A Randomized Trial of Atropine Regimens for Treatment of Moderate Amblyopia in Children

*The Pediatric Eye Disease Investigator Group**

Objective: To compare daily atropine to weekend atropine as prescribed treatments for moderate amblyopia in children younger than 7 years.

Design: Prospective, randomized multicenter clinical trial (30 sites).

Participants: One hundred sixty-eight children younger than 7 years with amblyopia in the range of 20/40 to 20/80 associated with strabismus, anisometropia, or both.

Intervention: Randomization either to daily atropine or to weekend atropine for 4 months. Partial responders were continued on the randomized treatment until no further improvement was noted.

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

Results: The improvement in VA of the amblyopic eye from baseline to 4 months averaged 2.3 lines in each group. The VA of the amblyopic eye at study completion was either (1) at least 20/25 or (2) better than or equal to that of the sound eye in 39 children (47%) in the daily group and 45 children (53%) in the weekend group. The VA of the sound eye at the end of follow-up was reduced by 2 lines in one patient in each group. Stereoacuity outcomes were similar in the 2 groups.

Conclusions: Weekend atropine provides an improvement in VA of a magnitude similar to that of the improvement provided by daily atropine in treating moderate amblyopia in children 3 to 7 years old. *Ophthalmology 2004;111:2076–2085 © 2004 by the American Academy of Ophthalmology.*

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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. Atropine and other cycloplegic drops have been considered alternatives. We recently reported a randomized clinical trial in which we found that substantial improvement in the visual acuity (VA) of the amblyopic eye occurred with either daily patching or daily atropine treatment regimens, and that the difference between the patching and daily atropine regimens was clinically insignificant after 6 months.[3] Simons et al reported that intermittent atropine therapy (1 or 2 days a week) was as successful as daily atropine therapy in a retrospective study.[4] This could be true because the cycloplegic effect of topical atropine usually lasts for several days.[5] To address the clinical question of how often atropine needs to be administered, we conducted a randomized clinical trial to compare atropine administered on weekend days only (weekend atropine) with atropine administered daily for treatment of moderate amblyopia in children younger than 7 years who were able to complete standardized optotype VA testing.

Patients and Methods

Our study, supported through a cooperative agreement with the National Eye Institute of the National Institutes of Health, was conducted by the Pediatric Eye Disease Investigator Group at 30 clinical sites. The protocol and informed consent forms were approved by institutional review boards, and the 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 criteria for the trial included age < 7 years, VA in the amblyopic eye between 20/40 and 20/80 inclusive, VA in the sound eye of 20/40 or better, intereye acuity difference of ≥ 3 logarithm of the minimum angle of resolution (logMAR) lines, a history of strabismus or the presence of an amblyogenic factor meeting study-specified criteria for strabismus and/or anisometropia, and the wearing of optimal spectacle correction for a minimum

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Correspondence to Michael S. Repka, MD, Jaeb Center for Health Research, 15310 Amberly Drive, Suite 350, Tampa, FL 33647. E-mail: rbeck@jaeb.org.

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

*See "Appendix" for the Writing Committee and a list of the members of the Group participating in the trial.

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of 4 weeks at the time of enrollment (the protocol for correction of refractive error has been published).[6] Children with myopia greater than −6.00 diopters (D) in the amblyopic eye, myopia greater than −0.50 D in the sound eye, or Down syndrome were excluded. A complete listing of the eligibility and exclusion criteria can be reviewed in the online supplementary material available at http://www.ophsource.com/periodicals/ophtha. Based on a postrandomization review, 2 patients in the daily group and 2 patients in the weekend group were enrolled with presumed amblyopia but did not have a study-defined amblyogenic factor (data were included in the analyses).

Treatment Protocols

Each patient was randomly assigned with equal probability to either daily or weekend (Saturday and Sunday) atropine. 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.

At enrollment, patients were prescribed atropine sulfate 1%, which was provided by the study. Sunglasses were provided, which were to be worn with a brimmed hat when the child was in sunlight. If an allergy to atropine developed, topical homatropine 5% could be substituted. If reverse amblyopia was suspected, atropine use could be reduced or discontinued at the discretion of the investigator. Before the 4-month masked examination, patching or alternate therapies for amblyopia were not to be prescribed, even if there was no response to treatment. For patients in the daily atropine group, daily use was continued, unless the VA in the amblyopic eye was equal to or better than that of the sound eye, in which case the frequency could be reduced to a minimum of 2 times a week.

At each visit, the parent was queried about side effects of treatment and adherence to the treatment protocol. Adherence was assessed by having the parent record on a calendar the days atropine was administered. 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%; 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).

Follow-up Schedule

Follow-up visits were performed at 5 weeks and 17 weeks within a specified 2-week time window. The latter visit served as the primary outcome for assessing amblyopic eye acuity. After the 17-week visit, atropine was discontinued, and the patient returned 2 to 4 weeks later to assess the sound eye acuity and binocularity (referred to below as the sound eye outcome visit). Patients whose VA in the sound eye was reduced (worse) by ≥1 lines compared with baseline were retested the same day. If there was still a reduction, a cycloplegic refraction was performed; new glasses were prescribed, if necessary; and the patient returned in 1 to 4 weeks for repeat acuity testing.

After completion of these visits, study participation ended for patients who met any of the following criteria: (1) the amblyopic eye VA was 20/25 or better, (2) the amblyopic eye VA was equal to or better than the sound eye VA, (3) the amblyopic eye VA had not improved at least 2 lines from baseline, or (4) the amblyopic eye had received patching or other nonstudy alternative treatment. Patients whose amblyopic eye had improved ≥2 lines from baseline but still had VA worse than 20/25 and worse than the sound eye acuity resumed atropine and had study-specified visits every 8 weeks as long as the amblyopic eye VA was ≥1 lines better than the acuity at the prior visit.

Examination Procedures

At enrollment and at each follow-up visit, VA was measured in each eye by a study-certified vision tester using the Amblyopia Treatment Study VA-testing protocol (which uses single-surrounded HOTV optotypes) on an electronic visual acuity tester.[7,8] Additional baseline testing included (1) a cycloplegic refraction; (2) an ocular examination; (3) measurement of ocular alignment with a simultaneous prism and cover test at distance and near fixation; (4) assessment of binocularity with the Titmus Test (fly only), the Randot Suppression Test (the R, +, and L symbols of the Randot Stereotests), and the Randot Preschool Stereoacuity Test (Stereo Optical Co., Chicago, IL); and (5) measurement of near VA in each eye before cycloplegia and in the sound eye after cycloplegia (ATS4 Near Visual Acuity Test, Precision Vision, La Salle, IL).

The near acuity test consists of a series of flip cards with single-surrounded HOTV optotypes beginning at 20/400 and ending at 20/20 in 0.1-logMAR intervals. A matching card and a 40-cm test distance measuring cord are attached. Spectacles are worn, if prescribed. The testing procedure consists of (1) a screening phase asking the patient to identify the first HOTV optotype on each line, starting with 20/400 and continuing until a letter is identified incorrectly, and (2) a threshold phase, which begins at the lowest correct line on screening: if 3 of 3 or 3 of 4 are correct, the test continues with smaller optotypes until 2 on a line are missed; otherwise larger optotypes are tested until 3 of 3 or 3 of 4 on a line are correct. The smallest line read with 3 of 3 or 3 of 4 letters correct is recorded as the near VA.

At the 5-week visit, a questionnaire designed to assess the impact of the pharmacologic amblyopia treatment on the quality of life of the child and family (Amblyopia Treatment Index[9,10]) was completed by the parent. At the 17-week (4-month) outcome examination, VA testing was conducted by a study-certified vision tester who was masked as to the patient's treatment group. At the post–17 week sound eye outcome examination (completed after atropine was discontinued for at least 2 weeks), the following tests performed at baseline were repeated: near acuity in each eye (without cycloplegia), measurement of ocular alignment (usually performed after VA testing, but the timing was not standardized and the examiner was not always the same examiner who made the baseline measurement), and assessment of binocularity.

Statistical Methods*

The trial was designed to assess whether one treatment regimen was superior to the other. Using data from the atropine treatment group in our previous study,[3] 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 0.17 for the 4-month amblyopic eye acuity scores, a mean difference between groups of 0.1 logMAR units (1 line of acuity), a correlation between the

*Additional details can be found in the online supplementary material available at http://www.ophsource.com/periodicals/ophtha.

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 subgroup analyses based on the cause of amblyopia. With this sample size and the above assumptions, there was 99% power for the primary analysis.

The primary outcome was the 4-month amblyopic eye logMAR VA score. The treatment groups were compared in an analysis of covariance model in which the logMAR acuity scores were adjusted for baseline acuity. Confounding was evaluated by including covariates of interest in the model, and interaction between baseline factors and treatment group on the 4-month outcome acuity was assessed by including interaction terms in the model. Methods used to analyze the amblyopic eye logMAR acuity scores at the 5-week visit paralleled the analyses conducted on the 4-month data.

The treatment group difference in sound eye logMAR VA score 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 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. The associations of baseline factors with improvement in the 4-month amblyopic eye acuity were evaluated with linear regression controlling where indicated for baseline acuity.

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). Within treatment groups, the change in acuity from baseline is reported in lines. Treatment group comparisons are reported as differences in mean logMAR acuity. All reported *P* values are 2 tailed. Analyses were conducted using SAS.[11]

Results

Between June 2002 and April 2003, 168 patients entered the trial, with 83 assigned to the daily atropine group and 85 assigned to the weekend atropine group. The number of patients enrolled per site at the 30 sites ranged from 1 to 28 (median, 3). The average age of the patients was 5.3 years; 39% were female, and 79% were white. The mean VA in the amblyopic eye at enrollment was 0.46 logMAR (approximately 20/63), with a mean difference in acuity between eyes of 4.0 lines. The baseline characteristics of the 2 groups are provided in Table 1.

Patient Follow-up and Treatment

The primary outcome examination was completed by 77 (93%) of the 83 patients in the daily group and 83 (98%) of the 85 patients in the weekend group (Fig 1). The vision tester was masked as to treatment group for 97% of these examinations (99% in the daily group and 95% in the weekend group). Before the 4-month outcome examination, patients in each group had a similar number of follow-up visits (mean number of visits, 1.2±0.5 in the daily group and 1.1±0.4 in the weekend group, respectively; $P = 0.60$).

Among the patients completing the 4-month outcome examination, the treatment was the same throughout follow-up for 66 (86%) of the 77 patients in the daily group and for 79 (95%) of the 83 patients in the weekend group. In 3 patients in the daily group and 2 patients in the weekend group, treatment was stopped or reduced because acuity in the amblyopic eye was the same as or better than that of the sound eye acuity. In 4 patients in the daily group, treatment was stopped or reduced because of possible treatment side effects. Two patients in the daily group were prescribed patching without ever starting atropine. Two patients in the daily group and 2 in the weekend group were switched to patching after initially using atropine (all changes to patching were at parents' request).

After 4 months, 26 (34%) patients in the daily group and 32 (39%) patients in the weekend group met the study criteria to continue in the study on treatment (amblyopic eye acuity had improved ≥2 lines from baseline but was still worse than 20/25 and worse than the sound eye acuity at enrollment). Five patients met criteria for continued treatment at the 4-month outcome visit, but had no further follow-up (4 in the daily group and 1 in the weekend group). Among the 53 patients with additional treatment, the average duration of additional treatment beyond the 4-month visit was 10 weeks in both the daily and weekend groups, with a maximum of 26 and 20 weeks, respectively.

During the initial 4 months of treatment, patient adherence with the prescribed treatment was judged by the investigator to be excellent in 75%, good in 20%, fair in 4%, and poor in 1% of patients in the daily group, and to be excellent in 68%, good in 26%, fair in 4%, and poor in 2% of patients in the weekend group.

Effect of Treatment on Visual Acuity in the Amblyopic Eye

A similar amount of improvement in the amblyopic eye VA occurred from baseline to 4 months in both the daily and weekend groups (Fig 2; see also supplementary Table 2 available at http://www.ophsource.com/periodicals/ophtha), and the course of acuity improvement seemed similar in the 2 treatment groups (Fig 3). At 5 weeks, improvement in amblyopic eye VA averaged 1.6 lines in the daily group and 1.7 lines in the weekend group (mean difference in acuity between groups, 0.01 logMAR; 95% confidence interval, −0.03 to 0.05), and at 4 months improvement averaged 2.3 lines in each group (mean difference in acuity between groups, 0.00 logMAR; 95% confidence interval, −0.04 to 0.04). The results were not altered when adjusted for the imbalance between groups in race or iris color (data not shown).

Results in subgroups based on cause of amblyopia (strabismus, anisometropia, or combined) were similar to the overall result; the mean line change from baseline ranged from 2.1 to 2.5 in the 6 subgroups based on cause and treatment ($P = 0.83$ for an interaction between cause and treatment group). Additionally, there was no evidence for an interaction between treatment group and gender ($P = 0.57$), age ($P = 0.72$), iris color ($P = 0.11$), baseline amblyopic eye acuity ($P = 0.59$), prior amblyopic treatment ($P = 0.65$), or sound eye refractive error ($P = 0.11$).

Patients who continued on treatment beyond the 4-month outcome examination improved an average of 0.8 additional lines of amblyopic eye acuity (0.7 lines among the 22 daily group patients with additional follow-up and 0.8 lines among the 31 weekend group patients with additional follow-up). Ten (45%) of the 22 patients in the daily group and 16 (52%) of the 31 patients in the weekend group improved at least 1 additional line of acuity in the amblyopic eye.

At the time of study completion, 39 (47%) of the patients in the daily group and 45 (53%) in the weekend group had an amblyopic

Table 1. Baseline Characteristics According to Treatment Group

	Daily (n = 83) [n (%)]	Weekend (n = 85) [n (%)]	Overall (n = 168) [n (%)]
Gender (female)	29 (35)	37 (44)	66 (39)
Age (yrs)			
<3	1 (1)	3 (4)	4 (2)
3–<4	12 (14)	14 (16)	26 (15)
4–<5	18 (22)	14 (16)	32 (19)
5–<6	27 (33)	31 (36)	58 (35)
6–<7	25 (30)	23 (27)	48 (29)
Mean (SD)	5.3 (1.1)	5.3 (1.1)	5.3 (1.1)
Race/ethnicity			
White	58 (70)	74 (87)	132 (79)
Black	5 (6)	2 (2)	7 (4)
Hispanic/Latino	14 (17)	6 (7)	20 (12)
Asian	2 (2)	1 (1)	3 (2)
American Indian/Alaskan Native	1 (1)	0	1 (1)
More than one	1 (1)	1 (1)	2 (1)
Unknown/not reported	2 (2)	1 (1)	3 (2)
Iris color			
Blue	27 (33)	37 (44)	64 (38)
Brown	45 (54)	36 (42)	81 (48)
Hazel (green)	11 (13)	8 (9)	19 (11)
Mixed	0	4 (5)	4 (2)
Prior treatment for amblyopia			
None	67 (81)	71 (84)	138 (82)
Patching (skin)	9 (11)	9 (11)	18 (11)
Patching (glasses)	5 (6)	1 (1)	6 (4)
Atropine (or other cycloplegic drops)	1 (1)	1 (1)	2 (1)
Patching and atropine	1 (1)	2 (2)	3 (2)
Other	0 (0)	1 (1)	1 (1)
Cause of amblyopia*			
Strabismus	27 (33)	29 (34)	56 (33)
Anisometropia	33 (40)	36 (42)	69 (41)
Strabismus and anisometropia	21 (25)	18 (21)	39 (23)
Distance visual acuity, amblyopic eye			
20/80	16 (19)	18 (21)	34 (20)
20/63	34 (41)	31 (36)	65 (39)
20/50	14 (17)	18 (21)	32 (19)
20/40	19 (23)	18 (21)	37 (22)
Mean (SD) logMAR	0.46 (0.10)	0.46 (0.11)	0.46 (0.10)
Distance visual acuity, sound eye			
20/40	0	2 (2)	2 (1)
20/32	18 (22)	12 (14)	30 (18)
20/25	22 (27)	28 (33)	50 (30)
20/20	32 (39)	30 (35)	62 (37)
20/16	11 (13)	13 (15)	24 (14)
Mean (SD) logMAR	0.06 (0.10)	0.05 (0.10)	0.05 (0.10)
Intereye acuity difference (lines)			
3	31 (37)	28 (33)	59 (35)
4	33 (40)	34 (40)	67 (40)
5	9 (11)	16 (19)	25 (15)
6	8 (10)	5 (6)	13 (8)
7	2 (2)	2 (2)	4 (2)
Mean (SD)	4.0 (1.1)	4.1 (1.0)	4.0 (1.0)
Refractive error in amblyopic eye (spherical equivalent in diopters)			
<+1.00	7 (8)	10 (12)	17 (10)
+1.00–<+2.00	5 (6)	4 (5)	9 (5)
+2.00–<+3.00	7 (8)	14 (16)	21 (13)
+3.00–<+4.00	14 (17)	13 (15)	27 (16)
≥+4.00	50 (60)	44 (52)	94 (56)
Mean (SD)	4.37 (2.29)	4.08 (2.45)	4.22 (2.37)
Refractive error in sound eye (spherical equivalent in diopters)			
<+1.00	10 (12)	15 (18)	25 (15)
+1.00–<+2.00	21 (25)	20 (24)	41 (24)
+2.00–<+3.00	10 (12)	15 (18)	25 (15)
+3.00–<+4.00	15 (18)	11 (13)	26 (15)
≥+4.00	27 (33)	24 (28)	51 (30)
Mean (SD)	3.11 (2.10)	2.95 (2.23)	3.03 (2.16)

logMAR = logarithm of the minimum angle of resolution; SD = standard deviation.
*Four patients (2 in the daily group and 2 in the weekend group) did not meet criteria for any of the 3 study-specified causes of amblyopia.

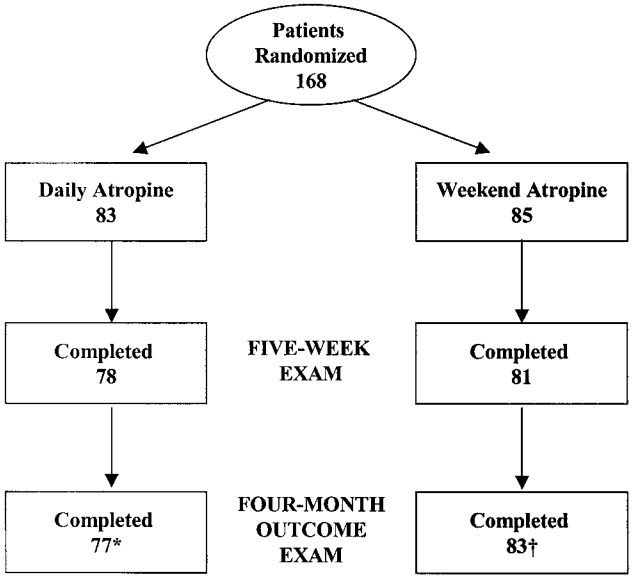


Figure 1. Flow chart showing study completion in each treatment group. *Daily group: among the 6 patients with incomplete follow-up, 2 were enrolled but had no further follow-up, and 4 completed a follow-up visit but then dropped out. Of the completed visits, 63 were completed in window (16–18 weeks), 3 were early (13 to <16 weeks), and 11 were late (>18 to 26 weeks). †Weekend group: among the 2 patients with incomplete follow-up, 1 was enrolled but had no further follow-up, and 1 completed a follow-up visit but then dropped out. Of the completed visits, 68 were completed in window (16–18 weeks), 1 was early (13 to <16 weeks), and 14 were late (>18 to 26 weeks).

eye acuity that was either (1) 20/25 or better or (2) the same as or better than the sound eye acuity, provided that the sound eye acuity had not decreased from enrollment (Table 3). The mean amblyopic eye acuity at study completion was 0.23 logMAR in the daily group and 0.21 logMAR in the weekend group (approximately 20/32). For comparison to assess the degree of residual amblyopia, the mean sound eye VA at enrollment was 0.05 logMAR (approximately 20/25), with 81% of the sound eyes having acuity of 20/25 or better.

Among patients who improved ≥2 lines from baseline during the study, 30% of patients achieved their best acuity at 5 weeks, 50% at 4 months, 7% at 6 months, 10% at 8 months, and 3% at 10 months. These results were similar in the 2 treatment groups.

Adverse Effects of Treatment

At 4 months, the sound eye VAs were similar in the 2 groups (mean logMAR VA score, 0.02 in the daily group and 0.02 in the weekend group; $P = 0.52$) (Table 4). Visual acuity in the sound eye was decreased from baseline by ≥2 lines in 2 patients (3%) in the daily group and in 2 patients (2%) in the weekend group ($P = 0.99$; see Table 4 for case details).

Ocular side effects, most commonly light sensitivity, were reported by 13 (16%) patients in the daily group and 25 (29%) patients in the weekend group. However, these symptoms did not lead to a change in treatment. Facial flushing and fever were reported for 2 patients in the daily group, one of whom remained on atropine and the other of whom was switched to homatropine.

Ocular Alignment

Assessment of distance ocular alignment at the outcome examination revealed that among patients with no ocular deviation at baseline, 6 patients in the daily group and 5 patients in the weekend group were noted to have small-angle esotropia (1–8 Δ) at distance fixation, whereas 2 patients in the daily group and none in the weekend group developed an esotropia of >8 Δ. Two patients in the daily group and 1 patient in the weekend group had a preexisting strabismus that increased by >10 Δ. Two patients in the daily group and 3 patients in the weekend group who at baseline had small-angle strabismus (1–8 Δ) at distance fixation had no deviation at 17 weeks. Three patients in the daily group and 4 patients in the weekend group had preexisting esotropia that decreased by ≥10 Δ.

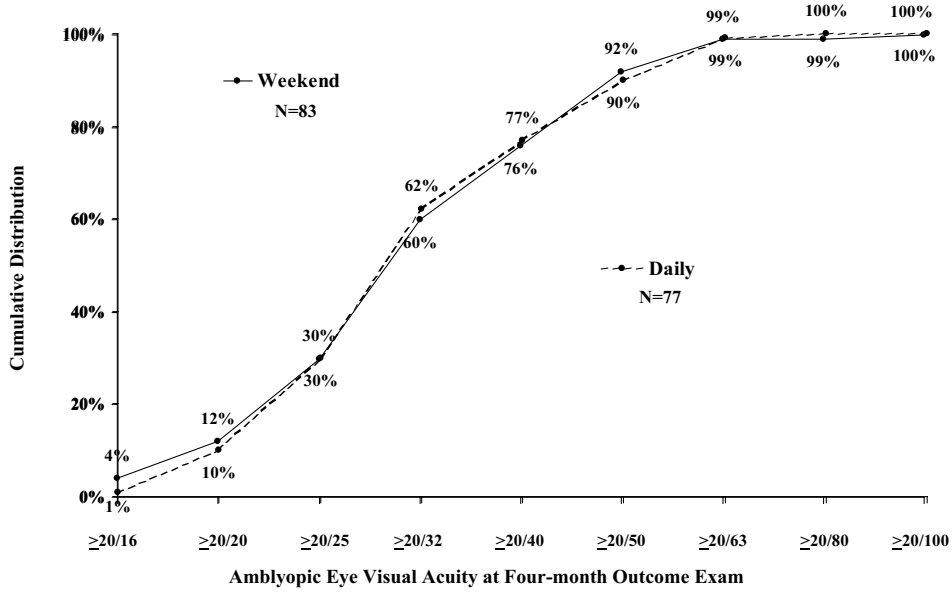
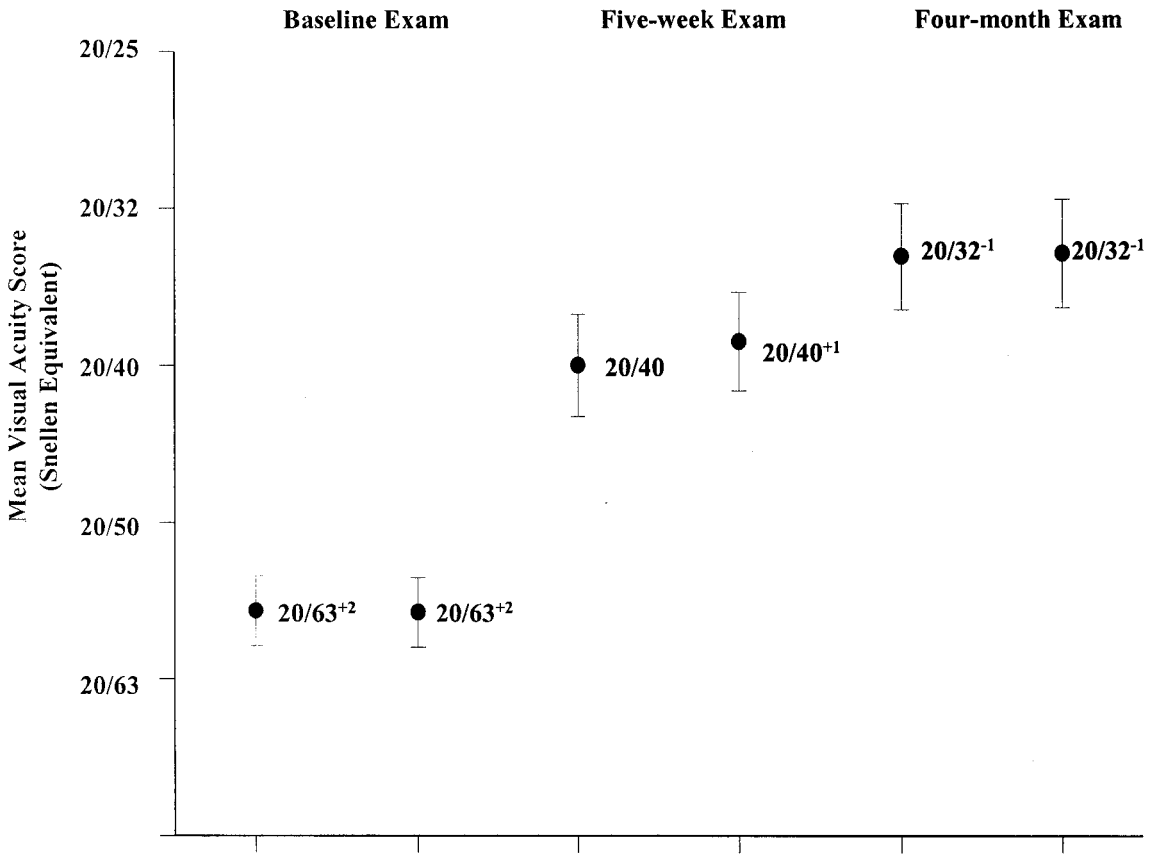


Figure 2. Cumulative distribution of amblyopic eye visual acuity scores at 4-month outcome examination according to treatment group.



	Daily Atropine N=83	Weekend Atropine N=85	Daily Atropine N=78	Weekend Atropine N=81	Daily Atropine N=77	Weekend Atropine N=83
20/125						
20/100			3%			1%
20/80	19%	21%	1%	4%	1%	
20/63	41%	36%	14%	11%	9%	7%
20/50	17%	21%	13%	16%	13%	16%
20/40	23%	21%	28%	26%	14%	16%
20/32			29%	25%	32%	30%
20/25			9%	16%	19%	18%
20/20			3%	2%	9%	8%
20/16					1%	4%
Mean logMAR (SD)	0.46 (0.10)	0.46 (0.11)	0.30 (0.15)	0.29 (0.14)	0.23 (0.15)	0.23 (0.16)
Mean Lines Change (SD)	-	-	1.6 (1.3)	1.7 (1.3)	2.3 (1.4)	2.3 (1.3)

Figure 3. Amblyopic eye visual acuity in each group at baseline, 5 weeks, and 4 months. The point estimates and 95% confidence intervals are shown. logMAR = logarithm of the minimum angle of resolution; SD = standard deviation.

Table 3. Visual Acuity (VA) in the Amblyopic Eye at the Time of Study Completion by Treatment Group

	Daily Group (n = 83) [n (%)]	Weekend Group (n = 85) [n (%)]
Distribution of VA scores at study completion*		
20/100	1 (1)	0
20/80	1 (1)	1 (1)
20/63	7 (8)	7 (8)
20/50	8 (10)	10 (12)
20/40	11 (13)	10 (12)
20/32	29 (35)	24 (28)
20/25	17 (20)	20 (24)
20/20	8 (10)	9 (11)
20/16	1 (1)	4 (5)
Mean logMAR (SD)	0.23 (0.16)	0.21 (0.16)
Improvement from baseline to study completion [mean lines (SD)]	2.3 (1.5)	2.5 (1.5)
Amblyopic eye VA at study completion either (1) 20/25 or better or (2) better than or equal to sound eye VA [mean lines (SD)]	39 (47)	45 (53)
95% confidence interval for difference† between treatment groups	−21% to 9%	

logMAR = logarithm of the minimum angle of resolution; SD = standard deviation.
*For 55 patients in the daily group and 52 patients in the weekend group, the study completion amblyopic eye acuity was the acuity measured at the 4-mo outcome examination. For the 22 patients in the daily group and 31 patients in the weekend group who continued on treatment beyond 4 mo, the study completion amblyopic eye acuity was obtained at a visit after 4 mos. For patients who did not complete the study (6 patients in the daily group and 2 patients in the weekend group), the amblyopic eye VA at the last follow-up visit was used, or if no follow-up, the acuity at enrollment was used.
†Daily atropine group minus the weekend atropine group.

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

	Daily Group (n = 77)	Weekend Group (n = 83)
Line change from baseline to outcome examination [n (%)]		
−2	2 (3)	2 (2)
−1	2 (3)	3 (4)
0	53 (69)	45 (54)
+1	11 (14)	28 (34)
+2	9 (12)	5 (6)
Mean* (SD)	0.3 (0.8)	0.4 (0.8)
Distribution of VA scores at outcome examination [n (%)]		
20/50	1 (1)	0
20/40	0	1 (1)
20/32	9 (12)	9 (11)
20/25	14 (18)	18 (22)
20/20	36 (47)	30 (36)
20/16	17 (22)	25 (30)
Mean* logMAR (SD)	0.02 (0.10)	0.02 (0.10)

logMAR = logarithm of the minimum angle of resolution; SD = standard deviation.
$P = 0.52$ for difference in mean sound eye VA at 4 mos between treatment groups from analysis of covariance model controlling for baseline sound eye VA. Among the 4 patients with a ≥2-line reduction in sound eye acuity with further follow-up off treatment, the sound eye tested equal to baseline in 2 patients (1 of 2 in the daily group and 1 of 2 in the weekend group). Two patients remained 2 lines worse than baseline (1 patient in the daily group tested 20/20 at baseline, 20/32 at 4 mos, and 20/32 again at 5 mos before being lost to follow up, and 1 patient in the weekend group tested 20/20 at baseline, 20/32 at 4 mos, and 20/32 at 8 mos).
*A positive mean indicates that the sound eye VA at the 4-mo outcome examination was better than the sound eye VA at baseline.

Binocularity

The 2 groups tested similarly on the binocularity tests at baseline and at the 4-month outcome (supplementary Table 5, available at http://www.ophsource.com/periodicals/ophtha). There was no difference between treatment groups in responses recorded at the outcome examination for the Randot Preschool Stereoacuity Test ($P = 0.69$), the suppression portion of the Randot Stereotests ($P = 0.39$), or the Titmus fly stereotest ($P = 0.99$).

Parental Questionnaire

For the patients completing the 5-week visit, the Amblyopia Treatment Index was completed by 71 of 78 (91%) in the daily group and by 76 of 81 (94%) of the parents in the weekend group. In both treatment groups, the questionnaire results indicated that treatment was well tolerated. The questionnaire scores were similar in the daily and weekend groups on the Adverse effects subscale (median, 2.00 vs. 2.00; $P = 0.25$) and Social stigma treatment subscale (median, 2.00 vs. 2.00; $P = 0.98$), but on the Compliance subscale, the scores were slightly worse in the weekend group than in the daily group (median, 2.10 vs. 2.00; $P = 0.05$).

Factors Associated with Improvement in Amblyopic Eye Acuity

Data were assessed overall and within treatment group to evaluate whether any patient factors were associated with the amount of VA improvement from baseline to 4 months (supplementary Table 6 available at http://www.ophsource.com/periodicals/ophtha). Amblyopic eye acuity improved a similar amount within subgroups based upon gender, age, cause of amblyopia, iris color, prior amblyopia treatment, and refractive error in the sound eye. The amblyopic eye also improved a similar amount regardless of whether the baseline sound eye acuity under cycloplegia at near fixation was the same as, better than, or worse than the baseline amblyopic eye acuity.

Overall, patients who started with worse amblyopic eye acuity at baseline improved more on average than patients who started with better acuity (2.0 mean line improvement in patients with baseline amblyopic eye VA of 20/40–20/50, vs. a 2.5 mean line improvement in patients with baseline amblyopic eye VA of 20/63–20/80; $P<0.001$) (supplementary Table 7 available at http://www.ophsource.com/periodicals/ophtha).

Discussion

We compared the effectiveness of prescribing weekend and daily atropine regimens for the sound eye in the treatment of moderate amblyopia (20/40–20/80) in 168 children younger than 7 years. The study, which was conducted in both university and community-based practices, was designed to approximate usual 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 VA. We found that amblyopia improved with both atropine regimens and that there was no demonstrable advantage to the daily administration of atropine either in the rapidity of improvement or in the magnitude of improvement after 4 months of treatment. Furthermore, there was no difference between groups in the improvement achieved with additional protocol treatment beyond the 4-month outcome.

The magnitude of improvement after 4 months was 2.3 lines with both daily and weekend atropine regimens. These treatments may have had an equal effect because of the prolonged cycloplegic action of atropine and consequent optical defocus. This improvement was strikingly similar to the 2.4-line improvement after the same time interval we found in a previous clinical trial for regimens of 2 hours of patching per day and 6 hours of patching per day for amblyopic patients with nearly identical eligibility criteria and baseline characteristics.[12]

At the 4-month outcome examination, there was no difference between treatment groups in the mean sound eye VA score or in the proportion of eyes in each group whose sound eye VA tested ≥2 lines worse than baseline. Two patients had a 2-line reduction in sound eye acuity (1 in each group) at 4 months that was present at the last follow-up visit. There was no difference between treatment groups in the development, worsening, or improvement of strabismus or in stereoacuity measured with the Randot Preschool Stereoacuity Test. Overall, at 4 months, 10% of patients were found to have had a new strabismus or a preexisting angle of strabismus that had increased by ≥10 Δ, and 8% were found to have had their strabismus resolved or an angle of strabismus reduced by ≥10 Δ compared with baseline. In a prior study,[3] we reported that the risk of new-onset strabismus after 6 months of treatment was similar in patients treated with atropine and patients treated with patching.

Although the parent questionnaire completed after the first 5 weeks of treatment indicated that both atropine regimens were well tolerated, the parents of the patients in the weekend group reported more concern with compliance than did the parents of patients in the daily group. We speculate that the daily routine of administering the atropine drops is easier for the parents to remember and for the children and parents to accept treatment, thereby easing compliance concerns. Parents also reported more frequent light sensitivity with weekend atropine than with daily atropine. This may be due to patients on daily atropine becoming acclimated to the drug's effects, including light sensitivity, and, therefore, being less likely to report it than patients treated on the weekend only. The clinician may wish to balance these results related to weekend atropine therapy with the advantage of prescribing less medication.

To estimate the maximum improvement from each regimen, the trial design maintained patients on their randomized therapy if the amblyopic eye acuity had improved ≥2 lines by 4 months, was worse than 20/25, and was worse than the baseline sound eye acuity. The continued treatment was prescribed for about a third of all patients and averaged 10 weeks in both treatment groups. This additional treatment was sufficient to increase the improvement from therapy for these patients by approximately 0.8 lines, on average. This finding supports the continuation of treatment in patients who improve but have residual amblyopia after 4 months of treatment. However, our study design is such that we cannot provide a recommendation as to how long beyond 4 months treatment should be continued after no improvement is noted to reach maximum improvement in VA.

In this study we analyzed the outcomes with regard to iris color and cycloplegic near VA in the sound eye to determine whether these factors might be predictive of a response to treatment. We hypothesized that patients with darker colored irides might have had a shortened duration of cycloplegia from atropine. However, we saw no difference in the treatment response related to iris color. We enrolled too few black patients to assess whether race would impact the response to treatment. We also speculated that for patients to improve with atropine treatment they would need their near acuity in the amblyopic eye to be better than that in the cyclopleged sound eye. However, the VA of the amblyopic eyes improved an amount similar to the overall treatment benefit, even when the sound eye with cycloplegia had better near acuity than the amblyopic eye. Perhaps the amblyopic eye is being used for some portion of the day or under conditions other than those tested with the near acuity test. These findings are consistent with our study that compared atropine to patching therapy, in which a switch of near fixation to the amblyopic eye was not necessary for improvement.[3]

We could identify no sources of bias or confounding to explain our findings. The follow-up visit rate was high in both groups, and data missing from patients who dropped out of the study did not influence the interpretation of the results. Baseline amblyopic eye acuity was similar in the 2 groups. There was a slight imbalance between groups in the distribution of race and blue iris color; however, adjusting for this in analysis indicated that this did not confound the results. Although the patients, parents, and investigators were by the nature of this study unmasked to the treatment group assignments, masking of the primary VA outcome measurement was achieved in 97% of cases. Visual acuity testing was performed by a standardized protocol using a VA testing instrument developed specifically for this study to ensure consistency of testing across our sites.[7,8] With the actual sample size of 160 patients (number completing the 4-month outcome visit) and using the observed data as the basis for the standard deviation of the outcome acuity scores, statistical power for the primary analysis was 90% to detect a treatment group difference of 0.08 logMAR (about 1 line). Thus, it is unlikely that a true benefit of meaningful magnitude between weekend and daily atropine exists but was not detected in this study.

We know of no prospective clinical trial that has compared differing atropine treatment regimens. However, these results confirm the retrospective case series of Simons et al, who reported that intermittent atropine therapy could effectively treat amblyopia.[13] They reported 1.9 lines of improvement in the intraocular acuity difference in 73 patients

treated with intermittent therapy (no specific frequency), compared with 2.7 lines of improvement in 38 patients treated with daily treatment. We did not believe that we feasibly could include an untreated control group in this trial. Thus, our conclusion that both atropine regimens improved VA 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 2.3 lines on average at 4 months) substantially exceeded any potential learning effect or age effect.[7,8,14] The magnitude of any learning/age effect on the VA of the amblyopic eyes in this study may likely be similar to the observed improvement from baseline to the 4-month examination in the acuity in the sound eyes of patients in the patching group of our previously reported trial of atropine versus patching for moderate amblyopia (mean change, 0.3 lines).[3,12] A slight overestimate of the amount of improvement attributable to 4 months of atropine 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 have no bearing on our conclusions, they could have produced a slight overestimate of the amount of improvement from atropine experienced by such patients in both treatment groups.

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 deprivation amblyopia) younger than 7 years who developmentally were able to perform an HOTV optotype VA 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. A 3-line difference in 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. 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 about treatment 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 clinical practice.

In summary, prescribed weekend atropine appears to be as effective as prescribed daily atropine in treating children ages 3 to <7 years old with moderate amblyopia in the range of 20/40 to 20/80. The magnitude of improvement was similar to that previously reported for patching prescribed either 2 or 6 hours per day. A reduced frequency of atropine treatment is another method for parents and clinicians to consider when treating moderate amblyopia.

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Appendix

Writing Committee

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

Scheiman, OD, David R. Stager, Sr, MD, David K. Wallace, MD.

The Pediatric Eye Disease Investigator Group

Clinical Sites That Participated in This Protocol. Sites are listed in order by number of patients enrolled into the study, which is noted in parentheses and preceded by the site's location and name. I = Investigator; C = Coordinator; V = Visual Acuity Tester.

Erie, Pennsylvania—Pediatric Ophthalmology of Erie (28): N. Sala (I), R. Hodde (C), C. Tanner (V).

Anchorage, Alaska—Ophthalmic Associates (15): R. Arnold (I), M. Armitage (C), N. Brusseau (V), M. Gindling (V).

Lancaster, Pennsylvania—Family Eye Group (15): D. Silbert (I), E. Singman (I), D. Blackburn (I), N. Matta (C), S. Butler (V), C. Corradino (V), T. Hosey (V), D. Jostes (V), A. Keene (V), S. Kilgore (V), T. Nelson (V), W. Piper (V), S. Weit (V), S. Wright (V).

Miami, Florida—Bascom Palmer Eye Institute (11): S. Tamkins (I), E. Olivares (C), N. Oviedo (C), B. Bailey (V), C. Cannon (V), M. Garcia (V), G. Patsiopoulos (V).

West Des Moines, Iowa—Wolfe Clinic (10): D. Suh (I), H. Sipes (C), K. Walters (C), L. Fergus (V), R. Swisher (V).

Dallas, Texas—Pediatric Ophthalmology, P.A. (8): D. Stager, Sr (I), D. Stager, Jr (I), P. Berry (I), J. Felius (C), S. Morale (C), J. Whalen (C).

Lake Worth, Florida—Palm Beach Eye Foundation/Visual Health and Surgical Center (8): L. Friedman (I), K. Seale (C), L. Mancino (V).

Providence, Rhode Island—Rhode Island Eye Institute (8): J. Donahue (I), N. Waterman (C), C. Bazinet (V), P. Reale (V), M. Silvia (V).

Saint Paul, Minnesota—Associated Eye Care (8): S. Schloff (I), A. Brown (C), V. Olson (C).

Fullerton, California—Southern California College of Optometry (7): S. Cotter (I), C. Barnhardt (I), R. Chu (I), M. Nguyen (V), S. Shin (I), E. Song (V), Y. Flores (C), L. Asiain (C).

Birmingham, Alabama—University of Alabama at Birmingham School of Optometry (6): R. Rutstein (I), W. Marsh-Tootle (I), K. Niemann (I), C. Baldwin (C), P. Garjales (V).

Indianapolis, Indiana—Indianapolis Eye Care Center (6): D. Lyon (I), M. Varvel (C), J. Downey (V), B.Sutton (V).

Providence, Rhode Island—Pediatric Ophthalmology and Strabismus Associates (6): D. Robbins Tien (I), G. Bulan (I), H. Christ (C), L. DeWaele (C).

Columbus, Ohio—Pediatric Ophthalmology Associates, Inc. (5): R. Hertle (I), D. Bremer (I), M. McGregor (I), G. Rogers (I), V. Hill (C), R. Murray (C), C. King (V)

Baltimore, Maryland—Wilmer Institute (3): M. Repka (I), S. Broome (C), C. Goodman (C), X. Liu (C).

Calgary, Canada—Alberta Children's Hospital (3): W. Astle (I), M. del Pilar Echeverri (I), A. Ells (I), T. Beer (C), C. Hayduk (C), A. Ingram (C), C. Kerr (C), S. McMullen (C), H. Peddie (C), H. Vibert (C).

Dallas, Texas—UT Southwestern Medical Center (3): D. Weakley, Jr (I), C. Dias (C).

Grand Rapids, Michigan—Pediatric Ophthalmology, P.C. (3): P. Droste (I), R. Peters (I), J. Hilbrands (C), C. Vanravenswaay (V).

Albuquerque, New Mexico—Eye Associates of New Mexico & Southwest Colorado (2): F. Durso (I), S. Calhoun (C), S. Cohen (V), W. Lacoursiere (V).

Cinnaminson, New Jersey (2): M. Gallaway (I), A. Bacho (V).

Columbus, Ohio—The Ohio State University (2): M. Kulp (I), T. Kitts (C), M. Ackerman (V), A. Toole (V).

Minneapolis, Minnesota—University of Minnesota (1): G. Summers (I), S. Christiansen (I), A. Holleschau (C), J. Lavoie (V), K. Merrill (V).

New York, New York—State University of New York, College of Optometry (1): R. Duckman (I), D. FitzGerald (I).

Norfolk, Virginia—Eastern Virginia Medical School (1): E. Crouch, Jr (I), K. Ruark (C), G. Ventura (V).

Palm Harbor, Florida—Specialty Eye Care (1): C. Burns (I), L. Lawrence (C).

Philadelphia, Pennsylvania—Pennsylvania College of Optometry (1): M Scheiman (I), J. Bailey (I), B. Scombordi (I), K. Zinzer (I), A. Grossman (C), K. Pollack (V).

Rockville, Maryland (1): S. Glaser (I), P. Glaser (C), A. Matazinski (C), M. Schroyer (C).

St. Louis, Missouri—Cardinal Glennon Children's Hospital (1): O. Cruz (I), B. Davitt (I), E. Miyazaki (C), A. Zimmerman Moya (C).

Waterbury, Connecticut—The Eye Care Group, PC (1): A. Levada (I), D. Comstock (C), T. Matchett (C), S. Weiss (V).

Wichita, Kansas—Grene Vision Group (1): D. Johnson (I), R. Dannar (C).

PEDIG Coordinating Center—Tampa, Florida. R. Beck, N. Boyle, C. Cagnina-Morales, E. Cardosa, D. Chandler, Q. Donahue, H. Gillespie, J. Gillett, K. Grant, R. Kraker, S. Mares, H. McCombs, P. Moke.

National Eye Institute—Bethesda, Maryland—D. Everett.

PEDIG Executive Committee—M. Repka (Chair), J. Holmes (Vice-Chair), R. Beck, E. Birch, S. Cotter, D. Everett, P. Moke.

Amblyopia Treatment Study Steering Committee—R. Beck, E. Birch, S. Cotter, D. Everett, R. Hertle, J. Holmes, P. Moke, G. Quinn, M. Repka, M. Scheiman.

Data and Safety Monitoring Committee—W. Barlow (Chair), E. Buckley, B. Davis, V. Dobson, J. Keltner, H. Osman, E. Palmer, D. Phelps.

Eligibility and Exclusion Criteria

Eligibility Criteria

- Age < 7 years
- Able to measure visual acuity (VA) using the ATS VA testing protocol on the EVA Tester (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)
- Visual acuity in the amblyopic eye of $\leq$20/40 and $\geq$20/80
- Visual acuity in the sound eye of $\geq$20/40
- Intereye acuity difference of $\geq$3 logarithm of the minimum angle of resolution lines
- No amblyopia treatment (other than spectacles) in the month before enrollment and no more than 1 month of amblyopia treatment in the 6 months before enrollment (any treatment more than 6 months before enrollment was acceptable)
- Refractive error corrected for at least 4 weeks
- 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 $\geq$0.50 diopters (D) of spherical equivalent (SE) or $\geq$1.50-D difference in astigmatism in any meridian, with no measurable heterotropia at distance or near fixation, which persisted after at least 4 weeks 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 $\geq$1.00-D SE or $\geq$1.50-D difference in astigmatism in any meridian, which persisted after at least 4 weeks of spectacle correction

Exclusion Criteria

- Ocular cause for reduced VA
- Myopia more than a SE of -6.00 D in the amblyopic eye
- Myopia more than a SE of -0.50 D in the sound eye
- Bifocal glasses
- Down syndrome
- Prior intraocular surgery
- Known allergic reaction to atropine

Additional Statistical Methods

Patients were included in the primary analysis if they had a visual acuity (VA) 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 VA measurement that was no more than 3 weeks before or 2 months after this time window. Four additional analyses were conducted: 1 included only those patients having an examination within the prespecified 4-month time window, 1 excluded patients treated with patching before the outcome examination, 1 used the best amblyopic eye acuity measured at any visit rather than the 4-month acuity, and 1 included all patients using the last observation carried forward method to impute for missing data (i.e., for patients missing the outcome examination, the VA recorded at the last follow-up examination was used as the outcome acuity; for patients with no follow up, the baseline acuity was used). Results of these 4 analyses were virtually identical to those of the primary analysis (see table).

Difference between Treatment Groups in Mean Logarithm of the Minimum Angle of Resolution Acuity at Outcome Examination*

Cohort	Difference (95% CI)
Primary analysis as reported in article	0.00 (−0.04 to +0.04)
Additional analyses	
Including only patients with an examination within a prespecified time window	0.00 (−0.05 to +0.05)
Excluding patients treated with patching before the outcome examination	−0.01 (−0.05 to +0.03)
Using best amblyopic eye acuity at any visit up to and including 4 mos	+0.01 (−0.04 to +0.05)
Including all patients with last observation carried forward method to impute for missing data	+0.01 (−0.03 to +0.05)

CI = confidence interval.
*Adjusted for baseline visual acuity in analysis of covariance model. A negative difference indicates that the daily group scores were better than weekend group scores.

Patients were included in the 5-week visit analysis if they had a VA measurement in the amblyopic eye within the time window of the 5-week visit or, in the absence of such a visit, if they had a VA measurement that was no greater than 8 weeks from randomization.

The amblyopic eye acuity at the time of study completion was used to determine whether a patient was a complete responder, which was defined as amblyopic eye acuity either (1) 20/25 or better or (2) equal to or better than sound eye acuity (if sound eye acuity at the time of study completion was worse than baseline, then amblyopic eye acuity must have been equal to or better than baseline sound eye acuity), in the absence of treatment with patching. For patients who did not complete the study, the VA recorded at the last follow-up examination was used for this categorization. An exact 2-sided 95% confidence interval was computed for the difference in complete responder percentages between the 2 groups.

Table 2. Visual Acuity in the Amblyopic Eye at the 4-Month Outcome Examination by Treatment Group

Lines of Improvement from Baseline to Outcome Examination	Daily Group (n = 77) [n (%)]	Weekend Group (n = 83) [n (%)]
−3	0	1 (1)
−2	0	0
−1	2 (3)	1 (1)
0	4 (5)	3 (4)
+1	15 (19)	18 (22)
+2	25 (32)	22 (27)
+3	16 (21)	22 (27)
+4	11 (14)	15 (18)
+5	4 (5)	1 (1)

Table 5. Binocularity Testing at Baseline and at the 4-Month Outcome Examination by Treatment Group

	Baseline		4-Month Outcome		
	Daily Group	*Weekend Group*	*Daily Group*	*Weekend Group*	**P Value***
Randot Preschool (arc sec) (cumulative %)	n = 74	n = 75	n = 71	n = 74	0.69
≥800	42	39	49	47	
≥400	32	29	23	36	
≥200	22	24	21	27	
≥100	11	13	13	18	
≥60	8	5	8	7	
≥40	0	1	3	4	
Titmus fly (arc sec) (cumulative %)	n = 78	n = 78	n = 75	n = 80	0.99
3000 (positive fly)	59	67	67	68	
Randot Suppression Test (%)	n = 83	n = 84	n = 77	n = 81	0.39
No suppression	40	48	57	57	
Suppression of sound eye	6	6	12	9	
Suppression of amblyopic eye	37	27	21	30	
No response	17	19	10	5	

n = number of patients able to perform each test.
*For Randot Preschool testing, from Wilcoxon rank sum test for difference in distribution between treatment groups at 4 mos; for Titmus fly and Randot Suppression testing, from the Fisher exact test for difference in proportions between treatment groups at 4 mos.

Table 6. Visual Acuity (VA) Improvement in the Amblyopic Eye at 4 Months According to Patient Characteristics with Treatment Groups Combined

Characteristic	n	Mean Baseline VA (logMAR)*	Mean Line Improvement from Baseline to 4 Months	*P* Value†
Overall	160	0.46	2.3	—
Gender				0.75
Male	96	0.46	2.3	
Female	64	0.46	2.3	
Age (yrs)				0.66
<4	28	0.49	2.4	
4–<5	30	0.50	2.3	
5–<6	56	0.45	2.4	
6–<7	46	0.42	2.0	
Cause of amblyopia‡				0.71
Strabismus	53	0.46	2.2	
Anisometropia	65	0.45	2.4	
Strabismus and anisometropia	38	0.47	2.3	
Iris color				0.71
Blue	62	0.46	2.2	
Brown	76	0.46	2.4	
Other	22	0.43	2.2	
Prior amblyopia treatment				0.51
Yes	29	0.43	2.1	
No	131	0.46	2.3	
Refractive error in sound eye				0.21
<+2.00 D	60	0.45	2.3	
+2.00–<+4.00 D	50	0.46	2.3	
≥+4.00 D	50	0.47	2.2	
Near acuity in sound eye at baseline after cycloplegia compared with amblyopic eye at baseline before cycloplegia§				0.67
Sound eye better	36	0.48	2.6	
Sound eye same	20	0.44	2.2	
Sound eye worse	63	0.44	2.3	

D = diopters; logMAR = logarithm of the minimum angle of resolution.
*20/63 is Snellen equivalent of logMAR of 0.50.
†For the association between patient factor and 4-mo acuity from a linear regression model, with 4-mo logMAR acuity score as a dependent variable and patient factor and baseline logMAR acuity score as independent variables (baseline acuity, age, and refractive error were analyzed as continuous variables).
‡Four patients did not meet criteria for any of the 3 causes of amblyopia.
§Forty-one patients enrolled at sites without near acuity testing at the time of enrollment are not included.

Table 7. Visual Acuity (VA) in the Amblyopic Eye at 4 Months According to Baseline Acuity in the Amblyopic Eye with Treatment Groups Combined

Amblyopic Eye VA at 4 Months	**Amblyopic Eye VA at Baseline (Cumulative %)**				
	20/80 (n = 32)	*20/63 (n = 63)*	*20/50 (n = 30)*	*20/40 (n = 35)*	*Overall (n = 160)*
≥20/100			100		100
≥20/80		100	97		99
≥20/63	100	98	97		99
≥20/50	78	90	93	100	91
≥20/40	50	73	87	97	76
≥20/32	25	54	73	97	61
≥20/25	3	21	37	66	30
≥20/20	0	5	23	23	11
≥20/16	0	0	3	9	3
Mean logMAR	0.34	0.26	0.19	0.11	0.23
Mean line change from baseline	2.6	2.4	2.1	1.9	2.3

logMAR = logarithm of the minimum angle of resolution.
$P \leq 0.001$ from analysis of variance for difference in mean 4-mo acuity according to baseline acuity.