

Treatment Dose–Response in Amblyopia Therapy: The Monitored Occlusion Treatment of Amblyopia Study (MOTAS)

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PURPOSE. Amblyopia is the commonest visual disorder of childhood. Yet the contributions of the two principal treatments (spectacle wear and occlusion) to outcome are unknown. This study was undertaken to investigate the dose–response relationship of amblyopia therapy.

METHODS. The study comprised three distinct phases: baseline, in which repeat measures of visual function were undertaken to confirm the initial visual deficit; refractive adaptation: an 18-week period of spectacle wear with six weekly measurements of logarithm of the minimum angle of resolution (logMAR) visual acuity; occlusion: in which participants were prescribed 6 hours of “patching” per day. In the latter phase, occlusion was objectively monitored and logMAR visual acuity recorded at 2-week intervals until any observed gains had ceased.

RESULTS. Data were obtained from 94 participants (mean age, 5.1 ± 1.4 years) with amblyopia associated with strabismus ($n = 34$), anisometropia ($n = 23$), and both anisometropia and strabismus ($n = 37$). Eighty-six underwent refractive adaptation. Average concordance with patching was 48%. The relationship between logMAR visual acuity gain and total occlusion dose was monotonic and linear. Increasing dose rate beyond 2 h/d hastened the response but did not improve outcome. More than 80% of the improvement during occlusion occurred within 6 weeks. Treatment outcome was significantly better for children younger than 4 years ($n = 17$) than in those older than 6 years ($n = 24$; $P = 0.0014$).

CONCLUSIONS. Continuous objective monitoring of the amount of patching therapy received has provided insight into the dose–response relationship of occlusion therapy for amblyopia. Patching is most effective within the first few weeks of treatment, even for those in receipt of a relatively small dose. Further studies are needed to elucidate the neural basis for the dose–response functions. (*Invest Ophthalmol Vis Sci.* 2004;45:3048–3054) DOI:10.1167/iops.04-0250

Amblyopia is the commonest childhood vision disorder, with a prevalence of 1% to 5%.¹ It carries an increased lifetime risk (at least three times that of the general population)

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of serious vision loss of the fellow eye.² The condition is characterized by reduced visual functions and, usually but not invariably, affects one eye. Amblyopia is found in association with one or more of the following: refractive error (which may be unilateral or bilateral); strabismus; or, more rarely, conditions that preclude the formation of a clear retinal image (e.g., infantile cataract). Primate models of amblyopia have repeatedly shown the primary visual cortex (area V1) to be dysfunctional.³ Functional imaging studies confirm processing abnormalities in area V1 of humans and hint at deficits within higher cortical areas.⁴

Research in the 1960s and 1970s demonstrated that the developing visual system is highly sensitive to deprivation.⁵ This led to the concept of a visual sensitive period, ending at approximately 6 to 7 years, which, if interrupted by any obstacle such as blurred vision and/or strabismus, results in amblyopia. The clinical upshot of this research was the belief that amblyopia should be both identified and treated in early childhood. This critical notion has influenced health service management in many countries, so that in the United Kingdom at least, national screening for strabismus and amblyopia is recommended in children aged between 4 and 5 years⁶ and overall, approximately 90% of children’s eye services work is amblyopia related. Such a massive investment requires that amblyopia therapy be both effective and efficient.⁷

The mainstay treatment for more than 250 years has been occlusion of the better eye by an opaque patch (“patching”), to promote visual function in the amblyopic eye. Therapeutic regimens lack standardization and range from patching for a few minutes a day to all waking hours. Treatment may last many months.

To date, no study has been able to provide quantitative insight into the dose–response relationship of occlusion therapy, an important precursor to establishing the effectiveness of a treatment regimen. We consider this observation to be attributable to a lack of consideration of the following factors: refractive adaptation, objective measurement of occlusion dose, and appropriate definitions of treatment outcome.

First, most children with amblyopia require refractive correction by spectacles as well as patching. Both interventions may generate considerable visual improvement; however, until recently,⁸ the period over which what is referred to as either adaptation to spectacle wear or refractive adaptation occurs was not defined. Although the importance of fully differentiating the beneficial effects of spectacle wear from those of occlusion is now recognized,⁹ in practice both treatments are often prescribed concurrently.

Second, objective measurement of concordance (compliance) with treatment has only recently become available.^{10–12} Hitherto, any notion of treatment dose was subjective and unquantifiable with regard to the amount of actual patching received (as opposed to that prescribed).

Third, critical to evaluation of therapeutic effectiveness is a meaningful definition of treatment outcome. Published success rates span a broad range from 19% to 93%,^{13–20} but in the

absence of an agreed convention of recording outcome, they cannot be rigorously compared. Two broad approaches to quantifying outcome have been employed. The first defines outcome by visual acuity achieved at the end of treatment, often 20/20, 20/30, or 20/40. The attainment of 20/20 presupposes, incorrectly, that visual acuity is a single value, rather than a range. The use of subnormal values (20/30 or 20/40) is arbitrary. The second approach defines outcome by the number of visual acuity chart lines of treatment-generated improvement, but has the drawback that it offers no indication of how close outcome is to "normal," or how much of the amblyopia deficit has been corrected. We consider that the optimum outcome of amblyopia therapy for unilateral amblyopia is the achievement of equal visual acuity in both eyes, on the basis that binocular vision is best promoted by equal visual input from each eye. Utilizing this approach informs both how close to normal acuity the treatment achieves and the proportion of the visual deficit that is corrected.²¹

Herein, we present the results of the Monitored Occlusion Treatment of Amblyopia Study (MOTAS), with the purpose of determining the dose-response relationship of occlusion therapy as a function of age and type of amblyopia. Most studies have yielded low-grade evidence of treatment effectiveness, generating a plea²² for randomized controlled trials (RCTs). Four such studies have now been completed²³⁻²⁶; however, given that treatment success has been claimed for such a wide range of unmonitored occlusion doses, those regimens chosen for evaluation by RCT can only have been selected on a pragmatic basis. We propose that knowledge of the dose-response function gleaned by a study incorporating objective treatment monitoring (MOTAS) would greatly inform the design of future RCTs while providing interim guidance on clinical best practice.

This study is the first to investigate treatment dose-response in amblyopia therapy and was innovative in that it fully differentiated the effects of refractive adaptation from those of patching, used objective monitoring of occlusion, and used rational methods of quantifying outcome.

METHODS

Study Design

The design for this prospective study has been reported in detail elsewhere.²⁷ Briefly, it comprised three phases: baseline, refractive adaptation, and occlusion, depicted in detail in Figure 1.

Before study entry, all children had a full ophthalmic assessment including cycloplegic retinoscopy and fundoscopy. The baseline phase comprised a minimum of two consecutive assessments to be certain that the first measure of function was robust. Children who needed spectacle correction entered the refractive adaptation phase. Those not needing spectacle correction entered the occlusion phase. Children were instructed to wear spectacles (where prescribed) full time and were scheduled to return for vision assessment at 6-weekly intervals from week 0 (onset of spectacle wear) until 18 weeks of refractive adaptation was completed—a period that our published pilot research indicated would allow for all significant improvement attributable to spectacle wear to have occurred.⁸ Children remaining eligible, by still meeting the study's operational definition of amblyopia (described later), entered the occlusion phase and were prescribed 6 hours' occlusion per day. Occlusion episodes were recorded to the nearest minute by an occlusion dose monitor (ODM).¹⁰ The ODM, a device developed and extensively piloted by us, consists of an eye patch with two small electrodes attached to its undersurface that are connected to a battery-powered data logger by a plastic-encapsulated wire lead.^{10,11,28} In this phase, both visual function and monitored occlusion dose were recorded at 2-week intervals until acuity ceased to improve (two inflections in an acuity-against-time plot or identical

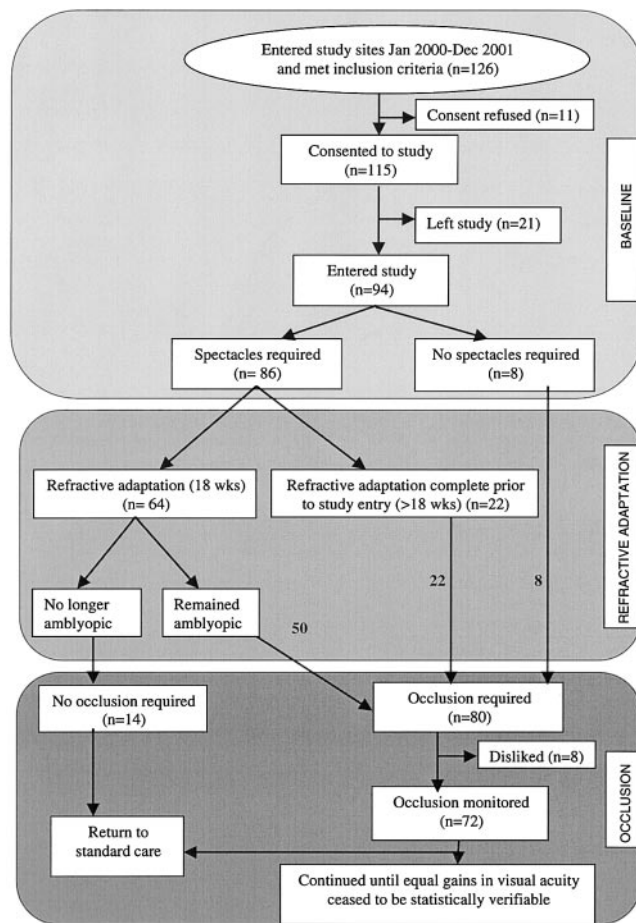


FIGURE 1. An organization flow chart showing progression of participants through the study.

measurements on three consecutive visits).²⁷ On completion of the occlusion phase, participants returned to standard clinical care.

Study Participants

Children were recruited from two London hospitals between January 2000 and December 2001. Inclusion eligibility criteria were: 3 to 8 years of age; anisometropia and/or strabismus; an interocular acuity difference of at least 0.1 logarithm of the minimum angle of resolution (logMAR; e.g., right 20/20; left <20/25, in Snellen notation); and no history of previous occlusion therapy, ocular disease, or learning difficulties. Rationale of inclusion criteria and definitions of anisometropia and strabismus are discussed elsewhere.²⁷ Written parental consent was a prerequisite of enrollment. The study was administered according to the Helsinki Declaration II and approved by Hillingdon and St. Marys Hospital National Health Service (NHS) Trusts Local Research Ethics Committees.

Outcome Measures

Assessment of Visual Function. The primary measure of visual function outcome measurement was logMAR visual acuity,^{29,30} scored by letter. Three letter logMAR visual acuity charts were used: ETDRS, crowded, and single logMAR charts. The chart used depended on the reading ability of the child and was generally age dependent. The visual acuity test used at the first study session was used throughout the study period.

Objective Monitoring of Occlusion. The occlusion dose was monitored with an ODM as described earlier. At the start of the occlusion phase, the investigator explained to the parents and child

the practicalities of wearing the monitor. At each subsequent visit, data from the ODM were downloaded to a computer, and parents were given the opportunity to review their child's concordance.

Definition of Optimum Outcomes. Visual outcome was expressed in two ways: first, by calculating the residual amblyopia (acuity difference between the amblyopic and fellow eye at outcome); and second, by calculating the proportional improvement (proportion of the visual deficit corrected). This second method sets the visual acuity of the fellow eye as the target to be achieved and also accounts for natural visual development during the study period. This approach informed us how close to normal the treatment brings the eye with amblyopia and also how much of the amblyopic visual deficit is corrected.²¹ A score of 100% proportional improvement and 0.0 log units residual amblyopia represented the optimum outcomes, where the amblyopic deficit had been fully corrected, and the visual acuities of the two eyes were equal.

Statistical Analysis

The principal objective of the statistical analysis was to identify the functional form of the dose-response relationship between occlusion dose and improvement in logMAR acuity of the amblyopic eye. The most general formulation involves recording the total (accumulated) occlusion dose (D), and the total improvement in visual acuity (y); the dose-response relationship is then encapsulated in the function (f) where $y = f(D)$, which depends on unknown parameters and explanatory variables such as type of amblyopia, age at occlusion, and initial visual acuity. In addition, a calibration mechanism through fellow eye logMAR measurement at the start and end of occlusion may be introduced. We considered both dose and dose rate (dose per day) as important predictors of response.

Statistical Models and Methods

In this article, we consider the nonparametric modeling of the dose-response function, using locally weighted scatter plot smoothed (LOWESS) regression.³¹ Uncertainty intervals are obtained using bootstrap resampling. We also consider parametric linear and nonparametric regression modeling. To identify significant terms in the model, we use parametric tests (analysis of variance) and nonparametric tests that allow the parametric assumptions to be relaxed. The nonparametric tests are performed in an exact setting using permutation methods (SPlus; Mathsoft, Inc., Cambridge, MA).³²

In this analysis, we provide a summary of the data and inference results, using the simplest models in an attempt to give a general overview of the various relationships uncovered. In particular, we use a multiple linear regression for the overall treatment response, using amblyopia type as a discrete factor, and age and total dose as covariates. We inspect R^2 values to assess adequacy of fit, and coefficient estimates, and standard errors. Note that all probabilities are two-sided. A stringent criterion is adopted, because of the noise present in the data, and because of the multiple testing of hypotheses in our report: we deem a significance level of 1% to be appropriate in our analyses, but report probabilities exactly.

To assess whether the dose-response differed as a function of amblyopia type we have to capture the difference in an appropriate goodness of fit measure, based on residual sums of squares (RSS), between the best-fitting models. The spline regression (fit using the LOWESS function in a statistical package [SPlus; Mathsoft, Inc.] on a default specification) can be used to obtain a model fit, and hence the RSS, for any data subset. Therefore, let R be the RSS for the whole data set, and let R_1 , R_2 , and R_3 be the RSS for each of the three data subsets defined by anisometropia, mixed (anisometropia and strabismus), and strabismus, respectively. An appropriate measure of the improvement in fit from fitting amblyopia type as a factor in the regression is $T = (R_1 + R_2 + R_3)/R$. We use T as a test statistic in a spline-ANOVA type assessment. We compute the exact null distribution of the test statistic using simulation-based methods, in particular, randomization tests, based on randomization of the type label among the dose-response

data. We test in the left tail of the randomization distribution only, and compute the simulation probability in the usual way by evaluating the proportion of sampled (permuted) results no larger than the observed test statistic.

RESULTS

Of the 126 eligible participants, 94 (75%) parents gave consent for their children to participate at a mean (SD) age of 5.2 ± 1.4 years. Amblyopia was associated with anisometropia in 23 participants (5.6 ± 1.2 years), strabismus in 34 (4.7 ± 1.2 years), and mixed (anisometropia with strabismus) in 37 (5.3 ± 1.5 years). The 32 children whose parents refused consent were not significantly different ($P = 0.78$) in age (4.9 ± 1.4 years) or in severity of amblyopia ($P = 0.56$) than the consenting group mean (range) 0.59 ± 0.34 (1.3-0.15) and 0.65 ± 0.41 (1.6-0.14), respectively.

Of the 94 participants, 86 (91%) had refractive errors requiring correction. Twenty-two (25%) had undergone full refractive adaptation before study entry and passed straight from baseline to the occlusion phase. Thus, 64 (75%) participants underwent refractive adaptation before entering the occlusion phase.

Refractive Adaptation Phase

In this phase, the mean \pm SD (range) visual acuity for amblyopic eyes improved from 0.65 ± 0.41 (1.6-0.14) to 0.43 ± 0.37 (1.3 to -0.08) logMAR, a mean \pm SD (range) improvement of 0.22 ± 0.18 (0.0-0.6) log units (Fig. 2). Visual acuity change was not significantly different ($P = 0.29$) for each type of amblyopia (anisometropia 0.22 ± 0.13 log units; mixed 0.18 ± 0.14 log units; strabismic 0.27 ± 0.24 log units) nor were there significant differences ($P = 0.38$) for each age group (under 4 years, 0.23 ± 0.18 log units; 4 to 6 years, 0.24 ± 0.20 log units; more than 6 years, 0.16 ± 0.23 log units). During refractive adaptation, visual acuity in 14 children improved to an extent that they were no longer eligible for occlusion.

Occlusion Phase

Eighty children entered this phase. Eight left the study (five disliked wearing the ODM and three did not attend) leaving complete data for 72 participants. Mean \pm SD (range) visual acuity in the amblyopic eye improved from 0.50 ± 0.36 (1.6-0.0) to 0.15 ± 0.25 (1.02 to -0.15) logMAR, a change of 0.35 ± 0.19 (0.0-1.2) log units (Fig. 2). With the exception of three participants, all improvement took place in the first 12 weeks with most of this occurring by the first 4 weeks (46% by week 2, 65% by 4 weeks, 82% by 6 weeks, 93% by 8 weeks). The mean \pm SD improvement in visual acuity (log units) increased significantly with decreasing age (under 4 years [$n = 17$], 0.43 ± 0.25 ; 4 to 6 years [$n = 31$], 0.29 ± 0.19 ; over 6 years [$n = 24$], 0.19 ± 0.12 ; $P = 0.0014$). After age had been taken into consideration, mean \pm SD change in visual acuity (log units) was not significantly different ($P = 0.03$) for each type of amblyopia (anisometropia 0.18 ± 0.16 ; mixed 0.34 ± 0.22 ; strabismic 0.30 ± 0.20).

Concordance. Mean concordance with the prescribed occlusion dose rate (6 h/d) was 2.8 hours (48%). Only 10 (14%) of participants achieved an average concordance within 30 minutes of the prescribed dose rate. Inter- and intraparticipant variation was considerable (0%-100%; Fig. 3).

Dose-Response. The total occlusion dose required to achieve the observed gains in logMAR visual acuity was described by a monotonic function, which for all categories of amblyopia appeared to be linear with an approximate dose-response rate of 0.1 log unit (1 chart line) improvement per 120 hours of occlusion (Fig. 4A). The overall response did not differ significantly for each amblyopia type ($P > 0.1$).

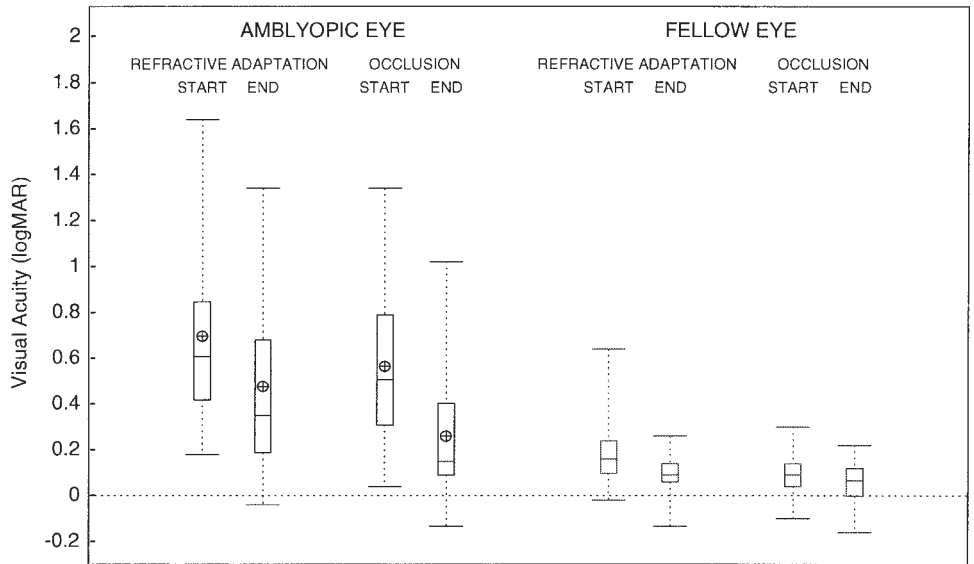


FIGURE 2. Box plots of visual acuity at start and end of refractive adaptation ($n = 64$) and occlusion ($n = 72$) phases. Fourteen participants gained equal visual acuity with refractive adaptation and did not enter the occlusion phase, hence apparent deterioration of visual acuity between the end of refractive adaptation and the start of occlusion. Thirty participants were added at the start of occlusion; 22 had undergone full refractive adaptation before study entry, and 8 did not require any spectacle correction. Circles: the mean, central bars: median values; whiskers: the 97.5 and 2.5 percentiles.

Dose rates of 2 h/d and over had a similar impact on outcome (Fig. 4B), but greater dose-rates reduced the number of weeks of occlusion necessary to achieve the best acuity.

Regression Model. In an exploratory linear regression analysis with age, visual acuity at start of study, total occlusion dose, and amblyopia type as predictors, a reasonable fit to the data was obtained with a multiple linear regression ($R^2 = 0.87$). Wald tests of the coefficients in the model indicated that total dose, visual acuity at start of study, and age were all influential predictors, but that there was no difference between amblyopia types.

Visual Outcome. Considering the outcome of all study participants, the amount of deficit corrected was full in 30% of participants, 75% to <100% in 24%, 50% to <75% in 23%, and 25% to <50% in 13%; whereas in 10%, less than 25% of the amblyopic deficit was corrected.

In general, total doses over 200 hours were associated with residual amblyopia less than 0.2 log units and more than 75% of the deficit corrected (Table 1).

Outcome by Intervention. The contribution to outcome attributable to the refractive adaptation and occlusion phases, and the amount of amblyopia that remained at study outcome is shown in Table 2. The contribution by refractive adaptation was greater in anisometric amblyopia than in the other amblyopia types, and the final outcome for this group was also better. Although study participants with strabismic and mixed amblyopia showed some improvement with refractive adaptation (correcting 27%–30% of the deficit) occlusion had a proportionately greater effect.

DISCUSSION

In this study, we quantified the dose-response function(s) of amblyopia treatment and the contributions to outcome attributable to refractive adaptation and occlusion. Objective monitoring of occlusion found overall concordance with treatment to be 48%, but there was considerable variation within and

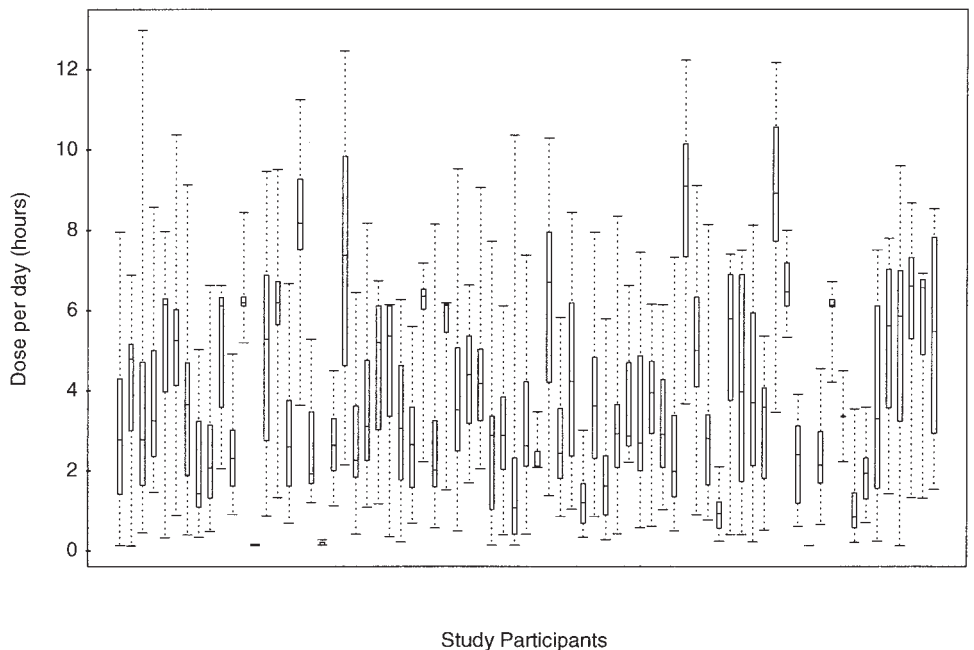


FIGURE 3. Box plots of occlusion doses worn over the duration of treatment for each study participant. Central bars: median values; whiskers: the 97.5 and 2.5 percentiles.

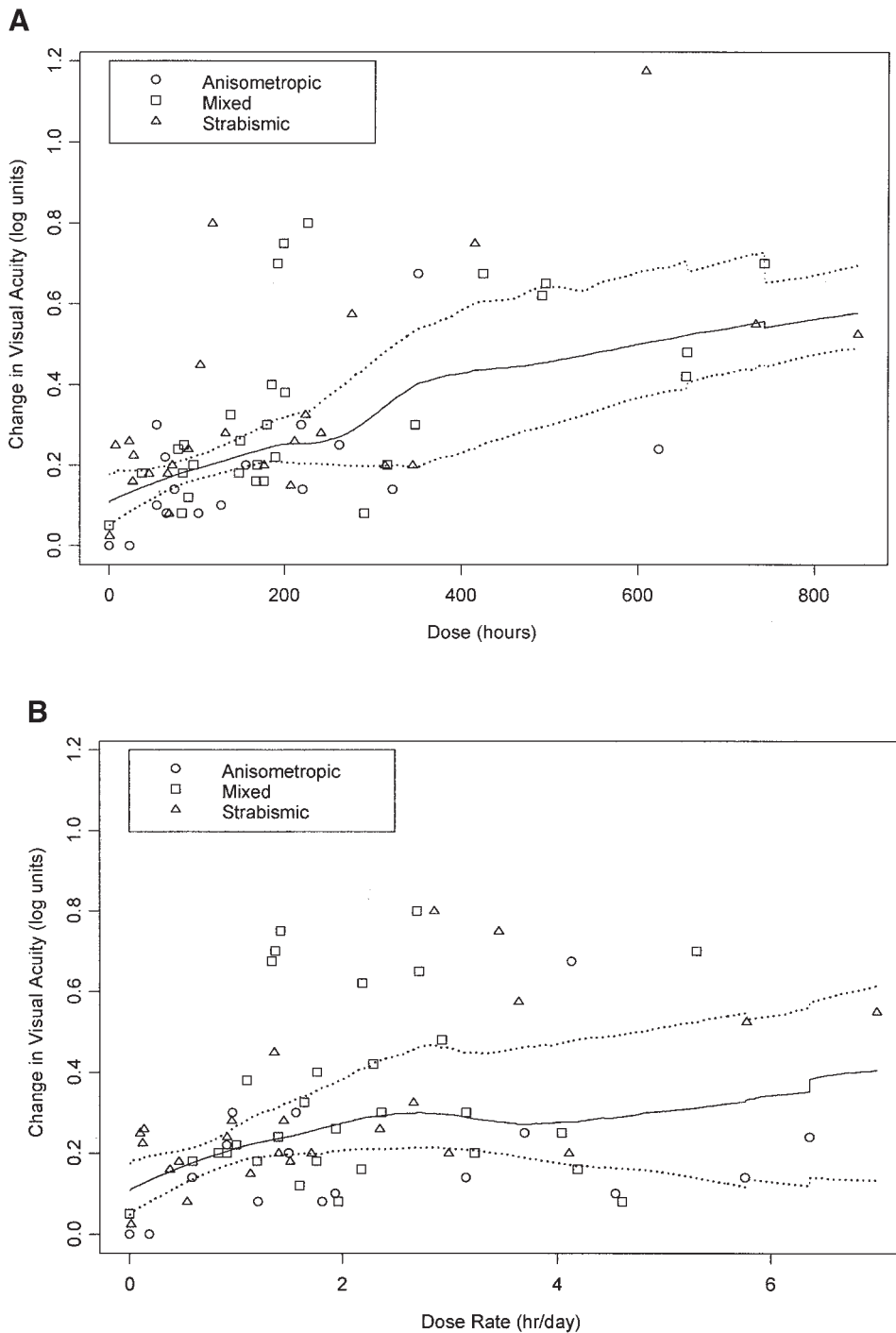


FIGURE 4. Change in visual acuity of the amblyopic eye as a function of (A) total dose accumulated to achieve best acuity for the first time and (B) dose rate. Fitted lines: default LOWESS line of best fit, with 95% confidence intervals (computed point-wise using 5000 bootstrap resamples from the original data) included for guidance.

between participants. The relationship between visual acuity and treatment dose was monotonic, with 82% of the improvement being achieved by 6 weeks of patching, but with some further improvement up to 12 weeks. Children younger than 4 years of age fared better than those older than 6 years.

In current clinical practice, dose rates range from 10 minutes a day to all waking hours, and treatment may take many months.^{10,19,20,23,33} We have found that dose rates of 2 to 6 h/d generate equal final outcomes, although those with a high dose rate achieved a successful outcome more rapidly. This finding is in agreement with a recent trial in which it was reported that daily prescribed patching of 2 hours generates a similar final improvement to that of 6 hours.²³ This study did not include

full refractive adaptation, and the patching was not objectively monitored. Thus, as was acknowledged by the authors,²³ the actual dose received by the child was unknown.

Although it is a long-held clinical belief that amblyopia therapy is more successful in the earlier stages of visual development,³⁴ there is little supportive evidence of this.^{19,35} Indeed, Hiscox et al.¹³ and Lea and Rubenstein³⁶ demonstrated no significant difference in the effectiveness of occlusion treatment commencing at any time between 3 and 7 years of age. We have provided further evidence that treatment age *is* a factor that influences the effectiveness of occlusion, although sample size limitations do not allow us to stratify this effect in detail. Nonetheless, our findings may contribute to the current

TABLE 1. Visual Outcome of Study Participants According to Total Dose Received

	Total Patching Dose Worn to Achieve Best Acuity (h)				
	0-99 (n = 25) n (%)	100-199 (n = 19) n (%)	200-399 (n = 17) n (%)	≥400 (n = 11) n (%)	Total (n = 72) n (%)
Residual amblyopia					
≤0.6	23 (92)	19 (100)	15 (88)	10 (91)	63 (88)
≤0.4	19 (76)	17 (89)	14 (82)	7 (64)	57 (79)
≤0.2	13 (56)	13 (68)	11 (65)	7 (64)	44 (61)
≤0.1	9 (36)	11 (58)	10 (59)	6 (55)	36 (50)
0.0	4 (16)	3 (16)	6 (35)	1 (9)	14 (19)
Mean (SD) residual amblyopia	0.26 (0.26)	0.16 (0.19)	0.20 (0.32)	0.25 (0.32)	0.25 (0.26)
Proportional improvement					
Any	25 (100)	19 (100)	17 (100)	11 (100)	72 (100)
>25%	19 (76)	19 (100)	15 (100)	11 (100)	64 (89)
>50%	13 (52)	15 (79)	14 (85)	9 (82)	51 (71)
>75%	10 (40)	8 (42)	9 (53)	7 (64)	34 (47)
Full (100%)	7 (28)	4 (21)	5 (15)	2 (18)	18 (23)
Mean (SD) proportional improvement	58% (37)	70% (25)	72% (30)	76% (22)	67% (30)

Data are the number of participants, with the percentage of the total in parentheses.

debate on the best age(s) at which to conduct childhood vision screening.

Refractive adaptation is a distinct component of amblyopia treatment and, in some cases, the only modality needed. We recognize that not everyone would use the term amblyopia to describe the visual deficit that improves slowly with refractive correction, but currently we have no better term. It is speculated that the response during refractive adaptation is a non-competitive activity-dependent process in response to the increase in the high-spatial-frequency content of the retinal image on correction of refractive error.⁸ This may explain why this improvement takes many weeks to complete. Understanding the kinetics of refractive adaptation has practical implications, for if it is allowed to run its course, children commence patching at a higher acuity level. This has benefits for the child; for some, unnecessary patching is avoided. It is less disabling than if it had been commenced when visual acuity was worse, and perhaps adverse psychosocial consequences³⁷ of patching are minimized, potentially enhancing concordance. The methodology of this study has enabled us to differentiate the therapeutic gains due to occlusion from those due to refractive adaptation and has demonstrated that these two modalities contribute in an additive fashion to the final outcome. This suggests that separate neural substrates and mechanisms are involved in the response by the visual system to each of these interventions. Future research should be directed toward identifying the underlying neural activity that underpins these responses, in which functional neuroimaging has undoubtedly an important role to play.⁴

TABLE 2. Proportion of Amblyopic Deficit Corrected by Intervention for Each Type of Amblyopia

	Refractive Adaptation	Occlusion	Deficit Corrected
All types of amblyopia (n = 48)	32 ± 6	47 ± 6	78 ± 5
Anisometropia (n = 15)	44 ± 5	42 ± 6	86 ± 5
Strabismus (n = 10)	30 ± 8	50 ± 9	80 ± 6
Mixed (n = 23)	27 ± 5	50 ± 5	77 ± 5

Data are percentage of visual acuity improvement, according to intervention. Includes only children who completed refractive adaptation and occlusion phases. n = 48.

We have described the dose-response relationship of occlusion therapy. This will enable clinicians to discuss the components of treatment (spectacle wear and patching) and broad time scales for each intervention with parents. We now have knowledge of occlusion doses likely to provide a therapeutic response. Future RCTs are required to determine optimum treatment regimens; however, we now have knowledge of viable regimens to evaluate, and a validated model of methodology to incorporate into RCT design.

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