent years, there has been mounting evidence supporting the effectiveness of amblyopia treatment in patients older than 12 years of age. PEDIG showed that amblyopia could be successfully treated in patients at least up to 17 years old. In their cohort of 507 patients with moderate to severe amblyopia, approximately 25% showed improvement in visual acuity with optical correction alone. Subsequent patching may also result in additional gains. Khan, et al., also showed that two to four hours of occlusion therapy per day could improve visual acuity in their study population of 61 patients, ages 12-30 years old, with anisometropic amblyopia. In their study, over half of the patients showed a post-treatment visual acuity of 20/20, and almost a quarter showed a post-treatment acuity of 20/25. Thus, amblyopia treatment may benefit patients beyond what has been previously considered to be the “sensitive period.” This also provides evidence that the brain and visual system possesses significant neural plasticity in adulthood.

**What Treatment Directions Show Promise?**

The following treatment directions – perceptual learning tasks, videogame play, binocular dichoptic training, and direct stereoacuity training – have shown favorable results in small-scale studies. However, it should be noted that these treatment modalities are not yet available for use in clinical settings.

*Monocular perceptual learning tasks and videogame play may also effectively treat amblyopia.*

One treatment paradigm that shows increasing promise is perceptual learning (PL). Psychologist Eleanor Gibson, who is often known for her “visual cliff” experiments, defined perceptual learning as “any relatively permanent and
consistent change in the perception of a stimulus array following practice or experience with this array.” In the context of amblyopia treatment, perceptual learning refers to the concept that practicing certain visual tasks can lead to long-lasting improvements. This is considered to be a form of neural plasticity, and its outcome appears to be independent of age. In PL, subjects are learning how to make the amblyopic visual system more efficient by making better use of more important cues and ignoring extraneous visual noise. PL tasks are generally targeted, intensive and supervised with feedback. They require the active attention of the visual system, rather than depending on passive daily life experiences.

The fact that active visual attention is important in amblyopia treatment is not new; it is a concept that has been used in clinical practice for many years. It has also been used in optometric vision therapy for patients with amblyopia and other active monocular and binocular amblyopia treatment therapies. However, in this case, visual stimulation is provided through a different medium.

But, there are limitations to PL tasks. First, they tend to be specific: training on one task may not necessarily transfer to performance on related tasks. Training for contrast sensitivity detection, crowding and stereoacuity has been shown to have some positive effects on visual acuity in patients with amblyopia. However, this transfer of learning may be incomplete. It may be particular to the orientation of the trained stimulus. In addition, PL tasks tend to require thousands of trials. Subjects may find these tasks boring and repetitive, which leads to decreased motivation and poorer compliance.

Videogames, on the other hand, aim to overcome these limitations. They tend to be engaging, immersive and, like PL tasks, require high levels of visual discrimination. In adults with normal vision, they have been shown to enhance visual attention. Recent studies have shown that PL tasks and videogame play may be more efficient than patching in recovering vision: 120 hours of occlusion has been shown to be needed for one line of improvement in visual acuity, whereas only 20-40 hours are needed with videogame play and monocular PL tasks.

While certainly some improvement in vision is due to patching, studies suggest that patching with the visual demand associated with videogames gives an extra benefit in terms of improving visual acuity. For example, Li, et al., showed in their study utilizing a crossover experimental design that the visual acuity improvement is not simply due to occlusion therapy. In the first phase of their study, seven adults with amblyopia were asked to perform visually demanding activities such as reading a book, knitting, surfing the Internet or watching television while wearing a patch. Their acuity was measured after 20 hours and compared to that measured from a group of nine adults with amblyopia who played videogames while also wearing a patch for the same amount of time. The group who performed patching while performing visually demanding activities showed no significant change in visual acuity, whereas the group who played videogames for the same length of time showed significant improvement in visual acuity. This suggests that the improvement in visual acuity seen with monocular PL and videogame play may be due to more than just the treatment effects from occlusion.

**Binocular dichoptic (antisuppression) training may also provide effective amblyopia treatment.**

Classically, amblyopia has been considered a monocular condition. However, binocular imbalance and inhibition, suppression and impaired binocular vision are also considered important characteristics of amblyopia. Targeting these first in amblyopia treatment via binocular dichoptic training, rather than after occlusion therapy, may better address a number of decreased visual functions affected with amblyopia. This treatment modality has also shown to be effective in remedying visual acuity.

Binocular dichoptic training involves presenting a separate image to each eye simultaneously, using a mirror haploscope, a head-mounted video display like the Oculus Rift, or an iPad. This aims to equilibrate the visual
information sent from each eye. For example, the better-seeing eye may receive an image with reduced contrast or blurred detail to match what the amblyopic eye perceives. Like PL tasks, binocular antisuppression therapy, such as red-filter or red-green anaglyphic activities, is not new and has also been used clinically in optometric vision therapy for patients with amblyopia. The use of electronic aids, on the other hand, provides newer mediums for which therapy may be delivered.

For example, Hess et al. has reported improved binocular vision function in their subjects who have undergone binocular dichoptic training one hour a day, four to six days a week, for four to six weeks. Stereaoctuity and monocular visual acuity were also found to independently improve. Interestingly, age and type of amblyopia appeared to have no impact – positive or negative – on treatment outcome. Furthermore, they report that no patients reported experiencing diplopia post-therapy. In addition, Birch et al. have also reported in their study involving 50 preschool children with amblyopia, that binocular dichoptic iPad games using red-green anaglyphic glasses are effective in improving visual acuity. Approximately one line of Snellen acuity improvement - 20/54 to 20/44 - was found after four weeks of iPad play, four hours a week (therefore, 16 hours of iPad play in total). However, they reported no significant improvements in stereoacuity.

Conclusion

Overall, amblyopia is a common vision disorder that, if left untreated, can result in visual impairment. The Amblyopia Treatment Studies conducted by PEDIG have provided evidence to guide monocular treatment paradigms used in current clinical practice. These include the amount of visual acuity recovery expected with the use of optical correction alone, comparison of patching to atropine and Bangerter filter use, patching dose and frequency, and factors that may cause a patient to be more susceptible for regression.

Furthermore, recent research provides promising evidence supporting the efficacy of perceptual learning tasks, videogame play, and binocular dichoptic antisuppression activities in recovering acuity and other binocular functions in patients with amblyopia. In addition, there is mounting evidence that amblyopia treatment can be beneficial in older patients who have surpassed their “critical period” of visual development. Although these newer treatment directions are not yet approved for widespread clinical use, they show potential for possible use in the future.

Disclosures:

The author has no commercial or financial disclosures.

Table 1: Factors that may give rise to amblyopia.

<table>
<thead>
<tr>
<th>Strabismus</th>
<th>Unilateral Constant or high frequency intermittent</th>
<th>Often associated with esotropia Rarely associated with intermittent exotropia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractive</td>
<td>Anisometropic</td>
<td>Myopia &gt;-3.00D Hyperopia &gt;+1.00D Astigmatism &gt;1.50D</td>
</tr>
<tr>
<td></td>
<td>High isoametropic</td>
<td>Myopia &gt;-8.00D Hyperopia &gt;+5.00D Astigmatism &gt;2.50D</td>
</tr>
<tr>
<td>Stimulus or form deprivation</td>
<td>Along visual axis</td>
<td>e.g., ptosis or surgical lid closure, corneal opacities, cataract</td>
</tr>
<tr>
<td>* May have secondary eso- or</td>
<td>Along visual pathway</td>
<td>e.g., coloboma, optic nerve atrophy</td>
</tr>
</tbody>
</table>
Table 2: Recommendations for patching based on findings from PEDIG’s Amblyopia Treatment Studies. 12, 16, 17

<table>
<thead>
<tr>
<th>Mild amblyopia</th>
<th>Moderate amblyopia</th>
<th>Severe amblyopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better than 20/40</td>
<td>20/40 to 20/100</td>
<td>Worse than 20/100</td>
</tr>
<tr>
<td>2 hours daily</td>
<td>2 hours daily</td>
<td>6 hours daily</td>
</tr>
</tbody>
</table>

Table 3: Pros and Cons of Atropine versus Patching. 18, 21-23

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atropine</strong></td>
<td><strong>Only works for certain clinical profiles</strong></td>
</tr>
<tr>
<td>• No option to remove</td>
<td>• Stinging on instillation</td>
</tr>
<tr>
<td>• Better compliance once drops are in</td>
<td>• Use of a pharmaceutical</td>
</tr>
<tr>
<td>• No occlusion of light</td>
<td>• Side effects possible</td>
</tr>
<tr>
<td>• Less social stigma</td>
<td>• May need ADD Rx</td>
</tr>
<tr>
<td><strong>Patching</strong></td>
<td><strong>Social stigma</strong></td>
</tr>
<tr>
<td>• Does not involve pharmaceuticals</td>
<td>• Poor compliance: e.g., peeking; remove /lose patch</td>
</tr>
<tr>
<td>• No light sensitivity</td>
<td>• Skin sensitivity to adhesive</td>
</tr>
</tbody>
</table>

References


CE@Home January/February Questions
"Updates in Amblyopia Treatment,"
by Debora Lee Chen, OD

Answer the following 10 questions to the best of your ability. To receive CE credit, please fax in your answers to 916-448-1423 or mail them to California Optometric Association, Attn: CE, 2415 K Street, Sacramento, CA 95816. Answers are due March 15, 2016. Test submissions are entered every Friday; transcripts are available every Saturday morning.

1. The prevalence of amblyopia is approximately than 2% to 4% of the population.
   a. True
   b. False

2. If left untreated, which of the following factors may lead to development of amblyopia? (For the refractive errors listed, please assume that they were determined under cycloplegic conditions.)
   a. OD -5.00DS, OS -6.00DS
   b. Intermittent alternating exotropia
   c. OD +4.00DS, OS +1.00DS
   d. OD -1.00 -0.75 x180, OS -1.50 -1.25 x180
   e. b and c

3. When treating amblyopia, it is recommended to start with optical correction and patching of the non-amblyopic eye for four hours a day.
   a. true
   b. false

4. In the Amblyopia Treatment Studies, approximately how many patients were shown to have a two or more line improvement in visual acuity using optical correction alone?
   a. ~25%
   b. ~50%
   c. ~75%
   d. ~90%

5. How many hours of patching per day are recommended for a patient who has a best-corrected visual acuity of 20/60 in the amblyopic eye?
   a. Two hours daily
   b. Four hours daily
   c. Six hours daily
   d. Not enough information

6. What is one benefit of atropine use over patching for amblyopia treatment?
   a. It is painless and does not sting
   b. It involves the use of pharmaceuticals
   c. Less social stigma
   d. There are no side effects

7. Which of the following factors place a patient at risk for experiencing regression of visual acuity?
   a. Constant alternating exotropia
   b. Greater magnitude of visual acuity improvement
   c. Poor stereoacuity
   d. b and c
   e. None of the above

8. Amblyopia treatment has been proven to be ineffective for patients older than 12 years of age.
   a. True
   b. False

9. Which of the following are considered limitations to perceptual learning tasks?
   a. They tend to be specific
   b. They tend to require high levels of visual discrimination skill
   c. They tend to be repetitive, which may decrease compliance
   d. a and b
   e. a and c

10. The gains in visual acuity seen from monocular perceptual learning tasks and videogame play are likely due to patching, and not due to any additional treatment effects.
    a. True
    b. False