Predictors and a Remedy for Noncompliance with Amblyopia Therapy in Children Measured with the Occlusion Dose Monitor

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PURPOSE. Noncompliance is one of the limiting factors in the success of occlusion therapy for amblyopia. Electronic monitoring was used to investigate predictors of noncompliance, and, in a prospective randomized clinical trial, determined the effectiveness of an educational program.

METHODS. Compliance was measured electronically during 1 week every 3 months in 310 newly diagnosed amblyopic children. The family’s demographic parameters and the child’s clinical parameters were assessed for their influence on the level of compliance. In addition to standard orthoptic care, children were randomized to receive an educational cartoon story, reward stickers, and an information sheet for the parents (intervention group), or a picture to color (reference group). These and the electronic device were distributed during home visits by researchers. The primary outcome measure was the percentage of compliance (actual/prescribed occlusion time) in the two groups. The secondary outcome measure was the influence of demographic and clinical factors on compliance.

RESULTS. Compliance was associated with parental fluency in the national language, country of origin, level of education, and initial visual acuity of the child. During the first 1-week measurement period children in the intervention group had better compliance than the reference group had (78% vs. 57% ± 40%; P < 0.001), and fewer children were not occluded at all (3 vs. 23 in the reference group; P < 0.0001). This difference remained throughout the study period.

CONCLUSIONS. Poor parental fluency in the national language, a low level of education, and poor acuity at the start of treatment were predictors of low compliance. An educational program primarily aimed at the child improved compliance and reduced

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mblyopia, with a prevalence of 3.5%,1–3 is loss of visual function, usually unilaterally, caused by strabismus, anisometropia, and/or visual deprivation. It is commonly treated with patching of the nonamblyopic eye, preferably before the age of 6. Approximately one third of the affected children do not reach visual acuity of 6/12 in the ambylocopic eye,2,4 thereby increasing the risk of bilateral visual impairment due to loss of vision in the nonamblyopic eye1–7 and decreasing quality of life in adulthood.8 Treatment effectiveness was questioned in a report published by Snowdon and Stewart-Brown9 in 1997 that contributed to the setup of five randomized controlled trials (RCTs).10–14 These produced evidence of treatment effectiveness. Many other studies have suggested that one of the factors influencing outcome with treatment is the level of compliance.15–25 Low compliance was found to be associated with social deprivation24 and lower attendance rates were reported among amblyopic patients from more deprived areas.26

In general, compliance is referred to as the degree of correspondence between the recommendations from the healthcare provider and the patients’ actual dosage.27 Poor compliance decreases the effectiveness of treatment and increases costs to the healthcare system.28 Especially in pediatric patients, low levels of compliance have been found across a range of treatments and is an important obstacle to providing effective healthcare in long-term treatments.29–32

Reported rates of compliance depend on the mode of measurement: pill count, patients’ report, appointment-keeping behavior, blood tracers, or electronic measurements, for example.33–36 Since the development of the Occlusion Dose Monitor (ODM) by Fielder and Moseley,15 compliance with occlusion therapy for amblyopia can be measured electronically. By means of the ODM, it has been demonstrated that, generally, compliance with amblyopia treatment is low and treatment success is related to the level of compliance.14,16,22,25,37 Therefore, programs designed to improve compliance are being distributed, and it has been concluded that increasing parents’ understanding of the disease may contribute to improved compliance.38,39 However, no study has provided evidence of whether compliance can be improved in concurrence with the electronic monitoring of that compliance. The primary purpose of this study was, by means of electronic monitoring, to assess the effectiveness of a newly developed educational cartoon story explaining to the child, without text, the rationale for treatment, combined with reward stickers and an information sheet for the parents. As a secondary purpose, it identified demographic and clinical factors determining compliance.

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METHODS

Patient Selection

Children were recruited from four clinics by six treating orthoptists in The Hague between July 2001 and December 2003. The study area consisted of The Hague (approximately 442,000 inhabitants), the third largest city in The Netherlands. It is a very ethnically and culturally diverse city, with 58% of the population having Dutch nationality; 10% of Surinam, 6% of Turkish, and 5% of Moroccan nationality; and 21% of other nationalities. Additional children were recruited in Frankfurt am Main (Germany) and Leicester (UK).

Included were all children with newly diagnosed amblyopia (i.e., never treated for amblyopia) with an interocular difference in visual acuity of at least 0.2 logMAR (logarithm of the minimum angle of resolution) that persisted after 6 weeks of spectacle correction, strabismus, and/or anisometropia (>1.0 D) or a deprivation in the absence of additional ocular or neurologic diseases.

Exclusion criteria were previous treatment for amblyopia, a neurologic disorder, other eye disorders, and diminished acuity due to medication, brain damage, or trauma. The Ethics Committee of Erasmus University Rotterdam and the boards of the participating clinics approved the protocol and informed consent forms. Written informed consent by the parents or guardian was a prerequisite for participation. The research adhered to the tenets of the Declaration of Helsinki.

Standard Orthoptic Care

Eligible children received a routine ophthalmic examination and explanation of diagnosis and treatment by the treating orthoptist. Binocular vision, ocular motility, cycloplegic refraction, and visual acuity were assessed. For this study, the charts used to assess visual acuity depended on the age: children aged 2.5 to 4 years: Amsterdam Picture Chart (uncrowded, linear optotypes; Medical Workshop, Oculi, Groningen, The Netherlands); children aged 4 to 5 years: E-chart (uncrowded, linear optotypes; Medical Workshop, Oculi); children aged 5 and older: Landolt-C (uncrowded; linear; Medical Workshop, Oculi). In children younger than 2.5 years or otherwise unable to cooperate with the visual acuity tests, decimal equivalents were used, only for analysis of the relationship between acuity and compliance, for the following categories: far eccentric fixation and no pursuit when looking monocularly, fierce protest when covering the better eye, 0.1; eccentric fixation and hardly any pursuit when looking monocularly, considerable protest when covering the better eye, 0.3; cannot maintain fixation and saccadic pursuit when looking monocularly, some protest when covering the better eye, 0.5; prefers fixation with the other eye and almost smooth pursuit when looking monocularly, 0.7; alternating freely and smooth pursuit when looking monocularly, no dominance found in +PD base-out tests, 0.9. The severity of amblyopia was expressed as the ratio (in decimals) between the acuity in the amblyopic eye and the better eye, to minimize the influence of possible differences in testing conditions. The acuity data were expressed as decimal scores.

Anisometropic amblyopia was defined as amblyopia in the presence of anisometropia >1.0 D of spherical equivalent or >1.50 D difference in astigmatism in any meridian, with no measurable heterotropia at distance or near fixation. Spectacles were prescribed in case of anisometropia >1.0 D, astigmatism >1.5 D, hypermetropia (spherical equivalent) >1.5 D. Occlusion therapy commenced after a minimum of 6 weeks’ adaptation to the spectacles.

Few guidelines exist when prescribing a certain number of occlusion hours; therefore, in this study, the duration of occlusion (number of hours per day) for the first prescription was standardized in a focus group consisting of the treating orthoptists, as experts in the field. They were given example cases of persons in whom diagnosis, visual acuity, and age varied and were asked to prescribe the number of occlusion hours per day. Diagnosis proved to be of little importance and the relationship between the two other parameters (visual acuity and age) could be represented by: \(-6.63 \times \text{ratio acuity anisometropic eye/} \text{acuity better eye} + 0.5 \times \text{age (years)} + 4.97\). For example, for a 3-year-old child with an acuity ratio of 0.6, the number of hours would then be: \(-6.63 \times 0.6 + 0.5 \times 3 + 4.97\), which equals \(\approx2.5\) hours of occlusion per day. A table was then developed from which the orthoptists could directly read off the daily number of occlusion hours to be prescribed. It was not possible to standardize subsequent prescriptions of occlusion therapy, as the treating orthoptists wished to proceed on an individual basis, dependent on treatment success. All children were seen by the treating orthoptist for routine assessment every 3 to 4 months. This schedule continued independently of the electronic recordings of compliance. After each examination, the treating orthoptist completed and forwarded a standard examination form to the research center. Occlusion therapy was terminated when the interocular difference in visual acuity was 1 logMAR line or less on two consecutive visits to the orthoptist.

The researchers visited the participating orthoptists at their clinic 10 times over a 1-year period (January 2002-January 2003). The total time spent on taking patient history, examining the child, and explaining the diagnosis and treatment was recorded per child. A distinction was made between children who visited the orthoptist for the first time and follow-up visits.

Randomization

After the first visit to the treating orthoptist, parents of children with newly diagnosed amblyopia were contacted by telephone by the researchers to obtain verbal consent and an appointment for a home visit. Before the home visit, each patient was randomized to either the intervention group or the reference group, using permuted blocks of length six: That is, when six children were randomized, three were allocated to the intervention group and three to the reference group, in random order. Children in the intervention group received the educational program; children in the reference group received a picture to color. During the home visit, the researcher explained the nature and possible consequences of the study and use of the ODM, and full written informed consent was obtained.

Compliance was measured with the ODM, in all children during an entire week every 3 months. It was attached to the front of the occlusion patch with double-sided adhesive tape and measured the temperature difference between the front and back of the ODM every 2 minutes. The device has been extensively tested, including the ability to differentiate between measurements on the eye and on other parts of the body, and has been found satisfactorily reliable. In case of an unsuccessful recording due to battery failure (no data at all or less than 7 days of data), a broken or lost ODM, the 1-week measurement with the ODM was repeated the subsequent week.

The study was designed as a prospective, single blind, randomized clinical trial. The researcher who made the home visits was aware of randomization. The treating orthoptist, however, was blind to group assignment, and randomization took place after the first visit to the orthoptist. Time spent on each home visit was approximately equal for children in both groups—that is, 45 minutes for a first home visit and 10 minutes for a following visit, and all parents were given the same explanation. The distribution of the ODM via home visits minimized the number of dropouts from the study. Home visits continued even when the parents failed to attend their clinic appointments.

Assessment of Demographic and Clinical Factors Affecting Compliance

The socioeconomic and ethnic background of the families was assessed via a 23-item questionnaire registering the highest level of education of either parent (scores from 1 to 5, with 1 representing ‘no education’ and 5 ‘university’); the mother’s native country; material factors including housing and employment status; religion; family structure; age of the parents; and the parents’ marital status. The highest level of education of either parent indicated the socioeconomic status. This questionnaire was filled in during the first home visit. The mothers’ fluency in the national language was rated by the
regression analysis on the data from the first entire 1-week measurement with the ODM only, because it was certain that at this moment the number of occlusion hours had been prescribed according to protocol and that the orthoptist was unaware of randomization. The results of the univariate analysis are presented first; the influence of potential confounding is corrected for in the multivariate analysis. \( P < 0.05 \) indicated statistical significance. The percentage of the variation in compliance that could be ascribed to the different factors involved was defined as the ratio of the percentage of the variance explained by the model, with and without the factor in question.

It would have been desirable to have final visual acuity as an outcome measure; however, the statistical noise between compliance and visual acuity increase, as measured in current orthoptic practice, would have led to the treatment groups’ becoming excessively large. Therefore, the primary outcome measure was restricted to electronically measured compliance.

Children were included in the analysis when they had received at least one entire 1-week measurement. When parents refused further participation in the study after the first 1-week measurement, they were asked their consent as to whether the previous ODM measurement(s) and their child’s baseline characteristics could be used for analysis. Only the data of the children whose parents agreed remained in the study (\( n = 6 \); intervention group; \( n = 5 \); reference group). Children who moved out of the area and consequently received no further ODM measurements were included in the analysis.

**Results**

**Study Population**

Of the 418 recruited children, 310 (74%) were eligible for analysis (Fig. 1). Of these, 20 children were recruited in Frankfurt (18 participated) and 4 in Leicester. There was no difference in frequency of withdrawal of participants between the clinics. Throughout the study, 12 children from the intervention group no longer attended their appointments in the clinic; of those, 5 also refused further study participation. In all, parents of 13 children refused further study participation. In the reference group, 17 children no longer attended their appointments in the clinic; of those, 8 also refused further study participation. In all, parents of 19 children refused further study participation. During the study, four children (two from either group) were lost to follow-up (moved out of the area). The birth rate in The Hague was approximately 5071 children in the year during which most of the children in the study were born (i.e., 1997). In this study, 394 were registered for a period of 2.5 years, indicating that 3.1% of the children born were included in the study.

In case the ODM was lost or broken or the recording failed, the 1-week measurement was repeated the subsequent week. During the study period, 13 parents lost the ODM and 11 broke it (e.g., tore it apart when removing the double-sided adhesive tape), and in 29 cases, the ODM had incomplete data. Because of measurement failure, 15 parents refused further participation, but 40 children received a measurement the subsequent week.

Table 1 depicts the baseline characteristics of the included children according to their randomization; both randomization groups were comparable for the baseline characteristics, including the number of prescribed occlusion hours per day by the orthoptist. The mean age of the included children was 4.6 ± 2.0 years; 56% were boys. Amblyopia was associated with anisometropia in 140 children (mean age, 5.3 ± 1.9), with strabismus in 88 (mean age, 3.5 ± 1.9) and with both anisometropia and strabismus in 46 children (mean age, 4.7 ± 1.9). Five children had deprivation amblyopia (mean age, 3.9 ± 1.7). In 31 children, a difference in visual acuity of only 0.2 logMAR

**Outcome Measures and Statistical Analysis**

Calculation of the sample size was based on previous compliance studies of other diseases that used electronic monitoring to measure compliance.33–36 These results showed a normally distributed relationship between the number of patients and the percentage of compliance with a maximum at approximately 80%–90%, an average of 68% and a SD of 22%. To reach an effect size of 3%, a sample of \( 2 \times 150 \) patients was necessary.

The main outcome was the level of compliance in the two treatment groups, defined as the actual occlusion time measured with the ODM divided by the prescribed occlusion time and expressed as a percentage. This calculation was made for each child separately for each week of measurement with the ODM. The recruitment of patients continued for 30 months. On average, a child received three electronic measurements (ranging from one to a maximum of seven measurements) during, on average, 8 months of treatment. The effect of the educational program on compliance was determined in a multilevel analysis in which all available weeks of ODM monitoring were used, corrected for the differences in the number of observations during follow-up. This analysis was used to estimate compliance of all included children throughout the treatment. The difference in percentages of compliance in the two treatment groups was assessed with least-squares regression analysis. Testing for an unequal distribution of baseline characteristics between the randomization groups was performed with logistic regression (Wald test).

The second research question was the influence of demographic and clinical factors on the level of compliance. We used least-squares

**Intervention Protocol**

**Intervention Group.** Children received the educational cartoon story, a calendar with reward stickers, and a one-page information sheet for the parents.

The cartoon story was designed for this study by two artists specializing in art for sick children (José Vingerling and Gerard de Bruyne), together with two specialists from the Municipal Health Service, The Hague (Karen Bree and Nicole Goedee). The educational program was developed considering the most efficient way to transmit the message and whether to target the parent or the child. It was designed as a cartoon story, without text, as most of the children treated for amblyopia are too young to read. The cartoon depicts the orthoptic examination of a preschool child, subsequent patching therapy, and the reasons for therapy seen from the perspective of the child. As no animal figures were included, the children were more able to identify themselves with the child depicted in the story. The cartoons could not be linked to a certain ethnic or cultural group. A sheet containing general information about amblyopia and its treatment for the parents was made in eight languages and distributed with the cartoon story only during the first home visit.

**Reference Group.** Children were given a picture to color (e.g., Mickey Mouse or Winnie the Pooh) that was also considered a reward, but did not contain the educational message.

At the three monthly home visits, the ODM was delivered and the children were given the next episode of the cartoon story (intervention) or a different picture to color (reference). No specific instructions were given for the use of the cartoon story, the calendar with stickers, and the information sheet or, in the case of the reference group, the information sheet for the parents.

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at baseline was found: the treating orthoptist had commenced occlusion therapy, although anisometropia was mild (≤ 1 D), and there was no strabismus in these cases (mean age, 4.9 ± 1.2).

**Study Outcome**

**Predictors of Compliance.** This analysis was performed on the entire study population, using the data obtained from the first 1-week measurement, as the two treatment groups were comparable for the different baseline characteristics (Wald test for logistic regression).

Fluency in the national language by the mother was a significant predictor of the level of compliance ($P = 0.018$). Mean compliance ranged from 56% in the group who did not speak the national language at all to 72% in the group who spoke it excellently (Table 1, right-hand column). Univariate analysis also demonstrated the country of origin of the mother to be significant ($P = 0.018$). The highest level of education...
attained by either parent was also significant \((P = 0.021)\). Mean compliance ranged from 60% in the group with no education to 75% in the group with an academic education.

The child’s visual acuity at the start of treatment was the only significant clinical factor \((P = 0.003)\). Mean compliance ranged from 58% in children with the lowest visual acuity to 79% in children with the highest visual acuity. Compliance was not significantly related to the degree of binocular vision \((P = 0.667)\), the type of amblyopia \((P = 0.219)\), gender \((P = 0.057)\), and age at start of treatment (although the latter was borderline significant: \(P = 0.050)\).

After multivariate analysis the child’s visual acuity \((P = 0.031)\) and country of origin remained significant \((P = 0.035)\), level of education and fluency in the national language were not selected. However, the correlation between country of origin and fluency in the national language was too strong to be able to separate the effects of either variable \((P < 0.001)\). Adjusted analysis for the country of origin demonstrated that per 10% visual acuity increase or decrease, compliance would increase or decrease 2%. Adjusted analysis for visual acuity (at a median level of 0.6) demonstrated levels of compliance to be 75%, 51%, 71%, and 77%, for Native, Turkish, Moroccan or, Surinam children, respectively, and 65% for children from other countries.

After correction for the intervention applied, 12% of the variation in compliance could be explained by the demographic and clinical factors investigated in the study.

**Effect of the Educational Program on Compliance.**
During the first one-week measurement, mean overall compliance in the intervention group was 78% ± 32% compared with 57% ± 40% in the reference group \((P < 0.0001; \text{Table 1})\). Compliance decreased over the 2-year study period on each subsequent ODM measurement, more so in the reference group than in the intervention group \((P = 0.003; \text{see Fig. 2})\). There was no difference in the number of prescribed occlusion hours per day, neither for the first nor for the subsequent

<table>
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<th>Characteristic</th>
<th>Number of Children (%)</th>
<th>Mean Compliance (%)</th>
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<tr>
<td></td>
<td>Intervention Group</td>
<td>Reference Group</td>
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<tr>
<td>Overall compliance</td>
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<td>Number of occlusion hours per day*</td>
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<td>3:00 ± 1:38</td>
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<td>Visual acuity ratio†</td>
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<td>Country of origin‡</td>
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<td>35 (22)</td>
</tr>
<tr>
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<td>6 (4)</td>
<td>4 (3)</td>
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</table>

* Mean ± SD.
† Degree of amblyopia was expressed as the ratio (in decimals) between the visual acuity in the amblyopic eye and the better eye.
‡ Characteristics significantly affecting compliance after multivariate analysis \((P < 0.05)\).
§ Fluency in the national language subjectively assessed by a researcher. Excellent, native speaker; good, nonnative, but fluent; moderate, understandable and able to engage in conversation; poor, scarcely fluent; none; not spoken at all.
∥ Characteristics significantly affecting compliance after univariate analysis \((P < 0.05)\).
measurements. Figure 2 shows the relationship between mean compliance (measured with the ODM) and the period of treatment (in months) for the children in the two treatment groups. Mean compliance in the intervention group and the reference group at a certain time point could be calculated using the formulas shown in the legend for Figure 2. There was no modification in the effect of the educational program for visual acuity of the child \( (P = 0.59) \), country of origin \( (P = 0.57) \), or fluency in the national language \( (P = 0.48) \).

There was considerable variation in the level of compliance between the children and within each child, as indicated by the ODM measurements. The SD of mean compliance during the first 1-week measurement of all children \((n = 310)\) was 37%. The mean of all the standard deviations of mean compliance in each child during that week was 28%.

In the intervention group, three (2%) children were not occluded at all during the first ODM measurement (mean age, 4.3 ± 0.8) compared with 23 (15%; mean age 4.6 ± 2.0) in the reference group \((P < 0.0001; \chi^2; \text{Fig. 3})\). Children who did not comply with occlusion at all and children who did were comparable for clinical parameters. However, there were differences in the level of parental education, country of origin, and fluency in the national language.

The questionnaire designed to estimate the usage of the educational program or the picture to color showed that the cartoon story was used by 87% of the families. Mean time was 25 minutes per week (range, 5-180; number of observations, 123). The calendar and stickers were used by 80% of the families. Mean time was 10 minutes per week (range, 2-15; number of observations, 125). The information sheet was read by 67% of the parents. Mean time was 6 minutes (range, 2-10; number of observations, 123).

In the reference group, the picture was colored by 71% of the children. Mean time was 12 minutes (range, 5-20; number of observations, 131).

In 26 patients, the researchers recorded time spent on explaining the diagnosis and treatment during the first visit to the orthoptist. It averaged 234 seconds in non-native patients, and 416 seconds in native patients. During follow-up visits to the orthoptist these averages were 116 seconds and 233 seconds, respectively (62 patients).

**DISCUSSION**

This study identified the following demographic parameters as primary predictors for noncompliance: parental fluency in the national language, level of education and the country of origin. Although country of origin was selected in the multivariate model to be most significant, we cannot exclude the possibility that fluency in the national language and level of education (being significantly correlated with the country of origin) may be the causal factors. The most important clinical parameter was the initial visual acuity of the amblyopic eye. The educational program featuring the cartoon story that explained without words the rationale for treatment to the child significantly improved compliance throughout the study, limiting in particular the number of children who were not occluded at all (3 in the intervention group vs. 23 in the reference group). The electronic monitoring performed by the researchers, who were working independently from the treating orthoptists as they distributed the ODMs during home visits, enabled us to detect these striking differences between the two treatment groups.

The study was designed as a single-blind, randomized clinical trial. The treating orthoptists were unaware of randomization, but the researcher distributing the educational program or the picture to color was not. Efforts were made to ensure that time spent explaining the study was equal in both groups. Randomization took place after the first visit to the orthoptist. Main results of this study were based on the data obtained from the first ODM measurement, thereby excluding any possible biases of a treating orthoptist later on in the study.

As compliance was measured in the week after the home visit, it would be reasonable to expect that compliance would be higher in the week it was monitored, and we cannot exclude that the ODM itself acted as an intervention. This bias applied to children in both groups. The study found that compliance was moderate despite the fact that parents knew...
that compliance was being monitored. This finding was also made in one of the previous pilot studies, in which compliance was monitored for longer periods (Simonsz HJ, et al. IOVS 2001;42:ARVO Abstract 4152). For this reason, it was decided that compliance would be measured on a regular basis: 1 week every 3 months, also making the study more feasible for both parents and the researchers. Mean compliance in our reference group during the measurements was similar to that reported by the MOTAS (Monitored Occlusion Treatment of Amblyopia Study) Cooperative,22 who objectively monitored occlusion for a longer consecutive period.

Visual acuity at the start of treatment was the clinical parameter most significantly correlated with compliance. This finding is in agreement with other studies17,18,22,24,25 and is explained by the fact that the acceptance of the patch is less when acuity is low. The decrease in compliance during treatment, as found in our study, is partly due to a selection bias: Children with low visual acuity at the start of treatment were less compliant, therefore wore patches for a longer period, and consequently were recorded more often. The influence of treatment age on compliance has been a point of debate17,22,25; our study found the treatment age to be borderline significant, with younger children tending to have better compliance.

Having established this large study group of more than 300 children, the research group intends to proceed to an analysis of their visual acuity outcome. For this, the children’s final acuity will be assessed in a standardized fashion by the research orthoptist after the children have completed their patching treatment.

Apparently, native parents received more lengthy explanations at diagnosis and treatment than non-native parents did. Several factors may have contributed to this observation (e.g., cultural background, language skills, confidence, assertiveness, education, interests). Also, in The Netherlands, the time an orthoptist can spend on a patient varies and is sometimes limited to 15 minutes for a new patient.

Although occlusion therapy in amblyopia has been the primary treatment for centuries14,12 and clinically is an effective treatment, its success is limited, by, among other factors, noncompliance.14,20,22,25 In this study, we confirmed, using electronic monitoring, that lack of understanding of the disease and treatment in pediatric medicine are obstacles that can be remedied by an educational program: the cartoon story, reward stickers, and an information sheet. Important demographic predictors for low compliance included poor parental fluency in the national language, country of origin, and a low level of education. Education, primarily aimed at the child, improved compliance and reduced the number of children who did not comply with occlusion at all.

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