Atropine vs Patching for Treatment of Moderate Amblyopia
Follow-up at 15 Years of Age of a Randomized Clinical Trial

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**IMPORTANCE** Initial treatment for amblyopia of the fellow eye with patching and atropine sulfate eyedrops improves visual acuity. Long-term data on the durability of treatment benefit are needed.

**OBJECTIVE** To report visual acuity at 15 years of age among patients who were younger than 7 years when enrolled in a treatment trial for moderate amblyopia.

**DESIGN, SETTING, AND PARTICIPANTS** In a multicenter clinical trial, 419 children with amblyopia (visual acuity, 20/40 to 20/100) were randomly assigned to patching (minimum of 6 h/d) or atropine sulfate eyedrops, 1% (1 drop daily), for 6 months. Treatment after 6 months was at the discretion of the investigator. Two years after enrollment, an unselected subgroup of 188 children were enrolled into long-term follow-up.

**INTERVENTION** Initial treatment with patching or atropine with subsequent treatment at investigator discretion.

**MAIN OUTCOMES AND MEASURES** Visual acuity at 15 years of age with the electronic Early Treatment Diabetic Retinopathy Study test in amblyopic and fellow eyes.

**RESULTS** Mean visual acuity in the amblyopic eye measured in 147 participants at 15 years of age was 0.14 logMAR (approximately 20/25); 59.9% of amblyopic eyes had visual acuity of 20/25 or better and 33.3%, 20/20 or better. Mean interocular acuity difference (IOD) at 15 years of age was 0.21 logMAR (2.1 lines); 48.3% had an IOD of 2 or more lines and 71.4%, 1 or more lines. Treatment (other than spectacles) was prescribed for 9 participants (6.1%) aged 10 to 15 years. Mean IOD was similar at examinations at 10 and 15 years of age (2.0 and 2.1 logMAR lines, respectively; \( P = .39 \)). Better visual acuity at the 15-year examination was achieved in those who were younger than 5 years at the time of entry into the randomized clinical trial (mean logMAR, 0.09) compared with those aged 5 to 6 years (mean logMAR, 0.18; \( P < .001 \)). When we compared subgroups based on original treatment with atropine or patching, no significant differences were observed in visual acuity of amblyopic and fellow eyes at 15 years of age (\( P = .44 \) and \( P = .43 \), respectively).

**CONCLUSIONS AND RELEVANCE** At 15 years of age, most children treated for moderate amblyopia when younger than 7 years have good visual acuity, although mild residual amblyopia is common. The outcome is similar regardless of initial treatment with atropine or patching. The results indicate that improvement occurring with amblyopia treatment is maintained until at least 15 years of age.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00000170
Amibloipa is an important cause of monocular visual impairment.1-2 Refractive correction, patching, atropine sulfate eyedrops, and Bangerter filters to the fellow eye have been shown to improve the vision of the amblyopic eye.3-6 Regression after cessation of treatment for amblyopia occurs in some patients, thereby reducing the lifetime benefit of therapy.7-12 Prospective long-term outcome data evaluating the durability of the treatment benefit are important.

The Pediatric Eye Disease Investigator Group (PEDIG) initiated a randomized clinical trial (RCT) in 1999 comparing patching (6 h/d to full-time daily patching in the fellow eye) with atropine sulfate eyedrops, 1% (1 drop daily in the fellow eye), as treatments for moderate amblyopia (20/40 to 20/100) in children younger than 7 years.3 After 6 months, mean improvement of about 3 logMAR lines in the visual acuity of the amblyopic eye was present in both treatment groups. After the initial 6-month treatment phase, the investigators at their discretion could switch, combine, or adjust the dosage of amblyopia treatment. From 6 months to 2 years, additional improvement in visual acuity (mean of 0.7 logMAR lines) occurred in both original treatment groups. However, only approximately 50% of amblyopic eyes were 20/25 or better at the 2-year outcome.13 At the next study outcome examination at 10 years of age, the treatment benefit was maintained, with 46% of amblyopic eyes having visual acuity of 20/25 or better.14 In this report we evaluate visual acuity of the amblyopic and fellow eyes and stereoacuity for the participants when examined at 15 years of age.

Methods

The full study protocol has been detailed in prior publications.1-3 A brief summary of the protocol follows. The protocol and informed consent forms compliant with the Health Insurance Portability and Accountability Act were approved by the institutional review boards of the clinical sites. The study adhered to the tenets of the Declaration of Helsinki, and oversight was provided by an independent data and safety monitoring committee. Written informed consent was obtained from the parent or the guardian for the RCT and updated to continue follow-up through 15 years of age.

Eligibility criteria for the RCT included being younger than 7 years, having visual acuity in the amblyopic eye of 20/40 to 20/100 and visual acuity in the fellow eye of 20/40 or better, interocular acuity difference (IOD) of 3 or more logMAR lines, and the presence or the history of an amblyogenic factor meeting the study-specified criteria for strabismus and/or anisometropia.3

The RCT included 419 children randomly assigned to patching (6 h/d to full-time daily at the discretion of the investigator) or atropine sulfate eyedrops, 1%, 1 drop daily. During the first 6 months, the children continued to receive their randomized treatment. A protocol-specified masked outcome examination was conducted 6 months after randomization. From 6 months to 2 years, the protocol allowed amblyopia treatment at the discretion of the investigator but specified that participants were to be examined at least once every 6 months, with another masked outcome examination occurring 2 years after randomization.

At the time of the 2-year examination, parents of children from a subset of participating sites (those with ≥5 children enrolled and continuing with other PEDIG protocols) were invited to enter a long-term extension phase; parents of 188 children agreed to continued participation. All treatment prescribed after the first 2 years was determined by the investigator. Testing conducted at 10 and 15 years of age (10- and 15-year examinations) included measurement of visual acuity, manifest and cycloplegic refractions (as described below depending on visual acuity and changes in refraction), assessment of ocular alignment using the simultaneous prism and cover test at distance and near fixation, and an assessment of stereoacuacity with the Randot Preschool Stereoacuity Test (Stereo Optical Company).

Visual Acuity Testing

During the initial phase of the study through 2 years of follow-up, visual acuity was measured with the single-surrounded Amblyopia Treatment Study protocol (ATS-HOTV).15 At 10 and 15 years of age, visual acuity was measured by a study-certified vision tester with an electronic modification of the testing protocol developed for the Early Treatment Diabetic Retinopathy Study (electronic ETDRS).16

At the 15-year examination, if visual acuity in either eye was worse than 20/20 (<83 letters) or if an IOD between the eyes of 5 or more letters was found, a manifest refraction was performed that included dry retinoscopy with subjective refinement. Acuity testing was repeated using the manifest refraction for an eye that had a difference between the manifest refraction and the correction used for initial testing that met 1 or more of the following criteria: decrease of at least 0.25 diopters (D) in hyperopia; increase of at least 0.25 D in myopia; change of at least 0.50 D in cylinder power; and change of at least 10° in axis.

If visual acuity on the initial test and after retest using the manifest refraction was worse than 20/20 or if the difference between the initial and retest visual acuities was at least 5 letters, a cycloplegic refraction was performed after completing stereoacuity and ocular motility testing. Visual acuity was tested a third time in eyes that had a difference between the manifest refraction and the cycloplegic refraction that met the same criteria as noted above. The best visual acuity obtained at the visit was used in the analysis.

Statistical Analysis

Differences in participant characteristics for those completing the 15-year examination vs those randomized who did not complete the 15-year examination were evaluated to assess the potential for bias. Visual acuities in the amblyopic and fellow eyes were compared between randomized treatment groups as continuous variables in analysis-of-covariance models adjusted for baseline acuity. A logistic regression model was used to compare the proportions of eyes in each treatment group with visual acuity in the amblyopic eye of 20/25 or better. Five participants who completed the 15-year outcome examination but had visual acuity tested with a method other than the...
The 15-year examination was completed by 152 of the 188 participants (80.9%). Their mean age was 5.1 (range, 2.6-7.0) years at enrollment and 15.3 (range, 14.8-17.1) years at the time of the 15-year examination; 41.5% were female. The mean visual acuity in the amblyopic eye at the 15-year examination was 0.08 logMAR in participants originally prescribed atropine (42.1% vs 41.1%) and male (59.9% vs 58.5%). However, participants who completed the 15-year examination had better visual acuity in the amblyopic eye at the 2-year outcome examination than those who did not (mean logMAR acuity, 0.13 vs 0.19) and were more likely to be white (89.1% vs 80.1%) and male (58.5% vs 50.4%).

### Treatment Prescribed
Between the 10- and 15-year examinations, 9 participants (6.1%) were prescribed treatment for amblyopia other than optical correction (4, patching only; 2, atropine only; 1, patching and atropine; and 2, patching, atropine, and Bangerter filters). No participant was prescribed amblyopia treatment at the 15-year examination.

### Visual Acuity
The mean visual acuity in the amblyopic eye at the 15-year examination in 147 patients was 0.14 logMAR (approximately 20/160) in 59.9% of amblyopic eyes had acuity of 20/25 or better and 33.3% had 20/20 or better (Table 1). The mean visual acuity in the fellow eye was −0.07 logMAR (approximately 20/16). The mean IOD was 0.21 logMAR (2.1 logMAR lines), with 48.3% having an IOD of 2 or more lines and 71.4% having an IOD of 1 or more lines (Table 2).

### Results
The 15-year examination was completed by 152 of the 188 participants (80.9%). Their mean age was 5.1 (range, 2.6-7.0) years at enrollment and 15.3 (range, 14.8-17.1) years at the time of the 15-year examination; 41.5% were female. The mean visual acuity of the amblyopic eyes at the time of entry into the RCT was 0.53 logMAR (approximately 20/60), with a mean IOD of 4.5 lines. This cohort was comparable to randomized participants who did not complete the 15-year examination in terms of age, cause of amblyopia (anisometropia, strabismus, or a combination), baseline visual acuities in the amblyopic and fellow eyes, baseline IOD in visual acuity, baseline mean spherical equivalent refractive error, treatment before randomization, and randomized treatment group (Supplement eTable 1). Participants who completed the 15-year examination had better visual acuity in the amblyopic eye at the 2-year outcome examination than those who did not (mean logMAR acuity, 0.13 vs 0.19) and were more likely to be white (89.1% vs 80.1%) and male (58.5% vs 50.4%).

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### Visual acuity in the amblyopic eye at the 15-year examination was similar in the 2 original treatment groups (difference in mean visual acuity between the treatment groups adjusted for baseline acuity +0.02 logMAR [95% CI, −0.03 to +0.07]; P = .44 for difference in mean visual acuity) (Table 3). Visual acuity in the amblyopic eye was 20/25 or better in 61% of participants originally prescribed patching and 58% of participants originally prescribed atropine (P = .27). Mean visual acuity in the fellow eye was −0.08 logMAR in participants origi-
nally prescribed patching and −0.07 logMAR in participants originally prescribed atropine eyedrops (approximately 20/16); the difference in mean visual acuity of the fellow eyes between the treatment groups adjusted for baseline acuity was +0.01 logMAR (95% CI, −0.01 to +0.03; P = .43).

The mean IOD measured with the electronic ETDRS protocol was similar at the 10- and 15-year examinations (2.0 and 2.1 logMAR lines, respectively; P = .39) (Figure). A small improvement from 10 to 15 years of age was noted for the amblyopic eye (mean, 0.3 [95% CI, 0.1–0.4] logMAR lines or about 1.5 letters) and the fellow eye (mean, 0.4 [0.2–0.5] logMAR lines or about 2 letters) (Supplement [eTable 2 and eFigure 1]).

In a multivariate model, younger age at the time of entry into the RCT was associated with better amblyopic eye visual acuity at the 15-year examination. Mean visual acuity in the amblyopic eye at the 15-year examination was 0.09 logMAR (approximately 20/25) in the 63 participants younger than 5 years at randomization compared with 0.18 logMAR (approximately 20/25) in the 83 participants aged 5 to 6 years (P < .001) (Supplement [eFigure 2]). Better baseline visual acuity in the amblyopic eye was associated with better visual acuity at 15 years of age (P < .001) (Supplement [eTable 3]). No apparent relation existed between the cause of amblyopia (strabismus, anisometropia, or a combination), sex, or whether or not treatment was prescribed before study enrollment and the visual acuity outcome at 15 years of age (P = .33, P = .63, and P = .13, respectively) (Supplement [eTable 3]).

Stereocuity at the 15-Year Examination

Results of the Randot Preschool Stereoacuity Test at the 15-year examination were better than 800 arcseconds in 42.5% of all participants and better than 800 arcseconds in 64.2% of participants classified at 15 years of age as having no ocular deviation at distance or near. Stereocuity of 60 arcseconds or better was found in 13.7% of all participants and in 23.5% classified as having no ocular deviation at distance or near. Re-
results were similar for the 2 treatment groups ($P = .44$ for all participants and $P = .85$ for those with no ocular deviation at 15 years of age) (Table 4).

**Discussion**

The improvement achieved with patching or atropine treatment for moderate amblyopia (20/40 to 20/100) due to strabismus, anisometropia, or both when initiated before age 7 years was maintained from 10 to 15 years of age. We found no deterioration in the visual acuity of the amblyopic eye between the 10- (mean, 0.16 logMAR) and 15-year (mean, 0.14 logMAR) examinations. The mean visual acuity of amblyopic eyes was about 20/25. Almost 60% of amblyopic eyes had visual acuity of 20/25 or better.

The maintenance of improvement seen in our study is similar to that seen in prior studies of long-term follow-up of amblyopia treatment. Leiba et al\textsuperscript{10} reported mean amblyopic eye logMAR visual acuities of 0.90 at the start of occlusion treatment. Bowman et al\textsuperscript{17} found mean visual acuity in the amblyopic eye of 0.47 logMAR at the time of presentation (mean age, 4.1 years), 0.23 at the end of treatment (mean age, 7.5 years), and 0.18 at a mean age of 12.3 years in 88 participants.

Outcomes were similar in the original atropine and patching treatment groups. As at 10 years of age, the visual acuity outcome at 15 years of age was slightly better in participants who were aged 3 to 4 years at enrollment compared with those aged 5 to 6 years.\textsuperscript{14} Younger age at initiation of treatment might be advantageous if plasticity decreases with age or if a shorter duration of amblyogenic insult reduces the severity of the effect on the visual sensory system, resulting in the significant effect of younger age on treatment outcomes at the 10- and 15-year examinations. Although we did not observe an age relationship between age at initiation of treatment and final visual acuity at 6 months and 2 years after randomization in the full randomized cohort,\textsuperscript{3,13} a meta-analysis from 4 other PEDIG studies found greater improvement with younger age.\textsuperscript{18} Our data suggest that the younger participants continued to improve after the 2-year postrandomization examination.

Our study design included measurement of stereoacuity to determine whether amblyopia treatments had different effects on the development of binocularity. Simons et al\textsuperscript{19} suggested a beneficial effect of atropine in a nonrandomized study using various atropine dosages. Conversely, Kushner\textsuperscript{20} voiced concern about a possible negative effect of persistent cycloplegia on binocularity. At the 10-year outcome examination, a previous PEDIG study\textsuperscript{14} found no difference in stereoacuity outcome between children originally treated with patching and those originally treated with atropine. The results at the 15-year examination are similarly reassuring because they show no difference in stereoacuity by original treatment for the entire cohort or for participants with no ocular deviation at 15 years of age.

In a previous report from the PEDIG\textsuperscript{3} after 6 months of treatment, more participants in the atropine-treated group than in the patching group had a transient reduction in visual acuity of the fellow eye. The investigators concluded

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**Figure. Interocular Acuity Difference (IOD) at the 10- vs 15-Year Examinations**

Examinations were conducted at 10 and 15 years of age. The diagonal line represents the line of equivalence; markers, participants. Participants represented below the line had a larger IOD at the 10-year examination.

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**Table 4. Randot Preschool Stereoacuity Test Results at the 15-Year Examination**

<table>
<thead>
<tr>
<th>Test Result, arcs</th>
<th>Combined (n = 146)</th>
<th>Patching (n = 73)</th>
<th>Atropine (n = 73)</th>
<th>$P$ Value$^c$</th>
<th>Combined (n = 81)</th>
<th>Patching (n = 40)</th>
<th>Atropine (n = 41)</th>
<th>$P$ Value$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 800$</td>
<td>71 (48.6)</td>
<td>32 (43.8)</td>
<td>39 (53.4)</td>
<td></td>
<td>55 (67.9)</td>
<td>26 (65.0)</td>
<td>29 (70.7)</td>
<td></td>
</tr>
<tr>
<td>$\geq 400$</td>
<td>62 (42.5)</td>
<td>29 (39.7)</td>
<td>33 (45.2)</td>
<td>.44</td>
<td>52 (64.2)</td>
<td>24 (60.0)</td>
<td>28 (68.3)</td>
<td>.85</td>
</tr>
<tr>
<td>$\geq 200$</td>
<td>44 (30.1)</td>
<td>22 (30.1)</td>
<td>22 (30.1)</td>
<td></td>
<td>38 (46.9)</td>
<td>19 (47.5)</td>
<td>19 (46.3)</td>
<td></td>
</tr>
<tr>
<td>$\geq 100$</td>
<td>35 (24.0)</td>
<td>18 (24.7)</td>
<td>17 (23.3)</td>
<td></td>
<td>31 (38.3)</td>
<td>17 (42.5)</td>
<td>14 (34.1)</td>
<td></td>
</tr>
<tr>
<td>$\geq 50$</td>
<td>20 (13.7)</td>
<td>9 (12.3)</td>
<td>11 (15.1)</td>
<td></td>
<td>19 (23.5)</td>
<td>9 (22.5)</td>
<td>10 (24.4)</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>13 (8.9)</td>
<td>6 (8.2)</td>
<td>7 (9.6)</td>
<td></td>
<td>13 (16.0)</td>
<td>6 (15.0)</td>
<td>7 (17.1)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: arcs, arcsecond.

$^a$ Includes no ocular deviation at distance and near at the 15-year examination.

$^b$ Assigned at the time of randomization.

$^c$ Calculated from the exact Wilcoxon rank sum test for a difference in distribution between treatment groups.
that much of this reduction was due to persistent cycloplegia and consequently incorrect spectacle correction at the time the vision was measured. Further support for this conclusion comes from the absence of a difference in visual acuity in the fellow eye by treatment group at each of the planned 2-year,13 10-year,14 and 15-year outcome examinations.

Our results are subject to potential selection bias in that participants had better visual acuity in the amblyopic eye at the 2-year outcome examination than nonparticipants (mean of about 3 letters better).14 As a result, our observed visual acuity in the amblyopic eyes at the 15-year examination may be slightly biased toward better acuity. We could not identify other sources of bias to explain our findings. Visual acuity testing was performed with a standardized protocol to ensure consistency across sites.

Conclusions

The improvement in visual acuity achieved in amblyopic eyes by 10 years of age is maintained at age 15 years, although mild residual amblyopia is common, after treatment for amblyopia initiated before age 7 years. The outcome is similar regardless of whether the initial treatment prescribed consisted of atropine eyedrops or patching.

Clinical Sites: The following PEDIG members participated in the study and are listed by clinical site (number of patients completing the 15-year examination):

Nicholas A. Sala, (investigator [I]), Rhonda M. Hodde (coordinator [C]), Veda L. Zeto (C), and Jeanine M. Romeo (C), Pediatric Ophthalmology of Erie, Erie, Pennsylvania (19); William F. Astle (I), Anna L. Ellis (I), Christine M. Millar (C), Heather N. Sandusky (C), Emi N. Sanders (C), and Charlene D. Gillis (visual acuity examiner [E]), Alberta Children’s Hospital, Calgary, Alberta, Canada (14); David R. Tien (I), Samantha J. Garner (C), Myra B. McGuinness (C), and Shannon M. Lees (C), Pediatric Ophthalmology and Strabismus Associates, Providence, Rhode Island (14); Robert W. Arnold (I) and Mary D. Armitage (C), Ophthalmic Associates, Anchorage, Alaska (13); Stephen R. Glaser (I), Tracey L. Cossens (C), Noga Senderowitch (C), and Laura L. Graham (C), Stephen R. Glaser, MD, PC, Rockville, Maryland (12); Michael X. Repka (I), Alex Christoff (C), Carole R. Goodman (C), and Xiaonong Liu (C), Wilmer Ophthalmological Institute, The John Hopkins University, Baltimore, Maryland (10)*; Susan A. Cotter (I), Raymond H. Chu (I), Lernik Mesropian (I), Tawna L. Roberts (I), and Susan M. Park (I), School of Optometry, Arizona State University, Tempe, Arizona (11)*; Richard P. Golden (C), Linsenbardt (C), Children’s Medical Center, Dallas, Texas (2); Daniel J. Karr (I), Paula K. Rauch (C), Pamela H. Berg (E), Yelena M. Bubnov (E), and Albert Remo (E), Casey Eye Institute, Portland, Oregon (2); James B. Rubin (I) and Dipti Desai (C), The Permanente Medical Group, Roseville, California (2); Marjean T. Kulp (I) and Freda D. Dallas (C), The Ohio State University College of Optometry, Columbus (2); David I. Silbert (I) and Noelle S. Matta (C), Family Eye Group, Lancaster, Pennsylvania (I); Scott R. Lambert (I), Judy L. Brower (C), and Rachel A. Robb (C), The Emory Eye Center, Atlanta, Georgia (I); Sean P. Donahue (I) and Lisa A. Fraine (C), Vanderbilt Eye Center, Nashville, Tennessee (I)*; and Earl R. Crouch Jr (I) and Gaylord G. Ventura (C), Department of Ophthalmology, Eastern Virginia Medical School, Norfolk (I). *Center received support used for this project from an unrestricted grant from Research to Prevent Blindness Inc. PEDIG Coordinating Center: Raymond T. Kraker, Roy W. Beck, Christina M. Cagnina-Morales, Danielle L. Chandler, Courtney L. Conner, Quayleen Donahue, Brooke P. Fimbels, James E. Hoepner, Curtis R. Koh, Elizabeth L. Lazar, B. Michele Mela, Diana E. Rosas, and Jennifer A. Shah. National Eye Institute, Bethesda, Maryland: Donald F. Everett.


Wyburn-Mason Syndrome

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