

A Randomized Trial of Atropine vs Patching for Treatment of Moderate Amblyopia in Children

The Pediatric Eye Disease Investigator Group

ARCHIVES EXPRESS

Objective: To compare patching and atropine as treatments for moderate amblyopia in children younger than 7 years.

Methods: In a randomized clinical trial, 419 children younger than 7 years with amblyopia and visual acuity in the range of 20/40 to 20/100 were assigned to receive either patching or atropine at 47 clinical sites.

Main Outcome Measure: Visual acuity in the amblyopic eye and sound eye after 6 months.

Results: Visual acuity in the amblyopic eye improved in both groups (improvement from baseline to 6 months was 3.16 lines in the patching group and 2.84 lines in the atropine group). Improvement was initially faster in the patching group, but after 6 months, the difference in visual acuity between treatment groups was small and

clinically inconsequential (mean difference at 6 months, 0.034 logMAR units; 95% confidence interval, 0.005-0.064 logMAR units). The 6-month acuity was 20/30 or better in the amblyopic eye and/or improved from baseline by 3 or more lines in 79% of the patching group and 74% of the atropine group. Both treatments were well tolerated, although atropine had a slightly higher degree of acceptability on a parental questionnaire. More patients in the atropine group than in the patching group had reduced acuity in the sound eye at 6 months, but this did not persist with further follow-up.

Conclusion: Atropine and patching produce improvement of similar magnitude, and both are appropriate modalities for the initial treatment of moderate amblyopia in children aged 3 to less than 7 years.

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AMBLYOPIA IS the most common cause of monocular visual impairment in both children and young and middle-aged adults.¹⁻³ Most cases are associated with strabismus, usually esotropia in infancy or early childhood. Less frequently the cause is anisometropia (difference in refractive error between the two eyes), a combination of strabismus and anisometropia, or visual deprivation.^{4,5} About 25% of patients have a visual acuity in the amblyopic eye worse than 20/100, and about 75% have an acuity of 20/100 or better.^{4,6-8} Although some authors have reported benefits of treating amblyopia even in adulthood,⁹⁻¹¹ it is generally held that the response to treatment seems best when instituted at an early age^{12,13} and is poor after age 8 years.¹⁴⁻¹⁶

Occlusion therapy with patching of the sound eye has been the mainstay of amblyopia treatment despite the lack of meaningful data demonstrating its superiority compared with other modalities. Opinions vary on the number of hours of patch-

ing per day that should be prescribed, ranging from a few hours to all waking hours.^{17,18} Compliance is often cited as a major problem because of patients' dislike of occlusion owing to skin irritation and visual, social, and psychological reasons. Reported rates of compliance range widely from 49% to 87%.^{4,13,18-25} Not unexpectedly, the success of occlusion therapy is reported to be dependent on compliance.^{2,26}

See also pages 281 and 387

Although less widely prescribed, pharmacologic penalization is an alternative to occlusion therapy for amblyopia. This method involves the instillation of a long-acting topical cycloplegic agent, such as atropine sulfate, into the sound eye. The cycloplegia prevents accommodation, blurring the sound eye at near fixation. When the sound eye is hyperopic, the penalization effect is potentially augmented if less than full plus spectacle correction is prescribed for the cycloplegic sound eye, effectively blurring its vision at both near and distance fixation. Pharmacologic penaliza-

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PATIENTS AND METHODS

The study, supported through cooperative agreements with the National Eye Institute of the National Institutes of Health (Bethesda, Md) was conducted by the Pediatric Eye Disease Investigator Group at 47 clinical sites. The protocol and informed consent forms were approved by institutional review boards, and the parent or guardian (hereafter referred to 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 visual acuity in both eyes using the Amblyopia Treatment Study visual acuity testing protocol (see "Examination Procedures"), a cycloplegic refraction, an ocular examination, and an ocular motility examination. Procedures were performed according to the investigator's usual routine except for the visual acuity testing protocol. Visual acuity testing was required to be performed within the 7 days prior to randomization; the remainder of the examination could be completed within 2 months prior to randomization.

Eligibility criteria for the trial included age younger than 7 years, visual acuity in the amblyopic eye from 20/40 to 20/100, visual acuity in the sound eye of 20/40 or better, intereye acuity difference of 3 or more logMAR lines, the presence or history of an amblyogenic factor meeting study-specified criteria for strabismus or anisometropia, and the wearing of optimal spectacle correction for a minimum of 4 weeks at the time of enrollment (**Table 1** has a complete list of the eligibility and exclusion criteria). Details of the protocol for correction of refractive error have been published previously.⁴⁹

Based on a postrandomization review, 10 patients (3 in the patching group and 7 in the atropine group) did not fully meet the visual acuity or amblyogenic factor eligibility criterion: 1 patient had an amblyopic eye acuity of 20/125, 4 had an intereye acuity difference less than 3 lines (1 of whom had a 20/30 amblyopic eye acuity), and 5 were presumed to have amblyopia but did not have a definite amblyogenic factor. These patients remained in the study, and their data were included in the analyses.

SYNOPSIS OF STUDY DESIGN

After informed consent was obtained, each patient was randomly assigned with equal probability to either the patching or atropine treatment group. Randomization was accomplished on the study's Web site using a permuted-blocks design of varying block sizes with a separate sequence of computer-generated random numbers for each investigator.

Visual acuity in the amblyopic eye was the primary efficacy outcome measure, and acuity in the sound eye was the primary safety outcome measure. Protocol-specified follow-up visits were conducted after a period of 5±2 weeks, 16±2 weeks, and 26±1 weeks (primary outcome). Additional visits could be performed at the investigator's discretion. After the 6-month outcome examination, patients continue to receive follow-up for an additional 18 months, during which there is no specific visit schedule except for the requirement of at least 1 visit every 6 months.

TREATMENT PROTOCOLS

Both treatment groups followed a structured treatment protocol until the 6-month outcome examination. Prior to this point, patients in the patching group were not to be prescribed atropine, and patients in the atropine group were not to be prescribed patching. A patient was considered to be successfully treated with regard to the protocol when the amblyopic eye's visual acuity was 20/30 or better or had improved 3 or more lines from baseline. If a treatment-related decrease in the sound eye visual acuity (reverse amblyopia) was suspected, treatment was at the investigator's discretion.

Patching Protocol

The patching protocol was designed to be similar to the investigator's usual practice subject to the following stipulations: (1) the initial patching time was a minimum of 6 hours per day (maximum, all waking hours); (2) assuming that reverse amblyopia did not develop, this minimum remained in effect through the 6-month outcome examination unless the criteria for successful treatment were met; (3) if criteria for successful treatment were met, patching time could be reduced but needed to be at least 7 hours per week as long as the visual acuity in the amblyopic eye was 1 or more lines worse than that in the sound eye; (4) if the visual acuity in the two eyes became equal, patching could be discontinued; and (5) if criteria for successful treatment were not met by the 16-week visit, and patching time had been less than 12 hours per day, patching time was increased to 12 or more hours per day for 2 months prior to the 6-month outcome examination. Adhesive skin patches provided by the study (Coverlet Eye Occlusors; Beiersdorf-Jobst Inc, Rutherford College, NC) were used unless there was skin allergy or irritation nonresponsive to both local treatment with a skin emollient and a change in the brand of patch, in which case a spectacle occluder could be prescribed.

Atropine Protocol

At enrollment, patients were prescribed 1 drop per day of atropine sulfate 1%, which was provided by the study. Sunglasses were also provided, with the advice that they be worn with a hat when the child was in sunlight. Daily atropine use was continued unless the visual acuity in the amblyopic eye met criteria for successful treatment, in which case (at the investigator's discretion) the frequency could be reduced to a minimum of 2 times a week and could be discontinued if the acuities became equal in the two eyes. For patients with hyperopia in the sound eye, if the amblyopic eye was not successfully treated by the 16-week visit, the spectacle lens was reduced to plano for 2 months prior to the 6-month outcome examination. If an allergy to atropine developed, topical homatropine 5% could be substituted instead.

EXAMINATION PROCEDURES

At baseline and each protocol-specified visit, visual acuity was measured in both eyes using the Amblyopia Treatment Study visual acuity testing protocol⁵⁰ administered by a study-certified vision tester. The test was administered either on the

Continued on next page

Baylor Video Acuity Tester or the Electronic Visual Acuity Tester.⁵¹ The acuity testing protocol consists of the presentation of single-surround HOTV optotypes in 4 steps: a screening phase, followed by a first-threshold determination (phase 1), reinforcement phase, and second-threshold determination (phase 2). In the screening phase, starting from either 20/100 or 20/400, a single letter at each logMAR level is shown until one is missed. In phase 1, letters are shown starting 2 logMAR levels above the missed level in screening to determine the lowest level at which 3 of 3 or 3 of 4 letters are correctly identified. In the reinforcement phase, to get the child with drifting attention back on track, 3 larger letters are shown (but not scored) starting 2 levels above the lowest correct level in phase 1. In phase 2, the child is given a second chance on the last level missed in phase 1; if 3 of 3 or 3 of 4 are correctly identified, the test continues at the next-smallest level until a level is failed. When 2 letters are missed (of a maximum of 4 presentations), testing stops. The visual acuity score is the lowest level passed in phase 1 or phase 2. Quality control measures for the visual acuity testing included (1) a formal standardized training, certification, and recertification program; (2) a calibration check of optotype size on the monitor prior to each masked examination; and (3) a review of visual acuity testing score sheets at the coordinating center to evaluate whether the protocol had been properly followed.

At the 5-week visit, a questionnaire designed to assess the effect of amblyopia treatment on the child and parent (Amblyopia Treatment Index⁵²) was completed by the parent. The questionnaire consists of 18 items, each scored from 1 to 5, with 5 representing the most difficult. Three subscales measured the adverse effects of treatment (8 items), difficulties with compliance (5 items), and social stigma of treatment (3 items), with internal consistency reliabilities of 0.86, 0.86, and 0.76, respectively. Items were summed to compute each subscale score, then scaled to a common range from 1 to 5.

At the 6-month outcome examination, visual acuity testing of the amblyopic eye was conducted by a tester masked to the patient's treatment group. To conceal the treatment group assignment, a patch was placed over the sound eye by site staff prior to the examination to avoid unmasking either from a dilated pupil due to atropine or from skin changes due to patching. For patients receiving daily treatment, treatment was continued until the day prior to the testing of the amblyopic eye's visual acuity. Outcome examination testing also included the measurement of visual acuity in the sound eye and assessment of ocular alignment using a simultaneous prism and cover test at distance and near fixation. For patients in the patching group, this testing typically was done on the same day as the amblyopic eye visual acuity testing, whereas for patients in the atropine group, testing was performed at a second visit after atropine had been discontinued for 7 days.

ADHERENCE TO THE TREATMENT PROTOCOL

Adherence to the treatment protocol by the patient was assessed by having the parent maintain a calendar on which the treatment received each day was logged. The calendars were reviewed at follow-up visits, and at each visit 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%; and poor, 25% or less). An average compliance score was computed for each patient from the adherence assess-

ment 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 (\leq 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 feedback was provided to the investigator as indicated.

ADVERSE REACTIONS

At each study visit, the parent was asked about specific adverse effects of treatment. For the patching group, this related to skin irritation. For the atropine group, information was elicited at each visit on the development of local adverse effects, such as ocular irritation, and systemic adverse effects, such as dry skin and mouth, tachycardia, fever, flushing, and irritability.

Visual acuity in the sound eye at 6 months was the primary safety outcome. For patients whose sound eye acuity was reduced from baseline (acuity < 20/20 and decreased by 1 or more lines from baseline), subsequent follow-up data were used to evaluate whether the decrease represented a real and/or permanent reduction.

STATISTICAL METHODS

The sample size was based on whether the visual improvement at 6 months with atropine was equivalent to that with patching. The equivalence limit, which represents the end of the 95% confidence interval (CI) for the difference in mean visual acuity between groups, was set to be 0.1 logMAR unit (a difference of 0.1 logMAR unit is equivalent to 1 line of acuity). Monte Carlo simulations, based on projected scenarios for the data, were used to establish a sample size of 400 such that there would be at least 80% power, with an α level of .05 for assessments of the treatment group differences in each of 3 subgroups based on cause of amblyopia (strabismus, anisometropia, and combined-mechanism). With this sample size, the power for the primary overall analysis was 99%.

The primary outcome was the 6-month amblyopic eye visual acuity score in logMAR units. The treatment groups were compared in an analysis-of-covariance model in which the logMAR acuity scores were adjusted for baseline acuity. Patients were included in the primary analysis if they had a visual acuity measurement in the amblyopic eye within the time window of the 6-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 window. Two additional analyses were conducted on the 6-month amblyopic eye logMAR acuity scores: one analysis included only patients who had an examination within the 6-month window, and the other analysis included all patients using the method of last observation carried forward to impute for missing data (for patients missing the outcome examination, the visual acuity recorded at the last follow-up examination was used; for patients with no follow-up, the baseline acuity was used). Results of these 2 analyses were similar to the primary analysis (data not shown). Interaction between baseline factors (cause of amblyopia, age, and amblyopic eye acuity) and treatment group on the outcome acuity was assessed by including interaction terms in the analysis-of-covariance models. Methods used to analyze the amblyopic eye logMAR acuity scores at the 5-week

and 16-week visits paralleled the analysis conducted on the 6-month data. Within treatment groups, the change in visual acuity from baseline was reported in lines. Treatment group comparisons were reported as differences in logMAR acuity.

A prespecified secondary outcome (treatment success) was defined as a 6-month visual acuity of 20/30 or better and/or that had improved from baseline by 3 or more lines. A patient was classified as a treatment failure if the success criteria were not met or if the nonassigned treatment was received for at least 1 week (ie, if a patient in the atropine group received patching or a patient in the patching group received atropine). An exact 2-sided 95% CI was computed for the difference in success percentages between the 2 groups.

Treatment group differences in the questionnaire subscale scores were assessed with a Wilcoxon rank sum test. The treatment group difference in the proportion of patients with a decreased 6-month visual acuity in the sound eye was assessed with a Fisher exact test. Post-6-month sound eye visual acuity results include data received at the coordinating center through December 31, 2001.

All analyses followed the intention-to-treat principle (ie, 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.

tion has generally been advocated only for mild and moderate amblyopia (20/100 or better) because the blurring effect on the sound eye may be insufficient when visual acuity in the amblyopic eye is worse than 20/100.²⁷⁻³⁵ Clinical experience has found that pharmacologic penalization has a high acceptability to patients and parents, and consequently high rates of compliance.^{33,35}

Despite the wealth of articles that have been written about amblyopia therapy, the amount of meaningful data on the response to treatment is extremely limited. In primarily retrospective studies, success rates (with varying definitions of success) for treatment of moderate amblyopia in children have ranged from about 40% to 90% for both patching and atropine.* Only a few studies have compared atropine and patching, all of which have been either retrospective⁴⁵ or, if prospective, have had too small a sample size to provide meaningful data.^{34,46} A treatment-related reduction in visual acuity in the sound eye has been reported to occur rarely with both atropine and patching treatments and has usually been reversible.^{28,30,32-35,44,47,48}

An unpublished survey of the Pediatric Eye Disease Investigator Group conducted in 1997 found that for patients who met the eligibility criteria for this trial, only 3% of the investigators prescribed atropine or some other form of penalization therapy as their primary treatment modality, whereas the other 97% prescribed patching. As a secondary treatment when patching was unsuccessful, 41% prescribed penalization.

*References 4, 13, 19, 26, 28, 31-33, 35-44.

To determine optimal treatment for moderate amblyopia, we conducted a randomized controlled clinical trial to assess whether treatment with atropine drops was as effective as patching for this condition (20/40 to 20/100 in the amblyopic eye) in children younger than 7 years who were able to complete standardized optotype visual acuity testing.

RESULTS

Between April 1999 and April 2001, 419 patients entered the trial, with 215 assigned to the patching group and 204 to the atropine group. The number of patients enrolled per site ranged from 1 to 35 (median = 5 patients). The mean \pm SD age of the patients was 5.3 ± 1.1 years; 47% were girls, and 83% were white. The mean visual acuity in the amblyopic eye at enrollment was 0.53 logMAR units (approximately 20/63), with a mean difference in acuity between eyes of 4.4 lines. The baseline characteristics of the 2 groups were similar (**Table 2**). Additional baseline data were reported previously.⁴⁹

PATIENT FOLLOW-UP

The primary-outcome examination was completed by 97% of the patients in the patching group and 95% in the atropine group (**Figure 1**). The vision tester was masked to treatment group for 97% of these examinations (97% in the patching group and 98% in the atropine group). Prior to the outcome examination, patients in each group had a similar number of follow-up visits (mean \pm SD number of visits, 2.6 ± 1.0 and 2.7 ± 1.1 in the patching and atropine groups, respectively; *P* = .52).

TREATMENT

Patching Group

The number of hours of patching prescribed at enrollment was 6 hours in 43% of patients, 8 hours in 30%, 10 hours in 7%, and 12 or more hours in 20%. The maximum number of patching hours prescribed at any time prior to the outcome examination was 6 or 7 hours in 30% of patients, 8 or 9 hours in 27%, 10 or 11 hours in 10%, and 12 or more hours in 33%. For 80% of the patients, the number of patching hours prescribed at baseline was the maximum amount of patching prescribed during the 6-month follow-up period. For 26 patients, patching time during follow-up was increased from a lesser initial amount to 12 or more hours per day. Six additional patients should have been (but were not) prescribed at least 12 hours of patching per day as dictated by the protocol for an incomplete response to a lesser amount of patching.

Patient adherence to the prescribed treatment was judged by the investigator to be excellent in 49%, good in 34%, fair in 13%, and poor in 5% of patients. A spectacle occluder was prescribed as a substitute for patching in 9 patients who could not tolerate the skin patches. Four patients in the patching group were switched to atropine prior to the primary-outcome examination because of noncompliance with patching (parental decision in 2 cases and investigator's decision in 2 cases).

Table 1. Eligibility and Exclusion Criteria***Eligibility criteria**

- Age <7 y
- Able to measure visual acuity using the Amblyopia Treatment Study visual acuity testing protocol
- Visual acuity in the amblyopic eye $\leq 20/40$ and $\geq 20/100$
- Visual acuity in the sound eye $\geq 20/40$
- Intereye acuity difference ≥ 3 logMAR lines
- No more than 2 mo of amblyopia therapy in the past 2 y (any treatment more than 2 y ago was acceptable)
- Refractive error corrected for at least 4 wk
- 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 ≥ 0.5 -D spherical equivalent or ≥ 1.50 -D difference in astigmatism in any meridian, with no measurable heterotropia at distance or near fixation, that persisted after at least 4 wk 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 ≥ 1.00 -D spherical equivalent or ≥ 1.50 -D difference in astigmatism in any meridian that persisted after at least 4 wk of spectacle correction.

Exclusion criteria

- Presence of an ocular cause for reduced visual acuity
- Prior intraocular surgery
- Myopia (spherical equivalent of -0.50 D or more) in either eye
- Down syndrome
- Known skin reaction to patch or bandage adhesive, or allergy to atropine or other cycloplegics

*D indicates diopters.

Atropine Group

All patients were prescribed 1 drop of atropine 1% per day at baseline. The amount of induced distance optical blur in the sound eye while the patient was wearing spectacles (spherical equivalent of cycloplegic refraction minus spherical equivalent of spectacle lens) was 0.50 diopter (D) or less for 66% of patients, greater than 0.50 to 1.00 D for 19%, greater than 1.00 to 2.00 D for 14%, and greater than 2.00 D for 1%. A plano spectacle lens was prescribed for the sound eye during follow-up for 56 patients, inducing distance optical blur as defined previously of greater than 0.50 to 1.00 D for 3 patients, greater than 1.00 to 2.00 D for 9, and greater than 2.00 D for 44 patients. Four patients should have been (but were not) prescribed a plano lens for the sound eye as dictated by the protocol for an incomplete response to atropine.

Patient adherence to the prescribed treatment was judged by the investigator to be excellent in 78% of patients, good in 18%, fair in 3%, and poor in 1%. Homatropine 5% was prescribed as a substitute in 2 patients who developed an adverse reaction to atropine. Two patients in the atropine group were switched to patching prior to the primary-outcome examination (parental decision in both cases).

Table 2. Baseline Characteristics According to Treatment Group*

	Total (N = 419)	Patching Group (n = 215)	Atropine Group (n = 204)
Sex: F	196 (47)	101 (47)	95 (47)
Age, y			
<3	7 (2)	4 (2)	3 (1)
3 to <4	64 (15)	32 (15)	32 (16)
4 to <5	83 (20)	41 (19)	42 (21)
5 to <6	140 (33)	67 (31)	73 (36)
6 to <7	125 (30)	71 (33)	54 (26)
Mean (SD)	5.3 (1.1)	5.3 (1.1)	5.2 (1.1)
Race			
White	349 (83)	175 (81)	174 (85)
African American	23 (5)	12 (6)	11 (5)
Hispanic	25 (6)	13 (6)	12 (6)
Asian	8 (2)	4 (2)	4 (2)
Mixed	7 (2)	7 (3)	0
Other	7 (2)	4 (2)	3 (1)
Prior treatment for amblyopia			
None	309 (74)	159 (74)	150 (74)
Patching (skin)	82 (20)	45 (21)	37 (18)
Atropine (or other cycloplegic)	8 (2)	3 (1)	5 (2)
Patching and atropine	1 (0.2)	0	1 (0.5)
Other†	19 (5)	8 (4)	11 (5)
Cause of amblyopia‡			
Strabismus	159 (38)	83 (39)	76 (37)
Anisometropia	155 (37)	82 (38)	73 (36)
Strabismus and anisometropia	100 (24)	49 (23)	51 (25)
Visual acuity, amblyopic eye§			
20/100	95 (23)	49 (23)	46 (23)
20/80	96 (23)	42 (20)	54 (26)
20/60	93 (22)	56 (26)	37 (18)
20/50	88 (21)	48 (22)	40 (20)
20/40	45 (11)	20 (9)	25 (12)
Mean (SD), logMAR units	0.53 (0.13)	0.52 (0.13)	0.53 (0.14)
Visual acuity, sound eye			
20/40	39 (9)	17 (8)	22 (11)
20/30	85 (20)	41 (19)	44 (22)
20/25	116 (28)	62 (29)	54 (26)
20/20	150 (36)	82 (38)	68 (33)
20/15	29 (7)	13 (6)	16 (8)
Mean (SD), logMAR units	0.09 (0.11)	0.08 (0.11)	0.09 (0.11)
Intereye acuity difference, lines			
3	132 (32)	67 (31)	65 (32)
4	117 (28)	59 (27)	58 (28)
5	79 (19)	39 (18)	40 (20)
6-8	87 (21)	48 (22)	39 (19)
Mean (SD)	4.4 (1.3)	4.4 (1.4)	4.3 (1.3)
Refractive error in amblyopic eye¶			
<+1.00	23 (5)	13 (6)	10 (5)
+1.00 to <+3.00	72 (17)	40 (19)	32 (16)
>+3.00	324 (77)	162 (75)	162 (79)
Mean (SD)	4.46 (2.13)	4.29 (2.09)	4.64 (2.16)
Refractive error in sound eye¶			
<+1.00	68 (16)	46 (21)	22 (11)
+1.00 to <+3.00	176 (42)	89 (41)	87 (43)
>+3.00	175 (42)	80 (37)	95 (47)
Mean (SD)	2.82 (2.00)	2.66 (1.95)	2.99 (2.05)

*Data are presented as number (percentage) unless otherwise indicated.

†“Other” category includes spectacle occluder and fogging (Bangerter filters, tape, or optical).

‡Five patients (1 in the patching group and 4 in the atropine group) did not meet the criteria for any of the 3 categories.

§Amblyopic eye acuity was 20/30 in 1 patient and 20/125 in 1 patient (both in atropine group).

||Intereye acuity difference less than 3 lines in 4 patients (2 in each group).

¶Spherical equivalent in diopters.

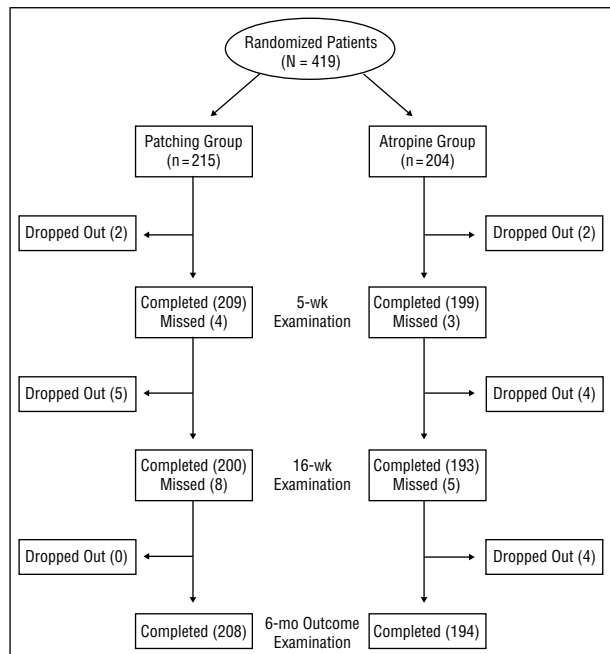


Figure 1. Flowchart showing visit completion and the timing of dropouts. Of the 208 patients in the patching group who completed the 6-month outcome examination, 169 patients were in the 6-month window (25-27 weeks), 7 were early (21 to <25 weeks), and 32 were late (>27 to 40 weeks). Among the 7 patients with incomplete follow-up, 4 patients were lost to follow-up, and 3 were withdrawn at the request of the parent. Of the 194 patients in the atropine group who completed the 6-month outcome examination, 164 patients were in the 6-month window (25-27 weeks), 5 were early (21 to <25 weeks), and 25 were late (>27 to 40 weeks). Among the 10 patients with incomplete follow-up, 6 were lost to follow-up, and 4 were withdrawn at the request of the parent.

EFFECT OF TREATMENT ON VISUAL ACUITY IN THE AMBLYOPIC EYE

Substantial improvement in visual acuity from baseline to 6 months occurred in both the patching group and the atropine group (**Table 3**). The mean change in visual acuity from baseline was 3.16 lines (95% CI, 2.95-3.37) in the patching group and 2.84 lines (95% CI, 2.61-3.07) in the atropine group. The mean treatment group difference in the 6-month logMAR acuity was 0.034 (95% CI, 0.005-0.064). Seventy-nine percent of the patching group and 74% of the atropine group met our criteria for treatment success (95% CI for difference in percentages, -4% to 13%).

Although differences in amblyopic eye acuity between treatment groups at 6 months were small, visual acuity in the amblyopic eye showed greater initial improvement with patching than with atropine (**Figure 2**). At the 5-week visit, visual acuity had improved from baseline by a mean of 2.22 lines in the patching group and 1.37 lines in the atropine group (mean difference in logMAR acuity between groups, 0.087; 95% CI, 0.060-0.113). By 16 weeks, the difference between groups had narrowed, but the patching group still had slightly greater improvement (mean change from baseline, 2.94 lines in the patching group and 2.42 lines in the atropine group; mean difference in logMAR acuity between groups, 0.053; 95% CI, 0.026-0.080).

For all 3 causes of amblyopia (strabismus, anisometropia, and combined-mechanism) and in subgroups based on patient age and baseline acuity in the amblyopic eye,

Table 3. Visual Acuity in the Amblyopic Eye at Outcome Examination by Treatment Group*

	Patching Group (n = 208)	Atropine Group (n = 194)
Lines of improvement from baseline to outcome examination		
<-1	1 (0.5)	2 (1)
-1 to +1	26 (13)	32 (16)
+2	35 (17)	44 (23)
≥+3	146 (70)	116 (60)
Mean (SD)	3.16 (1.6)	2.84 (1.6)
Distribution of visual acuity scores at outcome examination		
≤20/125	2 (1)	2 (1)
20/100	2 (1)	2 (1)
20/80	6 (3)	5 (3)
20/60	4 (2)	9 (5)
20/50	20 (10)	26 (13)
20/40	42 (20)	47 (24)
20/30	47 (23)	47 (24)
20/25	52 (25)	34 (18)
20/20	27 (13)	20 (10)
20/15	6 (3)	2 (1)
Difference between treatment groups in mean visual acuity at outcome examination, † logMAR units		
		0.034
95% confidence interval		
		(0.005 to 0.064)
Treatment success‡		
	164 (79)	144 (74)
95% confidence interval for difference between treatment groups, %		
		(-4 to 13)

*Data are presented as number (percentage) unless otherwise indicated.

†Adjusted for baseline visual acuity in analysis of covariance model.

‡Treatment success defined as outcome examination with a visual acuity of 20/30 or better or 3 or more lines of improvement from baseline (crossovers to alternate treatment considered treatment failures).

the effect of each treatment appeared consistent with the effect in the overall group. In both treatment groups, all subgroups showed at least a 2.3-line mean improvement in amblyopic eye acuity from baseline to the primary-outcome examination. Statistically, there was no significant interaction between any of these baseline factors and treatment group on the outcome acuity in the amblyopic eye (*P* values for interaction were .68 for cause of amblyopia, .84 for age, and .59 for baseline amblyopic eye acuity).

EFFECT OF TREATMENT ON VISUAL ACUITY IN THE SOUND EYE

At the 6-month examination, visual acuity in the sound eye was decreased from baseline by 1 line in 14 patients (7%) in the patching group and 30 patients (15%) in the atropine group and by 2 or more lines in 3 patients (1%) and 17 patients (9%), respectively (*P*<.001). Only 1 patient (in the atropine group) was actively treated for a presumed treatment-related decrease in sound eye acuity, with a return of visual acuity to its baseline level.

In the atropine group, many of the excess cases of decreased sound eye acuity appeared to be related to improper refractive correction combined with a residual cycloplegic effect of the atropine (including 9 cases in which the testing was done with a plano lens prescribed for therapeutic effect rather than the proper lens), although data

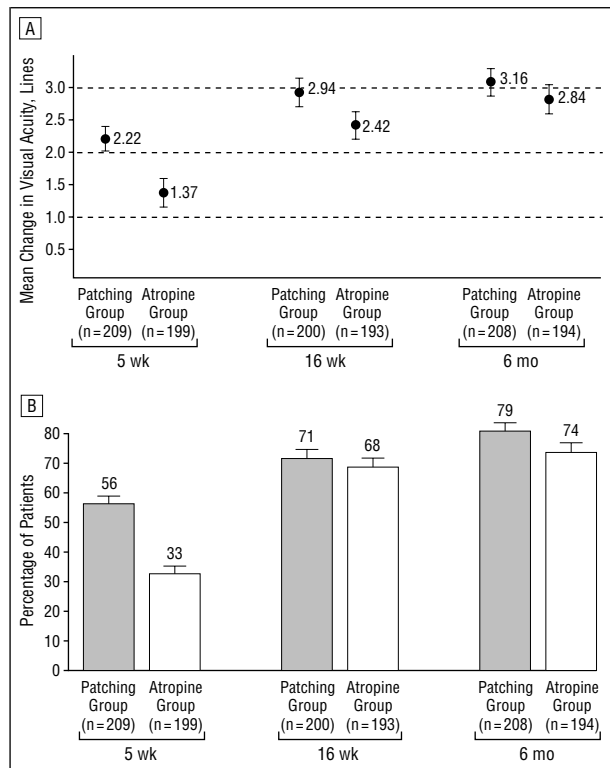


Figure 2. Visual acuity results in each treatment group for the amblyopic eye at the 5-week, 16-week, and 6-month visits. A, Mean line change from baseline. B, Percentage of patients meeting criteria for successful treatment (visual acuity of 20/30 or better and/or 3 or more lines of improvement from baseline). The point estimates and 95% confidence intervals are shown.

did not fully document this in all cases. Among the 47 patients in the atropine group with a decrease of 1 or more lines at 6 months, subsequent follow-up examinations were performed for 45. Visual acuity on the subsequent testing was the same or better than that at baseline in 40 of the 45 patients: 20 while still receiving atropine treatment (10 with the same refractive correction and 10 with a different refractive correction) and 20 after atropine was discontinued (6 with the same refractive correction and 14 with a different refractive correction). In the other 5 patients, acuity on subsequent testing was decreased from baseline by 1 line (3 taking atropine; 2 not taking atropine). The 2 patients who have not had further follow-up both had a 1-line decrease from baseline at 6 months.

Among the 17 patients in the patching group with a decreased sound eye acuity, subsequent follow-up examinations were performed for 13. Visual acuity on the subsequent testing was the same or better than that at baseline in 11 of the 13 patients; the other 2 had a 1-line decrease from baseline. The 4 patients who have not had further follow-up all had a 1-line decrease from baseline at 6 months.

OTHER ADVERSE EFFECTS

In the patching group, mild skin irritation was reported at least once for 41% of the patients, and moderate or severe irritation for an additional 6%.

In the atropine group, an ocular adverse effect was reported at least once for 26% of patients, most commonly light sensitivity (18%), lid or conjunctival irrita-

tion (4%), and eye pain or headache (2%). Facial flushing was reported for 2 patients, one of whom continued taking atropine with no further problems and one of whom was switched to homatropine.

During the 6-month treatment period, among patients with no history of strabismus, a new distance ocular deviation of more than 8 Δ developed in 1 patient in the patching group (20- Δ esotropia) and in 1 patient in the atropine group (10- Δ esotropia). Two patients in the patching group and 3 patients in the atropine group had a preexisting esotropia that increased by more than 10 Δ (in 1 patient in the atropine group, this occurred after a plano lens was prescribed for the sound eye). Among patients with no distance ocular deviation at baseline, a small-angle strabismus (1-8 Δ) at distance fixation was noted at 6 months in 12 (12%) of 97 patients in the patching group and 11 (12%) of 90 patients in the atropine group. Among patients with a baseline 1- to 8- Δ strabismus at distance fixation, no distance deviation was noted at 6 months in 12 (24%) of 50 patients in the patching group and 8 (17%) of 47 patients in the atropine group.

PARENT QUESTIONNAIRE

For patients completing the 5-week visit, the Amblyopia Treatment Index was completed by 192 (92%) of the parents in the patching group and 181 (91%) in the atropine group. In both treatment groups, the questionnaire results indicated that treatment was well tolerated. However, the questionnaire scores were consistently higher (worse) on all 3 subscales in the patching group compared with the atropine group (adverse effects: median=2.25 vs 2.00; $P=.002$; difficulty with compliance: median=2.20 vs 1.80; $P<.001$; and social stigma: median=3.00 vs 2.00; $P<.001$). The full questionnaire results will be reported in a separate article.

COMMENT

We evaluated the comparative effectiveness of patching and atropine as treatments for moderate amblyopia (visual acuity of 20/40 to 20/100) in 419 children younger than 7 years. The study, which was conducted in both university and community-based practices, was designed to approximate clinical practice, with the exceptions being (1) the use of randomization to determine the treatment prescribed, and (2) the use of a standardized protocol to measure visual acuity. Substantial improvement in the visual acuity of the amblyopic eye occurred with both the patching and atropine treatment regimens. Improvement was more rapid in the patching group, but by 6 months the difference in mean visual acuity between groups was small (about one third of a line) and clinically inconsequential. The difference between groups in the percentage of patients meeting our criteria for successful treatment (visual acuity of 20/30 and/or 3 or more lines of improvement from baseline) was also small (79% in the patching group vs 74% in the atropine group).

In the patching group, most patients received no more than 6 or 8 hours of patching per day, and only 33% were treated for 12 or more hours per day. In the atropine group,

15% of patients had more than +1.00 D of distance optical blur in the sound eye at the start of treatment (comparing the lens correction with the cycloplegic refraction), and an additional 25% were prescribed a plano lens to maximize the optical blur during follow-up.

Both treatments were well tolerated, and few patients required alteration of treatment because of adverse effects. One patient in each group developed an esotropia greater than 8 Δ that was not present at baseline. Approximately equal numbers of patients manifested a small-angle strabismus ($\leq 8 \Delta$) at 6 months that was not noted at baseline and a small-angle strabismus at baseline that was not noted at 6 months; this likely reflects the variability of testing for microtropia rather than a true improvement or worsening in the ocular alignment related to treatment. Although no definite cases of a persistent treatment-related decrease in the sound eye acuity occurred in either group, more patients in the atropine group than the patching group had a measured reduction of visual acuity in the sound eye at the 6-month outcome examination. However, in nearly all cases with follow-up information after the first 6 months, visual acuity in the sound eye returned to its prestudy level; there were 5 patients in the atropine group and 2 patients in the patching group in whom the sound eye acuity was 1 line worse than baseline at the last follow-up visit. This is consistent with the variability of the testing^{50,51} and presumably does not represent a true decrease. In many cases, the reduced sound eye acuity at 6 months was likely related to the residual cycloplegic effect of atropine and/or an improper refractive correction. Most of the patients were tested at 6 months with the same refractive correction in use at study entry, not accounting for the possible effect of 6 months of atropine treatment on undercorrected latent hyperopia. Because the cycloplegic effect of even a single drop of atropine has been reported to last for up to 14 days,^{53,54} in retrospect we should have discontinued atropine for longer than 7 days before the 6-month visual acuity measurement. Thus, our data are inconclusive about whether atropine may cause a treatment-related reduction of acuity in the sound eye more often than patching. However, even if this is true, we are reasonably confident that our cohort experienced no lasting adverse effect on visual acuity of the sound eye. One potential concern with atropine use would be the light exposure of the retina from the dilated pupil. Although we provided sunglasses to our patients and recommended hat wear outdoors to minimize the sunlight exposure, we believe that a few months of atropine use does not have a deleterious effect on the retina. Atropine has been used long-term to prevent the progression of myopia without an apparent adverse effect on acuity,⁵⁵⁻⁵⁷ and as noted previously, our post-6-month data do not suggest permanent impairment in the sound eye acuity. We will be able to provide definitive long-term safety data on the completion of 2-year follow-up. At that time we also will assess differences between groups in stereoacuity and fusion.

The burden to administer amblyopia treatment in children falls on the parent. One of the rationales for atropine use has been that it has a higher degree of acceptability by patients and parents than patching.^{33,35} This premise was supported in our parent questionnaire data

obtained at the 5-week follow-up visit. However, whereas atropine was better accepted, the treatment group differences, although highly statistically significant, were small. In both groups, the questionnaire results indicated that the initial month of treatment was usually well tolerated by the patient and parent.

We could identify no apparent sources of bias or confounding to explain our findings. The follow-up visit rate was high in both groups, and missing data from patients who dropped out of the study did not influence the interpretation of the results. There was a slight imbalance in baseline visual acuity between groups (the atropine group had slightly worse acuity), but this was accounted for in analysis. Although the patients, parents, and investigators were unmasked to the treatment group assignments, masking of the primary visual acuity outcome measurement was achieved in 97% of cases. Visual acuity testing was performed using a standardized protocol developed specifically for this study to ensure consistency of testing across our many sites.⁵⁰ The sample size for the trial was selected to have sufficient power to evaluate the treatment effect in subgroups based on cause of amblyopia. As a result, for the overall primary analysis, statistical power approached 100%. Thus, it is unlikely that a substantially larger treatment group difference than we found exists, and we can conclude with a high degree of confidence that both patching and atropine produce an improvement in visual acuity of a similar magnitude.

We could not ethically include an untreated control group in this trial. Thus, our conclusion that both treatments improved visual acuity is based on overwhelming clinical experience indicating that substantial improvement of amblyopia rarely occurs without treatment, and the fact that the amount of observed improvement (about 3 lines on average) substantially exceeded any potential learning effect or age effect.^{50,51,58} The magnitude of the learning and age effects on the visual acuity of the amblyopic eyes was likely similar to the observed improvement from baseline to the 6-month outcome in acuity in the sound eyes of the patients in the patching group (mean change, 0.6 lines). A slight overestimate of the amount of improvement could also 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 this would not have affected the relative treatment group comparison, it could have produced a slight overestimate of the absolute amount of improvement experienced by such patients in both treatment groups.

Improvement in the atropine group lagged behind that in the patching group. It is possible that if our primary outcome had occurred at a time point longer than 6 months, the atropine group might have shown further improvement, perhaps achieving the same proportion of patients with 20/30 or better amblyopic eye acuity as found in the patching group. In designing the trial, we recognized that 6 months might be too short a time for the full benefit of atropine to be manifested. However, we did not believe that it would be possible to sustain pa-

Clinical Sites

Listed in order of number of patients enrolled into the Amblyopia Treatment Study 1, with city, state, site name, and number of patients in parentheses. Personnel are listed as (I) for investigator, (C) for coordinator, and (V) for visual acuity tester.

Gaithersburg, Md (36): Stephen R. Glaser (I), Andrea M. Matazinski (C), David M. Sclar (V). *Erie, Pa; Pediatric Ophthalmology of Erie* (33): Nicholas A. Sala (I), Chrissy M. Vroman (C), Cindy E. Tanner (V). *Dallas, Tex; Pediatric Ophthalmology PA and the Center for Adult Strabismus* (26): David R. Stager, Sr (I), Priscilla M. Berry (I), David R. Stager, Jr (I), Joost Feliuss (C), Jennifer A. Wilkerson (C), Maria Petrova Pesheva, MD (C), Eileen E. Birch (V), Brett G. Jeffrey (V), Anna R. O'Connor (V). *Providence, RI; Pediatric Ophthalmology and Strabismus Associates* (25): David Robbins Tien (I), Glenn E. Bulan (I), Heidi C. Christ (C), Lauren B. DeWaele (C), David A. Young (V). *Calgary, Alberta, Canada; Alberta Children's Hospital* (24): William F. Astle (I), Anna L. Ells (I), Cheryl R. Hayduk (C), Catriona I. Kerr (C), Mary S. McAlester (C), Heather J. Peddie (C), Heather M. Vibert (C). *Bethesda, Md; National Eye Institute* (20): Richard W. Hertle (I), Susan D. Mellow (C), Ed J. Fitzgibbon (V), Guy E. Foster (V). *Anchorage, Alaska; Ophthalmic Associates* (20): Robert W. Arnold (I), Mary Diane Armitage (C), Nancy H. Brusseau (V). *Milwaukee; Medical College of Wisconsin* (18): Mark S. Ruttum (I), Jane D. Kivlin (I), Veronica R. Picard (C), Merelyn J. Chesner (V). *Fullerton; Southern California College of Optometry* (17): Susan A. Cotter (I), Carmen N. Barnhardt (I), Susan M. Shin (I), Raymond H. Chu (I), Lourdes Asiain (C), Yvonne F. Flores (C), Gen Lee (C), John H. Lee (V), Sherene C. Fort (V), Jennifer L. Slutsky (V). *Houston; Texas Children's Hospital* (14): Evelyn A. Paysse (I), David K. Coats (I), Kathryn M. Brady-McCreery (I), Alma D. Sanchez (C), Viviana Corredor (C). *Nashville, Tenn; Vanderbilt Eye Center* (13): Sean Donahue (I), Cindy Foss (C), Julie A. Ozier (C), Ronald J. Biernacki (V), Evelyn Tomlinson (V). *Portland, Ore; Casey Eye Institute* (12): David T. Wheeler (I), Kimberley A. Beaudet (C), Christin L. Bateman (V), Michele A. Hartwell (V). *Sacramento, Calif; Permanente Medical Group* (11): James B. Ruben (I), Dipti Desai (C), Sue Ann Parrish (C), Tracy D. Louie (V). *University of Alabama at Birmingham School of Optometry* (10): Robert P. Rutstein (I), Wendy L. Marsh-Tootle (I), Cathy H. Baldwin (C), Kristine T. Becker (V). *Baltimore, Md; Wilmer Institute* (10): Michael X. Repka (I), David G. Hunter (I), Jana S. Mattheu (C), Sheena O. Broome (V), Carole R. Goodman (V). *Indianapolis; Indiana University Medical Center* (9): Daniel E. Neely (I), David A. Plager (I), Derek T. Sprunger (I), Donna J. Bates (C), Jay Galli (C), Michele E. Whitaker (C). *Fort Lauderdale, Fla; NOVA Southeastern University* (9): Susanna M. Tamkins (I), Michele Gonzalez (C), Siby Jacobs (V). *Baltimore, Md; Greater Baltimore Medical Center* (7): Mary Louise Z. Collins (I), Cheryl L. McCarus (C), Jaime N. Brown (V), Dorothy B. Conlan (V). *Atlanta, Ga; Emory Eye Center* (7): Scott R. Lambert (I), Lucy Yang (C), Alexander T. Elliott (V), Nicole Fallaha (V). *St Louis, Mo; Cardinal Glennon Children's Hospital* (6): Oscar A. Cruz (I), Bradley V. Davitt (I), Susan A. Havertape (C), Emily A. Miyazaki (C), Molly B. Bosch (C). *Waterbury, Conn; Ophthalmic Surgical Associates* (6): Andrew J. Levada (I), Tabitha L. Matchett (C), Angela Zimmerman Moya (C), Cara C. Mulligan (V), Shelley K. Weiss (V), Holly J. Pelletier (V). *Grand Rapids, Mich; Pediatric Ophthalmology PC* (6): Patrick J. Droste (I), Robert J. Peters (I), Jan Hilbrands (C), Kelli A. Sheeran (V), Deborah K. Smith (V), Corrie L. Vanraze-nswaay (U). *Dallas; UT Southwestern Medical Center* (6): David R. Weakley, Jr (I), Clare L. Dias (C). *Wichita, Kan; Grene Vision Group* (5): David A. Johnson (I), Ruth D. James (C), Patti G. Claes (V), Kelli K. Drake (V). *Rochester, Minn; Mayo Clinic* (5): Jonathan M. Holmes (I), Becky A. Nielsen (C), Marcela Garcia (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). *Philadelphia; Pennsylvania College of Optometry* (5): Mitchell M. Scheiman (I), Jo Ann T. Bailey (I), Kathleen T. Zinzer (V). *Columbus; Ohio State University College of Optometry* (5): Marjean T. Kulp (I), Tracy L. Kitts (C), Michael J. Earley (V). *Buffalo, NY; Children's Hospital of Buffalo* (4): Steven Awner (I), Scott E. Olitsky (V). *Lancaster, Pa; Family Eye Group/Eye Specialists of Lancaster* (4): David I. Silbert (I), Abbe E. Wagner (C), Kit M. Castillo (V), Noelle S. Matta (V), Tracy L. Meshey (V), Paulette Myers-Ely (V), Wendy L. Piper (V), Dena M. Scaringi (V), Pamela M. Snavelly (I), Lori J. Walker (V). *Palm Harbor, Fla; Specialty Eye Care* (4): Christine L. Burns (I), Magda Barsoum-Homsy (I), Le Ila C. Lawrence (C). *Chapel Hill; University of North Carolina, Department of Ophthalmology* (4): David K. Wallace (I), Marguerite J. Sullivan (C). *Tucson; University of Arizona* (4): Joseph M. Miller (I), Toby Ann Aparisi (C), Jenniffer Funk-Weyant (C), Megan Taylor (V), Sue Bulau (V). *Iowa City; University of Iowa Hospitals and Clinics* (4): William E. Scott (I), Wanda I. Ottar-Pfeifer (C), Pamela J. Kutschke (V), Keith M. Wilken (V). *Minneapolis; University of Minnesota* (4): C. Gail Summers (I), Stephen P. Christiansen (I), Ann M. Hollerschau (C), Sally M. Cook (C), Jane D. LaVoie (V), Kim S. Merrill (V). *Birmingham; Alabama Ophthalmology Associates PC* (3): Frederick J. Elsas (I), Thomas H. Metz, Jr (I), Michelle L. Mizell (C), Stephanie O. Roberts Bennett (V). *Norfolk; Eastern Virginia Medical School* (3): Earl R. Crouch, Jr (I), Kristen D. Ruark (C), Gaylord G. Ventura (V). *Mexico City, Mexico* (3): Miguel Paciuc (I), Marina M. Schnadower (C), Cecilio Velasco (V). *Temple, Tex; Scott and White Ophthalmology* (3): David C. Dries (I), V. Jeanne Vengco (C). *Salt Lake City; University of Utah/Moran Eye Center* (3): Richard J. Olson (I), Robert O. Hoffman (I), Susan F. Bracken (C), Pat L. Remington (V), Kimberly G. Yen (V). *Asheville, NC; Asheville Eye Associates* (2): Robert E. Wiggins, Jr (I), Sally A. Baumgartner (C), Mary Knecht (V). *Cincinnati, Ohio; Children's Hospital Medical Center* (2): Constance E. West (I), Shelley L. Benson (C), Laurie A. Hahn-Parrott (V), Walker E. Motley (V), Regina M. Poole (V). *Philadelphia, Pa; Children's Hospital of Philadelphia* (2): Brian J. Forbes (I), Graham E. Quinn (I), Melissa L. Ehnbohm (V), Michelle C. Maturo (V), David R. Phillips (V). *Washington, DC; Children's National Medical Center* (1): Marjean Michele Miller (I), Mitra Maybodi (I), Cori Greger (C). *Canton; Eye Centers of Ohio* (1): Elbert H. Magoon (I), Paula A. Kannam (C), Lynn A. McAtee (C), Margie Andrews (V), Caroline M. Hoge (V). *Charleston; Medical University of South Carolina, Storm Eye Institute* (1): Richard A. Saunders (I), Judy P. Hoxie (C), Lisa M. Langdale (C), Kimberly D. 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(continued)

tients who had persistent amblyopia in their treatment groups without permitting changes in therapy beyond this 6-month time point. We also do not have the data to de-

termine whether initiating distance optical blur concomitant with starting atropine therapy (by prescribing a plano spectacle lens for the sound eye) would have produced

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a more rapid response than atropine alone. At the end of 2-year follow-up, we will be able to determine whether there is any advantage regarding visual acuity to the initiation of treatment with either patching or atropine.

For the treatment protocols used in this study, the cost of the atropine regimen is likely to be less than that of the patching regimen. Assuming a cost of \$0.35 per patch and the need to use an average of 1.5 patches a day, the cost for 3 months of daily patching would be about \$50 and for 6 months about \$100. A 15-mL bottle of atropine 1% costs about \$10 and lasts for 6 months. With our protocol, about 25% of atropine-treated patients will need to be prescribed a plano spectacle lens because of an inadequate response to atropine alone. Assuming a cost of \$50 for the lens, the cost of the atropine plus the lens change is still less than that of a 6-month course of patching.

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 moderate strabismic and/or anisometropic amblyopia (specifically excluding deprivational amblyopia and myopia) younger than 7 years who were developmentally able to perform optotype visual acuity testing. This effectively set 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 previously treated for amblyopia or had received no more than 2 months of treatment in the prior 2 years. The visual acuity limit for the amblyopic eye was set at 20/

100 because atropine is not thought to be as effective a treatment for worse acuities.^{33,35} A 3-line difference in visual acuity between eyes was required (1) to assure that a true reduction in acuity was present, and (2) to have a sufficient depth of amblyopia to be able to assess improvement with treatment. Myopia was an exclusion to assure visual blur at near fixation for patients in the atropine group. In designing the trial to mirror a real-world situation, we limited compliance aids to those commonly used in clinical practice: an instruction sheet about treatment and a calendar to record the treatment received each day. Nevertheless, we recognize that patients participating in a clinical trial may differ from those in everyday practice, and our patients' level of compliance may have been better than what may be achieved in the real world.

In summary, both atropine and patching are effective treatments for moderate amblyopia in children aged 3 years to less than 7 years. Patching has the potential advantages of a more rapid improvement in visual acuity and possibly a slightly better acuity outcome, whereas atropine has the potential advantages of easier administration and lower cost. Our data are inconclusive about whether atropine may cause a transient treatment-related reduction of visual acuity in the sound eye more often than patching. However, we are reasonably confident that in our cohort, atropine did not have a lasting adverse effect on the acuity of the sound eye. Because incomplete responders to one treatment could later be given the other treatment, our results indicate that the initial choice of patching or atropine can be made by the eye

care provider and parent. Both patching and atropine are appropriate modalities for the initial treatment of moderate amblyopia in children.

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