**Assessing interventions to increase compliance to patching treatment in children with amblyopia: A Systematic Review and Meta-analysis**

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**Word Count: 3297ABSTRACT**

**Background/Aims**

Amblyopia is the most common condition affecting visual acuity in childhood. Left untreated it will not resolve itself, leading to increased risk of blindness. Occluding the good eye with a patch is a highly effective treatment if carried out before age 7 but compliance is a major problem. This systematic review addresses the question: How effective are existing interventions at increasing compliance to patching treatment in amblyopic children?

**Methods**

Electronic searches were carried out in June 2014 and updated in April 2015 to identify studies reporting primary data on interventions to increase patching compliance. Data screening, extraction and quality ratings were performed independently by two researchers.

**Results**

Nine papers were included. Interventions including an educational element (5 studies) significantly increased patching compliance and had higher quality ratings than interventions that changed aspects of the patching regime (3 studies) or involved supervised occlusion (1 study). Meta-analysis was conducted on four studies and indicated that overall interventions involving an educational element have a significant small effect r = 0.249, p < .001.

**Conclusions**

Interventions to increase patching compliance should include educational elements. High quality research is needed to further assess the effectiveness of specific elements of educational interventions and additional behaviour change techniques.

**BACKGROUND**

Amblyopia is the most common condition that affects visual acuity in childhood, [1] affecting up to 5% of the population.[2] It can lead to an increased risk of blindness[3] and impairments in functional abilities, such as slower reading speed and poorer fine motor skills.[2] Due to these negative outcomes, and the fact that left untreated amblyopia will not resolve itself and significant vision loss may occur,[4] it is important that amblyopia is treated early. The current treatment recommendations, based on Pediatric Eye Disease Investigator Group (PEDIG) trials, are a period of spectacle correction followed by therapy via atropine penalisation or occlusion via patching, with the most popular method of patching being the disposable adhesive patch.[5] Research indicates that patching has been overprescribed in the past and full time patching is no longer supported by the evidence base [6]. However, patching has been found to be extremely effective,[7] and remains the most common choice of first line treatment by orthoptists.[4] To maximise treatment effectiveness work is being carried out to model dose-response in amblyopia [8] and to trial personalised dosing strategies.[9] Given that patching is widely prescribed in the treatment of amblyopia and is used by the majority of orthoptists as the first line treatment for amblyopia,[4] it is the focus of the present review.

Several factors affect the success of patching treatment.[7] One critical factor is compliance to the treatment regime,[10] with non-compliance being a major barrier.[11,12] Patching treatment has been associated with a number of negative outcomes, for example, parental concerns, perceived social impact, emotional distress and the visual impact causing the child to struggle with everyday life.[1] However, to ensure the best vision outcome in the minimum treatment time, it is important that the prescribed amount of patching is complied with.

Large amounts of research to investigate non-compliance to occlusion therapy has been carried out since 1994 when the first objective occlusion dose monitor was developed [13] and it is now generally accepted that treatment compliance is important for improvement in visual acuity. [14] Over 90 studies have been carried out to identify factors that predict compliance ([15,16]) and/or to explore individuals’ experiences of patching ( [1,17]). Furthermore a large survey of orthoptists in the UK reported that orthoptists are aware of the need to address non-compliance and do this by using a variety of techniques, including giving written information, using colourful patches and reward charts.[4] However, despite research exploring predictors of non-compliance, [14] there is a lack of clarity on the effectiveness of interventions that have been developed and tested to improve compliance. In order to progress in this area a systematic review is required to provide evidence for the types of interventions that are most successful and to allow future optimal interventions and guidelines for orthoptists to be developed.

**Review question**

The current systematic review addresses the question: How effective are existing interventions at increasing compliance to patching treatment in amblyopic children?

**METHOD**

**Inclusion/Exclusion Criteria**

The search was carried out on the 27th June 2014 and updated on 21st April 2015. All studies published prior to this, which met the following criteria, were included in the review:

1. Study includes an intervention to increase patching compliance

2. Primary data are reported

3. Participants have a diagnosis of amblyopia

4. Participants have been prescribed patching treatment

5. Study includes a direct measure of time spent patching

The following exclusion criterion was used:

1. Entirely qualitative study

These criteria were designed to include both randomised controlled trials (RCTs) and non-RCTs to ensure a thorough review of the literature. Excluding studies on the sole basis that they are not RCTs is not advocated because valuable information can be missed. [18] Furthermore including non RCTs is recommended when scoping exercises indicate there are low numbers of RCTs, [19] as was found in the scoping exercise for this review.

**Search Strategy**

The search strategy allowed for both published and grey literature to be identified. Eight databases (PsycInfo, Web of Science, CINAHL plus full text, PsychArticles, PubMed, Science Direct, Cochrane Library, Cochrane controlled trials register) were searched using the following terms:

(Compliance OR Adherence OR Non-concordance) AND (Occlusion therapy OR Patching OR Treatment) AND (Lazy eye OR Amblyopi\*) AND (Intervention OR Improv\* OR Increas\*)

Two authors (SD and JR) independently screened each title, and abstract if required, to identify studies for potential inclusion. These studies were obtained in full text and screened for inclusion. Disagreements were resolved through discussion. Once the list of studies for potential inclusion was compiled the reference list from each article was checked to ascertain whether any additional studies could be identified.

**Data extraction and quality rating**

For each of the included studies two authors (SD and JR) independently completed a data extraction sheet that was created for this review (available as a supplementary file). This included gathering data on the country the study was carried out in, type of participants (age, diagnosis, and other relevant information), a description of the intervention, the design of the study and the measure of patching compliance used. Where additional data was needed for inclusion in the meta-analysis the authors were contacted and all responded.

The same two authors also independently rated the quality of each study using the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies. [20] This tool is used to assess individual studies on several components, consisting of selection bias, study design, confounders, blinding, data collection methods and withdrawal and drop-outs. Ratings for each component are combined to give a global quality rating for the study of strong, moderate or weak.

**Summary Measures**

The primary outcome measure was percentage compliance to patching, calculated as the actual time spent patching divided by the prescribed patching time. Several studies also reported the actual number of hours spent patching and a small number of studies reported on the numbers of successful and unsuccessful “patchers”, with various criteria used, or reported on the number of participants who undertook no patching at all. Information on these outcome measures was included in the narrative review.

**Data Synthesis**

A narrative synthesis of the studies was conducted, followed by a meta-analysis on a sub-set of the studies. The meta-analysis was conducted according to Clark-Carter’s guidelines. [21] A fixed effects model was assumed but a random model would have been applied if heterogeneity had been detected. An effect size was calculated for each study and then converted to the common statistic, r. r values were converted to Z scores using Fishers’ Z transformation then used to calculate the combined effect size and confidence interval. To assess significance, z scores were calculated for each study and used to calculate the combined probability. A check for heterogeneity of effect sizes using chi-squared was carried out and tests to check for potential publication bias were run.

**RESULTS**

**Study Selection**

The flow chart for the exclusion and selection of studies is presented in Figure 1. The initial search yielded 424 results. Once duplications were removed 242 remained. An additional 6 papers were identified through an expanded search, resulting in 248 papers for title/abstract screening. Of these 28 were identified for potential inclusion and underwent full text screening. Nineteen papers were excluded, leaving 9 articles for inclusion in the systematic review.

Figure 1. Flow diagram of systematic review based on PRISMA guidelines

**Study Characteristics**

A summary of the data extraction is given in Table 1. In total there were 837 participants. These included children who were identified as not adhering to patching (2 studies [22,23]), children undergoing patching therapy (2 studies [11,24]), children who had not previously had substantial patching treatment (1 study [25]) and children with newly diagnosed amblyopia (4 studies [26–29]). Across the 9 studies all types of unilateral amblyopia were represented but the majority of children were diagnosed with either strabismic or anisometropic amblyopia. Just under half of the studies (4) were carried out in England, two involved children from low socioeconomic status (SES) in The Netherlands, one a mix of higher and lower SES children in Chile, one in Canada and one in India. The types of interventions included adjusting the patching regime, using physical properties to make non-compliance more difficult, and multifaceted interventions. Six of the studies contained an educational element. Six of the studies had parallel control groups, one had a between-subjects pre and post design and two did not have control groups. Based on the EPHPP criteria four studies were rated as low quality and five as moderate.

**Table 1: Characteristics of Included Studies.**

Table 1. Characteristics of Included Studies

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Authors and Country | Participants included in analysis | Intervention | Control Group | Who administered intervention | Method | Measure of Compliance | Quality Rating |
| Loudon, Fronius, Looman, et al.[26]The Netherlands (additional participants from Germany and England) | N: 310Age: M = 4.6 y (+/- 2.0 y)Newly diagnosed amblyopia.171 anisometropia, 88 strabismic, 46 anisometropia and strabismus, 5 deprivation.  | -Educational cartoons- Reward chart-Information sheet for parents | Received a cartoon to colour | Researcher | Prospective, single blind, randomized clinical trial | Objective. Percentage of nce measured via ODM for  | Moderate |
| Newsham, [11]England | N: 114Age: 2-7 yReceiving at least one hour of occlusion for amblyopia.All types of unilateral amblyopia included (none with stimulus deprivation presented) | -Educational leaflet for parents including written treatment regimen as a memory aid | Did not receive the educational leaflet | Orthoptist | Experimental, matched pairs with random allocation to either the intervention or control group. | Subjective. Concordance Index CI = recorded occlusion hours/prescribed occlusion hours measured via parental diary  | Moderate |
| Pradeep,Proudlock, Awan, Bush, Collier, &Gottlob, [27]England | N: 46 (62 for ITT)Age:,3.5-8.9 yM = 5.5 y, +/-1.2 yNewly diagnosed amblyopia. Prescribed to patch 10 hours a day for 6 days a week for 12 weeks.15 strabismic, 28 mixed, 19 anisometropic | -Illustrated book-Information booklets for parents, children, teachers, family and friends-Quotation booklet from parents and children undergoing treatment-Passport outlining results of each hospital visit.-Informational video-Session with orthoptist  | Did not receive the intervention | Orthoptist | Unmasked randomised controlled clinical trial with ITT | Objective. Percentage compliance measured with ODM. For ITT participants were coded as a success (patched at least 40% prescribed time) or failure.  | Moderate |
| Tjiam, Holtslag, Van Minderhout, et a.[29]The Netherlands | N = 88Age: 3-6 yLow SES area. Starting first occlusion therapyAmblyogenic risk factor, strabismus without alternating fixation, anisometropia or astigmatism | -One of three intervention components: cartoon, reward chart or parental information. | Given a picture to colour | Orthoptist | RCT | Objective. Actual occlusion hours per day. Percentage compliance based on ODM worn for one week | Moderate |
| Tjiam, Holtslag, Vukovic, et al.[28]The Netherlands | N: 130 Aged: 3-6 yLow SESNewly diagnosed starting first patching Amblyogenic risk factor: strabismus, anisometropia or astigmatism | - Cartoon story, reward chart, parental information sheet.-Orthoptists received compliance training. | Pre-implementation stage - standard orthoptic care | Orthoptists | Clinical, prospective, non-randomized, pre and post implementation study | Objective. Percentage of prescribed patching time achieved measured via ODM measured for 1 week | Moderate |
| El-Ghrably, Longville&Gnanaral. [22]England | N:30Age: 20-75m M = 47mPoor patching compliance.27 strabismic (6 also anisometropic), 3 anisometropic | -1 day Intensive supervised occlusion therapy -Parental education | No control group | Ophthalmology nurse | Retrospective case review | Subjective. Measured directly via parents’ history | Weak |
| Iturriaga, Zanolli, Damm et al.[24]Chile | N: 29 (30 for ITT)Age: M = 5.3y (+/-2.4y)Amblyopia type not specified | -Regular physician check-ups every 4-6 weeks | Attended on standard schedule | NA | Prospective, comparative, blind trial | Subjective. Physician’s rated percentage compliance | Weak |
| Rubab, French,& Levin [23]Canada | N: 5Age: 2-6 yearsAll attempts at occlusion therapy had failed.2 strabismic, 1 organic, 1 anisometropic, 1 sensory deprivation | -Cyanoacrylate glue applied to the patch | No control group | Clinic Staff | Pilot study, longitudinal case study with a non-experimental design. | Subjective. Time spent wearing the patch in hours. | Weak  |
| Sachdeva, Mittal, Kekunnaya, et al. [25]India | N: 68Age: 4-11 yNo amblyopia treatment in past month. No history of patching therapy for more than 1 monthAnisometropic amblyopia | - Split time  | Received standard continuous patching  | Orthoptist | Prospective, interventional, non-randomised (parental choice of condition) comparative pilot study. | Subjective. Compliance rate based on hours spent patching measured with the calendar method | Weak |

\*ITT = Intention to Treat Analysis, ODM = Occlusion Dose Monitor, N = number of participants included in analysis, M = Mean, m = months, y = years.

**Summary of Results**

An overview of the findings of the nine individual studies is presented here. More detail on individual study findings is available in a supplementary file (Table 2). Of the studies with interventions involving an educational element the following results were reported. Loudon et al. [26] found that children who received educational cartoons, a reward chart and information for parents, patched for significantly longer than children who did not receive the intervention. Newsham [11] similarly found better compliance in children whose parents received an educational leaflet. El-Ghrably et al. [22] reported that following one day of supervised occlusion with parental education the average duration that children patched for increased. In contrast Pradeep et al., [27] who trialled the most comprehensive intervention containing multiple components, did not report a significant difference in percentage compliance between the control and intervention groups. They did however report that there were significantly more successful patchers, those patching for at least 50% of the prescribed time, and fewer dropouts in the intervention group. Tjiam et al. [29] assessed three separate intervention components and found that compliance was higher in the educational cartoon intervention than in the reward chart intervention and control groups. In a separate study, Tjiam et al. [28] combined the same three intervention components alongside giving compliance training to orthoptists. They found that there was no significant difference in percentage compliance from pre to post intervention. They did however, find that post intervention there were significantly fewer children who were patching for less than 30% of their prescribed time or were not patching at all.

The three remaining studies involved changing aspects of the patching regime [23, 24, 25]. Rubab et al. [23] reported that adhering the patch to the children’s faces with cyanoacrylate glue increased the length of time they spent wearing the patch. However, Iturriaga [24] found that increasing the frequency of physician check-ups did not result in increased compliance, although the means were in the expected direction, and Sachdeva et al. [25] found no improvement in compliance when giving parents the option to do split time instead of continuous patching.

**Synthesis of Results**

The pattern of results in all 9 studies indicated that overall the interventions showed positive effects. Five studies had moderate quality and all reported significant improvements in compliance. As well as having the same quality rating, these studies were conceptually similar in intervention, with all of them involving an educational element for parents, children or both. Four studies received ‘weak’ quality ratings. Two of these interventions found no significant differences (split-patching [25] and more frequent follow-up [24]) and two studies did not report any statistical analysis (glue [23] and supervised patching [22]).

**Percentage Compliance**

For the key outcome measure, compliance with prescribed patching time, three of the moderate quality studies reported significant effects of the intervention. One for an intervention that included information for parents, information for children and a reward chart,[26] one that involved information for parents [11] and one that found a significant effect for child information but not for the parental information or reward chart. [29] Two moderate quality studies reported no significant effects on percentage compliance but the means are in the expected direction. [27] [28]

Meta-analysis

Due to their similar design, higher quality rating and common educational component, four studies were included in the meta-analysis [11,26,27,29] One of these studies [29] contained three separate interventions. The parental information intervention was selected for inclusion in the main analysis because this was the most similar to the interventions in the three other studies. This meant that each study in the meta-analysis included information for parents, two also included information for the children and one also included information for teachers and relatives.

The meta-analysis revealed that the interventions increased percentage compliance compared to controls. Individual effect sizes and 95% confidence intervals are presented visually in Figure 2. The combined effect size was r = 0.249, p < 0.001, (CI = 0.16 - 0.329), which is a significant small effect size.[21] The included studies were homogenous (X2 (3) = 1.558, p > 0.50) and there was no evidence of publication bias because 31 non-significant studies would be needed to render the results non-significant and it is likely that 30 exist.

Figure 2. Forest Plot showing the effect size r and associated 95% confidence intervals

Sensitivity analysis was conducted by running the meta-analysis three more times substituting in turn Tjiam et al.’s [29] child information, reward chart and a weighted mean that combined all three interventions. The results of these three meta-analyses were consistent with the main analysis, effect sizes ranging from r = 0.243 to r = 0.263, p values all < 0.001, with the largest effect size for the child information. The only difference was that the meta-analysis including the reward chart showed evidence of potential publication bias.

For the four lower quality studies, two did not report percentage compliance and two did not report significant differences between the intervention and control, though results of one approached significance [21] and for the other were significant when intention to treat (ITT) analysis was not used. [17]

**Number of hours spent patching**

Four of the studies reported actual number of hours spent patching. Of the two moderate quality studies the means showed the patching hours were higher in the intervention group but one reported no significant increase [28] and one reported no statistical analysis for this measure [29]. Two lower quality studies report there was an increase but provided no statistical justification.

**Additional outcome measures**

The five moderate quality studies also reported on additional outcome measures, most of which pertain to participants with poor compliance. Two studies reported that the intervention decreased the number of children who did not patch at all [26,28] and three studies reported fewer non-concordant patchers in the intervention group. However, the definitions of non-concordance varied across studies, from less than 80% [11], less than 40 % [27] to less than 30% [28] of prescribed occlusion time. Tjiam et al. [29] reported that no child who received the educational cartoon occluded less than 1 hour per day but a percentage of children in the control and two other intervention groups did. Tjiam et al. [28] also reported that pre-implementation most children occluded less than 1 hour but post-implementation most children occluded significantly more, at a rate of between 1 and 3 hours.

One study reported that compliance decreased more in the control than the intervention group across the data collection period [26] and one reported twice as many drop outs in the control than in the intervention [27].

**DISCUSSION**

In answer to the research question ‘How effective are existing interventions at increasing compliance to patching treatment in amblyopic children?’ it appears that the majority of interventions have been effective to some extent. The populations studied in the papers varied and it is promising that interventions have been found to be effective in different population groups, from different countries and with different levels of SES. There is most evidence to suggest that interventions involving an educational aspect for the parent or child are effective, with the meta-analysis revealing an overall significant small effect size. Adapting the patching regimen via increasing check-up frequency and using split-time patching did not improve compliance. However, these studies were of poorer quality, making it difficult to assess the effectiveness of the interventions. Given the limitations of these studies and current recommendations for orthoptists to increase the frequency of check-ups to combat non-compliance [4], future research should use RCTs to fully assess their effectiveness. It was reported that both supervised occlusion with parental education from a trained nurse and using glue to adhere the patch more tightly to the patient’s face increased compliance. However, these studies did not provide statistical justification to support their findings. Current UK guidelines are for orthoptists to prescribe 2 to 6 hours of patching per day and to reserve supervised out-patient patching and intensive occlusion programmes for patients whose poor compliance is impacting on their vision [4]. Therefore it is unlikely that either of these interventions will become widely used. Instead future research should focus on wider reaching and less costly interventions.

Five studies indicate that interventions involving an educational element for the parent and/or child can be effective in increasing compliance to patching treatment. Further research should be conducted to explore how best to present information on amblyopia and its treatment and who to target it towards. To date only one study [29] assessed information for parents and children separately. The evidence from this study indicates that information for children may be more effective than information for parents or reward charts at increasing compliance. In addition the effect size in the current meta-analysis was larger when the child intervention was included compared to the parent intervention. This finding demonstrates that giving information directly to children may be important in improving compliance, which is in line with current guidance that separate educational leaflets be provided for the parent and the child [4]. More research is needed to further assess the benefits of giving information directly to children.

Despite evidence that information giving can increase compliance with amblyopia treatment, this may be only the first step in improving compliance. Future research should explore additional behaviour change techniques that could be used both with children starting patching treatment and those showing poor compliance. Such techniques may include increasing social support, goal setting or setting reminders to patch. A wide array of barriers to patching treatment compliance have been identified, including stress and lack of motivation, poor patient-doctor communication and psychological distress associated with wearing the patch, [14] and there is evidence that different individuals have different reasons for non-compliance. [11] Therefore more tailored behaviour change interventions should be explored.

**Limitations of review studies**

There is a lack of high quality research to assess the effectiveness of interventions to increase compliance to patching treatment for amblyopia, and this is an area that future research should address. The limited number of studies meant analysis such as meta-regression and further exploration of potential publication bias was not possible. Further limitations within the current review include the different methods of measuring compliance, variation in time since diagnosis of participants and lack of consistency in the follow-up times of the studies. A limitation with studies involving an educational element is the possibility that not all participants who received information actually read and/or understood the information [4]. Additionally while the present systematic review was inclusive of all types of amblyopia, only a small number of participants had form deprivation amblyopia. This was unavoidable due to the low levels of research carried out on this condition.[30] Despite these limitations a core set of studies with moderate quality were identified and provide evidence that information giving is an effective method of improving compliance.

**Conclusions**

Compliance to patching treatment in amblyopic children is a substantial problem. Orthoptists use a variety of techniques to combat this and the current review provides evidence that educational interventions can be effective. Where possible orthoptists should ensure that both the child and parent/caregiver understand the importance of patching and provide written information tailored to both of them. Future high quality research is needed to assess the effectiveness of different elements of educational interventions and to explore the effectiveness of additional behaviour change techniques.

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Conflict of interest: None

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Appendices: None

Figure Legends:

Figure 1. Flow diagram of systematic review based on PRISMA guidelines

Figure 2. Forest Plot showing the effect size (r) and associated 95% confidence intervals