Cochrane Library

Cochrane Database of Systematic Reviews

Active treatments for unilateral amblyopia in adults (Protocol)

Suttle C, Conway M, Asper L, Shah R, Khuu S, Lawrenson JG

Suttle C, Conway M, Asper L, Shah R, Khuu S, Lawrenson JG.
Active treatments for unilateral amblyopia in adults (Protocol).
Cochrane Database of Systematic Reviews 2025, Issue 9. Art. No.: CD016116.
DOI: 10.1002/14651858.CD016116.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Protocol]

Active treatments for unilateral amblyopia in adults

Catherine Suttle[1a], Miriam Conway[1], Lisa Asper[2], Rakhee Shah[1], Sieu Khuu[2], John G Lawrenson[1]

[1]Centre for Applied Vision Research, School of Health and Medical Sciences, City St George's, University of London, London, UK. [2]UNSW Sydney, Sydney, Australia

[a]ORCID iD: https://orcid.org/0000-0001-8694-195X

Contact: Catherine Suttle, catherine.suttle.1@city.ac.uk.

Editorial group: Cochrane Central Editorial Service.
Publication status and date: New, published in Issue 9, 2025.

Citation: Suttle C, Conway M, Asper L, Shah R, Khuu S, Lawrenson JG. Active treatments for unilateral amblyopia in adults (Protocol). *Cochrane Database of Systematic Reviews* 2025, Issue 9. Art. No.: CD016116. DOI: 10.1002/14651858.CD016116.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of monocular and binocular (known as dichoptic) active treatments for unilateral amblyopia in adults.

BACKGROUND

Description of the condition

Amblyopia is a visual disorder which usually occurs unilaterally (affecting vision in only one eye) and affects about 1% to 5% of people globally [1]. It arises during infancy and childhood, and if untreated during these periods, prognosis is generally considered poor. This is because the visual system has neural plasticity as it develops; the neural pathways transmitting information between the eyes and brain are modifiable according to their environment and their stimulation [2]. Until recently, this plasticity was believed to diminish or disappear entirely by adulthood.

If visual stimulation during infancy and childhood is degraded in the form of blurred vision, such as by uncorrected refractive error, visual pathway development may be adversely affected. In particular, if the refractive error is anisometropic (significantly different between the two eyes), the eye with greater error may become amblyopic. Since we have two eyes, while the pathway relating to one eye is degraded, that of the fellow eye with normal stimulation (less or no uncorrected refractive error) is not affected in the same way. In addition to refractive error, amblyopia may be caused by a range of factors affecting visual stimulation in early life. A common cause is unilateral constant manifest strabismus (eye turn), in which the stimulation from the deviating eye is suppressed to avoid diplopia (double vision). Less commonly, deprivation amblyopia arises if the passage of light to the eye is impeded, such as in childhood cataract. In all causes, the effect is that the eye with the relatively degraded stimulation develops poorer vision than the fellow eye with better stimulation [3].

Conventionally, unilateral amblyopia is defined clinically as a two-line difference between visual acuity of the right and left eye, with an amblyogenic factor (such as history of childhood strabismus, as indicated above) and no other factors (such as disease or injury) that might explain the reduced vision [4]. Although visual acuity is used in this definition, it does not fully describe the visual deficit, and people may experience visual distortion, reduced perceived contrast, or both, when viewing with the amblyopic eye [5].

When viewing binocularly, the normal visual system has the advantage of good depth perception, important for many everyday tasks, leisure activities, and for some occupations. Unilateral amblyopes commonly suppress or 'ignore' the input from the amblyopic eye, so depth perception is often reduced. In addition, function of both eyes may be vital if one of them becomes affected by pathology or injury. This is a particularly important consideration in amblyopia, since the risk of visual impairment or blindness due to loss of the non-amblyopic eye has been found to be significantly higher than in the normal population [6, 7]. Therefore, treatment of amblyopia is important for a range of reasons, including optimisation of depth perception and minimisation of the risk of vision loss [8].

Description of the intervention and how it might work

Treatment of childhood amblyopia has for many years involved spectacle correction and occlusion or blurring of the non-amblyopic eye [9]. Blurring may be achieved by 'atropine penalisation', regular instillation of atropine eye drops to the non-amblyopic eye to prevent accurate focus. Both methods allow the amblyopic eye periods of time to develop and refine its neural connections along the visual pathway unimpeded by competition from the other eye. A Cochrane review found that both methods achieve similar visual acuity improvements [10]. However, the visual system has far less plasticity in older children and adults than in infants and young children and is therefore less amenable to treatment [11]. In addition, research suggests an age-related increase in the necessary duration of occlusion, which may reduce the feasibility and appeal of treatment for adults [12]. Thus, treatment of amblyopia in adults has been considered unfeasible and is not routinely practised clinically. Since amblyopia occurs in about 1% to 5% of adults [1], there may be many individuals globally who would benefit from an effective treatment (due to their career choice, or loss of vision in the non-amblyopic eye). Reports of visual improvement in the amblyopic eyes of adults who have developed pathology in their fellow eye suggest that treatment may indeed be possible at any age [13], and numerous studies have investigated amblyopia treatment in adults or in older children, beyond periods of neural plasticity (reviewed by Levi 2020) [14]. Those studies have largely focused on developing and testing the efficacy of methods that may be considered active (requiring the individual to undergo an activity) as opposed to passive (such as occlusion or wearing spectacles, requiring no specific activity).

Active treatment takes several forms, all of which are based on the concept of perceptual learning, in which visual function improves following a period of training on a visual task. Improvements of this kind have been demonstrated after training on letter identification, face recognition, movement detection, contrast discrimination, and other tasks. In the context of amblyopia, active methods involve visual tasks ranging from paper-based dot-to-dot or similar activities, to electronic tasks such as video games. In some cases, tasks are carried out while the non-amblyopic eye is occluded, so active and passive treatments are applied simultaneously. Other tasks involve binocular vision, with no occlusion. The binocular methods used in active amblyopia treatment are known as 'dichoptic' methods, indicating that the right and left eye are simultaneously stimulated using different images. Many dichoptic treatments involve central parts of the visual scene being viewed by the amblyopic eye, while peripheral parts are viewed by the fellow eye. This differential stimulation of each eye is achieved using filters or goggles which are worn over any required spectacle correction. Some dichoptic methods involve adjustment of the right and left eye stimuli so that their perceived contrast is equal, to discourage suppression of the amblyopic eye (see Papageorgiou 2019 for a review [11]) and reduce the effect of 'interference' of the fellow eye on the amblyopic eye. Active methods of amblyopia treatment, the subject of our review, may be carried out in a clinic under the supervision of an eye care practitioner such as an optometrist, or may be carried out in the individual's home. The frequency and duration of training sessions varies, but typically, studies that have shown the efficacy of active methods have involved one to two hours of training per day over one to ten weeks [15, 16].

Passive amblyopia treatment using occlusion only is intended to prevent stimulation of the non-amblyopic eye and allow the amblyopic eye, without competition from the fellow eye, to more fully connect with the visual pathway. However, occlusion may be associated with poor adherence, limiting its effectiveness and risking the long-term negative outcome of reduced self-esteem [8, 17]. In addition, occlusion treatment requires a regular, long-term commitment with the patch being worn for two to six hours

per day over a period of four to six months [18]. Active forms of amblyopia treatment were introduced to improve adherence and enhance outcomes, and are each intended to work in different ways. As outlined above, a common characteristic of the amblyopic visual system is that neural activity in response to stimulation of the amblyopic eye is suppressed, and in this state binocular stimulation may not be helpful. Therefore, as indicated above, active dichoptic methods may involve the amblyopic eye being stimulated by central targets (imaged on the central, most sensitive part of the eye) while the fellow eye is stimulated by more peripheral parts of the visual scene. These are perceived as a whole visual scene so that the two eyes are functioning together with the aim of improving binocular as well as monocular vision. Some dichoptic methods also involve matching the right and left eyes' perceived contrast levels so that amblyopic eye suppression is lifted to enhance that eye's input to and connection with the visual cortex [19]. Active monocular methods involve occlusion of the non-amblyopic eye, while the amblyopic eye is stimulated by patterns and tasks ranging from simple paper-based puzzles [20], to computer-based grating detection, discrimination of shapes, or face recognition. The computer-based methods may be presented in a video game format, and in fact, commercially available video games have been used in amblyopia treatment research [21]. Active methods are intended to reduce the total time needed for treatment, reduce the possibility of negative psychosocial outcomes of occlusion (such as low social acceptance), and to improve effectiveness by increasing treatment adherence and reducing suppression of the amblyopic eye.

The neural mechanism by which such treatments may work has been investigated and involves a reduction in neural noise (activity other than the response to the stimulus) and an increase in sampling efficiency (neural response to spatial detail in the stimulus) [22]. The mechanism varies between amblyopic individuals, perhaps due to the range of causes and ages of onset of the condition [22].

Why it is important to do this review

A 2019 systematic review estimated that 99.2 million people were amblyopic worldwide, with an overall prevalence of 1.44%, 3.29% in adults over 20 years of age, and less than 2% in children under 10 years [1]. While prevalence estimates depend on the criteria used by included studies, these values demonstrate that amblyopia occurs in significant numbers worldwide. The review analysis predicted an increase in the amblyopic population to 175.2 million by 2030 and 221.9 million by 2040. Adults with amblyopia may want to improve vision in their amblyopic eye due to vision requirements in their target profession or reduced vision in their non-amblyopic eye. In addition, as outlined above, amblyopia treatment may decrease the risk of visual impairment or blindness due to loss of vision in the fellow eye. Active treatment methods have been developed and tested in numerous studies, but their safety and effectiveness for adult amblyopia treatment remains questionable, with no clear guidelines and limited high level evidence. For example, the most recent American Academy of Ophthalmology Preferred Practice Pattern guidelines, referring to treatment of childhood and adult amblyopia, state that research on dichoptic treatment is 'ongoing' and will be used to 'delineate use of binocular therapy for treatment of amblyopia' [4].

Questions of safety are related to the difference in visual perception between the two eyes. When viewing a target with both eyes, the level and quality of vision depends on that of the non-amblyopic eye, with little or no contribution from the amblyopic eye. This is because input from the amblyopic eye is usually suppressed so that a blurred or diplopic (doubled) image is not perceived. A goal of active binocular or dichoptic treatment for amblyopia is to lift this suppression, but if this occurs, the amblyopic eye begins to contribute to binocular, everyday vision, and adverse effects such as diplopia may be experienced. Further, due to reduced plasticity, it may not be possible for the mature visual system to regain suppression, so these effects may be permanent. Despite a lack of clear evidence on efficacy and safety, such treatments are widely marketed and available for individuals to access online and use either in a clinic or at home [23]. The treatments are expensive (for example, about 300 pounds sterling (GBP) for a six-month program [24]), making access difficult for those with limited means, so it is important for individuals to know whether they would be beneficial. The efficacy of methods on which these treatments are based, such as perceptual learning, has been tested in numerous studies with a range of results, with some randomised, controlled trials reporting little or no difference in the outcomes (see Tsirlin 2015 for a systematic review and meta-analysis [25]).

In view of the high prevalence of unilateral amblyopia, its potential impact on affected individuals, and the lack of clarity on efficacy and safety of treatment in adults, this review is important as a source of robust, high-quality, regularly updated evidence.

OBJECTIVES

To assess the benefits and harms of monocular and binocular (known as dichoptic) active treatments for unilateral amblyopia in adults.

METHODS

Criteria for considering studies for this review

Types of studies

The review will include randomised controlled studies on the efficacy of active treatments for unilateral amblyopia in adults. To avoid excluding potentially relevant data, we will also consider for inclusion quasi-randomised controlled studies (e.g. where participants are allocated using methods that are not truly random, such as by date of birth or medical record number).

Types of participants

Studies that include unilateral amblyopes, 18 years of age or older, will be eligible for inclusion in the review. We will place no restrictions on gender, ethnicity, severity of amblyopia, or amblyopia treatment history. For studies that include some eligible participants (such as a proportion of participants in our age range and some children), we will include the eligible data if published by the authors, or contact the authors to obtain these data. If we are unable to obtain this information, we will proceed with the available data. Studies including participants with anisometropic, strabismic, mixed (anisometropic and strabismic), or deprivation amblyopia (a less common cause of amblyopia due to occlusion such as cataract) will be eligible for inclusion. For this purpose, we define unilateral amblyopia as an interocular difference in letter acuity of at least two lines on a standard clinical chart, no pathology to explain this difference, and history of an amblyogenic factor.

Types of interventions

The review will include studies which, following optical treatment (a period of time, usually at least three to four months, wearing full refractive correction), have trialled monocular or dichoptic active treatments for amblyopia. These treatments require active involvement by the participant, such as playing a video game or performing a paper-based activity (e.g. a crossword), as opposed to more passive treatments such as eye patching, in which participants are required to do no particular activity. The requirement for optical treatment ensures that any improvements in vision are not explained simply by wearing spectacles [26]. Monocular active treatments may be carried out using the amblyopic eye while the non-amblyopic eye is occluded or blurred, the latter by pharmacological penalisation (cycloplegic eye drops) or optical (e.g. blurring lens) means. Studies using the following monocular and dichoptic active treatments used alone or in combination will be eligible for inclusion in the review.

- Monocular: active treatments including paper-based activities such as drawing or computer-based perceptual learning with any visual task such as pattern detection, discrimination, or face recognition.
- Dichoptic: active binocular treatments involving the use of viewing systems such as goggles which allow different stimuli to be presented to each eye. Active tasks range widely and may include object detection or computer gaming with a variety of designs, their common feature being that both eyes must be used together to complete the task successfully.

Comparator treatments may include occlusion, blurring (both passive), no treatment, or sham active treatment such as watching movies.

There are no restrictions on the duration or frequency of treatment.

Outcome measures

In selecting our outcome measures, we drew on the body of literature on amblyopia treatment in adults and a core outcome set for amblyopia [27, 28].

Critical outcomes

We will assess the mean change from baseline in monocular best corrected visual acuity (BCVA) using standard logMAR (logarithm of the minimum angle of resolution) or Snellen charts at conclusion of treatment, up to six months after conclusion of treatment (T1), and at 12 to 24 months after conclusion of treatment (T2). This will allow us to assess whether any treatment effect is sustained in the short and longer term, respectively.

Important outcomes

We will assess the following important outcomes as change from baseline to conclusion of treatment, and any further change up to six months (T1) and 12 to 24 months (T2) after conclusion of treatment.

- Change in binocular function from baseline measured by mean difference in stereoacuity according to the stereopsis test used in the study.
- Other tests of visual function such as mean change from baseline in contrast sensitivity or contour perception. These measurements are based on the participant's ability to discriminate low contrast or similar shapes. The unit of measurement of contrast sensitivity is the reciprocal of the contrast threshold, while contour perception may be measured in a number of ways, including the smallest perceptible change in orientation of part of a given shape. Measurements of this kind are used in some, but not most, studies on amblyopia treatment.
- Mean change from baseline in quality of life (using any validated tool). A range of tools have been developed and validated for assessment of vision-related quality of life, such as the Visual Function Questionnaire-39 (VFQ-39, with 39 items) and the National Eye Institute Visual Function Questionnaire-25 (NEIVFQ-25, with 25 items). Each provides a percentage score, but they include different sets of domains, so they may reflect different aspects of life. In the event that we find eligible studies that assess participants' quality of life, we will consider whether the quality of life measurements can be included in any meta-analysis.
- Adherence to treatment will be assessed over the treatment period specified in the study.
- Harms, including diplopia, perceived superimposition of right and left eye images of different clarity, or aesthenopic symptoms (related to poorly compensated strabismus, for example) arising by the end of the study.

Search methods for identification of studies

Electronic searches

We will search the following databases:

- Cochrane Central Register of Controlled Trials via OVID Online from 1999;
- MEDLINE via OVID Online from 1946;
- Embase via OVID Online from 1974;
- Allied and Complementary Medicine database (AMED) via OVID Online from 1985;
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) via EBSCOHost from 1961;
- Latin American and Caribbean Health Sciences Literature via WHO Global Index Medicus from 1986;
- Web of Science via Clarivate from 1970;
- ClinicalTrials.gov via National Library of Medicine from 2000;
- International Clinical Trials Registry Platform via the World Health Organization (WHO) from 2005.

See Supplementary material 1 for the MEDLINE search strategy.

For grey literature, we will search the Bielefeld Academic Search Engine and doctoral thesis registries DART and EThOS. We will impose no restrictions on language or publication date. An Information Specialist will perform the searches and remove duplicates.

Searching other resources

We will search the reference lists of the included studies and any relevant systematic reviews to identify additional studies meeting the inclusion criteria. We will contact the authors for missing data if indicated.

Prior to extracting data from the included studies, we will search for errata or retractions related to the studies using PubMed and

Retraction Watch. If we identify any, we will follow Cochrane guidance on managing potentially problematic studies [29].

Data collection and analysis

Selection of studies

The City St Georges, University of London librarian will perform the search, remove duplicates, and upload the titles to Covidence [30]. Two review authors will independently screen the titles and abstracts using the specified eligibility criteria, categorising each as Yes, No, or Maybe. We will retrieve the full texts of all titles and abstracts categorised as Yes or Maybe, and two review authors will independently review each article and classify each as 'include' or 'exclude' and document reasons for exclusion. We will resolve any disagreement between authors on how to categorise a study by discussion based on the predefined criteria.

Data extraction and management

Two authors will independently extract the data listed below using a pre-piloted data extraction form developed and used within Covidence [30], following guidelines in Chapter 5 of the *Cochrane Handbook for Systematic Reviews of Interventions* [31].

- Geographical location of study
- Inclusion and exclusion criteria
- Participant mean age, age range, gender, and ethnicity
- Number of participants randomised
- Active treatment method
- Comparator
- Duration of treatment
- Sustainability/durability of treatment
- Critical and important outcomes and follow-up periods
- Exclusions and losses to follow-up
- Conflicts of interest
- Funding

The form will include the following for extraction where available, to allow consideration of factors that contribute to health inequities [32]: participant location of residence, occupation, religion, disability, education, socioeconomic status, and social capital.

We will contact study investigators to request clarification or missing information. If the investigator does not provide data or clarification within eight weeks, we will proceed with the data available.

Risk of bias assessment in included studies

Working independently, two review authors will assess the risk of bias in included studies using the Cochrane risk of bias 2 (RoB 2) tool for randomised trials [33], following the instructions outlined in the *Cochrane Handbook* [34]. We will assess the risk of bias for the critical and important outcomes (see Outcome measures). The RoB 2 tool includes signalling questions relating to bias arising from the following domains:

- the randomisation process;
- deviations from intended interventions;
- missing outcome data;
- bias in the measurement of the outcome;
- bias in the selection of the reported result.

Using signalling questions, we will assess each domain as low risk, 'some concerns', or high risk. We will use the RoB 2 algorithm to assign the overall risk of bias based on judgements for the five domains.

We will resolve disagreement in the RoB 2 assessments by discussion and consensus.

For all outcomes, we will assess the effect of assignment to intervention (the intention-to-treat effect).

Measures of treatment effect

We will conduct analyses following the approach described in Chapter 10 of the *Cochrane Handbook* [35].

For continuous outcomes (e.g. BCVA and stereoacuity), we will extract data on the change in treatment effects from baseline to our pre-defined timeframes as means and standard deviations (SDs). We will express treatment effects as mean difference with 95% confidence intervals. Note that Snellen or decimal visual acuity scores, which are measured on ordinal scales, should not be averaged and then converted to logMAR, as this can lead to inaccurate results [36]. Instead, individual visual acuity measurements should first be converted to logMAR values before calculating the mean. We anticipate that authors of the included studies will have followed this procedure. If not, we will contact the study authors to request individual participant data in order to correctly compute the average change in logMAR units. While our critical and important outcomes are changes in visual function over time (e.g. mean difference in acuity from baseline), if eligible studies have reported final (post-treatment) measures only, we will include the means and SDs of these measures in meta-analysis, presented as a subgroup separate from mean difference (change) data for clarity.

For dichotomous outcomes (e.g. adverse events), we will extract the numbers of events and participants in each study group to estimate the risk ratios (RRs) and 95% confidence intervals (CIs).

Unit of analysis issues

The primary unit of analysis will be the participant with observation/measurement of one amblyopic eye at baseline and a specified time point. We may find multi-arm RCTs that are relevant to our research question, and in this case, we will make pairwise comparisons of only those groups of individuals relevant to this review. Where appropriate, we will consider combining groups to create a single pairwise comparison to avoid a unit-of-analysis error for a study that could contribute multiple, correlated data.

Dealing with missing data

We will not attempt to impute missing data; we will analyse available case data only and assume that data are missing at random. We plan to obtain missing data by contacting the authors of included papers; if we do not receive a response within eight weeks, we will analyse the studies based on available data.

Reporting bias assessment

We plan to assess selective or incomplete reporting using the RoB 2 tool. If we include at least 10 studies in our planned meta-analysis, we will assess potential publication bias using funnel plots, following the guidelines in Chapter 13 of the *Cochrane Handbook*. We plan to conduct statistical tests for funnel plot asymmetry, such as Egger's test or Harbord's test, where appropriate [37, 38].

Synthesis methods

We will compare active (dichoptic or monocular, computer or paper-based) treatment to a control or standard care (such as patching or no treatment). We will conduct meta-analysis if we judge participants, interventions, and comparisons are reasonably similar. We will conduct a random-effects meta-analysis using Review Manager (RevMan) [39], as we anticipate clinical heterogeneity. To estimate between-study variance (heterogeneity), we will use the restricted maximum likelihood (REML) method, in line with the updated guidance in the *Cochrane Handbook* [35]. If we include more than two studies in the analysis, we will calculate the confidence interval for the summary effect using the Hartung-Knapp-Sidik-Jonkman method, as suggested in the *Cochrane Handbook,* Chapter 10 [35]. If there are two trials, we will use a fixed-effect model. We will use other synthesis methods if necessary (for example, if search and extraction processes identify limited data), following Cochrane guidance [40].

Investigation of heterogeneity and subgroup analysis

We plan to investigate statistical heterogeneity according to the guidelines provided in Chapter 10 of the *Cochrane Handbook* [35]. We will assess clinical and methodological heterogeneity in meta-analysis by comparing the characteristics of included studies and by visual inspection of forest plots. We will assess statistical heterogeneity quantitatively using the Chi^2 test and the I^2 values. The latter provides an estimate of the percentage of the data variability that is due to heterogeneity rather than chance. We will consider I^2 values between 0% to 40% as not important; 30% to 60% as representing moderate heterogeneity; 50% to 90%, substantial heterogeneity; 75% to 100%, considerable heterogeneity.

If sufficient studies are available, we plan to explore the heterogeneity through subgroup analysis via a formal test of heterogeneity to assess whether differences between subgroups are likely to be explained by chance. Subject to sufficient data being available, we will analyse the following subgroups.

- Aetiology of amblyopia: strabismus; anisometropia; mixed (strabismus and anisometropia); deprivation
- Participant age: dependent on age groups in included studies but may include groups categorised as 18 to 30 years, older than 30 to 50 years, and older than 50 years
- Treatment type: possible subgroups if sufficient studies are available include home-based versus practice- or lab-based treatment, frequency of intervention (one versus two or more hours of gaming per week), and types of video game such as action-adventure video games (e.g. first-person shooter games) versus puzzle video activities (e.g. Sudoku).

Equity-related assessment

The subject of this review, amblyopia and its treatment, may impact people differentially due to variations in access to treatment, including remote location of residence, disability, inability to take time off from work, and lack of awareness of the condition and treatment (an aspect of education). More pertinent to this review, active treatment is unlikely to be available free of charge and may be prohibitively expensive (see Background), so may be less accessible to those with low socioeconomic status. We therefore plan to apply the PRO EDI tool, which is based on the PROGRESS framework, to ensure that we explicitly consider factors (participants' geographical location of residence, race/culture, disability, occupation, sex, religion, education, socioeconomic status, and social capital) that contribute to health inequities [32]. We will complete a PRO EDI participant characteristics table for each study using the available interpretation guidance [41].

Sensitivity analysis

We will conduct sensitivity analysis where appropriate; for example, to assess the impact of including studies in which not all participants are within our specified age range (see Types of participants) or those found to be at high risk of bias.

Certainty of the evidence assessment

Two review authors will independently assess the certainty of the evidence for comparisons of active treatments (computer-based monocular therapy, dichoptic therapy, or paper-based therapy) versus control or standard therapy for the following outcomes, which will be reported in a summary of findings table.

- Mean change in BCVA at conclusion of treatment
- Mean change in BCVA up to six months after conclusion of treatment
- Mean change in BCVA 12 to 24 months after conclusion of treatment
- Mean change in stereoacuity at conclusion of treatment
- Mean change in stereoacuity up to six months after conclusion of treatment
- Mean change in stereoacuity 12 to 24 months after conclusion of treatment
- Harms (such as diplopia, see Important outcomes) at conclusion of treatment

In the certainty of evidence evaluation, we will consider factors such as risk of bias, inconsistency, imprecision in effect estimates, indirectness of evidence, and potential publication bias [42]. If the two review authors disagree, a third author will resolve the dispute. We will initially rate the certainty of evidence from randomised controlled trials (RCTs) as high, but we may downgrade it by up to three levels depending on the severity of study limitations. We will present the results in tables generated using GRADEpro software (GRADEpro GDT) [43], following the guidance in Chapter 14 of the *Cochrane Handbook* [44]. We will report estimates from the meta-analysis according to GRADE methods.

Consumer involvement

Due to limited resources, consumers will not be involved in this review, although critical and important outcomes are based on a core outcome set that included patients in its development [28].

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016116.

Supplementary material 1 Search strategies

ADDITIONAL INFORMATION

Acknowledgements

We are grateful to Stephen O'Driscoll and the City St George's, University of London Library for discussions on search strategies and for providing the MEDLINE search strategy for this protocol.

Editorial and peer-reviewer contributions

Cochrane supported the authors in the development of this protocol.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Jennifer R Evans, Associate Professor, International Centre for Eye Health, London School of Hygiene & Tropical Medicine (LSHTM);
- Managing Editor (provided editorial guidance to authors, edited the article): Anupa Shah, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, selected peer reviewers, collated peer-reviewer comments and supported editorial team): Andrew Savage, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Faith Armitage, Cochrane Central Production Service;
- Peer-reviewers (provided comments and recommended an editorial decision): Mario Triosi (patient and public review); Tom Patterson, Cochrane Evidence Production and Methods Directorate (methods review); Jo Platt, Central Editorial Information Specialist (search review).

Contributions of authors

The review was conceived by author CS. Authors LA, CS, MC, and RS were involved in writing the Background section. Authors SK, JL, CS, and LA were involved in writing the data analysis sections of the Methods in the main text, with assistance from a university librarian on the search strategy. CS, RS, and MC were involved in writing other aspects of the Methods. CS, LA, and JL wrote the review criteria and analyses sections.

Declarations of interest

John Lawrenson received grant income from the National Institute for Health Research (NIHR) and the UK College of Optometrists for projects outside the submitted review. He is employed by his institution and is a Senior Editor with Cochrane Eyes and Vision, but had no involvement in the editorial process for this review protocol.

Catherine Suttle and Lisa Asper were co-authors on a non-randomised study (doi: 10.1016/j.visres.2006.08.017) related to amblyopia treatment.

Catherine Suttle authored a narrative review (doi: 10.1111/j.1444-0938.2010.00486.x) on active treatments for amblyopia, and works as an optometrist in community practice.

Miriam Conway works as an orthoptist at City St Georges, University of London.

Sources of support

Internal sources

- City St George's, University of London, Library, UK

  University librarian has committed to assist with searches for this review.

External sources

- No external source of support, Other

  No external source

Registration and protocol

Cochrane approved the proposal for this review in January 2024.

Data, code and other materials

Data sharing is not applicable to this article as it is a protocol, so no datasets were generated or analysed.

REFERENCES

1. Fu Z, Hong H, Su Z, Lou B, Pan C, Liu J. Global prevalence of amblyopia and disease burden projections through 2040: a systematic review and meta-analysis. *British Journal of Ophthalmology* 2019;**104**:1164-70. [DOI: 10.1136/bjophthalmol-2019-314759]

2. Tailor VK, Schwarzkopf DS, Dahlmann-Noor AH. Neuroplasticy and amblyopia: vision at the balance point. *Current Opinion in Neurology* 2017;**30**:74-83. [DOI: 10.1097/WCO.0000000000000413]

3. Maurer D, McKee SP. Classification and diversity of amblyopia. *Visual Neuroscience* 2018;**35**:e012. [DOI: 10.1017/S0952523817000190]

4. American Academy of Ophthalmology. Amblyopia Preferred Practice Pattern (PPP) 2022 - Updated 2024. https://www.aao.org/education/preferred-practice-pattern/amblyopia-ppp-2022; December 2022 (accessed 16 May 2024).

5. Barrett BT, Pacey IE, Bradley A, Thibos LN, Morrill P. Nonveridical visual perception in human amblyopia. *Investigative Ophthalmology and Visual Science* 2003;**44**:1555-67. [DOI: 10.1167/iovs.02-0515]

6. Tommila V, Tarkkanen A. Incidence of loss of vision in the healthy eye in amblyopia. *British Journal of Ophthalmology* 1981;**65**:575-7. [DOI: 10.1136/bjo.65.8.575]

7. Van Leeuwen R, Eijkemans MJ, Vingerling JR, Hofman A, De Jong PT, Simonsz JH. Risk of bilateral visual impairment in individuals with amblyopia: the Rotterdam study. *British Journal of Ophthalmology* 2007;**91**:1450-1. [DOI: https://doi.org/10.1136/bjo.2006.113670]

8. Webber AL. The functional impact of amblyopia. *Clinical and Experimental Optometry* 2018;**101**:443-50. [DOI: 10.1111/cxo.12663]

9. Loudon SE, Simonsz SJ. The history of the treatment of amblyopia. *Strabismus* 2005;**13**:93-106. [DOI: 10.1080/09273970590949818]

10. Li T, Qureshi R, Taylor K. Conventional occlusion versus pharmacologic penalization for amblyopia. *Cochrane Database of Systematic Reviews* 2019, Issue 8. Art. No: CD006460. [DOI: 10.1002/14651858.CD006460.pub3]

11. Papageorgiou E, Asproudis I, Maconachie G, Tsironi EE, Gottlob I. The treatment of amblyopia: current practice and emerging trends. *Graefes Archive of Clinical and Experimental Ophthalmology* 2019;**257**:1061-78. [DOI: 10.1007/s00417-019-04254-w]

12. Stewart CE, Moseley MJ, Stephens DA, Fielder AR. Treatment dose-response in amblyopia therapy: the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). *Investigative Ophthalmology and Visual Science* 2004;**45**:3048-54. [DOI: 10.1167/iovs.04-0250]

13. El Mallah MK, Chakravarthy U, Hart PM. Amblyopia: is visual loss permanent? *British Journal of Ophthalmology* 2000;**84**:952-56. [DOI: 10.1136/bjo.84.9.952]

14. Levi DM. Rethinking amblyopia. *Vision Research* 2020;**176**:118-29. [DOI: 10.1016/j.visres.2020.07.014]

15. Hess RF, Thompson B, Black JM, Machara G, Zhang P, Bobier WR, et al. An iPod treatment of amblyopia: an updated binocular approach. *Optometry* 2012;**83**:87-94.

16. Vedamurthy I, Nahum M, Huang SJ, Zheng F, Bayliss J, Bavelier D, et al. A dichoptic custom-made action video game as a treatment for adult amblyopia. *Vision Research* 2015;**114**:173-87. [DOI: 10.1016/j.visres.2015.04.008]

17. Stewart CE, Moseley MJ, Fielder AR, Stephens DA. Refractive adaptation in amblyopia: quantification of effect and implications for practice. *British Journal of Ophthalmology* 2004;**88**:1552-6. [DOI: 10.1136/bjo.2004.044214]

18. Chen AM, Cotter SA. The amblyopia treatment studies: implications for clinical practice. *Advances in Ophthalmology and Optometry* 2016;**1**:287-305. [DOI: 10.1016/j.yaoo.2016.03.007]

19. Hess RF, Mansouri B, Thompson B. A binocular approach to treating amblyopia: antisuppression therapy. *Optometry and Vision Science* 2010;**87**:697-704. [DOI: 10.1097/OPX.0b013e3181ea18e9]

20. Holmes JM, Lyon DW, Strauber MS. A randomized trial of near versus distance activities while patching for amblyopia in children aged 3 to less than 7 years. *Ophthalmology* 2008;**115**:2071-78. [DOI: 10.1016/j.ophtha.2008.06.031]

21. Li RW, Ngo C, Nguyen J, Levi DM. Video-game play induces plasticity in the visual system of adults with amblyopia. *PLoS Biology* 2011;**9**:e101135. [DOI: 10.1371/journal.pbio.1001135]

22. Li RW, Levi DM. Characterizing the mechanisms of improvement for position discrimination in adult amblyopia. *Journal of Vision* 2004;**4**:476-87. [DOI: 10.1167/4.6.7]

23. Accuvision. Amblyopia (lazy eye) treatment. https://www.accuvision.co.uk/amblyopia-treatment/ (accessed 9 November 2024).

24. AmblyoPlay. AmblyoPlay Vision Therapy Solution. https://www.amblyoplay.com/amblyoplay-vision-therapy-solution/ (accessed 7 March 2024).

25. Tsirlin I, Colma L, Goltz HC, Wong AM. Behavioral training as new treatment for adult amblyopia: a meta-analysis and systematic review. *Investigative Ophthalmology and Visual Science* 2015;**56**:4061-75. [DOI: 10.1167/iovs.15-16583]

26. Asper L, Watt K, Khuu S. Optical treatment of amblyopia: a systematic review and meta-analysis. *Clinical and Experimental Optometry* 2018;**101**:431-42. [DOI: 10.1111/cxo.12657]

27. Al Jabri S, Kirkham J, Row FJ. Development of a core outcome set for amblyopia, strabismus and ocular motility

disorders: a review to identify outcome measures. *BMC Ophthalmology* 2019;**47**:1-22. [DOI: https://doi.org/10.1186/s12886-019-1055-8]

28. Al Jabri S, Rowe FJ, Kirkham JJ. Core outcome set for three ophthalmic conditions: a healthcare professional and patient consensus on core outcome sets for amblyopia, ocular motility and strabismus (COSAMS study). *BMC Open* 2021;**11**:e042403. [DOI: 10.1136/bmjopen-2020-042403]

29. Cochrane. Cochrane Database of Systematic Reviews: editorial policies. https://www.cochranelibrary.com/cdsr/editorial-policies#problematic-studies (accessed 6 September 2025).

30. Covidence. Version accessed 12 November 2024. Melbourne, Australia: Veritas Health Innovation, 2024. Available at covidence.org.

31. Li T, Higgins JP, Deeks JJ, editor(s). Chapter 5: Collecting data. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from https://www.cochrane.org/authors/handbooks-and-manuals/handbook/archive/v6.4.

32. PRO EDI. Improving how equity, diversity and inclusion are handled in evidence synthesis. https://www.trialforge.org/trial-diversity/pro-edi/ (accessed 6 September 2025).

33. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

34. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from https://www.cochrane.org/authors/handbooks-and-manuals/handbook/archive/v6.4.

35. Deeks JJ, Higgins JP, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from https://www.cochrane.org/authors/handbooks-and-manuals/handbook/archive/v6.4.

36. Holladay JT. Proper method for calculating average visual acuity. *Journal of Refractive Surgery* 1997;**13**:388–91. [PMID: https://doi.org/10.3928/1081-597X-19970701-16]

37. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34.

38. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**:3443-57. [DOI: 10.1002/sim.2380]

39. Review Manager (RevMan). Version 9.10.0. The Cochrane Collaboration, 2025. Available at revman.cochrane.org.

40. McKenzie JE, Brennan SE. Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from https://www.cochrane.org/authors/handbooks-and-manuals/handbook/archive/v6.4.

41. PRO EDI. Using PRO EDI in a systematic review. PRO EDI interpretation guidance 25/4/2024. https://www.trialforge.org/wp-content/uploads/2024/04/PRO-EDI-interpretation-25-4-2024-Final.pdf (accessed 6 September 2025).

42. Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from https://gdt.gradepro.org/app/handbook/handbook.html 2013.

43. GRADEpro GDT. Version accessed 2025. Hamilton (ON): McMaster University (developed by Evidence Prime), 2025. Available at https://www.gradepro.org.

44. Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from https://www.cochrane.org/authors/handbooks-and-manuals/handbook/archive/v6.4.