A Randomized Trial of Prescribed Patching Regimens for Treatment of Severe Amblyopia in Children

*The Pediatric Eye Disease Investigator Group**

Objective: To compare full-time patching (all hours or all but 1 hour per day) to 6 hours of patching per day, as prescribed treatments for severe amblyopia in children younger than 7 years.

Design: Prospective, randomized multicenter clinical trial (32 sites).

Participants: One hundred seventy-five children younger than 7 years with amblyopia in the range of 20/100 to 20/400.

Intervention: Randomization either to full-time patching or to 6 hours of patching per day, each combined with at least 1 hour of near-visual activities during patching.

Main Outcome Measure: Visual acuity in the amblyopic eye after 4 months.

Results: Visual acuity in the amblyopic eye improved a similar amount in both groups. The improvement in the amblyopic eye acuity from baseline to 4 months averaged 4.8 lines in the 6-hour group and 4.7 lines in the full-time group ($P = 0.45$).

Conclusion: Six hours of prescribed daily patching produces an improvement in visual acuity that is of similar magnitude to the improvement produced by prescribed full-time patching in treating severe amblyopia in children 3 to less than 7 years of age. *Ophthalmology 2003;110:2075–2087 © 2003 by the American Academy of Ophthalmology.*

Amblyopia is the most common cause of monocular visual impairment in both children and young and middle-aged adults.[1,2] Occlusion therapy with patching of the sound eye has been the mainstay of treatment of amblyopia. However, opinions vary on the number of hours of patching per day that should be prescribed for amblyopia, ranging from as little as 1 or 2 hours a day to 24 hours a day.[3–5]

Severe amblyopia, worse than 20/100, has been estimated to occur in approximately 25% of all amblyopes.[6] There have been few previous studies that specifically addressed severe amblyopia, but both full-time patching and part-time patching have been advocated for its treatment.[7–9]

We recently conducted a randomized trial that evaluated patching regimens for *moderate* amblyopia.[10] Patients with visual acuity in the amblyopic eye ranging from 20/40 to 20/80 were randomized to patching either 2 hours per day or 6 hours per day, both combined with at least 1 hour of near-visual activities while patching. Improvement of visual acuity was found to be similar in both groups. In parallel with that study, we conducted a randomized trial to compare prescribing full-time patching (all hours or all but 1 hour per day) with prescribing 6 hours of patching per day combined with at least 1 hour per day of near-visual activities during patching for both severe strabismic and anisometropic amblyopia (20/100–20/400) in children younger than 7 years who were able to complete standardized optotype visual acuity testing.

Patients and Methods

Our study was supported through a cooperative agreement with the National Eye Institute of the National Institutes of Health and was conducted by the Pediatric Eye Disease Investigator Group[11] at 32 clinical sites. The protocol and informed consent forms were approved by institutional review boards, and a parent or guardian (referred to subsequently as "parent") of each study patient gave written informed consent. Study oversight was provided by an independent data and safety monitoring committee.

Patient Selection

Eligibility testing included measurement of best-corrected visual acuity in both eyes with the Amblyopia Treatment Study visual acuity testing protocol (which uses single-surround HOTV optotypes),[12,13] a cycloplegic refraction, an ocular examination including pupillary dilation, and an ocular motility examination. Except for the standardization of the visual acuity testing protocol across centers, procedures were performed according to the investigator's

Originally received: June 19, 2003.
Accepted: August 5, 2003. Manuscript no. 230394.

Supported by a cooperative agreement from the National Eye Institute (EY11751).

Correspondence to Roy W. Beck, MD, PhD, Jaeb Center for Health Research, 15310 Amberly Drive, Suite 350, Tampa, FL 33647. E-mail: rbeck@jaeb.org.

Reprint requests to PEDIG Coordinating Center, Jaeb Center for Health Research, 15310 Amberly Drive, Suite 350, Tampa, FL 33647. E-mail: pedig@jaeb.org.

*The writing committee and a list of the members of the Pediatric Eye Disease Investigator Group participating in the trial appear in the Appendix.

ISSN 0161-6420/03/$–see front matter
doi:10.1016/j.ophtha.2003.08.001

Table 1. Eligibility and Exclusion Criteria

Eligibility criteria
- Age <7 yrs
- Not in or within 4 mos of entering first grade
- Able to measure visual acuity using the Amblyopia Treatment Study visual acuity testing protocol on an electronic visual acuity tester*
- Visual acuity in the amblyopic eye between 20/100 and 20/400 inclusive
- Visual acuity in the sound eye 20/40 or better
- If amblyopia previously treated, no patching treatment within 6 mos of enrollment and no other amblyopia treatment of any type (other than spectacles) used within 1 mo of enrollment (any treatment more than 6 mos before enrollment was acceptable)
- Refractive error corrected for at least 4 wks
- Amblyopia associated with strabismus, refractive error/anisometropia, or both, meeting the following criteria:
  - ➢ *Strabismic amblyopia:* amblyopia (1) in the presence of either a heterotropia at distance and/or near fixation or a history of strabismus surgery (or botulinum) and (2) in the absence of refractive error meeting the criteria below for combined mechanism amblyopia
  - ➢ *Refractive/anisometropic:* amblyopia in the presence of anisometropia of ≥0.5 D of spherical equivalent or ≥1.50 D of difference in astigmatism in any meridian, with no measurable heterotropia at distance or near fixation, which persisted after at least 4 wks of spectacle correction
  - ➢ *Combined mechanism:* amblyopia in the presence of (1) either a heterotropia at distance and/or near fixation or a history of strabismus surgery (or botulinum) and (2) anisometropia of ≥1.00 D spherical equivalent or ≥1.50 D of difference in astigmatism in any meridian, which persisted after at least 4 wks of spectacle correction

Exclusion criteria
- Presence of an ocular cause for reduced visual acuity
- Myopia more than a spherical equivalent of −6.00 D
- Prior intraocular surgery
- Known skin reaction to patch or bandage adhesive

D = diopters.
*Moke PS, Turpin AH, Beck RW, et al. Computerized method of visual acuity testing: adaptation of the Amblyopia Treatment Study visual acuity testing protocol. Am J Ophthalmol 2001;132:903–9.

usual routine. Visual acuity testing was required to be performed within the 7 days before randomization, though the remainder of the examination could have been completed within 2 months before randomization.

The major eligibility criteria for the trial included age <7 years, best-corrected visual acuity between 20/100 and 20/400 inclusive in the amblyopic eye and 20/40 or better in the sound eye, the presence of or a history of an amblyogenic factor meeting study-specified criteria for strabismus and/or anisometropia, and the wearing of optimal spectacle correction for a minimum of 4 weeks at the time of enrollment (the protocol for correction of refractive error has been published[14]). Table 1 provides a complete listing of the eligibility and exclusion criteria. Based upon a postrandomization review, one patient in the full-time patching group was enrolled with presumed amblyopia but did not have a definitive amblyogenic factor (data were included in the analyses).

Treatment Protocols

Each patient was randomly assigned with equal probability to either 6 hours of daily patching or full-time patching (all hours or all but 1 waking hour). Randomization was accomplished on the study's website using a permuted-blocks design of varying block sizes, with a separate sequence of computer-generated random numbers for each clinical site.

Adhesive skin patches provided by the study (Coverlet Eye Occlusors, Beiersdorf-Jobst, Inc., Rutherford College, NC) were used unless there was skin allergy/irritation unresponsive to both local treatment with a skin emollient and a change in brand of patch, in which case a spectacle-mounted occluder could be prescribed. For both treatment groups, the protocol stipulated that the assigned patching regimen was to be used for the 4-month study duration, with the following exceptions: (1) if the acuity in the amblyopic eye improved to be the same as or 1 line worse than the acuity in the sound eye, patching could be continued at the initial number of hours or could be decreased at investigator discretion, provided it was at least 7 hours per week, and (2) if the acuity in the amblyopic eye became better than the acuity in the sound eye or if reverse amblyopia was considered by the investigator to have developed, then treatment could be continued, reduced, or stopped at investigator discretion. Before the 4-month masked outcome examination, additional hours of patching (for the 6-hour group) or alternate therapies for amblyopia were not to be prescribed, even if there was no response to treatment. For the 6-hour group, parents were advised that the daily hours of patching should be continuous, when possible, and that periods when the child was sleeping were not to be counted as patching time.

In addition to the patching, the parent was instructed to have the child spend at least 1 of the hours of patching time each day doing near-visual activities such as crafts, coloring, tracing, cutting out objects, connecting dots, hidden pictures and word finds, computerized videogames, reading, doing written homework assignments, or other activities requiring eye–hand coordination. The instruction to perform 1 hour of near activities was identical in the 6-hour and full-time patching groups.

Examination Procedures

Protocol-specified follow-up visits were conducted at 5±1 weeks and 17±1 weeks. Additional visits could be performed at investigator discretion. At baseline and at each protocol-specified visit, visual acuity was measured in both eyes using the Amblyopia Treatment Study visual acuity testing protocol,[12] administered by a study-certified vision examiner using an electronic visual acuity tester.[13]

At the 5-week visit, a questionnaire designed to assess the impact of the amblyopia treatment on the quality of life of the child and parent (Amblyopia Treatment Index[15,16]) was completed by the parent. The questionnaire consists of 19 Likert-type items, each scored from 1 to 5, with 5 representing the most difficulty. Three subscales measured the adverse effects of treatment (8 items), difficulties with compliance (6 items), and social stigma of treatment (3 items). Items were summed to compute each subscale score, and then scaled to a common range from 1 to 5.

At the 4-month outcome examination, visual acuity testing was conducted by a study-certified vision tester who was masked to the patient's treatment group. Additional testing done at this visit included assessment of ocular alignment with a simultaneous prism and cover test (the measurement was usually performed after visual acuity testing, but the testing order was not standardized and the examiner was not always the same examiner who made the baseline measurement) and measurement of stereoacuity with the Titmus Test (fly only), Randot Stereo Tests, and Randot Preschool Stereoacuity Test (Stereo Optical Co., Chicago, IL).

Adherence to the Treatment Protocol

Adherence to the treatment protocol was assessed by having the parent maintain a calendar on which the treatment (hours of

occlusion and completion of near activities) received each day was logged. The calendars were reviewed at each follow-up visit, and the investigator made an assessment of the patient's adherence to the prescribed treatment (excellent, 76–100% of prescribed treatment completed; good, 51–75%; fair, 26–50%; poor, ≤25%). An average compliance score was computed for each patient from the adherence assessment made at each visit while a patient was on treatment (assigning a value of 4 for excellent, 3 for good, 2 for fair, and 1 for poor). The average scores were then used to categorize each patient's adherence as excellent (>3.50), good (2.51–3.50), fair (1.51–2.50), or poor (≤1.50).

At the Coordinating Center, each follow-up examination form was reviewed to assess whether the investigator was properly prescribing the treatment protocol, and any necessary feedback was provided to the investigator.

Adverse Reactions

Visual acuity in the sound eye at 4 months was the primary safety outcome. For patients whose sound eye acuity was reduced from baseline by ≥2 lines, subsequent follow-up data (not part of the study protocol) were used to evaluate whether the decrease represented a real and permanent reduction. At each study visit, the parent was asked about skin irritation from the patching.

Statistical Methods

The primary outcome was the 4-month amblyopic eye logarithm of the minimum angle of resolution (logMAR) visual acuity score. Monte Carlo simulations were performed to estimate the sample size for a type 1 error rate of 5%, based on projecting a standard deviation of 0.34 for the 4-month acuity scores, a mean difference between groups of 0.2 logMAR units, a correlation between the baseline and outcome scores of 0.38, and a 5% loss to follow-up rate. A minimum sample size of 160 patients was selected to have 80% power for 2 subgroup analyses based on the cause of amblyopia ([1] strabismus with a deviation of ≥5 Δ or a history of strabismus surgery, with or without anisometropia, and [2] strabismus with a deviation of <5 Δ and no history of strabismus surgery, with or without anisometropia, or anisometropia alone). Patient recruitment continued until a prespecified ending date, and as a result of accrual being faster than anticipated, the final recruitment total exceeded the minimum sample size estimate.

The treatment groups were compared using an analysis of covariance model in which the 4-month logMAR acuity scores were adjusted for baseline acuity. Confounding and interaction between baseline factors (age, cause of amblyopia, and amblyopic eye acuity) and treatment group on the outcome acuity were assessed by including covariates and interaction terms in the analysis of covariance models. A difference between treatment groups in the variance of the change in amblyopic eye acuity from baseline to 4 months was evaluated with a Brown–Forsythe test for homogeneity of variances.

Patients were included in the primary analysis if they had a visual acuity measurement in the amblyopic eye within the time window of the 4-month visit or, in the absence of such a visit, if they had a visual acuity measurement that was no more than 1 month before or 3 months after this time window. An analysis including only those patients having an examination within the prespecified 4-month time window produced results similar to the primary analysis (i.e., no significant difference between groups). To assess for potential bias from incomplete follow-up, an analysis including all patients was conducted using the last-observation-carried-forward method to impute for missing data (i.e., for patients missing the outcome examination, the visual acuity recorded at the last follow-up examination was used as the outcome acuity; for patients with no follow-up, the baseline acuity was used).

Methods used to analyze the amblyopic eye logMAR acuity scores at the 5-week visit paralleled the analyses conducted on the 4-month data. Patients were included in the 5-week visit analysis if they had a visual acuity measurement within the time window of the 5-week visit or, in the absence of such a visit, if they had a visual acuity measurement no longer than 8 weeks after randomization.

The treatment group difference in sound eye visual acuity at 4 months was evaluated in an analysis of covariance model in which the logMAR sound eye acuity scores were adjusted for baseline acuity and age. The proportions of patients in each treatment group whose 4-month sound eye acuity was ≥2 lines worse than baseline were compared with a Fisher exact test.

The Amblyopia Treatment Index questionnaire subscale scores were compared between the 2 treatment groups with Wilcoxon rank sum tests. For the binocularity tests, the treatment groups were compared with Wilcoxon rank sum tests for continuous variables and with Fisher exact tests for categorical variables. The mean number of visits before the outcome examination in each group was compared with a *t* test. Factors predictive of improvement in amblyopic eye acuity were evaluated with linear regression controlling where indicated for baseline acuity and age. All analyses followed the intention-to-treat principle (i.e., the treatment group data were based on the randomization assignments, not on the actual treatment received or whether the treatment protocol was followed). All reported *P* values are 2 tailed. Analyses were conducted using SAS version 8.2 (SAS Institute Inc., Cary, NC).

Results

Between May 2001 and March 2003, 175 patients entered the trial, with 85 assigned to the 6-hour patching group and 90 assigned to the full-time patching group. The number of patients enrolled per site at the 32 sites ranged from 1 to 28 (median = 4). The average age of the patients was 4.8 years; 46% were female and 83% were white. The mean visual acuity in the amblyopic eye at enrollment was 0.90 logMAR (approximately 20/160), with a mean difference in acuity between eyes of 7.8 lines. Table 2 provides the baseline characteristics of each treatment group.

Patient Follow-up

The primary outcome examination was completed by 73 (86%) of 85 patients in the 6-hour group and by 84 (93%) of 90 patients in the full-time group (see Fig 1 for the number of patients completing the examination within the time window). The vision tester was masked to treatment group for 92% of these examinations (94% in the 6-hour group and 89% in the full-time group). Before the outcome examination, patients in each group had a similar number of follow-up visits (mean number of visits = 1.3 and 1.4 in the 6-hour and full-time groups, respectively, $P = 0.32$).

Treatment

Among the patients completing the outcome examination, the number of hours of patching prescribed at baseline was the same throughout follow-up for all but 1 of the patients in the 6-hour group whose patching hours were decreased because the amblyopic eye improved to be within 1 line of the sound eye. In the full-time group, the prescribed patching time was reduced for this reason in 8 patients and for other reasons (e.g., possible reverse amblyopia or skin irritation) in 6 patients. These 6 patients, for

Table 2. Baseline Characteristics According to Treatment Group

	Total (n = 175)	6-Hour Group (n = 85)	Full-time Group (n = 90)
Gender [female n (%)]	81 (46)	41 (48)	40 (44)
Age (yrs) [n (%)]			
<3	7 (4)	5 (6)	2 (2)
3–<4	35 (20)	21 (25)	14 (16)
4–<5	50 (29)	24 (28)	26 (29)
5–<6	58 (33)	23 (27)	35 (39)
6–<7	25 (14)	12 (14)	13 (14)
Mean (SD)	4.8 (1.1)	4.7 (1.1)	5.0 (1.0)
Race [n (%)]			
Caucasian	146 (83)	70 (82)	76 (84)
African-American	10 (6)	7 (8)	3 (3)
Hispanic	13 (7)	4 (5)	9 (10)
Asian	3 (2)	2 (2)	1 (1)
Mixed	1 (0.6)	0	1 (1)
Other	2 (1)	2 (2)	0
Prior treatment for amblyopia [n (%)]			
None	150 (86)	73 (86)	77 (86)
Patching (skin)	16 (9)	8 (9)	8 (9)
Atropine (or other cycloplegic drug)	1 (0.6)	0	1 (1)
Patching and atropine	5 (3)	3 (4)	2 (2)
Other	3 (2)	1 (1)	2 (2)
Cause of amblyopia 1* [n (%)]			
Strabismus	47 (27)	25 (29)	22 (24)
Anisometropia	60 (34)	30 (35)	30 (33)
Strabismus and anisometropia	67 (38)	30 (35)	37 (41)
Cause of amblyopia 2* [n (%)]			
Strabismus	91 (52)	44 (52)	47 (52)
Anisometropia–microtropia	83 (47)	41 (48)	42 (47)
Visual acuity, amblyopic eye n (%)			
20/400	10 (6)	4 (5)	6 (7)
20/320	10 (6)	6 (7)	4 (4)
20/250	14 (8)	6 (7)	8 (9)
20/200	32 (18)	17 (20)	15 (17)
20/160	24 (14)	11 (13)	13 (14)
20/125	39 (22)	14 (16)	25 (28)
20/100	46 (26)	27 (32)	19 (21)
Mean (SD) logMAR	0.90 (0.18)	0.89 (0.18)	0.90 (0.18)
Visual acuity, sound eye n (%)			
20/40	30 (17)	15 (18)	15 (17)
20/32	40 (23)	21 (25)	19 (21)
20/25	49 (28)	24 (28)	25 (28)
20/20	41 (23)	19 (22)	22 (24)
20/16	15 (9)	6 (7)	9 (10)
Mean (SD) logMAR	0.12 (0.12)	0.12 (0.12)	0.11 (0.12)
Interocular acuity difference (lines)			
Mean (SD)	7.8 (2.1)	7.7 (2.3)	7.9 (2.0)
Refractive error in sound eye (diopters)†			
Mean (SD)	2.91 (2.18)	3.18 (2.39)	2.66 (1.95)
Refractive error in amblyopic eye (diopters)†			
Mean (SD)	4.98 (2.58)	4.98 (2.86)	4.98 (2.31)

logMAR = logarithm of the minimum angle of resolution; SD = standard deviation.
*One patient in the full-time patching group was enrolled with indeterminate cause for amblyopia. Cause of amblyopia was categorized by 2 methods. See Table 1 for definitions of cause of amblyopia 1. For cause of amblyopia 2, the strabismus category is defined as strabismus with a deviation of ≥5 Δ or a history of strabismus surgery (with or without anisometropia), and the anisometropia–microtropia category is defined as either (1) strabismus with a deviation of <5 Δ and no history of strabismus surgery (with or without anisometropia) or (2) anisometropia alone (meeting criteria for anisometropia in Table 1).
†Spherical equivalent.

whom the prescribed patching time was reduced during follow-up from full-time to 6 to 10 hours, had a mean improvement from baseline to 4 months in amblyopia eye acuity of 4.5 lines, which was similar to the improvement seen in the rest of the full-time group.

Five patients (2 in the 6-hour group and 3 in the full-time group) were prescribed a spectacle-mounted occluder as a substitute for patching because of skin irritation. No patients in either group were prescribed a treatment other than occlusion (e.g., topical atropine sulfate 1%) during the 4-month follow-up period.

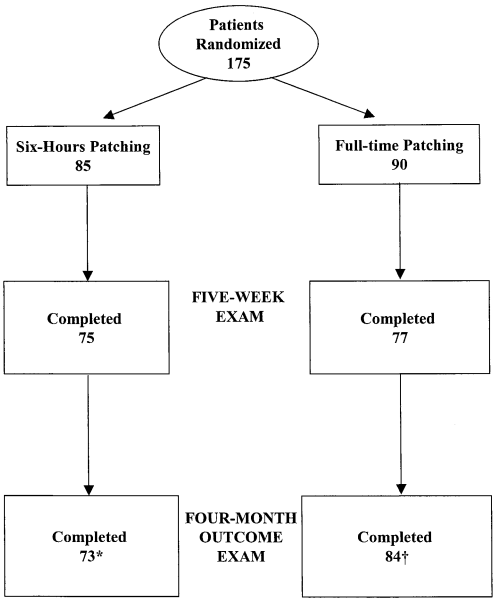


Figure 1. Flow chart showing visit completion for each treatment group. *Six-hour patching group: among the 12 patients with incomplete follow-up, 4 were enrolled but had no further follow-up, and 8 completed a follow-up visit but then dropped out. Of the completed visits, 59 were completed in window (16–18 weeks), 2 were completed early (12 to <16 weeks), and 12 were completed late (>18 to 31 weeks). †Full-time patching group: among the 6 patients with incomplete follow-up, 4 were enrolled but had no further follow-up, and 2 completed a follow-up visit, then dropped out. Of the completed visits, 61 were completed in window (16–18 weeks), 2 were completed early (12 to <16 weeks), and 21 were completed late (>18 to 31 weeks).

Patient adherence with the prescribed treatment was judged by the investigator to be excellent in 53%, good in 30%, fair in 11%, and poor in 5% of patients in the 6-hour group and excellent in 32%, good in 43%, fair in 15%, and poor in 10% of patients in the full-time group.

Effect of Treatment on Visual Acuity in the Amblyopic Eye

Substantial improvement in visual acuity from baseline to 4 months occurred in both the 6-hour group and the full-time group (Table 3, Fig 2), and the course of acuity improvement appeared similar in the 2 treatment groups (Fig 3).

At the 5-week visit, visual acuity had improved from baseline by an average of 3.5 lines in the 6-hour group and by 3.7 lines in the full-time group (mean difference between groups in logMAR acuity adjusted for baseline acuity = 0.02, 95% confidence interval = −0.04 to 0.07).

At the 4-month visit, improvement from baseline averaged 4.8 lines in the 6-hour group and 4.7 lines in the full-time group (mean difference between groups in logMAR acuity adjusted for baseline acuity = −0.03, 95% confidence interval = −0.11 to 0.05). The results were similar after adjusting for the imbalance between groups in age (mean difference between groups in logMAR acuity adjusting for age and baseline acuity = −0.01, 95% confidence interval = −0.08 to 0.07) and when the analysis used the best amblyopic eye visual acuity obtained at any visit during the 4-month follow-up period (mean difference between groups in logMAR acuity adjusting for baseline acuity = −0.01, 95% confidence interval = −0.08 to 0.07). The results also were similar to the primary analysis when the patients with incomplete follow-up were included in the analysis using the last-observation-carried-forward method as described in "Patients and Methods" (mean difference between groups in logMAR acuity adjusted for baseline acuity = −0.01, 95% confidence interval = −0.09 to 0.07).

For the 4-month amblyopic eye acuity results, there was no statistical evidence for an interaction between treatment group and baseline amblyopic eye acuity ($P = 0.24$), cause of amblyopia ($P = 0.34$), or age ($P = 0.94$) (Table 4). The change in amblyopic eye acuity from baseline to 4 months showed greater variability in the full-time group than in the 6-hour group (standard deviation of lines change from baseline to 4 months = 2.9 and 2.3 in the 2 groups, respectively, $P = 0.04$).

Adverse Effects of Treatment

Sound eye acuity scores on average were slightly better at 4 months versus baseline in the 6-hour group but not in the full-time group (mean change = 0.5 vs. 0.1 lines, $P = 0.04$; Table 5). This treatment group difference was apparent in both the younger and the older children (among patients <5 years old, mean change = 0.4 vs. 0.1; among patients ≥5 years old, mean change = 0.6 vs. 0.0). There were 3 patients (4%) in the 6-hour group and 9 patients (11%) in the full-time group whose sound eye tested ≥2 lines worse at 4 months compared with baseline ($P = 0.14$). With further follow-up, the sound eye acuity tested the same as or better than baseline for 9 of these 12 patients. One patient in the full-time group remained 1 line worse than baseline (20/25 vs. 20/20), and one patient in each group had no further follow-up.

Assessment of ocular alignment at the 4-month examination found that among patients with no ocular deviation at baseline, 2 patients in the 6-hour group and one patient in the full-time group were noted to have an intermittent exotropia at the 4-month examination, and 4 patients in the 6-hour group and 5 patients in the full-time group were noted to have a small-angle strabismus (1–8 Δ) at distance fixation. Three patients in the 6-hour group and one patient in the full-time group had a preexisting esotropia that increased by >10 Δ.

There was no difference between groups in binocularity at the outcome examination measured with the Randot Stereo Tests ($P = 0.90$ for contour test, $P = 0.15$ for random dot shapes test, and $P = 0.70$ for suppression test) or the Randot Preschool Stereoacuity Test ($P = 0.64$).

For the patients completing the 5-week visit, the Amblyopia Treatment Index was completed by 71 of 75 (95%) of the parents in the 6-hour group and by 74 of 77 (96%) in the full-time group. Median overall scores were 2.35 in the 6-hour group and 2.59 in the full-time group ($P = 0.12$), indicating that both treatments were perceived to be well tolerated on the 5-point Likert scale. The questionnaire scores were also similar between the 6-hour and full-time groups on all 3 subscales (*adverse effects* median = 2.25 vs. 2.50, $P = 0.06$; *treatment compliance* median = 2.33 vs. 2.42, $P = 0.64$; and *social stigma* median = 3.00 vs. 3.00, $P = 0.10$).

Factors Predictive of Improvement in Amblyopic Eye

Data were reviewed overall and within treatment group to evaluate whether any patient factors were associated with the amount of visual acuity improvement from baseline to 4 months. Patients improved a similar amount within subgroups based upon gender, race, and cause of amblyopia (data not shown). However, patients who started with worse amblyopic eye acuity improved more than patients who started with better acuity (5.9 lines of improvement in patients with 20/200–20/400 vs. 4.1 lines of improvement in

Table 3. Visual Acuity in the Amblyopic Eye at the 4-Month Outcome Examination by Treatment Group

	6-Hour Group (n = 73)	Full-time Group (n = 84)
Lines of improvement from baseline to outcome examination [n (%)]		
−2	0	1 (1)
−1	1 (1)	3 (4)
0	2 (3)	4 (5)
+1	2 (3)	5 (6)
+2	5 (7)	2 (2)
+3	7 (10)	16 (19)
+4	18 (25)	8 (10)
+5	11 (15)	10 (12)
+6	10 (14)	15 (18)
+7	9 (12)	8 (10)
+8	4 (5)	4 (5)
+9	2 (3)	4 (5)
+10	2 (3)	1 (1)
+11	0	3 (4)
Mean (SD)	4.8 (2.3)	4.7 (2.9)
Distribution of visual acuity scores at outcome examination [n (%)]		
20/400	0	0
20/320	2 (3)	1 (1)
20/250	1 (1)	2 (2)
20/200	0	2 (2)
20/160	2 (3)	3 (4)
20/125	1 (1)	3 (4)
20/100	4 (5)	6 (7)
20/80	3 (4)	6 (7)
20/63	9 (12)	9 (11)
20/50	14 (19)	16 (19)
20/40	19 (26)	15 (18)
20/32	12 (16)	15 (18)
20/25	5 (7)	5 (6)
20/20	1 (1)	0
20/16	0	1 (1)
Mean (SD)	0.40 (0.24)	0.44 (0.26)
Difference between treatment groups in mean logMAR acuity at outcome examination* (95% confidence interval for difference)	−0.03 (−0.11 to 0.05)	

logMAR = logarithm of the minimum angle of resolution; SD = standard deviation.
*Adjusted for baseline visual acuity in analysis of covariance model. A negative difference indicates that the 6-hr group scores were better than full-time group scores.

patients with baseline acuity of 20/100–20/160, $P<0.001$). Also, younger patients tended to show more improvement than older patients (5.5 lines of improvement in patients <5 years old vs. 3.8 lines of improvement in patients ≥5 years old, $P<0.001$). Among patients with baseline acuity of 20/100 to 20/160, patients <5 years old improved an average of 4.6 lines, compared with 3.6 lines of improvement in patients ≥5 years old. Among patients with baseline acuity of 20/200 to 20/400, patients <5 years old improved an average of 6.9 lines, compared with 4.4 lines of improvement in patients ≥5 years old ($P<0.001$ for association between outcome acuity and age, controlling for baseline acuity).

Discussion

We compared the effectiveness of prescribing 6 hours of daily patching to that of prescribing full-time patching (all hours or all but 1 hour per day) for the treatment of severe amblyopia (20/100–20/400) in 175 children younger than 7 years. The study was conducted in both university- and community-based practices and was designed to approximate usual clinical practice, with the exceptions of (1) the use of randomization to determine the treatment prescribed and (2) the use of a standardized protocol to measure visual acuity. We found that amblyopia improved with both patching regimens and that, overall, there was no demonstrable advantage to prescribing a greater number of hours of patching in either the rate or the magnitude of improvement after 4 months of treatment.

The parental questionnaire completed after the first 5 weeks of treatment indicated that both patching regimens were well tolerated. We found no difference between groups in the effect of treatment on ocular alignment or on binocularity. We did, however, find that, in the 6-hour group, sound eye acuity was about half a line better on average at 4 months than at baseline, whereas, in the full-time group, little change was seen. The change observed in the 6-hour group, which we presume is due to a learning effect, is greater than what we observed in our prior amblyopia studies of children in this age group. In our trial comparing atropine and patching for moderate amblyopia,[17] the mean

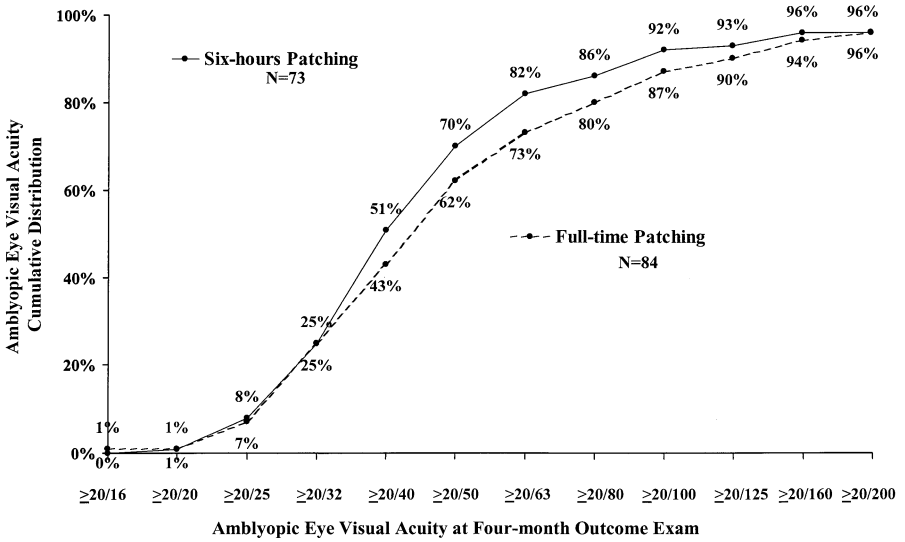


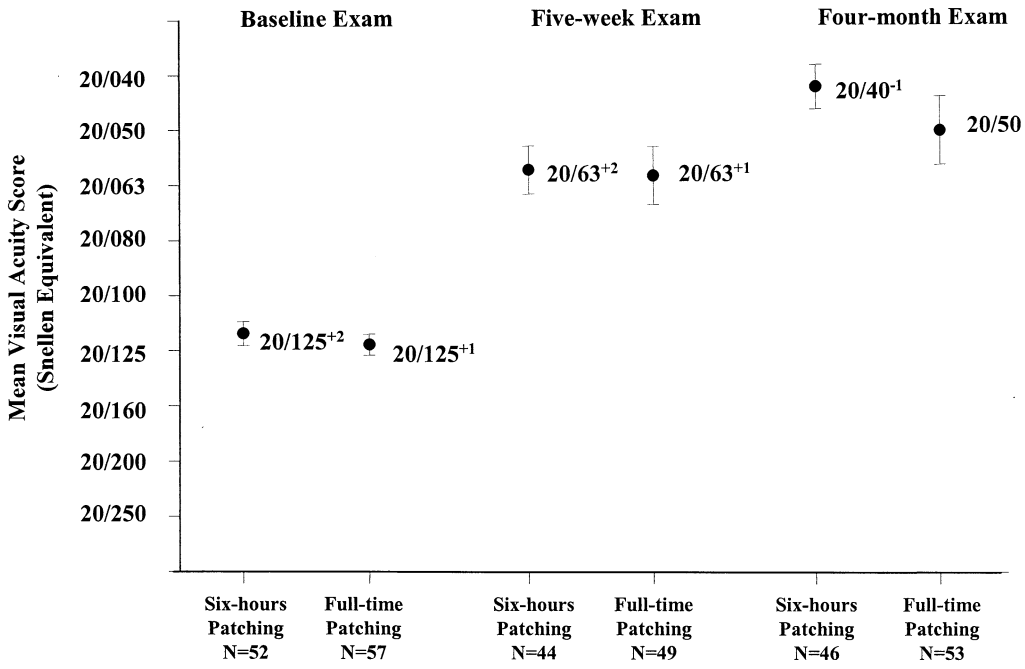
Figure 2. Cumulative distribution of amblyopic eye visual acuity scores at 4-month outcome examination according to treatment group.

change in sound eye acuity from baseline to 4 months in the patching group (most of whom were treated with 6–8 hours of patching per day) was 0.3 lines. In our trial comparing 2 hours and 6 hours of daily patching for moderate amblyopia,[10] the mean change in sound eye acuity from baseline to 4 months was 0.3 lines in the 2-hour group and 0.0 lines in the 6-hour group. In the current study, the difference in 4-month sound eye acuity between groups is principally due to the full-time group having a greater number of patients ≥5 years of age whose sound eye acuity decreased by 2 or 3 lines than did the 6-hour group. Because we would not expect older children to be more susceptible to reverse amblyopia than younger children, this finding reduces the plausibility of the treatment group difference being real rather than due to chance. However, we cannot rule out the possibility that full-time patching adversely affected the sound eye more often than did 6 hours of patching. Even if the effect on sound eye acuity induced by full-time patching was real, it appeared to be transient and resolved with further follow-up. In their retrospective series of 175 patients who underwent full-time occlusion therapy, Scott et al[9] reported that only one patient suffered irreversible occlusion amblyopia, and that "other cases of occlusion amblyopia reverted when the occlusion was stopped," occasionally requiring reverse patching. In a recent paper (Pfeifer WL, Keech RV, Kutschke PJ, Scott WE. Incidence and long term results of occlusion amblyopia with full time patching. Presented at: American Association for Pediatric Ophthalmology and Strabismus 29th Annual Meeting, March 24, 2003; Waikoloa, Hawaii), Scott's group reported a 25% incidence of occlusion amblyopia in 1541 patients treated with full-time occlusion, but they also reported that the risk of permanent visual loss was very low.

We did not include an untreated control group in the trial. Therefore, our conclusion that both 6 hours per day and full-time patching improved visual acuity is based on clinical experience indicating that substantial improvement of amblyopia rarely occurs without treatment, and that the amount of observed improvement (almost 5 lines, on average, at 4 months) substantially exceeded any potential learning effect or age effect.[12,13,18] A slight overestimate of the amount of improvement attributable to 4 months of patching could have occurred from including some patients with anisometropia who were wearing their optimal spectacle correction for only 4 weeks at the time of enrollment. Such patients might have experienced some on-study improvement due to the spectacles alone. Although these cases would not have affected the relative treatment group comparison and thus would have no bearing on our conclusions, their inclusion could have produced a slight overestimate of the absolute amount of improvement experienced by such patients in both treatment groups.

The amount of improvement that occurred during the 4 months of the trial should not be considered to be the maximum amount of improvement that can occur with patching for severe amblyopia. The 4-month follow-up period represented the maximum length of time we believed that the fixed treatment regimens (6 hours per day or full-time patching) could be prescribed before a change in the treatment might be necessary. In our previously reported trial comparing atropine and patching for moderate amblyopia,[17] among the patients in the patching group whose acuity was worse than 20/20 at 4 months, 46% improved at least 1 additional line at 6 months. Therefore, it is likely that neither group in the current study achieved the maximum possible improvement by 4 months, although we have no reason to believe that the full-time group would show greater additional improvement than the 6-hour group from subsequent therapy, if the fixed regimens had been sustained for a longer period of time.

We could identify no sources of confounding or bias to explain our findings. Baseline amblyopic eye acuity was similar in the 2 groups. There was a slight imbalance between groups in the distribution of patient ages, with the full-time group having a slightly older average age than the 6-hour group. However, adjusting for the difference in

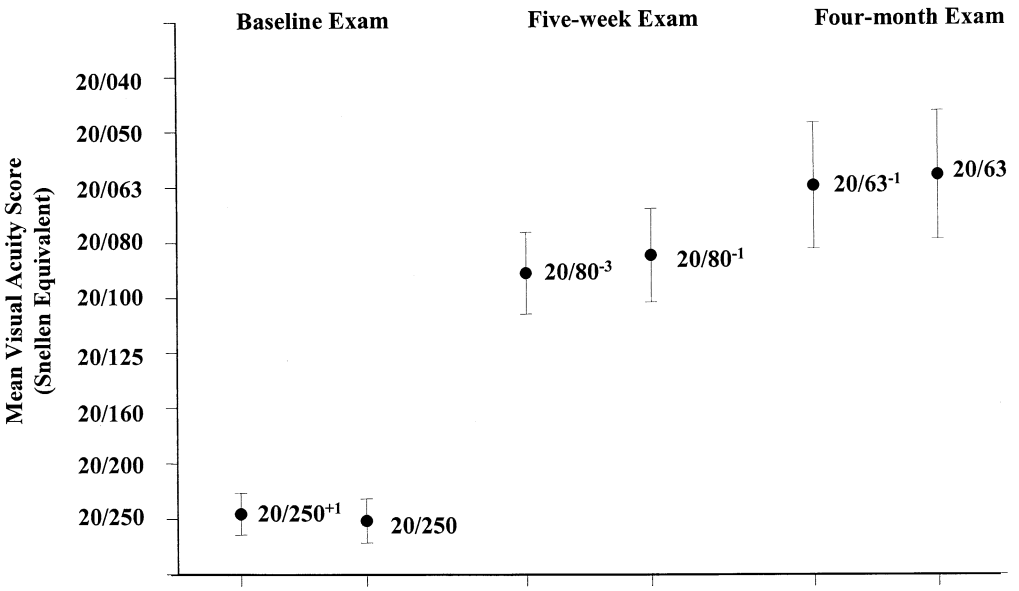


A

	Six-hours Patching N=52	Full-time Patching N=57	Six-hours Patching N=44	Full-time Patching N=49	Six-hours Patching N=46	Full-time Patching N=53
20/400						
20/320						
20/250						
20/200				2%		
20/160	21%	23%	2%			4%
20/125	27%	44%		8%		6%
20/100	52%	33%	7%	10%	4%	6%
20/80			18%	8%	2%	8%
20/63			34%	20%	15%	11%
20/50			14%	33%	17%	19%
20/40			20%	12%	30%	23%
20/32			5%	4%	22%	19%
20/25					9%	6%
20/20				2%		
20/16						
Mean logMAR (SD)	0.77 (0.08)	0.79 (0.07)	0.47 (0.15)	0.48 (0.19)	0.33 (0.15)	0.41 (0.21)

Figure 3. Amblyopic eye visual acuity in each group at baseline, 5 weeks, and 4 months; stratified by visual acuity at baseline: **A**, 20/100 to 20/160; **B**, 20/200 to 20/400. The point estimates and 95% confidence intervals are shown. Snellen equivalents are provided for the logarithm of the minimum angle of resolution (logMAR) scores. SD = standard deviation.

patient ages in analysis indicated that this did not confound the results. Likewise, an analysis to assess the impact of incomplete follow-up did not suggest that this was a source of bias. Although the patients, parents, and investigators were by the nature of this study unmasked to the treatment group assignments, masking of the primary visual acuity outcome measurement was achieved in 92% of cases. Visual acuity testing was performed by a standardized protocol using a visual acuity testing instrument developed specifically for this study to ensure consistency of testing across our many sites.[13] With the actual sample size of 157 patients (number completing the primary outcome visit) and using the observed data as the basis for the standard deviation of the outcome acuity scores, statistical power for the overall primary analysis was 90% to detect a treatment group difference of 0.12 logMAR (about 1 line). Thus, it is unlikely that a true benefit of meaningful magnitude from prescribing full-time patching versus prescribing 6 hours of



B

	Six-hours Patching N=33	Full-time Patching N=33	Six-hours Patching N=31	Full-time Patching N=28	Six-hours Patching N=27	Full-time Patching N=31
20/400	12%	18%				
20/320	18%	12%			7%	3%
20/250	18%	24%		4%	4%	6%
20/200	52%	45%	10%	7%		6%
20/160			13%	4%	7%	3%
20/125			10%	11%	4%	
20/100			16%	21%	7%	10%
20/80			16%	18%	7%	6%
20/63			23%	11%	7%	10%
20/50			6%	18%	22%	19%
20/40			6%	4%	19%	10%
20/32					7%	16%
20/25				4%	4%	6%
20/20					4%	
20/16						3%
Mean logMAR (SD)	1.09 (0.11)	1.10 (0.12)	0.66 (0.20)	0.63 (0.23)	0.52 (0.32)	0.50 (0.33)

Figure 3. Continued

patching exists but was not detected in this study. Our finding of similar improvement with part-time and full-time patching has been reported previously. In a selected retrospective case series, Elder[19] described similar "time to cure" and similar "proportions of patients cured" with part-time patching (6 hours per day) and full-time patching.

Why did we not find a difference between full-time patching and part-time patching in treating severe amblyopia? A number of possibilities exist, including (1) the 2 groups actually wore the patch for similar amounts of time and (2) there is a maximum rate of response to patching, which may be achieved with 6 or fewer hours per day, so there might be no incremental gain with full-time patching. Regarding the first possibility, we recognize that our results relate to the prescription of a specific number of hours of patching rather than to the actual number of hours of occlusion that were performed. Although we asked the parents to maintain a compliance calendar and although the investigators made an assessment of compliance at each visit, these data are insufficient for an analysis based on the actual number of hours of patching performed. It is possible that some of the patients prescribed full-time patching may have actually worn the patch far less than full time, and that, as a group, their average wearing time might have been close

Table 4. Treatment Effect at the 4-Month Outcome Examination According to Baseline Patient Characteristics

Baseline Characteristic	(6-Hour, Full-time)	Mean Lines of Improvement from Baseline to 4 Months in the Amblyopic Eye		*P* for Interaction*
		6-Hour Group	*Full-time Group*	
All patients	73, 84	4.8	4.7	
Gender				0.54
Male	35, 45	4.6	4.6	
Female	38, 39	5.1	4.7	
Race				0.42
Caucasian	59, 71	5.1	4.8	
Other	14, 13	3.6	3.7	
Age (yrs)				0.94
<4	21, 16	5.8	6.4	
4–<5	24, 23	5.3	4.9	
5–<6	20, 33	3.9	3.8	
6–<7	8, 12	3.1	4.3	
Baseline acuity				0.24
20/100 to 20/160	46, 53	4.4	3.8	
20/200 to 20/400	27, 31	5.6	6.1	
Prior amblyopia treatment				0.76
Yes	7, 13	3.1	3.5	
No	66, 71	5.0	4.9	
Cause of amblyopia 1†				0.34
Strabismus	20, 21	5.5	4.6	
Anisometropia	29, 28	5.0	4.6	
Strabismus and anisometropia	24, 34	4.1	4.9	
Cause of amblyopia 2†				0.28
Strabismus	35, 43	4.5	5.0	
Anisometropia–microtropia	38, 40	5.1	4.4	

*The *P* values are for the interaction between the characteristic and treatment group from an analysis of covariance model with the 4-mo amblyopic eye acuity score as the dependent variable and baseline amblyopic eye acuity, treatment group, the characteristic, and an interaction term between treatment group and the characteristic as independent variables. Age and baseline acuity are included in models as continuous variables.
†One patient in the full-time patching group was enrolled with indeterminate cause for amblyopia and is not included in the table. See Table 1 for definitions of cause of amblyopia 1, and Table 2 for definition of cause of amblyopia 2.

to the 6-hour group's duration. Preliminary data from Gottlob's group in Leicester, England (ARVO abstract available at: http://abstracts.iovs.org/cgi/content/abstract/44/5/4797), using an occlusion dose monitor, suggest that a longer duration of prescribed patching is associated with more variability in actual wearing time. This might explain our finding of increased variability of outcome visual acuity in the full-time group versus the 6-hour group. Additional studies await the widespread availability of a simple and acceptable occlusion dose monitor beyond the European research groups.[20–22]

Regarding the hypothesis of a "maximal rate of improvement" as a possible explanation of no difference between full-time and part-time patching, Cleary[23] found no difference between full-time and part-time patching during the first 200 hours of cumulative patching. Both Cleary's findings and ours are consistent with the speculation that recovery from amblyopia may be rate limited at a biochemical or biophysical level in the ocular–cortical pathway. Further studies designed to address this issue are warranted, and most likely would need to use an occlusion dose monitor, as discussed above.

Our results need to be viewed in the context of our instructions to have the children in both treatment groups perform near-visual activities for at least 1 hour per day while patched. We do not know to what extent performing near-visual tasks during a proportion of the patching time contributes to the improvement in visual acuity. We are planning a randomized trial to address this issue.

It is not known whether even fewer than 6 hours of patching per day might improve severe amblyopia. In our previous study of moderate amblyopia (20/40–20/80), we found that, when combined with at least 1 hour of near activities, 2 hours of prescribed patching per day resulted in improvement similar to that with 6 hours per day. In a future study, we will be evaluating whether 2 hours of daily patching can improve severe amblyopia.

In this study of severe amblyopia, we found a small age effect on success of amblyopia treatment; younger children (<5 years old) showed slightly more improvement than older children (5 to <7 years old). This age effect was not found in our previous studies of moderate amblyopia in the same age range.[10,17] Our results on the effect of patient age on outcome are consistent with previous retrospective studies suggesting older children respond less well to treatment.[24,25] We are currently conducting a randomized trial of amblyopia treatment in school-age children (7 to <18 years), which will better determine whether there is an upper age limit for effective treatment of amblyopia.

Regarding depth of amblyopia, we found greater im-

Table 5. Visual Acuity in the Sound Eye at the 4-Month Outcome Examination by Treatment Group

Lines of Change from Baseline to 4 Months in Sound Eye	6-Hour Group	Full-time Group
All patients [n (%)]	n = 73	n = 84
−4	1 (1)	0
−3	0	2 (2)
−2	2 (3)	7 (8)
−1	9 (12)	12 (14)
0	27 (37)	33 (39)
+1	22 (30)	24 (29)
+2	7 (10)	4 (5)
+3	4 (5)	2 (2)
+4	1 (1)	0
Mean (SD)	0.5 (1.3)	0.1 (1.2)
Patients <5 yrs old at enrollment [n (%)]	n = 45	n = 39
−3	0	1 (3)
−2	2 (4)	1 (3)
−1	5 (11)	8 (21)
0	18 (40)	15 (38)
+1	13 (29)	11 (28)
+2	6 (13)	3 (8)
+3	1 (2)	0
+4	0	0
Mean (SD)	0.4 (1.1)	0.1 (1.1)
Patients ≥5 yrs old at enrollment [n (%)]	n = 28	n = 45
−4	1 (4)	0
−3	0	1 (2)
−2	0	6 (13)
−1	4 (14)	4 (9)
0	9 (32)	18 (40)
+1	9 (32)	13 (29)
+2	1 (4)	1 (2)
+3	3 (11)	2 (4)
+4	1 (4)	0
Mean (SD)	0.6 (1.6)	0.0 (1.3)

SD = standard deviation.
*Among patients with a ≥2-line decrease in sound eye acuity, with further follow-up, sound eye acuity tested the same or better than baseline in 2 of 3 in the 6-hr group and 7 of 9 in the full-time group; one patient in the full-time group remained 1 line worse (20/25) than baseline (20/20), and one patient in each group had no further follow-up.

provement in visual acuity in the patients with worse baseline visual acuity (20/200–20/400) than in those with better visual acuity (20/100–20/160). This effect was seen in both the older and the younger children. However, the 4-month visual acuity was worse in those patients who started with worse baseline visual acuity. This finding is consistent with previous retrospective studies examining the relationship between baseline amblyopic visual acuity and success with patching.[25] Nevertheless, it is possible that, with further treatment in our patients, the outcome visual acuity might have been similar in those with worse and better baseline acuity.

We found that the degree of improvement in 4-month visual acuity did not depend on whether or not the cause for amblyopia was strabismus, anisometropia, or both. This similar response for the different types of amblyopia is consistent with that reported by Flynn et al.[25]

In translating our results into clinical practice, the findings must be viewed in the context of the clinical profile of the cohort enrolled in the study. The eligibility criteria for enrollment were broad, with the intention to include most children with severe strabismic and/or anisometropic amblyopia (specifically excluding deprivation amblyopia) and younger than 7 years who developmentally were able to perform an HOTV optotype visual acuity testing protocol, effectively setting a lower age limit of about 3 years. To avoid including prior treatment failures in the study, enrollment was restricted to children who either had not been treated for amblyopia previously or had not received patching treatment within 6 months of enrollment and had not received other amblyopia treatment of any type (other than spectacles) within 1 month of enrollment. In designing the trial to mirror a real-world situation, we limited compliance aids to those that are commonly used in clinical practice: an instruction sheet and a calendar on which to record at home the treatment received each day. Nevertheless, we recognize that patients participating in a clinical trial may differ from patients in usual practice, and our patients' level of compliance may have been better than what may be achieved in the real world.

In summary, 6 hours of prescribed daily patching seems to be as effective as prescribed full-time patching (all hours or all but 1 hour per day) in treating severe amblyopia in children 3 to less than 7 years of age. Prescribing fewer hours of daily patching may ease the implementation of patching therapy and monitoring of compliance for some parents.

References

1. Ederer F, Krueger DE. Report on the National Eye Institute's Visual Acuity Impairment Survey Pilot Study; Washington: National Eye Institute; 1984:81–4.
2. Attebo K, Mitchell P, Cumming R, et al. Prevalence and causes of amblyopia in an adult population. Ophthalmology 1998;105:154–9.
3. von Noorden GK. Binocular Vision and Ocular Motility: Theory and Management of Strabismus. 5th ed. St. Louis, Mo: Mosby; 1996:206–96.
4. Hiscox F, Strong N, Thompson JR, et al. Occlusion for amblyopia: a comprehensive survey of outcome. Eye 1992;6: 300–4.
5. Olson RJ, Scott WE. A practical approach to occlusion therapy for amblyopia. Semin Ophthalmol 1997;12:161–5.
6. Woodruff G, Hiscox F, Thompson JR, Smith LK. The presentation of children with amblyopia. Eye 1994;8:623–6.
7. Lithander J, Sjostrand J. Anisometropic and stabismic amblyopia in the age group 2 years and above: a prospective study of the results of treatment. Br J Ophthalmol 1991;75:111–6.
8. Newman DK, Hitchcock A, McCarthy H, et al. Preschool vision screening: outcome of children referred to the hospital eye service. Br J Ophthalmol 1996;80:1077–82.
9. Scott WE, Stratton VB, Fabre J. Full-time occlusion therapy for amblyopia. Am Orthopt J 1980;30:125–30.
10. Pediatric Eye Disease Investigator Group. A randomized trial of patching regimens for treatment of moderate amblyopia in children. Arch Ophthalmol 2003;121:603–11.
11. Beck RW. Clinical research in pediatric ophthalmology: the

Pediatric Eye Disease Investigator Group. Curr Opin Ophthalmol 2002;13:337–40.
12. Holmes JM, Beck RW, Repka MX, et al, the Pediatric Eye Disease Investigator Group. The Amblyopia Treatment Study visual acuity testing protocol. Arch Ophthalmol 2001;119: 1345–53.
13. Moke PS, Turpin AH, Beck RW, et al. Computerized method of visual acuity testing: adaptation of the Amblyopia Treatment Study visual acuity testing protocol. Am J Ophthamol 2001;132:903–9.
14. Pediatric Eye Disease Investigator Group. The clinical profile of moderate amblyopia in children younger than 7 years. Arch Ophthalmol 2002;120:281–7.
15. Cole SR, Beck RW, Moke PS, et al, the Pediatric Eye Disease Investigator Group. The amblyopia treatment index. J AAPOS 2001;5:250–4.
16. Pediatric Eye Disease Investigator Group. The impact of patching and atropine on the child and family in the amblyopia treatment study. Arch Ophthalmol. In press.
17. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. Arch Ophthalmol 2002;120:268–78.
18. Fern KD, Manny RE. Visual acuity of the preschool child: a review. Am J Optom Physiol Opt 1986;63:319–45.
19. Elder MJ. Occlusion therapy for strabismic amblyopia. Aust N Z J Ophthalmol 1994;22:187–91.
20. Fielder AR, Irwin M, Auld R, et al. Compliance in amblyopia therapy: objective monitoring of occlusion. Br J Ophthalmol 1995;79:585–9.
21. Simonsz HJ, Polling JR, Voorn R, et al. Electronic monitoring of treatment compliance in patching for amblyopia. Strabismus 1999;7:113–23.
22. Loudon SE, Polling JR, Simonsz HJ. A preliminary report about the relation between visual acuity increase and compliance in patching therapy for amblyopia. Strabismus 2002;10: 79–82.
23. Cleary M. Efficacy of occlusion for strabismic amblyopia: can an optimal duration be identified? Br J Ophthalmol 2000;84: 572–8.
24. Fulton AB, Mayer DL. Esotropic children with amblyopia: effects of patching on acuity. Graefes Arch Clin Exp Ophthalmol 1988;226:309–12.
25. Flynn JT, Woodruff G, Thompson JR, et al. The therapy of amblyopia: an analysis comparing the results of amblyopia therapy utilizing two pooled data sets. Trans Am Ophthalmol Soc 1999;97:373–90.

Appendix

Writing Committee

Lead authors: Jonathan M. Holmes, BM, BCh, Raymond T. Kraker, MSPH, Roy W. Beck, MD, PhD. Additional writing committee members (alphabetical): Eileen E. Birch, PhD, Susan A. Cotter, OD, Donald F. Everett, MA, Richard W. Hertle, MD, Graham E. Quinn, MD, MSCE, Michael X. Repka, MD, Mitchell M. Scheiman, OD, David K. Wallace, MD.

The Pediatric Eye Disease Investigator Group

Clinical Sites That Participated in This Protocol. Listed in order of number of patients enrolled into the study, with city, state, site name, and number of patients in parentheses. I = Investigator; C = Coordinator; V = Visual Acuity Tester.

Erie, Pennsylvania—Pediatric Ophthalmology of Erie (28): Nicholas A. Sala (I), Rhonda M. Hodde (C), Cindy E. Tanner (V), Chrissy M. Vroman (V).

Anchorage and Wasilla, Alaska—Ophthalmic Associates (17): Robert W. Arnold (I), Mary Diane Armitage (C), Nancy H. Brusseau (V), Maru V. Gindling (V), Karen M. Lowe (V).

Dallas, Texas—Pediatric Ophthalmology, P.A. (13): David R. Stager, Sr (I), George R. Beauchamp (I), Priscilla M. Berry (I), David R. Stager, Jr (I), Joost Felius (C), Sarah E. Morale (C), Anna R. O'Connor (V), Jennifer A. Wilkerson (C), William J. Franz (V), Shannon Sharp (V).

Providence, Rhode Island—Rhode Island Eye Institute (11): John P. Donahue (I), Nicole L. Waterman (C), Christine J. Bazinet (V), Melissa A. Corrente (V), Robin L. Darpino (V), Patricia Reale (V), Mary E. Silvia (V), Marisa F. Sousa (V).

Lancaster, Pennsylvania—Family Eye Group (9): David I. Silbert (I), Eric L. Singman (I), Don D. Blackburn (I), Noelle S. Matta (C), Shannon M. Butler (V), Suanne E. Carner (V), Kit M. Castillo (V), Cristina M. Corradino (V), Jessica D. Hince (V), Troy J. Hosey (V), Diane M. Jostes (V), Alyson B. Keene (V), Stephanie R. Kilgore (V), Wendy L. Piper (V), Sara L. Weit (V), Sylvia R. Wright (V).

Columbus, Ohio—Pediatric Ophthalmology Associates, Inc. (7): Richard W. Hertle (I), Don L. Bremer (I), Mary Lou McGregor (I), Gary L. Rogers (I), Vanessa Marie Hill (C), Rebecca A. Murray (C), Jane A. Blackburn (V), Rae R. Fellows(V), Ninon M. Greene (V), Chris J. King (V), Teresa M. Rhinehart (V), Nancy L. Roberts (V), Angela M. Serna (V), Laura Jean Shenberger (V), Cheryl L. Wynn (V).

Indianapolis, Indiana—Indiana University Medical Center (7): Daniel E. Neely (I), David A. Plager (I), Naval Sondhi (I), Derek T. Sprunger (I), Jay G. Galli (C), Michele E. Whitaker (C), Donna J. Bates (V), Donna G. Harper (V), Lisa K. Keenan (V).

Miami, Florida—Bascom Palmer Eye Institute (7): Susanna M. Tamkins (I), Jennifer E. Miranda (C), Eva M. Olivares (C), Paola Agnew (V), Bruce D. Bailey (V), Tom J. Carollo (V), Mirna Garcia (V), Georgia Patsiopoulos (V).

Calgary, Canada—Alberta Children's Hospital (6): William F. Astle (I), Maria del Pilar Echeverri (I), Anna L. Ells (I), Heather J. Peddie (C), Trena L Beer (C), Cheryl R. Hayduk (C), Catriona I. Kerr (C), Mary McAlester (C), Susan M. McMullen (C), Heather M. Vibert (C), April D. Ingram (V).

Providence, Rhode Island—Pediatric Ophthalmology and Strabismus Associates (6): David Robbins Tien (I), Glenn E. Bulan (I), Heidi C. Christ (C), Lauren B. DeWaele (C).

Rockville, Maryland (6): Stephen R. Glaser (I), Andrea M. Matazinski (C), Misti D. Schroyer (C), Sheena Broome (V), Anne M. Randall (V), Kelly A. Sirk (V).

Saint Paul, Minnesota—Associated Eye Care (6): Susan Schloff (I), Evan A. Ballard (I), Anthony R. Brown (C), Valori E. Olson (C).

St. Louis, Missouri—Saint Louis University Eye Institute (6): Oscar A. Cruz (I), Bradley V. Davitt (I), Emily A. Miyazaki (C), Angela Zimmerman Moya (C).

Fullerton, California—Southern California College of Optometry (5): Susan A. Cotter (I), Carmen N. Barnhardt (I), Raymond H. Chu (I), John H. Lee (I), Susan M. Shin (I), Lourdes Asiain (C), Tal A. Barak (V), Lisa M. Edwards (V), Erin Song (V).

Atlanta, Georgia—The Emory Eye Center (4): Scott R. Lambert (I), Rachel A. Reeves (C), Lucy Yang (C), Alexander T. Elliott (V), Nicole Fallaha (V), Rebecca E. Sands (V).

Birmingham, Alabama—University of Alabama at Birmingham School of Optometry (4): Robert P. Rutstein (I), Wendy L. Marsh-Tootle (I), Katherine K. Niemann (I), Cathy H. Baldwin (C), Kristine Becker (V), Paola M. Garjales (V), Bronwen N. Mathis (V).

West Des Moines, Iowa—Wolfe Clinic (4): Donny W. Suh (I), Kim S. Walters (C), Lisa M. Fergus (V), Susan D. Foster (V), Rhonda J. Swisher (V).

Dallas, Texas—UT Southwestern Medical Center (3): David R. Weakley, Jr (I), Clare L. Dias (C).

Philadelphia, Pennsylvania—Children's Hospital of Philadelphia (3): Brian J. Forbes (I), Monte D. Mills (I), Graham E. Quinn (I), Alexandra Huebner (C), Melissa L. Ehnbom (V), Michelle C. Maturo (V), David R. Phillips (V), Sonia Zhu (V).

Philadelphia, Pennsylvania—Pennsylvania College of Optometry (3): Mitchell M. Scheiman (I), Jo Ann T. Bailey (I), Brandy J. Scombordi (I), Kathleen T. Zinzer (I), Abby M. Grossman (C), Jason R. Hochreiter (V), Karen E. Pollack (V).

Waterbury, Connecticut—The Eye Care Group, PC (3): Andrew J. Levada (I), Tabitha L. Matchett (C), David N. Comstock (C), Nicole G. Rannazzisi (V), Lisa A. Marcil (V), Cheryl Schleif (V), Shelley K. Weiss (V).

Chapel Hill, North Carolina—UNC Department of Ophthalmology (2): David K. Wallace (I), Melissa W. Compton (C), Marguerite I. Sullivan (C), Madonna R. Petty (V).

Cincinnati, Ohio—Children's Hospital Medical Center (2): Constance E. West (I), Kathryn M. Carter (C), Shannen Nelson (C), Melissa Rickey (C), Laura E. Dickman (V), Stephanie C. Fort, (V), Sarah L. Grimm (V), Laurie A. Hahn-Parrott (V), Kelli N. Kinder (V), Debbie A. Meister (V), Walker W. Motley (V), Shannon R. Walsh (V).

Indianapolis, Indiana—Indiana University School of Optometry (2): Don W. Lyon (I), Michelle L. Varvel (C), Joseph V. DeSpirito (V), John P. Downey (V), Brad M. Sutton (V).

Lake Worth, Florida—Palm Beach Eye Foundation/Visual Health and Surgical Center (2): Lee S. Friedman (I), Kathy A. Seale (C), Linda L. Mancino (V).

Norfolk, Virginia—Eastern Virginia Medical School (2): Earl R. Crouch, Jr (I), Kristen D. Ruark (C), Gaylord G. Ventura (V).

Sacramento, California—The Permanente Medical Group (2): James B. Ruben (I), Dipti Desai (C), Sue Ann Parrish (C), Gerald C. Louie (V), Tracy D. Louie (V).

Mexico City, Mexico (1): Miguel Paciuc (I), Marina M. Schnadower (V), Cecilio Velasco (V).

Milwaukee, Wisconsin—Medical College of Wisconsin (1): Jane D. Kivlin (I), Mark S. Ruttum (I), Veronica R. Picard (C), Nahid F. Saadati (V).

Plattsburgh, New York—Eye Care for the Adirondacks, Associates in Ophthalmology, PC (1): Stanley W. Hatch (I), Lisa Lucia (V), Roxanne Rock (V).

Portland, Oregon—Casey Eye Institute (1): David T. Wheeler (I), Kimberley A. Beaudet (C).

Rochester, Minnesota—Mayo Clinic (1): Jonathan M. Holmes (I), Brian G. Mohney (I), Melissa L. Rice (I), Rebecca A. Nielsen (C), Julie A. Holmquist (V), Rose M. Kroening (V), David A. Leske (V), Marna L. Levisen (V), Deborah K. Miller (V), Debbie M. Priebe (V), Julie A. Spitzer (V).

Coordinating Center—Tampa, Florida. Roy W. Beck, R. Clifford Blair, Nicole M. Boyle, Esmeralda L. Cardosa, Danielle L. Chandler, Quayleen Donahue, Heidi A. Gillespie, Julie A. Gillett, Karalyn L. Grant, Raymond T. Kraker, Alisha N. Lawson, Holly J. McCombs, Shelly T. Mares, Pamela S. Moke.

National Eye Institute—Bethesda, Maryland. Donald F. Everett.

Executive Committee. Michael X. Repka (Chair), Jonathan M. Holmes (Vice-Chair), Roy W. Beck, Eileen E. Birch, Donald F. Everett, Pamela S. Moke.

Amblyopia Treatment Study Steering Committee. Michael X. Repka, Roy W. Beck, Eileen E. Birch, Donald F. Everett, Richard W. Hertle, Jonathan M. Holmes, Pamela S. Moke, Graham E. Quinn, Susan A. Cotter, Mitchell M. Scheiman.

Data and Safety Monitoring Committee. William Barlow (Chair), Edward G. Buckley, Barry Davis, Velma Dobson, John L. Keltner, Hana Osman, Earl A. Palmer, Dale L. Phelps.