Advances in Amblyopia: What Have We Learned From PEDIG Trials?

abstract

Amblyopia is the most common cause of preventable visual loss in children. This article reviews treatment options, durations, and efficacy in randomized multicentered trials conducted by the Pediatric Eye Disease and Investigator Group in the last decade. Parents and patients should be counseled that many forms of treatment are efficacious, allowing the option of choice of best-tolerated treatment method. Compliance is key to successful treatment. The course of treatment is likely at least 6–12 months, with yearly follow-up suggested once amblyopia has been treated to monitor for regression. Pediatrics 2013;131:1–8
Amblyopia is the most common cause of monocular visual loss in children and young adults with an incidence of 1% to 3.5% in developed countries. This visual disorder is potentially reversible if detected and treated at a young age. Amblyopia is the reduction in visual acuity attributable to neurologic deficits in the visual output of an eye. It is caused by inhibition of neurologic signals in the visual pathway of the amblyopic eye by the fellow eye during visual development. The inhibition results in anatomic changes visible in the lateral geniculate nucleus and in the occipital cortex. The areas in these structures receiving signal from the amblyopic eye are reduced in volume, as are binocularly driven cells in the occipital cortex. Amblyopia results from any etiology that creates a disparity in the vision from each eye. The most common causes of a visual disparity resulting in amblyopia are refractive error (a need for glasses), strabismic (ocular misalignment), other pathologies that occlude the visual axis, or a combination of these etiologies. Strabismic and refractive etiologies account for 90% of all amblyopia. Plasticity in the neurologic structures allows reassignment of the pathways from the amblyopic eye to the fellow eye, resulting in the visual deficit. This phenomenon only occurs during a sensitive time period from birth to ~6 to 8 years of age, called the critical window of visual development. Treatment within the critical window can also restore the vision to the amblyopic eye by altering the visual pathways. The neurologic pathways are more susceptible to treatment earlier in the critical window.

In 1997, the Pediatric Eye Disease and Investigator Group (PEDIG) was formed to investigate the treatment modalities for amblyopia by using randomized trials in a multicenter format. The group is a collaborative network with >80 participating sites and >120 practitioners participating with funding by the National Eye Institute. Although PEDIG has broadened its investigative subject matter, this review focuses on the results of the studies related to amblyopia.

COMPARING TREATMENT OPTIONS FOR AMBLYOPIA

The treatment of amblyopia centers on eliminating the inhibitory signal from the fellow eye to allow normal neurologic development of the amblyopic eye once refractive, strabismic, or occlusive etiologies have been resolved.

BEST REFRACTIVE CORRECTION ALONE

Best optical correction improves visual acuity, but amblyopia, or reduced vision despite best optical correction, was generally held to require more treatment. Some studies had suggested spectacle correction alone as treatment of anisometropic amblyopia, but a prospective study conclusively demonstrated the effectiveness of patching compared with spectacles alone. A group of 84 children between ages 3 and 7 with refractive etiology for amblyopia were treated with refractive correction alone. The vision was checked at 5-week intervals with plans for addition of patching or atropine if the vision failed to improve from the previous examination. Surprisingly, amblyopia improved with best refractive correction alone by ≥2 lines in 77% of patients. The average improvement in visual acuity was 2.9 lines. Most children reached maximum improvement in visual acuity after 15 weeks of spectacle usage. Twenty-seven percent of patients had complete resolution of their amblyopia. Amblyopia was most likely to resolve with glasses alone in the subgroups with better baseline visual acuity and in children with lesser magnitude of anisometropia. This study has shifted practice patterns of ophthalmologist to treat patients with amblyopia with glasses until the visual acuity stops improving with glasses alone with follow-up of patients at 5- to 6-week intervals before initiating patching or atropine treatment.

A similar improvement in visual acuity with spectacle correction alone in children aged 3 to 7 years old was seen in patients with strabismus as the etiology for the amblyopia. In this small study of 12 patients with untreated strabismic amblyopia, the visual acuity improved by at least 2 lines in 9 patients treated with spectacle correction alone. In older children aged 7 to 17, there is maximum improvement in visual acuity with penalization of the fellow eye compared with spectacle correction alone.

Patients with untreated severe bilateral refractive errors may develop bilateral amblyopia. A study of patients with both moderate and severe bilateral amblyopia revealed excellent improvement in visual acuity with glasses alone. The probability of binocular acuity of 20/25 after 1 year of treatment was 74%.

AMBLYOPIA TREATMENT

In the setting of residual visual disparity following the maximum improvement in visual acuity with spectacles, the treatment options for the remaining amblyopia include patching or atropine penalization of the fellow eye. Severe amblyopia with visual acuity worse than 20/100, is generally more difficult to treat than moderate amblyopia with beginning visual acuity better than 20/80. This is in part because of the difficulty of asking the child to continue his or her activities of daily living with the poor vision of the amblyopic eye while the fellow eye is occluded or atropinized.
These treatment options have advantages and disadvantages. Patching requires complete occlusion of 1 eye. Disposable adhesive patches are the most common patching method, although reusable spectacle-mounted eye patches or occluders are also popular. The number of hours of assigned patching may vary from 1 hour to essentially all day. Patching can be difficult because of the physical discomfort of the patch or its adhesive material, skin rashes or breakdown, compliance with the number of hours of patching, and social stigma related to the patch. Atropine inhibits the focusing ability of the eye, reducing visual acuity at near in all patients and distance vision in some, for potentially several days. Atropine can be given daily in the fellow eye, only on weekends, or any interval in between. Atropine causes mydriasis of the pupil, resulting in light sensitivity in some patients. Reduced near visual acuity may affect schoolwork. Potential complications of atropine also include a localized allergic reaction, inadvertent administration to the incorrect eye, and toxicities from overdose.

**PATCHING**

The control arm of the first PEDIG amblyopia trial was designed to determine the efficacy of aggressive patching (6 hours up to full-time daily). Aggressive patching was considered the gold-standard at that time. Children aged 3 to 7 years with moderate amblyopia (20/40 to 20/100) were treated with patching either 6 hours daily (43% of patients) or full-time (17% of patients) at the investigator’s discretion. The average visual acuity in the amblyopic eye was 20/63 at the beginning of treatment. The etiology of the amblyopia was strabismic in 38% of patients, anisometropic (difference in the refractive error between eyes) in 37%, and a combination of the 2 in 24%. After 6 months of treatment, 79% of patients had visual acuity of at least 20/30. The overall improvement of visual acuity was 3.16 lines. This provided the evidence-based guideline for expectations of improvement with amblyopia treatment.

Additional studies investigated the ideal number of hours of patching. Children 3 to 7 years of age with moderate amblyopia were assigned to 2 hours of patching compared with 6 hours of patching daily. After 4 months of treatment, there was no statistically significant difference in visual acuity between the 2 groups. Sixty-two percent of patients achieved either 20/30 visual acuity or at least 3 lines of improvement from baseline with either of the patching regimens. Initially there was a faster rate of improvement in the group patched 6 hours daily compared with 2 hours, but the final visual acuity was the same for both groups after 6 months of treatment. This study proved that a greater number of hours of patching does not have either a clinically or statistically significant effect after 6 months of treatment of moderate amblyopia.

Several authors have questioned the results of this study because compliance was monitored by self-reporting. Only 6% of patients assigned patching for 6 hours patched for the prescribed time 75% or less of the time. There would be no difference seen in effectiveness of treatment between 2 hours of patching and 6 hours, if children assigned to 6 hours of patching only patched 2 hours. Monitoring compliance with occlusion monitors reveals that far fewer hours of patching are preformed than reported to investigators. Additional PEDIG studies monitored compliance with logs, telephone calls, and self-reporting to attempt to address these concerns because electronic devices to measure compliance are not commercially available. The question regarding the effect of the actual number of hours patched still remains unanswered. However, these studies still provide useful information about the effect on vision of the prescribed number of hours of patching.

Other studies evaluated severe amblyopia (visual acuity 20/100 to 20/400). Children were randomized to 6 hours of patching compared with full-time patching. The etiologies of the amblyopia were similar to previous studies. The average visual acuity was 20/160 at the initiation of treatment. The average improvement in visual acuity was 4.8 lines in the group patching 6 hours daily and 4.7 lines in the group with full-time patching. Compliance with treatment was also subjectively assessed. Subgroup analysis of etiology revealed no statistically significant difference in the regimens.

Fewer hours of patching have not been compared with 6 hours of patching for severe amblyopia specifically, but in 1 study of patients with anisometropic amblyopia, 2 hours of patching for both moderate and severe amblyopia was compared with a control group with only spectacle correction. Patching 2 hours resulted in a 0.8-line improvement in visual acuity after 5 weeks of treatment compared with no improvement in the spectacle-only group, suggesting that 2 hours daily patching may treat severe amblyopia. In another study, visual acuity improved 3.7 lines in children with severe amblyopia treated with 2 hours of daily patching after ~4 months. Although the net improvement in vision was less than in the study comparing 6 hours and full-time patching in severe amblyopia cited earlier, the methods of treatment varied in the length of time, and best refractive correction was worn before the start of patching, making comparison difficult.

The effect of age on patching success was evaluated in a randomized trial and
in follow-up studies of previous randomized trials.\textsuperscript{4,17,18} Age <5 at the initiation of treatment had greater long-term success than older ages in degree and stability of visual recovery.\textsuperscript{17,18} In children aged 7 to 12 years, 53% had $\geq 10$ letters of improvement in visual acuity testing with glasses combined with patching 2 to 6 hours daily or atropine penalization.\textsuperscript{4} In older children, aged 13 to 17 years, only 25% of children had similar improvement if previous amblyopia treatment had been tried, but if their amblyopia had not been previously treated, 47% of this group had $\geq 10$ letters of improvement in visual acuity.\textsuperscript{4}

Addition of near activities while patching revealed no statistically significant difference compared with children performing distance activities while patching.\textsuperscript{16} Near activities included tasks such as crafts, reading, writing, or computer/handheld video games. Compliance with assigned activities was high, as indicated with monitored weekly logs, telephone interviews, and follow-up visit discussions. The improvement in visual acuity averaged 2.6 lines in the distance activities group compared with 2.5 lines in the near activities group.

Patchig does not affect the refractive error in the patched eye.\textsuperscript{19} There was only negligible change in the refraction in the patched eye over a 2-year period while patching. Patching may affect the ocular alignment after treatment. In 1 study, 16% of patients with no previous misalignment developed a microstrabismus after 6 months of patching, 13% of patients with strabismus had worsening of the alignment, and 16% of patients had resolution of their strabismus after treatment.\textsuperscript{20}

For both severe and moderate amblyopia, patching is an effective treatment. Compliance is generally improved with fewer required hours of patching, and fewer hours are equally effective in moderate and severe amblyopia after 6 months of treatment (Table 1).

### ATROPINE

The first PEDIG amblyopia trial compared atropine drops daily in the fellow eye with patching for moderate visual loss (20/40 to 20/100) in children 3 to 7 years old.\textsuperscript{6,21} Patching was prescribed for at least 6 hours daily. Compliance was monitored by subjective reporting at follow-up visits. The average age of patients was 5.3 years. Visual acuity improved by 3.16 lines in the patching group and 2.84 lines in the atropine group at 6 months. Although the improvement in visual acuity was faster for the patching group, both treatments resulted in a statistically equivalent visual acuity improvement at 6 months. Seventy-four percent of the atropine group achieved 20/30 visual acuity, as did 79% of the patching group after 6 months of treatment. There remained a 1.8-line difference between the amblyopic eye and the normal eye in both groups. There was no difference in success of treatment dependent on the etiology of the amblyopia. Neither patching nor atropine had unexpected side effects of treatment. Atropine had a higher degree of patient acceptability. In a follow-up study at 2 years, there continued to be no statistically significant difference in the improvement in vision between atropine treated groups and patched groups.\textsuperscript{22} Furthermore, in follow-up at 10 years of age, the mean visual acuity in the amblyopic eye was 20/32 for both atropine and patch-treated eyes.\textsuperscript{17} Forty-two percent of patients patched had 20/25 or better visual acuity compared with 49% of patients treated with atropine. Combining both groups, 64% of patients continued to have $>1$ line of interocular difference between their normal and amblyopic eye. The mean difference was 2.0 lines. Younger age at initiation of treatment was associated with better final visual acuity. There continued to be no difference in final visual acuity based on treatment. This led to the recommendation that patching 6 hours daily had equal efficacy to atropine penalization daily for the treatment of moderate amblyopia. Either modality could be used as the initial treatment of amblyopia because an individual patient may respond differently to treatment than the PEDIG group.

The Amblyopia Treatment Index was developed to assess the psychosocial impact on the child and family of amblyopia treatment.\textsuperscript{23} This 20-question test assesses quality-of-life issues with regards to differing treatments for amblyopia after 5 weeks of treatment. It has been internally validated with high reliability.\textsuperscript{23,24} The Amblyopia Treatment Index revealed that atropine treatment compared with patching was consistently better tolerated by the child and family with regard to 3 factors: adverse effects of treatment, difficulty with compliance, and social stigma.\textsuperscript{25} If fewer hours of patching were prescribed so that patching could be completed at home, away from peers and friends, the social stigma scores were not as negative.\textsuperscript{26} Assessing the psychosocial burdens of

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### TABLE 1 Comparison of Patching Regimes

<table>
<thead>
<tr>
<th>Degree of Amblyopia</th>
<th>Treatment: Hours of Patching</th>
<th>% with Vision 20/30 or Better</th>
<th>Lines of Improvement</th>
<th>Length of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe: Vision $&gt;20/100$</td>
<td>Full-time daily</td>
<td>25%\textsuperscript{14}</td>
<td>4.7 lines\textsuperscript{a}</td>
<td>4 mo</td>
</tr>
<tr>
<td>Severe: $&gt;20/100$</td>
<td>6 h daily</td>
<td>25%\textsuperscript{14}</td>
<td>4.8 lines\textsuperscript{a}</td>
<td>4 mo</td>
</tr>
<tr>
<td>Severe: $&gt;20/100$</td>
<td>2 h daily</td>
<td>0/13 patients\textsuperscript{15}</td>
<td>3.7 lines</td>
<td>17 wk</td>
</tr>
<tr>
<td>Moderate: $\leq 20/80$</td>
<td>6 h daily</td>
<td>62% to 79%\textsuperscript{6,8}</td>
<td>3.16 lines</td>
<td>4–6 mo</td>
</tr>
<tr>
<td>Moderate: $\leq 20/80$</td>
<td>2 h daily</td>
<td>62%\textsuperscript{6}</td>
<td>2.40 lines</td>
<td>4 mo</td>
</tr>
</tbody>
</table>

\textsuperscript{a} No statistically significant difference in degree of visual improvement.
treatment may increase compliance with treatment, ultimately resulting in better visual acuity.

Atropine is thought to function by its inhibition of accommodation, preventing the normal eye from being used at near. Eyes that are hyperopic or farsighted use accommodation, or focusing to present clear images to the retinas. In the presence of atropine, full cycloplegic correction of the hyperopia would be needed to maintain clear vision in the distance. Patients with severe amblyopia may be expected to continue using the normal eye at near if the vision in the amblyopic eye is worse than the blur achieved by the atropine. Yet a study monitoring the fixation preference at near revealed improvement in visual acuity in the amblyopic eye even without evidence of fixation switch to the amblyopic eye. The exact mechanism of atropine efficacy, therefore, remains to be determined.

In addition, although some studies initially suggested that the effect of atropine could be enhanced by prescribing less than the full cycloplegic refraction to the normal eye (no power in lens of fellow eye), this result was refuted by a randomized study designed to investigate this effect specifically. The improvement in moderate amblyopia was 2.8 lines in the atropine with optical undercorrection (no power in lens of fellow eye) group compared with 2.4 lines in the atropine with full optical correction group at 18 weeks. This difference was not statistically or clinically significant. This study did not specifically address whether undercorrected glasses could be effective if atropine treatment alone failed to produce improvement in the visual acuity. Although atropine was initially prescribed daily for amblyopia treatment, studies have compared daily atropine with weekend atropine for moderate amblyopia. Less frequent dosing should improve compliance with treatment with the expectation of preservation of visual acuity. The regression risk after cessation of treatment varies from 6% to 67% in previous studies. In the follow-up of children treated with either patching or atropine penalization, the visual acuity was monitored for 1 year after cessation of either treatment to assess for vision stability. Recurrence was considered a decrease in vision in the previously amblyopic eye of at least one-third of the treatment effect. The recurrence rate was 25% in children who discontinued patching and 21% in children discontinuing atropine. Recurrence was 4 times as likely in children who did not have a gradual taper of their treatment (ie, reducing patching from 6 hours daily to 2 hours daily before discontinuation) resulted in better outcomes than immediate cessation. Other factors linked to greater likelihood of recurrence included better visual acuity at the end of treatment, a greater number of lines of improvement in visual acuity during treatment, and previous history of recurrence. Excellent alignment, good stereoacuity, and younger age during treatment were not associated with reduced risk of recurrence.

The lack of protective effect with older age at cessation of treatment is particularly contradictory to previous beliefs regarding the plasticity of the visual system. Whereas treatment was previously often discontinued at age 6 to 8, the PEDIG study supports the continuous monitoring of visual acuity for at least 1 year after the cessation of amblyopia treatment. In an older

### CESSATION OF AMBYLIOPIA TREATMENT

After adequate recovery of visual acuity has occurred, the ophthalmologist must consider discontinuation of treatment with the expectation of preservation of visual acuity. The regression risk after cessation of treatment varies from 6% to 67% in previous studies. In the follow-up of children treated with either patching or atropine penalization, the visual acuity was monitored for 1 year after cessation of either treatment to assess for vision stability. Recurrence was considered a decrease in vision in the previously amblyopic eye of at least one-third of the treatment effect. The recurrence rate was 25% in children who discontinued patching and 21% in children discontinuing atropine. Recurrence was 4 times as likely in children who did not have a gradual taper of their treatment (ie, reducing patching from 6 hours daily to 2 hours daily before discontinuation) resulted in better outcomes than immediate cessation. Other factors linked to greater likelihood of recurrence included better visual acuity at the end of treatment, a greater number of lines of improvement in visual acuity during treatment, and previous history of recurrence. Excellent alignment, good stereoacuity, and younger age during treatment were not associated with reduced risk of recurrence.

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### TABLE 2 Results of Atropine Penalization

<table>
<thead>
<tr>
<th>Degree of Amblyopia</th>
<th>Atropine Dosage</th>
<th>% with Vision Better than 20/40</th>
<th>Lines of Improvement</th>
<th>Length of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe: vision &gt; 20/100</td>
<td>Weekend days only</td>
<td>21%</td>
<td>4.5 lines</td>
<td>18 wk</td>
</tr>
<tr>
<td>Moderate: ≥20/80</td>
<td>Daily drop</td>
<td>47%–75%</td>
<td>2.3–2.84 lines*</td>
<td>4-6 mo</td>
</tr>
<tr>
<td>Moderate: &lt;20/80</td>
<td>Weekend days only</td>
<td>53%</td>
<td>2.3 lines*</td>
<td>4 mo</td>
</tr>
</tbody>
</table>

* No statistically significant difference in degree of visual improvement.
group of children aged 7 to 12 treated for amblyopia, the recurrence rate for loss of ≥2 lines was only 7%.34 These authors speculate that some of the visual gain in this group may have been from better refractive correction, which would not be susceptible to reversal with cessation of amblyopia treatment. Importantly, however, most of the visual gain in this older age group is sustained, making treatment of amblyopia in this older age group worthwhile. In summary, a portion of the gains in visual acuity from amblyopia is vulnerable to regression with cessation of amblyopia treatment. Tapering of treatment improves the retention of visual acuity, but diligent monitoring of visual acuity after cessation of treatment is required.

FUNCTIONAL IMPACT OF AMBLYOPIA TREATMENT

Visual outcomes of amblyopia treatment are often limited to high contrast visual acuity (black letters on a white background) in the amblyopic eye. Visual function has many aspects such as varying contrast sensitivity, stereoacuity, reading fluency and reading comprehension that have recently been assessed.35–37

Contrast Sensitivity

Contrast sensitivity is reduced in amblyopic eyes. After treatment of the amblyopia, there continues to be a slight loss of contrast sensitivity with fine visual acuity (smaller letters) using low-contrast letters.35 Yet the overall distribution of contrast sensitivity is similar to children without amblyopia.

Stereoacuity

Computer-generated 3-dimensional entertainments have increased in popularity. Stereoacuity at near and distance is reduced in amblyopia. Stereoacuity can be measured with a series of tests such as the Preschool Randot Test, Distance Randot test, and Frisby-Davis distance and near test.38 The Frisby-Davis tests use real depth analysis compared with overlapping images discernable by each eye separately in the Randot testing. The testing methods greatly influence the outcomes. Studies of the effect on stereoacuity of successful amblyopia treatment using Randot testing reveal that stereoacuity remains lower in children with treated amblyopia than in nonamblyopic children of the same age.37 Amblyopia is less severe in eyes with better baseline stereoacuity and less anisometropia. After treatment of amblyopia, better stereoacuity was associated with better baseline stereoacuity and better visual acuity of the amblyopic eye at end of treatment. Therefore, the best chance of improving stereoacuity is successfully treating the amblyopia. Most children will have improvement in their ability to see computer generated 3-dimensional images with treatment of amblyopia, but these children will not have the same degree of computer-generated 3-dimensional ability as children without amblyopia. Functionally, however, tasks that require depth perception such as sports and driving are not affected by amblyopia, as shown by testing with the Frisby-Davis methods.

Reading

Reading is a crucial developmental requirement for school-age children. Reading fluency is a measure of both reading speed and accuracy. Reading was assessed monocularly in 10-year-old patients previously treated for amblyopia by using the Gray Oral Reading Test (4th edition).36 In this study, amblyopic eyes were slightly slower and less accurate than nonamblyopic eyes, but the reading comprehension was similar. Poorer visual acuity in the amblyopic eye or slower central processing by the brain may have contributed to this result. The type size used in the reading material was far larger than the visual acuity of the amblyopic eye, and the comprehension rates in the amblyopic eye were comparable to the fellow eye. Studies of binocular reading ability have shown contradictory results.39,40 Some studies have shown impaired binocular reading in children with amblyopia, and others have shown no correlation between amblyopia and binocular reading. There are many confounding variables that make comparisons of reading function with regard to amblyopia history difficult. This important function needs to be studied further to develop guidelines for children with regard to potential reading dysfunction.

CONCLUSIONS

In summary, amblyopia treatment is highly successful with ~75% of children <7 years of age achieving resolution of the amblyopia with either patching or atropine. Best optical re-refraction is essential to successful treatment. Patching and atropine penalization are equally effective for treatment of moderate amblyopia. If one treatment method fails, the alternative method may be initiated. Six hours of patching was equally efficacious to greater numbers of hours in moderate amblyopia in randomized trials. In severe amblyopia, all patching regimens have not been directly compared in randomized trials, but as little as 2 hours of patching was effective. Younger age is associated with better final visual acuity, but treatment should be attempted in older children without previous treatment because up to 47% of these patients had improvement in visual acuity that was sustained. Upon cessation of treatment, visual acuity needs to be monitored to identify and treat regression. Finally, amblyopia therapy has significant social and physical impact on the child and family. Decisions regarding treatment that factor in the wishes of the family and child are more likely to lead to successful outcome.
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