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Interventions for stimulus deprivation amblyopia

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Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.
Review content assessed as up-to-date: 26 November 2007.


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ABSTRACT

Background
Stimulus deprivation amblyopia (SDA) develops due to an obstruction to the passage of light, preventing clear formation of an image on the retina (e.g. cataract, ptosis). It is particularly severe and can be resistant to treatment, leading to poor visual prognosis. Precise estimates of SDA prevalence are difficult to come by but it probably constitutes less than 3% of all amblyopia cases. In developed countries, most patients present under the age of one; in less developed parts of the world, presentation is likely to be significantly later than this. The mainstay of treatment is occlusion of the better-seeing eye, but regimens vary, can be difficult to execute and are traditionally believed to lead to disappointing results.

Objectives
The objectives of this review were to evaluate the effectiveness of occlusion treatment for SDA, to establish the optimum treatment regimen, to determine the factors that may affect outcome, and to identify realistic treatment goals.

Search methods
We searched the Cochrane Central Register of Controlled Trials - CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) in The Cochrane Library (Issue 4, 2007), MEDLINE (1996 to November 2007), EMBASE (1980 to November 2007) and the Latin American and Caribbean Literature on Health Sciences (LILACS) (November 2007). The electronic databases were last searched on 27 November 2007. There were no date or language restrictions.

Selection criteria
Randomized and quasi-randomized controlled trials of participants with unilateral SDA, with visual acuity worse than 0.2 LogMAR or equivalent, were to be included. There were no restrictions with respect to age, gender, ethnicity, co-morbidities, medication use, and the number of participants.

Data collection and analysis
Two review authors independently assessed study abstracts identified by the electronic searches.

Main results
No trials were identified that met the inclusion criteria.
Authors’ conclusions

It is not possible to conclude how effective SDA treatment is or which treatment regimen produces the best results. There is a need for further study in this area.

**PLAIN LANGUAGE SUMMARY**

Treatment for amblyopia caused by obstructed vision in early childhood

Amblyopia or ‘lazy eye’ occurs when vision does not develop normally in early childhood. This may be due to strabismus, anisometropia (unequal refractive error) or obstruction of vision. Stimulus deprivation amblyopia (SDA), the type examined in this review, develops due to obstruction of vision in early childhood by conditions such as cataract (cloudy lens) or ptosis (droopy eyelid). Stimulus deprivation amblyopia is generally accepted to be the hardest type of amblyopia to treat. The prevalence of amblyopia varies from 1% to 5%, with SDA constituting less than 3% of all amblyopia cases. Health professionals or parents initially detect the accompanying signs of visual obstruction (e.g. leukocoria - whitish pupil associated with congenital cataract, droopy eyelid) when the patient is under the age of one. Amblyopia is then diagnosed after the causative factor has been treated and refractive correction has been given. The level of vision taken to be below normal varies; for this review, it was operationally defined as vision below 0.2 LogMAR or its equivalent, although typically the level of loss in SDA is much more severe. The aim of amblyopia treatment is to maximize visual recovery without adversely affecting the better-seeing eye. The rationale is to provide a good second eye should the better eye ever lose vision and to maximize stereopsis (binocular vision). Patching the better-seeing eye is the mainstay of treatment and amblyopia treatment is only effective in early childhood. Optimum treatment is unclear and prescribed regimens therefore vary. Reports of treatment success are inconsistent. Occlusion can be harrowing for parents and stressful for the child, making compliance an issue. Untreated or unsuccessfully treated amblyopia may affect employment in adult life. The aim of the review was to examine existing evidence to help establish realistic treatment outcomes and to determine the most effective treatment regimen(s). We searched for randomized controlled trials examining the effectiveness of patching or other treatment strategies for SDA, but did not find any that fulfilled our inclusion criteria. There remains a pressing need for better evidence of treatment effectiveness for this condition.

**BACKGROUND**

Description of the condition

Amblyopia derives from the Greek words “amblys” meaning blunt and “ops” meaning eye, thus bluntness of vision. Clinically, amblyopia denotes a reduction in vision in the absence of any retinal anomaly and any disorder of the afferent visual pathways (Duke-Elder 1973). Amblyopia can be bilateral, but is most commonly unilateral. Amblyopia is usually classified according to its cause:

- strabismic: as a result of squint (eye misalignment);
- anisometropic: unequal refractive (focusing) error;
- meridional: due to astigmatism (irregular corneal curvature);
- ammetropic: high refractive error in both eyes;
- stimulus deprivation: secondary to an obstruction in the anterior visual pathway.

Where more than one cause exists, it will often be described as mixed amblyopia; typically this is a combination of strabismic and anisometropic amblyopia. This review only appraised unilateral stimulus deprivation amblyopia (SDA); interventions for other types of amblyopia are currently being evaluated in a series of separate Cochrane reviews (Shotton 2005; Shotton 2008).

Pathophysiology

The organization of the adult visual cortex (brain) is determined by early visual experiences (Wiesel 1963). The time within which abnormal visual input can lead to a disruption of the normal pattern of development is called the ‘critical period’ (Hockfield 1998). There are several critical periods, each associated with different visual functions (Harwerth 1990), which probably reflect development of different parts of the brain. These critical periods do not end abruptly and can be considered as a continuum from extreme sensitivity to almost no sensitivity to external stimuli. Amblyopia finds its roots in these critical periods at young ages when the brain
and visual system are immature and connections between neurons are still being formed and stabilized. During the critical period, amblyopia is reversible, usually until the child is eight years old; this period of plasticity varies considerably among children and depends on the type of amblyopia.

Etiology
Stimulus deprivation amblyopia, also known as amblyopia ex anopsia, refers to the type of amblyopia where loss of vision results from disuse or lack of formation of clear retinal images, most commonly as a result of one of the following:

- unoperated infantile cataract (opacity of the lens);
- ptosis (droopy lid) (Dray 2002; Gusek 2000);
- hemangioma (blood-rich swelling on the lid) (Schulz 1982);
- vitreous hemorrhages (bleeding into the clear gel that fills the eye) (Ferrone 1994) or other obstructions in the vitreous such as persistent hyperplastic primary vitreous (PHPV);
- aphakia (absence of the natural lens);

The eye itself may be otherwise healthy or in some cases, there is co-existing pathology such as microphthalmos (small eye), coloboma (incomplete formation of the eye), optic nerve hypoplasia (under-developed optic nerve) or retinal abnormality. It can be very difficult to discern the extent of visual loss that is due to the amblyopia and what is due to other pathology. Co-existing disease will often limit the visual prognosis, making treatment harder to manage. The most commonly reported cause of SDA is unilateral congenital or infantile cataract. The affected eye is subjected to stimulus deprivation secondary to the cataract until the cataract is removed; stimulus deprivation continues until optical correction is provided. The aphakic eye may continue to be subjected to anisometropia and aniseikonia (unequal image size) even after optical correction (Enoch 1983). The early insult to the visual system seems to make this type of amblyopia particularly severe and resistant to treatment. The visual prognosis is reported to be poor (Kanski 1994; Taylor 1997).

Epidemiology
The prevalence of amblyopia in the general population ranges from 1% to 5% (Brown 2000; Hillis 1983). In European children, the prevalence ranges from 1% to 2.5% (Kvarnstrom 2001; Newman 2000). Amblyopia accounts for 29% of unilateral blindness in Copenhagen (Buch 2001) and as much as 8.3% of bilateral blindness in India following childhood cataract surgery (Dandona 2003). Stimulus deprivation amblyopia is seen in less than 3% of amblyopic patients (Hillis 1983). There is no known age, gender, race, or developing-developed country differences. These differences may also be due to varying definitions of amblyopia used in the studies.

Presentation
Routine health checks of babies and toddlers are carried out by a variety of health care personnel (e.g. pediatricians, nurses) and provide an opportunity for detection of the causative signs (e.g. ptosis, cataract) associated with SDA. However provision of such screening is not universal. Access to health care professionals and services may be limited, especially in the rural areas of developing countries. Stimulus deprivation amblyopia itself is not likely to be noticed, but parents may detect the signs associated with the cause of SDA such as leukocoria (whitish pupils) with congenital cataracts or the droopy eyelid (ptosis). Once poor vision in one eye is established, strabismus or squint (misalignment) may develop which may lead to a referral. In the developed world, most patients present for treatment while they are under a year old (Mein 1991); this is likely to be significantly later where healthcare is limited.

Diagnosis
There are four main steps in the diagnosis of SDA.

1. Visual acuity testing. Testing young children is largely reliant on objective observations that are limited by cognition and concentration. Qualitative methods (e.g. assessing fixation preference) may be used. However, quantitative tests (e.g. preferential looking) are more precise. Preferential looking tests rely on the observation that infants prefer to look at patterned rather than plain surfaces (Fanz 1958). If the child can discern the striped panel on the card presented, he will look at it. The degree of visual angle subtended by the stripes is known; therefore, a Snellen equivalent can be calculated. In older children, testing methods are more objective, relying on the child identifying pictures or letter optotypes in Snellen, decimal or LogMAR notation.

2. External and internal eye examination to identify any pathology. Some pathology, particularly optic nerve hypoplasia, needs to be carefully looked for in a child. Treatment may be inappropriate and unsuccessfully commenced if such visually limiting pathology remains undetected.

3. Cycloplegic refraction and corrective prescription if indicated. Amblyopia cannot be diagnosed unless any significant refractive error has been corrected.

4. Rechecking visual acuity with any prescribed refractive correction in place. Some improvement in visual acuity can be expected with spectacles alone. There should be a period of adjustment into spectacles before retesting. Traditionally this adjustment period has been four to six weeks, but studies on refractive and strabismic amblyopia show this may be as long as 24 weeks (Moseley 2002). Definitions of amblyopia vary largely due to the fact that there is little evidence as to what constitutes normal vision on many commonly used tests at different ages. It may be defined by comparing the eyes (inter-ocular difference) or by looking at monocular visual acuity alone. We have elected to define amblyopia as vision worse than 6/9 on a Snellen-based test, 0.2 LogMAR, or its equivalent in one eye.
Description of the intervention/How the intervention might work

Visual loss attributable to SDA can be severe. The aim of treatment is to maximize visual recovery without adversely affecting acuity in the better-seeing eye. The rationale for treatment is two-fold: to provide a good second eye should the better-seeing eye ever be visually compromised and to maximize stereopsis (binocular cooperation between the eyes). Untreated or unsuccessfully treated amblyopia may impact adult life. For individuals with amblyopia, the lifetime risk of serious visual impairment due to loss or damage of the better-seeing eye is estimated to be between 1.2% and 3.3% (Rahi 2002). In addition, there are implications for employment prospects and, therefore, income; the number of jobs barred to individuals with reduced vision increases with the severity of the deficit (Adams 1999).

Stages of treatment

(1) Correct the causative factor that is degrading the quality of the visual image (e.g. infantile cataract extraction, ptosis repair). In cases of early unilateral deprivation, correction must be undertaken in the first eight to 12 weeks of life if good visual acuity is to be obtained (Birch 1986; Birch 1988; Gregg 1992; Kanski 1994; McCulloch 1994; Taylor 1997)
(2) Prescribe any necessary refractive correction to maximize the quality of visual stimulation received by the child’s amblyopic eye. Intraocular implants, contact lenses or both may be used after cataract surgery.
(3) Occlusion therapy. Occlusion forces the use of the amblyopic eye, stimulating the formation of functional connections in the brain (Boothe 2000).

Occlusion regimen:

Protocols and practices vary considerably. Duration of occlusion therapy ranges from an hour to more than six hours (full-time). Factors affecting the amount prescribed include the level of visual deficit, the age of the child and the likely waiting time to the next appointment. Follow-up is recommended at intervals of one week per year of age during periods of aggressive patching (Simon 1987). Occlusion can be stopped when visual acuity becomes equal in the two eyes or if no progress has been made after three months of good compliance with occlusion (Pratt-Johnson 2001). It has been recommended that children in this situation are monitored up to the age of visual maturity (approximately seven years of age) to ensure that amblyopia does not recur. Some periods of maintenance occlusion may be required during that time (Mein 1991). The following have been used as additions to occlusion therapy, but appear not to be currently popular clinically:
(1) CAM visual stimulator: uses rotating high-contrast square wave gratings to stimulate the amblyopic eye.
(2) Pleoptics: employs after-images to encourage foveal fixation and normal projection in the amblyopic eye.

Types of occlusion:

Atropine penalization and optical penalization (use of lenses to reduce the acuity) are other forms of occlusion that encourage use of the amblyopic eye by diminishing visual form. These treatments for amblyopia are being evaluated in other Cochrane reviews currently underway (Li 2007).

This review examined the role of total occlusion to form and light as an intervention for SDA. Total occlusion, also known as conventional occlusion, is usually achieved by means of an opaque, adhesive patch on the better-seeing eye. Less commonly, occlusive contact lenses are employed. As mentioned previously, bilateral SDA is rare and not usually treated with occlusion therapy and therefore was not considered in this review.

Measuring outcomes

In order to quantify amblyopia, visual acuity must be measured. Qualitative methods for assessing vision in preverbal children are based on the observation of their fixation patterns. These methods are often unreliable and require highly trained examiners (Wright 1986; Zipf 1976). Final visual acuity assessed using an age-appropriate test (Fulton 1978; Sebris 1987) is the most commonly used outcome from treatment. Tests vary in the use of optotypes (picture, letter, or symbol) and may be with or without crowding; crowded visual acuity tests are harder to perform but are more sensitive to amblyopia than uncrowded tests.

Developmental changes in young children complicate the evaluation of actual change in acuity from pre- to post-treatment. Alternative methods of measuring change have been suggested in an attempt to overcome this (Schmidt 1994; Stewart 2003), but we aimed to compare post-treatment visual acuity values (defining restoration of normal visual acuity as better than or equal to 6/9 on Snellen, or 0.2 LogMAR or its equivalent).

Factors affecting outcome

Compliance with therapy is critical for successful treatment but can often be difficult to achieve. Young children can become distressed by being restricted to reduced visual acuity and from the discomfort of wearing an adhesive patch. It has been suggested that, if possible, compliance should be monitored to more effectively measure response to treatment. Devices to objectively measure compliance have been developed (Awan 2005; Stewart 2005) but are not commonly used; clinicians still generally depend on parental reports. Other factors thought to affect treatment success are duration of visual deprivation and age at onset of therapy (Maurer 1989): the earlier the onset, the longer the duration and the later treatment is commenced, the worse the visual prognosis.
Harm from occlusion therapy

Potential adverse effects from occlusion therapy include inducing amblyopia in the occluded eye, skin allergies, infections and/or corneal abrasions from contact lens wear, diplopia (double vision), and psychological effects (e.g. distress).

Why it is important to do this review

The reported success of treatment for SDA varies. There are studies reporting good levels of vision following early treatment (Gregg 1992; McCulloch 1994), but there is a lack of standardization and poor agreement among experts as to the optimum amount of occlusion needed to achieve good visual outcome. Commencing occlusion therapy in infants with very poor vision can be harrowing for the parents and stressful for the child. Realistic treatment goals are often poorly defined. It is thus necessary to establish the most effective occlusion regimen(s) for stimulus deprivation amblyopia and to define the degree of improvement that can be reasonably expected from this treatment.

OBJECTIVES

The principal objective was to evaluate the effectiveness of occlusion therapy for SDA in an attempt to establish realistic treatment outcomes. Where data was available, we also examined evidence for any dose/response effect and assessed the impact of the duration, severity and causative factor on the size and direction of the treatment effect.

METHODS

Criteria for considering studies for this review

Types of studies
This review included randomized and quasi-randomized trials.

Types of participants
- Unilateral SDA defined as best corrected visual acuity worse than 6/9 Snellen or its equivalent after treatment for the causative factor has been undertaken and ensuing refractive error has been corrected. (Other co-existing amblyogenic factors will be reported).
- No restrictions with respect to age, gender, ethnicity, comorbidity, medication use, and the number of participants.

Types of interventions
The following interventions were of interest:
- total occlusion by adhesive patch;
- total occlusion by occlusive contact lens;
- pleoptic treatment;
- partial occlusion (i.e. Bangerter filters);
- CAM visual stimulation.

The following comparisons were examined:
(1) total occlusion versus no occlusion;
(2) any means of total occlusion compared to another;
(3) any total occlusion plus pleoptic treatment versus total occlusion alone;
(4) any total occlusion plus CAM visual stimulator versus total occlusion alone;
(5) full-time occlusion (more than six hours / day) versus part-time occlusion (less than six hours / day);
(6) partial versus partial (e.g. two hours/day versus six hours/day)

Types of outcome measures

Primary outcomes
The primary outcome for this review was best-corrected visual acuity of the amblyopic eye, on an age-appropriate test, six months from cessation of occlusion. Although not directly equivalent, we planned to convert Snellen data into a LogMAR equivalent for ease of interpretation and analysis.

Outcomes were to be dichotomized:
(1) Normal = better than or equal to 0.2 LogMAR, 6/9 Snellen or its equivalent.
(2) Residual deficit = worse than 0.2 LogMAR.

Where possible, we planned to report mean values.

Secondary outcomes
The secondary outcomes for this review were:
(1) Visual acuity in the amblyopic eye at seven years of age or older.
(2) The proportion of the amblyopia deficit corrected (Stewart 2003).
(3) Any measure of stereoacuity (3-dimensional vision).

Cost data
We planned to summarize the comparative costs of treatment methods described in included trials.
Adverse effects
We planned to summarize adverse effects related to treatment that were reported in included trials:
Severe: occlusion amblyopia, contact lens-related problems (e.g. infection, corneal abrasions), adverse psychological effects (e.g. distress), treatment cessation due to poor compliance or failure to attend, or diplopia.
Minor: allergy to patches.

Quality of life measures
We planned to summarize any reports on quality of life measures in the included trials.

Follow up
A minimum of six months’ post-treatment follow-up was necessary for inclusion and analysis; any eligible studies with less follow-up were described.

Search methods for identification of studies

Electronic searches
We searched the Cochrane Central Register of Controlled Trials - CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) in The Cochrane Library, MEDLINE, EMBASE and Latin American and Caribbean Literature on Health Sciences (LILACS). There were no date or language restrictions. The databases were last searched on 27 November 2007. See: Appendices for details of search strategies for each database.

Searching other resources
No manual searches were undertaken for this review but will be carried out if possible in future updates. Manual searches will include searching Web of Science for other studies that cite included trials, and searching bibliography of included trials.

Data collection and analysis

Assessment of search results
Two review authors independently assessed the titles and abstracts of all reports identified by the electronic searches as per the ‘Criteria for considering studies for this review.’ The reviewers were unmasked to the report authors, institutions and trial results during this assessment.
The abstracts were classified as (a) definitely include, (b) unsure and (c) definitely exclude. Full copies of those classified as (a) definitely include and (b) unsure were obtained and re-assessed. The studies were then classified as (1) included, (2) awaiting clarification and (3) excluded. A third reviewer resolved any disagreements. Authors of studies classified as (2) awaiting assessment were contacted for further clarification. Details of studies identified by both reviewers as (3) excluded were documented in the relevant section of the review.

Methods for future updates
If any randomized or quasi-randomized trials are identified in future updates of this review we will adopt the following methods.

Assessment of methodological quality
Two review authors will independently assess the sources of systematic bias in trials according to methods set out in section 6 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006). The following parameters will be considered:
- quality of allocation concealment (selection bias);
- method of randomization;
- completeness of follow-up (i.e. attrition bias) - how many participants were lost to follow-up, how they were accounted for, whether follow-up rates for groups were similar;
- whether all participants were analyzed as randomized. If studies report that an intention-to-treat analysis (ITT) was performed, we will assess whether both a) participants where no outcome was collected, and b) those who only received some or none of their allotted treatment were included. We will only interpret a true ITT analysis to have been undertaken if both these criteria have been fulfilled.
- detection bias: whether assessment of outcome was concealed and if so, how adequately.

Each of the parameters will be graded as (A) Adequate or Yes, (B) Unclear or Not Reported, and (C) Inadequate or No. A third reviewer will resolve any disagreements. Masking of participants and care providers is not feasible in these trials and hence will not be used as a measure of quality. For trials categorized as (B) Unclear or Not Reported, the authors will be contacted for additional information. If the authors do not respond within four weeks, the reviewers assigned a grade to the trial based on the available information.

In addition to the parameters described above, other data will be extracted:
(1) Participants:
- numbers, age at onset and intervention, duration of stimulus deprivation, cause of stimulus deprivation, starting visual acuity, refractive correction;
- concomitant ocular pathology that may limit visual outcome (e.g. coloboma, optic nerve hypoplasia, retinal dystrophy). Studies including such participants will be subjected to a subgroup analysis;
- adjustment period into spectacle correction.
(2) Intervention: method of occlusion, regime, CAM, pleoptics.
(3) Outcomes: test(s) used, length of follow up, if, when and how compliance assessed.

Data extraction and management
Two review authors will independently extract data for the primary and secondary outcomes onto paper data collection forms developed by the Cochrane Eyes and Vision Group. Discrepancies will be resolved by discussion. Primary investigators will be contacted for missing data. One review author will enter data into RevMan 4.2. A second review author will independently re-enter the data, using the double data-entry facility to check for inaccuracies.

Measures of treatment effect
Data analysis followed the guidelines in section 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2006). For dichotomous outcomes, summary odds ratio will be calculated for rarer outcomes or risk ratio for more frequent outcomes. Weighted mean difference will be reported for continuous outcomes, for example, for trials that have measured vision using LogMAR tests throughout the study.

Unit of analysis issues
Statistical input from the Cochrane Eyes and Vision Group Editorial Base will be obtained for analysis of trials with multiple treatment groups, cross-over trials and cluster randomized trials.

Dealing with missing data
We will contact the investigators for more information on missing data. If they're unable to provide additional information, we will seek input from the Cochrane Eyes and Vision Group Editorial Base for guidance.

Assessment of heterogeneity
Forest plots will be examined for overlap of 95% confidence intervals of effect estimates for visual assessment of heterogeneity between effect estimates of included trials. I-square value will be calculated and the chi-square test for heterogeneity will be conducted. I-square values more than 50% will be considered substantial heterogeneity.

Data synthesis (meta-analysis)
If no statistical heterogeneity was detected or if there was no clinical heterogeneity within the trials, the results will be combined in a meta-analysis using a fixed-effect model. If there is statistical heterogeneity in the absence of clinical heterogeneity, a summary measure will be computed using a random effects model if I-square value is below 50%. In case of substantial statistical or clinical heterogeneity (I-square value greater than 50%), study results will not combined, but will be presented in a tabulated or narrative summary.

Investigation of heterogeneity
If sufficient numbers of trials are available and are stratified prior to randomization, the following subgroups will be explored:
- participants without any co-existing ocular pathology (that might be expected to limit visual prognosis) were analyzed separately from those with other pathology.
- participants with stimulus deprivation amblyopia associated with a unilateral congenital cataract were compared to stimulus deprivation amblyopia associated with any other unilateral etiology.

Sensitivity analysis
Sensitivity analyses will be conducted, if appropriate, to determine the size and direction of effect when excluding the following:
- Outcomes measured on uncrowded vision tests
- Studies where any parameter has been graded ‘C’ or ‘No’
- Excluding unpublished studies or industry-funded studies

Results

Description of studies
See: Characteristics of excluded studies.

Results of the search
The electronic searches conducted in 2004 identified 799 abstracts and titles of which seven appeared to be randomized controlled trials (RCTs) of interventions for amblyopia. Of these, three trials evaluated conventional occlusion therapy but did not include patients with SDA (Clarke 2003; Holmes 2003; Repka 2003). There were four studies (Keith 1980; Mehdorn 1981; Nyman 1983; Tylta 1981) on the CAM visual stimulator but after reading the full text of the studies and contacting the authors where necessary, it became apparent that only one trial (Nyman 1983) had included participants with SDA and the data relevant to this review were no longer available. All seven trials were therefore excluded (see table: Characteristics of excluded studies). Full text copies of 25 references were obtained because the initial search information was insufficient to establish whether the studies were eligible for inclusion or not. This was either because the title only was available, the abstract was unclear or the abstract or study was written in a language other than English. After further perusal or translation, all studies were found to be ineligible and
were excluded. Reasons for exclusion have been documented in the table: Characteristics of excluded studies. An updated search was done in November 2007 which yielded an additional 53 reports of studies. One RCT including five patients with SDA was found, but this investigated the effectiveness of an educational program on the predictors of noncompliance to occlusion therapy (Loudon 2006). Five additional RCTs investigated occlusion therapy (Hertle 2007; Repka 2007; Stankovic 2007; Stewart 2007; Wallace 2006), but these only included strabismic and/or amblyopia. Thus, the search did not identify any new trials which met the inclusion criteria for the review.

Risk of bias in included studies
We found no randomized or quasi-randomized trials eligible for inclusion in the review.

Effects of interventions
None of the studies identified in the searches were eligible for inclusion, highlighting a significant gap in the existing evidence for the treatment of stimulus deprivation amblyopia. In order to provide the reader with some insight into the basis for current practice, some of the non-randomized studies identified incidentally in the searches and others already known to the authors are discussed below.

Discussion
Since no RCTs were found, other relevant studies already known to the authors or identified in the searches have been described in order to comment on current practice. It is important to note that these were not systematically searched for, thus do not represent a systematic/comprehensive summary of existing evidence.

Treatment for strabismic and/or amblyopia has recently been subject to more rigorous scrutiny in high quality RCTs. These studies have helped clarify the level at which amblyopia treatment works and have provided useful information as to which occlusion regimens may work most effectively (Clarke 2003; Holmes 2003; Repka 2003; Stewart 2007). However, SDA is nearly always specifically excluded from these randomized or even from non-randomized trials. This is because SDA is generally accepted, not only to be more severe and therefore more resistant to treatment (Kanski 1994; Taylor 1997), but may also (based on animal studies) have a different pathophysiological mechanism from the other types (Mitchell 2002).

Treatment for SDA is confounded by many factors: possible co-existing pathology, the young age of the patient, limitations of clinical tests. These make it very difficult to quantify the degree of visual deficit, to establish how much is attributable to amblyopia and whether or not it is responding to treatment. The age of the patient and the severity of visual loss can also result in poor compliance with treatment and significant stress and distress for both parents and child. There is also a dearth of evidence as to what outcomes must be realistically expected.

Current evidence of treatment is largely derived from non-randomized studies of SDA caused by unilateral congenital cataract. A brief overview of some of these data is summarized below.

Occlusion type
The majority of studies we came across described the use of total or conventional occlusion for the treatment of SDA. Although it is not without disadvantages in terms of discomfort, it is relatively easy to control the dosage of treatment and is without the more complex side effects of occlusive contact lenses. One RCT (Nyman 1983) looked at the additional effect of CAM stimulation compared to total occlusion alone, but the data for SDA could not be isolated from the data for the other types of amblyopia. This treatment, though prevalent in the 1980s, has largely disappeared from current practice possibly due to the lack of evidence of long-term benefit and its time implications for both the patient and the clinician.

Occlusion regimens and treatment outcomes
Current practice generally favors aggressive patching in early life based on the knowledge that the visual system is much more sensitive to change at this age. Mayer 1989 reports a negative correlation between the number of hours patched and inter-ocular difference in acuity. Intensive or aggressive patching varies widely from a minimum of six hours per day to as much as 100% of waking hours. Birch 1988 reported 53% achieved a visual acuity of 20/80 (6/24) or better with this treatment. Lundvall 2002 found 20% attained visual acuity of 0.1 (6/7.5) or better and Drummond 1989 reported 43% achieved VA better than 20/50 (6/9). Robb 1987 found 46% achieved visual acuity of at least 20/70 (6/18). Although by no means comprehensive, this brief summary highlights the variable ‘success’ rate and also the different ways in which results can be categorized. This and other dissimilarities in study methodologies make it impossible to meaningfully compare results among these studies.

Less intense occlusion regimens, while being easier to execute, have been advocated because they promote more binocular interaction and stereoaucity. Brown 1999 reported good visual and binocular results with occlusion of one hour per day per month of age for the first six months of life. A more recent study (Stewart 2007) reported no difference in outcomes between patching for
six hours and 12 hours a day in children with strabismic and/or anisometropic amblyopia.

Compliance

Many, if not all, papers on occlusion treatment for SDA highlight the necessity of good compliance in order to achieve a satisfactory outcome. Unfortunately, compliance in treating SDA is extremely difficult to achieve. While it may not be too surprising that a treatment that visually compromises a child by means of an adhesive patch is not easy to deliver, justification of such a treatment must carefully consider any potential harm alongside evidence of benefit. In a culture where justifying intervention is increasingly required, the current absence of clear evidence of effectiveness in this area is concerning.

Compliance also affects interpretation of the dose-response treatment effect. Some studies on refractive and strabismic amblyopia have used objective methods to monitor how much occlusion is actually worn (Awan 2005; Loudon 2002; Stewart 2005). These show that the prescribed amount of occlusion is not always achieved and that lower doses of occlusion can be as effective as the more intense occlusion regimens. Studies have also used objective measurements of compliance to identify parental and demographic characteristics associated with poor compliance with occlusion therapy (Loudon 2006). To date, such information for SDA is lacking.

Authors’ Conclusions

Implications for practice

It is not possible to draw reliable conclusions from the available data since the study designs either do not compare treatment strategies or are subject to significant bias in the selection of participants for particular treatments. In addition, the variation between studies in treatment delivery and outcome measurement prevents the comparison or combination of results.

The general trend in practice (based on the proportion of papers we found reporting this treatment) appears to favor the more intensive occlusion therapy regimen to attain better visual outcomes, although this has not been thoroughly tested and has been linked to problems with compliance. There is some evidence that less intense treatment may have favorable results. The difficulties associated with treatment, the demand on resources and the potential impact on the patient need to be considered carefully against the current absence of real evidence of treatment benefit for SDA. It is currently difficult to objectively advise parents or to formulate evidence-based guidelines for the management of SDA. It remains uncertain what to realistically expect from treatment for SDA and how to best achieve this.

Implications for research

There is a clear and pressing need for higher quality studies in the management of SDA. While occlusion therapy currently remains the mainstay of treatment, withdrawing it for a time in the context of a RCT may be deemed unethical; it must also be studied whether it is worth continuing an intense and potentially traumatic treatment which does not have a clearly defined end-point or a strong evidence of effectiveness.

Unsuccessful treatment ultimately results in the same outcome as no treatment - blindness or partial sight in one eye. Exposure to treatment also carries with it the potential for harm, thus, future studies on treatment for SDA should report treatment effect and accurately measure any potential physical, emotional or psychological harm.

Specific questions that need to be addressed in prospective, randomized studies (with appropriate pre-randomization stratification for any subgroup analyses) are:

- duration of stimulus deprivation;
- the level of vision that can be realistically achieved; effect of age at onset and density of visual;
- optimum occlusion regimen occlusion;
- duration of treatment necessary to achieve optimum benefit;
- potential adverse effects from treatment;
- factors associated with satisfactory and unsatisfactory outcomes.

Acknowledgements

The Cochrane Eyes and Vision Group devised the search strategies for this review and carried out electronic searches.

We thank Richard Harrad, Carey Bunce, Sue Elliott and Suzanne Brodney-Folse for their peer review comments throughout the review process. We are also grateful to Milan Mathew for his guidance during the protocol stage. In addition, we thank Ruthy Acosta for her assistance with articles written in Spanish.
References to studies excluded from this review

Arruga 1966 [published data only]

Clarke 2003 [published data only]

Cuppers 1967 [published data only]

Cappers 1967 [published data only]

Fletcher 1969a [published data only]

Fletcher 1969b [published data only]

Flynn 1967 [published data only]

Flynn 1968 [published data only]

Fungini 1973 [published data only]

Hertle 2007 [published data only]

Holmes 2003 [published data only]

Iacobucci 1977 [published data only]

Keith 1980 [published data only]

Kuming 1982 [published data only]

Lang 1965 [published data only]

Lennonstrand 1983 [published data only]

Loudon 2006 [published data only]

Mackensen 1965 [published data only]

Malik 1970 [published data only]

Mehdorn 1981 [published data only]

Nyman 1983 [published data only]
Pistelka 1973 [published data only]

Prienigitz 1965 [published data only]

Repka 2003 [published data only]

Repka 2007 [published data only]

Schor 1983 [published data only]

Shroff 1983 [published data only]

Stankovic 2007 [published data only]

Stewart 2007 [published data only]

Stojevska 1975 [published data only]

Tomlinson 1973 [published data only]

Tommla 1969 [published data only]

Tommla 1974 [published data only]

Tylla 1981 [published data only]

Veronneau 1974 [published data only]

Wallace 2006 [published data only]

Widder 1967 [published data only]

Zang 1988 [published data only]

Additional references

Adams 1999

Awan 2005

Awaya 1973

Birch 1986

Birch 1988
Interventions for stimulus deprivation amblyopia (Review)

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Booth 2000

Brown 1999

Brown 2000

Buch 2001

Dandona 2003

Deeks 2006

Dray 2002

Drummond 1989

Duke-Elder 1973

Enoch 1983

Fanz 1958

Ferrone 1994

Fulton 1978

Glanville 2006

Gregg 1992

Gusek 2000

Harwerth 1990

Higgins 2006

Hillis 1983

Hockfield 1998

Kanski 1994

Kvarnstrom 2001

Li 2007

Loudon 2002
Lundvall 2002

Maurer 1989

Mayer 1989

McCulloch 1994

Mein 1991

Mitchell 2002

Moseley 2002

Newman 2000

Pratt-Johnson 2001

Rahi 2002

Robb 1987

Schmidt 1994

Schulz 1982

Sebris 1987

Shotton 2005

Shotton 2008

Simon 1987

Stewart 2003

Stewart 2005

Taylor 1997

Von Noorden 1973

Von Noorden 1981

Wiesel 1963

Wright 1986

Zipf 1976

* Indicates the major publication for the study
## CHARACTERISTICS OF STUDIES

### Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arruga 1966</td>
<td>Review, not a clinical trial.</td>
</tr>
<tr>
<td>Clarke 2003</td>
<td>Randomized controlled trial but stimulus deprivation amblyopia not included</td>
</tr>
<tr>
<td>Cramer 1966</td>
<td>Not a randomized controlled trial.</td>
</tr>
<tr>
<td>Cuppers 1967</td>
<td>Retrospective case-control study*</td>
</tr>
<tr>
<td>Fletcher 1969a</td>
<td>Randomized controlled trial but stimulus deprivation amblyopia not included</td>
</tr>
<tr>
<td>Fletcher 1969b</td>
<td>Retrospective chart review.</td>
</tr>
<tr>
<td>Flynn 1967</td>
<td>Retrospective chart review.</td>
</tr>
<tr>
<td>Flynn 1968</td>
<td>Retrospective study.</td>
</tr>
<tr>
<td>Hertle 2007</td>
<td>Randomized controlled trial but stimulus deprivation amblyopia not included</td>
</tr>
<tr>
<td>Holmes 2003</td>
<td>Randomized controlled trial but stimulus deprivation amblyopia not included</td>
</tr>
<tr>
<td>Iacobucci 1977</td>
<td>Review article.</td>
</tr>
<tr>
<td>Keith 1980</td>
<td>Trial of CAM vision stimulator; stimulus deprivation amblyopia not included</td>
</tr>
<tr>
<td>Kuming 1982</td>
<td>Before-after study with only 2 participants with stimulus deprivation amblyopia</td>
</tr>
<tr>
<td>Lang 1965</td>
<td>Case-series, non-comparative*</td>
</tr>
<tr>
<td>Lenerstrand 1983</td>
<td>No participants with stimulus deprivation amblyopia.</td>
</tr>
<tr>
<td>Loudon 2006</td>
<td>Randomized controlled trial on effectiveness of an educational program on the predictors for noncompliance to occlusion therapy</td>
</tr>
<tr>
<td>Mackensen 1965</td>
<td>Case-series, non-comparative*</td>
</tr>
<tr>
<td>Malik 1970</td>
<td>Cohort study.</td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Mehdorn 1981</td>
<td>Randomized controlled trial of CAM vision stimulator; stimulus deprivation amblyopia not included</td>
</tr>
<tr>
<td>Nyman 1983</td>
<td>Trial of CAM vision stimulator; data on stimulus deprivation amblyopia included but could not be extrapolated and no longer available</td>
</tr>
<tr>
<td>Priegnitz 1965</td>
<td>Non-comparative study*.</td>
</tr>
<tr>
<td>Repka 2003</td>
<td>Randomized controlled trial but stimulus deprivation amblyopia not included</td>
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<tr>
<td>Repka 2007</td>
<td>Randomized controlled trial but stimulus deprivation amblyopia not included</td>
</tr>
<tr>
<td>Schor 1983</td>
<td>Did not include participants with stimulus deprivation amblyopia</td>
</tr>
<tr>
<td>Stankovic 2007</td>
<td>Randomized controlled trial but stimulus deprivation amblyopia not included</td>
</tr>
<tr>
<td>Stewart 2007</td>
<td>Randomized controlled trial but stimulus deprivation amblyopia not included</td>
</tr>
<tr>
<td>Stojcevska 1975</td>
<td>Non-comparative study*.</td>
</tr>
<tr>
<td>Tommila 1969</td>
<td>Non-comparative study.</td>
</tr>
<tr>
<td>Tommila 1974</td>
<td>Review article.</td>
</tr>
<tr>
<td>Tyrla 1981</td>
<td>Trial of CAM vision stimulator; stimulus deprivation amblyopia not included</td>
</tr>
<tr>
<td>Veronneau 1974</td>
<td>Used historical controls.</td>
</tr>
<tr>
<td>Wallace 2006</td>
<td>Randomized controlled trial but stimulus deprivation amblyopia not included</td>
</tr>
<tr>
<td>Widder 1967</td>
<td>Non-comparative study*.</td>
</tr>
</tbody>
</table>

* - full-text articles of these studies published in non-English languages were reviewed and are noted in this table.
DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. CENTRAL search strategy used for Issue 4, 2007

#1 MeSH descriptor Amblyopia
#2 amblyop* or anopsi*
#3 MeSH descriptor Pupil Disorders
#4 MeSH descriptor Cataract
#5 cataract*
#6 MeSH descriptor Blepharoptosis
#7 blepharoptosis or prosis
#8 MeSH descriptor Vitreous Hemorrhage
#9 (haemorrhage* or hemorrhage*) near (vitreous)
#10 MeSH descriptor Hemangioma, Capillary
#11 (hemangioma or haemangioma) near (capillary)
#12 MeSH descriptor Aphakia
#13 aphaki*
#14 (stimul* or vision or visual or optical) near (deprivat*)
#15 (scar* or opac* or degenerat*) near (cornea*)
#16 media next opacit*
#17 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18 MeSH descriptor Sensory Deprivation
#19 patch* or shield*
#20 (stimul* or penalis*) near (optical*)
#21 (stimul* or penalis*) near (vis*)
#22 (therap* or treat* or lens* or complete* or partial*) near (occlus*)
#23 (therap* or treat* or lens* or complete* or partial*) near (pleoptic*)
#24 (#18 OR #19 OR #20 OR #21 OR #22 OR #23)
#25 (#17 AND #24)

Appendix 2. MEDLINE search strategy used on OVID up to November 2007

1 exp clinical trial/ [publication type]
2 (randomized or randomised).ab,ti.
3 placebo.ab,ti.
4 dt.fs.
5 randomly.ab,ti.
6 trial.ab,ti.
7 groups.ab,ti.
8 or/1-7
9 exp animals/
10 exp humans/
11 9 not (9 and 10)
12 8 not 11
13 exp amblyopia/
14 (amblyop$ or anopsi$).tw.
15 exp pupil disorders/
16 exp cataract/
17 cataract$.tw.
18 exp blepharoptosis/
19 (blepharoptosis or ptosis).tw.
20 exp vitreous hemorrhage/
21 ((haemorrhage$ or hemorrhage$) adj3 vitreous).tw.
22 exp hemangioma.capillary/
23 ((hemangioma or haemangioma) adj3 capillary).tw.
24 exp aphakia/
25 aphaki$.tw.
26 ((stimul$ or vision or visual or optical) adj3 deprivat$).tw.
27 ((scar$ or opac$ or degenerat$) adj3 cornea$).tw.
28 (media adj2 opacit$).tw.
29 or/13-28
30 exp sensory deprivation/
31 (patch$ or shield$).tw.
32 ((stimul$ or penalis$) adj3 optical$).tw.
33 ((stimul$ or penalis$) adj3 vis$).tw.
34 ((therap$ or treat$ or lens$ or complete$ or partial$) adj3 occlus$).tw.
35 ((therap$ or treat$ or lens$ or complete$ or partial$) adj3 pleoptic$).tw.
36 or/30-35
37 29 and 36
38 12 and 37
The search filter for trials at the beginning of the MEDLINE strategy was from the published paper by Glanville (Glanville 2006).

Appendix 3. EMBASE search strategy used on OVID up to November 2007

1 exp randomized controlled trial/
2 exp randomization/
3 exp double blind procedure/
4 exp single blind procedure/
5 random$.tw.
6 or/1-5
7 (animal or animal experiment).sh.
8 human.sh.
9 7 and 8
10 7 not 9
11 6 not 10
12 exp clinical trial/
13 (clin$ adj3 trial$).tw.
14 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15 exp placebo/
16 placebo$.tw.
17 random$.tw.
18 exp experimental design/
19 exp crossover procedure/
20 exp control group/
21 exp latin square design/
22 or/12-21
23 22 not 10
24 23 not 11
25 exp comparative study/
26 exp evaluation/
27 exp prospective study/
28 (control$ or prospectiv$ or volunteer$).tw.
29 or/25-28
30 29 not 10
31 30 not (11 or 23)
32 11 or 24 or 31
33 exp amblyopia/
34 (amblyop$ or anopsi$).tw.
35 exp pupil disorders/
36 exp cataract/
37 cataract$.tw.
38 exp blepharoptosis/
39 (blepharoptosis or ptosis).tw.
40 exp vitreous hemorrhage/
41 ((haemorrhage$ or hemorrhage$) adj3 vitreous).tw.
42 exp hemangiomacapillary/
43 ((hemangiom a or haemangiom a) adj3 capillary).tw.
44 exp aphakia/
45 aphaki$.tw.
46 ((stimul$ or vision or visual or optical) adj3 deprivat$).tw.
47 ((scar$ or opac$ or degenerat$) adj3 cornea$).tw.
48 (media adj2 opacit$).tw.
49 or/33-48
50 exp sensory deprivation/
51 (patch$ or shi eld$).tw.
52 ((stimul$ or penalis$) adj3 optical$).tw.
53 ((stimul$ or penalis$) adj3 vis$).tw.
54 ((therap$ or treat$ or lens$ or complete$ or partial$) adj3 occlus$).tw.
55 ((therap$ or treat$ or lens$ or complete$ or partial$) adj3 pleoptic$).tw.
56 or/50-55
57 49 and 56
58 32 and 57

Appendix 4. LILACS search terms used on 3 December 2007
amblyop$ and stimul$ or vis$ or viz$ optic$ and deprivat$

WHAT'S NEW
Last assessed as up-to-date: 26 November 2007.
**Date** | **Event** | **Description**
--- | --- | ---
13 October 2008 | Amended | Converted to new review format.

**HISTORY**

Protocol first published: Issue 1, 2005

Review first published: Issue 3, 2006

**Date** | **Event** | **Description**
--- | --- | ---
27 November 2007 | New search has been performed | An update search was done in November 2007; 6 RCTs were excluded but no new trials were included in the review
16 March 2006 | New citation required and conclusions have changed | Substantive amendment

**CONTRIBUTIONS OF AUTHORS**

Conceiving the review: AA

Designing the review: AA

Co-ordinating the review: AA, SSV

Data collection for the review

- Designing electronic search strategies: CEVG
- Undertaking searches: CEVG
- Screening search results: AA, CP, SSV
- Organizing retrieval of papers: AA, CP, SSV
- Screening retrieved papers against inclusion criteria: AA, CP, SSV, SH
- Appraising quality of papers: NA
- Extracting data from papers: NA
- Writing to authors of papers for additional information: NA
- Providing additional data about papers: NA
- Obtaining and screening data on unpublished studies: NA

Data management for the review

- Entering data into RevMan: NA
- Analysis of data: NA
Interpretation of data
- Providing a methodological perspective: SSV, SH
- Providing a clinical perspective: AA, CP, SH
- Providing a policy perspective: AA, CP, SH
- Providing a consumer perspective: AA, CP, SH
Writing the review: AA, CP, SH, SSV
Providing general advice on the review: AA, CP, SH, SSV
Securing funding for the review: SSV
Performing previous work that was the foundation of the current study: AA, CP, SH

DECLARATIONS OF INTEREST
None known

SOURCES OF SUPPORT

Internal sources
- Michigan State University, Department of Neurology and Ophthalmology, USA.
- Brown University, USA.
- Johns Hopkins University, USA.

External sources
- Contract N01-EY-2-1003, National Eye Institute, National Institutes of Health, USA.
- Sightsavers International, UK.
- Christian Blind Mission, Germany.

INDEX TERMS

Medical Subject Headings (MeSH)
* Occlusive Dressings; Amblyopia [etiologic; *therapy]; Blepharoptosis [complications]; Cataract [complications]; Treatment Outcome

MeSH check words
Child, Preschool; Humans; Infant