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[Intervention Review]

Binocular versus standard occlusion or blurring treatment for unilateral amblyopia in children aged three to eight years

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ABSTRACT

Background

Current treatments for amblyopia in children, occlusion and pharmacological blurring, have had limited success, with less than two-thirds of children achieving good visual acuity of at least 0.20 logMAR in the amblyopic eye, limited improvement of stereopsis, and poor compliance. A new treatment approach, based on the dichoptic presentation of movies or computer games (images presented separately to each eye), may yield better results, as it aims to balance the input of visual information from each eye to the brain. Compliance may also improve with these more child-friendly treatment procedures.

Objectives

To determine whether binocular treatments in children aged three to eight years with unilateral amblyopia result in better visual outcomes than conventional occlusion or pharmacological blurring treatment.

Search methods

We searched the Cochrane Eyes and Vision Group Trials Register (last date of searches: 14 April 2015), the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 3), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to April 2015), EMBASE (January 1980 to April 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials.

Selection criteria

Two review authors independently screened the results of the search in order to identify studies that met the inclusion criteria of the review: randomised controlled trials (RCTs) that enrolled participants between the ages of three and eight years old with unilateral amblyopia, defined as best-corrected visual acuity (BCVA) worse than 0.200 logMAR in the amblyopic eye, and BCVA 0.200 logMAR or better in the fellow eye, in the presence of an amblyogenic risk factor such as anisometropia, strabismus, or both. Prior to enrolment, participants were to have undergone a cycloplegic refraction and comprehensive ophthalmic examination including fundal examination. In addition, participants had to have completed a period of optical treatment, if indicated, and BCVA in the amblyopic eye had to

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remain unchanged on two consecutive assessments despite reportedly good compliance with glasses wearing. Participants were not to have received any treatment other than optical treatment prior to enrolment. We planned to include any type of binocular viewing intervention; these could be delivered on different devices including computer monitors viewed with LCD shutter glasses or hand-held screens including mobile phone screens with lenticular prism overlay. Control groups were to have received standard amblyopia treatment; this could include occlusion or pharmacological blurring of the better-seeing eye. We planned to include full-time (all waking hours) and part-time (between 1 and 12 hours a day) occlusion regimens.

Data collection and analysis

We planned to use standard methodological procedures expected by The Cochrane Collaboration. We had planned to meta-analyse the primary outcome, that is mean distance BCVA in the amblyopic eye at 12 months after the cessation of treatment.

Main results

We could identify no RCTs in this subject area.

Authors' conclusions

Further research is required to allow decisions about implementation of binocular treatments for amblyopia in clinical practice. Currently there are no clinical trials offering standardised evidence of the safety and effectiveness of binocular treatments, but results from non-controlled cohort studies are encouraging. Future research should be conducted in the form of RCTs, using acknowledged methods of visual acuity and stereoacuity assessment with known reproducibility. Other important outcome measures include outcomes reported by users, compliance with treatment, and recurrence of amblyopia after cessation of treatment.

PLAIN LANGUAGE SUMMARY

Treatments to stimulate eye co-operation versus standard patching or blurring treatment for amblyopia (lazy eye) in children aged three to eight years

Review question

Binocular versus standard occlusion or blurring treatment for unilateral amblyopia in children aged three to eight years.

Background

At present, amblyopia ('lazy eye') in children is treated with glasses, followed by either patching or blurring of the better-seeing eye with atropine eyedrops. These treatments are not popular with children, and the amount of patching or eye drops that parents and carers can apply is often less than what was prescribed. Less than two-thirds of children develop normal vision in the lazy eye, and three-dimensional vision also often does not improve. A new treatment that matches the visual information shown to the better eye to the level of vision in the lazy eye may yield better results. Children may find this approach easier to tolerate, as during treatment they play computer games or watch movies through special lenses or on modified computers.

We reviewed published reports about the success of this new treatment, compared with standard patching or eye drop blurring treatment, in children aged three to eight years with lazy eye. We searched all standard sources of information. Two review authors independently reviewed the results of this search. We planned to include only studies reporting results from randomised controlled trials (RCTs), that is those studies comparing the new treatment with a standard treatment, and where children were assigned treatment groups at random (like flipping a coin). Our main result was that we could not identify any such studies. Future updates of this review may include new studies.

We conclude that more research is needed to allow decisions about the new treatment. Whilst we did not find any RCTs, results from studies that did not include a control group are encouraging. We recommend that future research be done in the form of RCTs, and that researchers use acknowledged tests of visual acuity and three-dimensional vision to report the results. It will also be important to publish observations reported by children and families, how much the treatment was used, and if and when the vision in the lazy eye got worse after the treatment was stopped.

Search date

The evidence is current to 14 April 2015.

BACKGROUND

Description of the condition

Unilateral amblyopia is a developmental defect of vision. With a prevalence of between 2% and 5%, it is the most common cause of reduced vision in one eye in children in the UK (Carlton 2008; daCunha 1961; McNeil 1955; Powell 2009; Rahi 2006), and the second most common cause of functional low vision for children in low income countries (Gilbert 2008). The most common risk factors for the development of amblyopia are anisometropia (a difference in refraction or glasses prescription between the two eyes) and strabismus (misalignment of the visual axes) (Barrett 2004; McKee 2003); rarely, congenital or early childhood cataracts or other opacities of the ocular media can give rise to amblyopia by deprivation.

The imbalance of input to the brain from the two eyes results in a range of amblyopic defects in vision and gaze stability. This includes the definitive reduction in acuity or resolution and abnormal binocular function (Levi 1985; McKee 2003), with suppression of information from the amblyopic eye and poor stereopsis (three-dimensional vision) (Birch 2013; Greenwood 2012; Hess 2014; McKee 2003). This reduction in stereopsis can be associated with reduced motor skills, both in children and adults (Grant 2007; Grant 2011; Hrisos 2006; Niechwiej-Szwedo 2011; O'Connor 2010; Webber 2008a). The precise cause of amblyopia further influences the pattern of visual deficits, with anisometropic amblyopia producing additional reductions in contrast sensitivity (McKee 2003), while strabismic amblyopia yields a range of spatial disruptions including vulnerability to crowding (the disruptive influence of clutter on recognition) in the central visual field (Greenwood 2012; Levi 1985; Levi 2008; Song 2014), perceptual distortions (Barrett 2003; Mirabella 2011), and deficits in positional acuity (the ability to localise the relative position of an object in space) (Levi 1986; Neri 2006). Higher-order deficits in global-motion processing (Husk 2012; Simmers 2003) and spatial attention (the ability to direct visual attention to certain locations in the visual field) (Ho 2006; Sharma 2000) have also been reported.

If amblyopia persists into adulthood, affected individuals may be unable to take up professions that require depth perception, such as piloting aeroplanes or balancing on rooftops. Accidents affecting the better-seeing eye can lead to a severe loss of quality of life and independence (Rahi 2002). Children treated for amblyopia have lower social acceptance scores than their peers (Webber 2008b). Low self esteem and negative self image as a result of amblyopia and its treatment are common, as are feelings of depression, frustration, and embarrassment (Dixon-Woods 2006; Sinha 2008).

The distinct pattern of deficits in anisometropic and strabismic amblyopia are probably associated with specific alterations to the visual system (Birch 2000; Levi 1982; Levi 1985). Anisometropia causes blurred vision in one eye and defocused input to the visual

cortex, leading to selective loss of neurons tuned to high spatial frequencies (high resolution) (Kiorpes 1998; Kiorpes 1999). In strabismus, on the other hand, the focus of retinal images is clear but misalignment of the visual axes disrupts the input to binocular cortical neurons, leading to fixation preference for one eye and subsequent visual deficits in the other eye (Birch 2013; Kiorpes 1998; Kiorpes 1999).

The cortical changes associated with amblyopia are not fully understood. Best characterised are the disruptions of neural activity in the primary visual cortex (V1) in the occipital lobe (Sengpiel 2006; Victor 1994; Vorobyov 2013; Wiesel 1963). The imbalance of visual inputs appears to induce a reallocation of V1 neurons; those receiving input from the amblyopic eye shift their responsiveness to the better-seeing eye (Kiorpes 1998; Kiorpes 1999; Li 2007; Sengpiel 2011; Vorobyov 2013; Wiesel 1963). In strabismus, although V1 neurons receive input from both eyes, the number of V1 neurons responding to stimuli from both eyes is smaller than normal, as binocular neurons in V1 only mature when receiving matching input from both eyes (Mitchell 2009). However, these disruptions to V1 function are probably insufficient to account for the extent of visual deficits in amblyopia (Kiorpes 1999). Indeed, processing in extrastriate areas is also altered (Barnes 2001; Conner 2007; Zhang 2011), which may account for the deficits in crowding (Anderson 2012), positional acuity (Maus 2010), and spatial attention (Corbetta 1995). Both ventral (object recognition) and dorsal (motion processing and action) pathways may be affected (Goodale 1992), perhaps differentially for early- versus late-onset amblyopia (Davis 2006).

The development of the functional architecture or maps of the visual cortex occurs in stages (Espinosa 2012; White 2007). The phase of maturation of the functional maps of the visual cortex is called the "critical period". This is because imbalance or disruption in the form of visual deprivation causes dramatic changes to the strength and organisation of the functional maps (Espinosa 2012). Different aspects of visual processing have slightly different critical periods, though they may overlap (Daw 1998; Harwerth 1986; White 2007). Thus, for area V1, the selective characteristics of these neurons are refined and matched to the input from both eyes at an earlier stage than those of extrastriate areas. Imbalance of visual input could nonetheless affect the maturation of the functional maps in a range of cortical areas.

For a long time it was held that the critical period for amblyopia treatment is identical to that of visual development, and that after the end of the critical period amblyopia cannot be induced, nor can established amblyopia be reversed (Assaf 1982; Wiesel 1963). However, newer observations have challenged the concept of a complete loss of plasticity in the visual processing areas of the brain even in adulthood, though the quality of plasticity in adulthood may differ from that in childhood (Sato 2008). Recent reports indicate that suppression can be reversed and vision successfully improved even after the end of the conventional critical period (Evans 2011; Levi 2005; Levi 2009), though early intervention may

still deliver better visual outcomes (Eibschitz-Tsimhoni 2000).

Description of the intervention

Amblyopia is treated by first correcting any refractive error with glasses (optical treatment, refractive adaptation). Improvement in vision is typically greatest in the first few weeks of wearing glasses but can continue for up to four months and more (Cotter 2006; Cotter 2007; Stewart 2004b; Taylor 2014; Wallace 2006). If amblyopia persists, current treatment consists of patching (occluding) the better-seeing eye for two or six hours a day, depending on the severity of the amblyopia (Awan 2005; Holmes 2003; Loudon 2006; Repka 2003; Stewart 2004a; Stewart 2004b; Stewart 2005; Taylor 2014). Successful occlusion treatment leads to an improvement of visual acuity and stereopsis (Stewart 2013; Wallace 2011). Pharmacological blurring of the better-seeing eye using atropine eye drops appears to be equivalent to occlusion treatment (Li 2009; PEDIG 2002; Repka 2009; Scheiman 2008).

The main drawbacks of occlusion and pharmacological blurring are poor adherence to treatment and suboptimal treatment outcomes. Lack of adherence to occlusion treatment is common. Patching the better-seeing eye functionally incapacitates the child, and children often attempt to remove the patch. Figures reported for adherence range from 41% to 57% (Awan 2005; Loudon 2006), with compliance decreasing with both an increase in severity of amblyopia and an increase in the prescribed daily dose of occlusion (Awan 2005; Loudon 2006; Moseley 1995; Stewart 2002). A questionnaire tool has been developed to measure the burden of treatment to the child and the family (Felius 2010; Holmes 2008). Whether "poor parent knowledge" of the condition contributes to poor adherence to treatment is controversial, though educational interventions may be beneficial (Dixon-Woods 2006; Loudon 2006).

Even with the best current treatment, only a fraction of children achieve near-normal visual acuity in the amblyopic eye. Using best-corrected visual acuity (BCVA) after optical treatment as the baseline, around 25% of eyes with severe amblyopia and 58% of eyes with moderate amblyopia improve to a level of 0.2 logMAR or better with occlusion treatment (Holmes 2003; Repka 2003). After treatment is discontinued, visual acuity typically regresses (Hertle 2007; Holmes 2004), and a low-dose maintenance treatment is often used to 'wean' children off treatment. Nevertheless, two years after stopping treatment, BCVA in the amblyopic eye can still be 2 lines worse than in the better-seeing eye (Repka 2005). Regression to pretreatment BCVA may occur in 30% of cases (Malik 1975). This leaves a significant proportion of children at risk of severe functional impairment and loss of quality of life should they lose vision in the better-seeing eye at any stage during their life. In addition, stereoacuity (three-dimensional vision) improves in less than half of children (Stewart 2013).

In order to develop treatments that at the same time appeal more to children and improve not only visual acuity in the amblyopic

eye but also promote binocularity, several groups have designed methods of simultaneous binocular visual stimulation.

To date, three systems have been developed, as follows.

1. Anti-suppression therapy

Anti-suppression therapy presents the visual scene with reduced contrast to the better-seeing eye and with normal contrast to the amblyopic eye (Hess 2010a; Hess 2010b; Hess 2011; Hess 2012; Hess 2013). This approach aims to balance V1 input to overcome interocular suppression. The difference in input to the two eyes (dichoptic presentation) can be achieved with a mirror haploscope (Hess 2010a; Hess 2010b), a head-mounted video display (Knox 2012), or lenticular prism overlays on tablet computers or screens of other hand-held devices (To 2011). The observer then has to carry out a task that requires combination of the information from the two eyes. With improving performance, the contrast of the visual scene shown to the better-seeing eye is gradually increased until contrast is equal for both eyes. A popular task is the Tetris game in which a series of falling blocks have to be fitted together to form complete lines (Black 2011). Training dose is one to two hours a day. Improvement of visual acuity and binocular vision can occur within weeks of training in adults (Hess 2010a; Hess 2012; To 2011) and children (Knox 2012).

2. Balanced binocular viewing

BBV uses Gaussian blur to degrade the image seen by the better-seeing eye and to balance input into the visual cortex area V1 (Bossi 2014). Children watch movies at home for an hour while wearing LCD shutter glasses. Visibility of the content across the two eyes is balanced by applying sufficient Gaussian blur to the image seen by the better-seeing eye to reduce its resolution to that of the amblyopic eye.

3. I-BiT™

The I-BiT™ shutter glasses system presents different parts of a two-dimensional visual scene to either eye via shutter glasses, combined with a task that requires combination of the two images (Eastgate 2006; Foss 2013; Herbison 2013; Waddingham 2006). Images are viewed with both eyes, but parts of the image can only be seen with the amblyopic eye. Presentation of the visual scene is not stereoscopic; the shutter glasses present a distinct but visually related image to both eyes (Foss 2013). The material viewed consists of videos and interactive games aimed at children aged eight years and younger.

Results of non-RCT studies published to date

The results of published cohort studies are limited by methodological factors, including the lack of a control group, the use of different testing protocols for visual acuity, stereoacuity and other psychophysical assessments, and the enrolment of participants from different age groups, different subtypes of amblyopia, and those with and without prior treatment. Nonetheless, we can still gain some insight into the likely effectiveness of these interventions. Indeed, despite these methodological limitations, a

summary view of the published data demonstrates that binocular treatments of childhood amblyopia may be a promising new modality that merits further investigation. In [Table 1](#) we have presented the details of these studies, including the treatment type, participant characteristics, treatment dose, and visual outcomes. These studies all involve the dichoptic presentation of images, either through head-mounted displays, hand-held devices overlaid with a lenticular layer, stereo-shutter glasses, or anaglyph glasses. The approaches diverge in terms of the content viewed during treatment, the method of binocular image adjustment, treatment durations, etc. The largest number of publications to date derive from studies using anti-suppression training, initially in adults and more recently in children ([Hess 2010a](#); [Hess 2010b](#); [Hess 2012](#); [Knox 2012](#); [Li 2014](#); [To 2011](#)). All these studies used active game-playing via a Tetris game during treatment. The next-most reported technique is the I-BiT approach, which uses either computer games or DVD viewing during treatment ([Eastgate 2006](#); [Cleary 2009](#); [Foss 2013](#); [Herbison 2013](#); [Waddingham 2006](#)). Finally, the balanced binocular viewing method involves movie watching with a simple game interspersed to monitor the level of interocular suppression and the difference in perception of blur ([Bossi 2014](#)).

[Table 1](#) includes details of the reported improvements in visual acuity and stereoacuity. Across the anti-suppression studies, the mean improvement in amblyopic eye acuity ranged from 0.08 to 0.26 logMAR ([Hess 2010a](#); [Hess 2010b](#); [Hess 2012](#); [Knox 2012](#); [Li 2014](#); [To 2011](#)). Improvements in acuity of 0.177 to 0.25 logMAR have been reported with the I-BiT system ([Cleary 2009](#); [Herbison 2013](#); [Waddingham 2006](#)), whilst the BBV approach has produced a 0.26 logMAR improvement in anisometric participants ([Bossi 2014](#)). These values are comparable with the mean improvement from standard occlusion treatments, recently re-evaluated as equal to 0.22 (standard deviation: 0.16) at six months after occlusion, following either patching or atropine ([Repka 2014](#)). Regarding stereopsis, 67% of cases studied showed an improvement within 200 seconds of arc following anti-suppression therapy, with movement from unmeasurable to measurable stereo levels in 24% of cases ([Black 2012](#); [Hess 2011](#); [Hess 2012](#); [Knox 2012](#); [To 2011](#)). The BBV approach has also shown a mean gain in stereoacuity of 165 seconds of arc. This can be considered to be a real change, defined as a change of more than one octave on the Frisby test in all but one participant ([Adams 2009](#); [Bossi 2014](#)). Stereoacuity improvements have not yet been documented with the I-BiT approach. These improvements in logMAR acuity and stereopsis have been observed over a range of treatment durations using the anti-suppression approach, though no link between treatment duration (5 to 40 hours) and the subtype of amblyopia has been found ([Hess 2014](#)). Recent studies have also begun to pair these treatments with non-invasive techniques to directly stimulate brain activity (either repetitive transcranial magnetic stimulation or transcranial direct current stimulation), which may temporarily disrupt interocular suppression and thus accelerate the effect of

therapeutic training ([Hess 2013](#); [Spiegel 2013a](#); [Spiegel 2013b](#)). Binocular treatments may also have beneficial effects beyond the observed improvements in visual acuity and stereoacuity. In particular, the use of computer games or videos in these approaches is likely to engage children's attention and may thus improve compliance with treatment, which is notoriously difficult with occlusion treatment and pharmacological blurring ([Wallace 2013](#)). Indeed, high compliance with binocular treatments has been reported: 80.6% of prescribed period for I-BiT games, 92.3% for I-BiT videos ([Herbison 2013](#)), and 93% for BBV ([Bossi 2014](#)). The absence of control groups in the above-reported studies makes it difficult to assess whether these improvements in compliance will translate into improved visual outcomes, although compliance and acuity improvements do correlate strongly for patching treatments ([Woodruff 1994](#)). In addition, through treating the fundamental binocular imbalance of amblyopia, binocular approaches may promote a lower recurrence than with conventional treatment. So far, recurrence of amblyopia after cessation of treatment is reportedly low, for example 0.055 logMAR at 10 weeks with I-BiT, [Herbison 2013](#), and 0.02 logMAR at 14 weeks with BBV, [Bossi 2014](#).

How the intervention might work

Binocular treatments have been developed against a background of studies on the effect of perceptual learning on amblyopia ([Levi 2005](#)). A range of studies has shown that targeted practice of a specific task, such as Vernier acuity, can improve performance on that task. Although this often does not transfer to other tasks or stimulus configurations ([Levi 1986](#)), in some cases training on one task does improve performance on others. For instance, training on tasks for contrast detection ([Polat 2004](#)), crowding ([Hussain 2012](#)), and stereopsis ([Xi 2014](#)) have all been found to produce improvements in the acuity of those with amblyopia. This pattern of transfer is somewhat complex; while training on a contrast task can transfer to acuity, acuity training does not transfer to contrast detection ([Astle 2011](#)). It is possible that by identifying and targeting the fundamental deficit in amblyopia, a range of amblyopic deficits could be improved at once.

Binocular treatments based on dichoptic stimulus presentation balance the input to V1 from right and left eye, either by reducing the contrast of the visual scene viewed with the better-seeing eye, or by blurring it to match the perception with the amblyopic eye. The I-BiT approach does not modify contrast or sharpness, but presents different parts of the visual scene to the amblyopic and to the better-seeing eye, and requires the user to combine the information provided to successfully play a computer game. In other words, these systems based on dichoptic presentation of images specifically target binocular summation. It is known that balancing visibility in both the amblyopic and better-seeing eye can allow both binocular summation and binocular interactions in tasks such as motion coherence and orientation discrimination ([Baker 2007](#); [Baker 2008](#); [Mansouri 2008](#)). Given that the binoc-

ular imbalance is a fundamental component of amblyopia, it is likely that the specific targeting of this deficit will lead to improved outcomes for a range of amblyopic visual deficits.

Why it is important to do this review

Binocular treatments address the causal mechanisms underlying amblyopia and may deliver better outcomes than current standard treatments. In addition, these new treatment modalities are more child-friendly than conventional treatment. With home-based treatments becoming available, these new treatments may soon enter clinical use. A robust framework is required to facilitate the evaluation of RCT results and provide evidence on the benefits and harms of these treatments.

OBJECTIVES

To determine whether binocular treatments in children aged three to eight years with unilateral amblyopia result in better visual outcomes than conventional occlusion or pharmacological blurring treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include RCTs only in this review.

Types of participants

We planned to include participants between the ages of three and eight years old with unilateral amblyopia, defined as BCVA worse than 0.200 logMAR in the amblyopic eye and BCVA 0.200 logMAR or better in the fellow eye, in the presence of an amblyogenic risk factor such as anisometropia, strabismus, or both. In practice, an interocular difference in visual acuity of 0.200 logMAR or greater is usually required for a diagnosis of amblyopia.

Prior to enrolment, participants would have undergone a cycloplegic refraction and comprehensive ophthalmic examination including fundal examination. In addition, participants would have completed a period of optical treatment, and BCVA in the amblyopic eye would have remained unchanged on two consecutive assessments despite reportedly good compliance with glasses wearing. Participants would not have received any treatment other than optical treatment prior to enrolment.

Types of interventions

We planned to include any type of binocular viewing intervention; these could have been delivered on different devices including computer monitors viewed with LCD shutter glasses or hand-held screens including mobile phone screens with lenticular prism overlay.

Control groups would have received standard amblyopia treatment; this could have included occlusion or pharmacological blurring of the better-seeing eye. We planned to include full-time (all waking hours) and part-time (between 1 and 12 hours a day) occlusion regimens.

Types of outcome measures

Primary outcomes

The primary outcome for this review is mean distance BCVA in the amblyopic eye at 12 months after the cessation of the interventions in logMAR units on an age-appropriate acuity test. These tests are typically administered at a distance of 3 m in young children; we also included measurements at 4 m or 6 m.

Secondary outcomes

1. Main secondary outcome: mean distance BCVA in the amblyopic eye at any time point during or after cessation of treatment in logMAR units on an age-appropriate acuity test. These tests are typically administered at a distance of 3 m in young children; we also included measurements at 4 m or 6 m.
2. Proportion of change in BCVA defined by the equation: $\frac{\text{BCVA of amblyopic eye at start} - \text{BCVA of amblyopic eye at end of treatment}}{\text{BCVA of amblyopic eye at start} - \text{BCVA of fellow eye at end of treatment}}$ (Stewart 2003).
3. Stereopsis 12 months after cessation of treatment in seconds of arc.
4. Stereopsis at any time point during or after cessation of treatment in seconds of arc.
5. Proportion of participants achieving normal stereoacuity score of 60 seconds of arc or better 12 months after cessation of treatment.
6. Proportion of participants achieving normal stereoacuity score of 60 seconds of arc or better at any time point during or after cessation of treatment.
7. Proportion of participants with improvement in stereoacuity of 2 log levels or more (with 2 levels being the test-retest variability for stereoacuity tests) at 12 months after cessation of treatment (Adams 2009; Wallace 2011).
8. Proportion of participants with improvement in stereoacuity of 2 log levels or more at any time point during or after cessation of treatment.
9. Mean change in stereoacuity in log seconds of arc defined as: stereoacuity at start minus stereoacuity at end of treatment

10. Compliance or adherence to interventions as daily dose in hours/day, determined by occlusion dose monitors, electronic compliance measures of binocular treatments, or parental treatment diaries (ratio of received dose/prescribed daily dose).

11. Compliance or adherence to interventions as total dose, determined by occlusion dose monitors, electronic compliance measures of binocular treatments, or parental treatment diaries (ratio of received dose/prescribed total dose).

12. Impact of treatment on quality of life measured by a validated tool such as Child Amblyopia Treatment Questionnaire, [Carlton 2013](#), or Amblyopia Treatment Index, [Felius 2010](#).

13. Proportion of participants experiencing adverse events such as diplopia (double vision) or loss of BCVA greater than 1 line in either eye.

14. Proportion of participants experiencing regression of BCVA in the amblyopic eye to baseline level, [Malik 1975](#), or recurrence defined as a 2 or more logMAR lines (0.2 logMAR) deterioration in amblyopic eye BCVA, [Holmes 2004](#), 12 months after cessation of treatment.

15. Where available, we included analysis of cost-effectiveness or cost-utility of treatments.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Eyes and Vision Group Trials Register (last date of searches: 14 April 2015), the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 3), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to April 2015), EMBASE (January 1980 to April 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials.

See: Appendices for details of search strategies for CENTRAL ([Appendix 1](#)), MEDLINE ([Appendix 2](#)), EMBASE ([Appendix 3](#)), ISRCTN ([Appendix 4](#)), ClinicalTrials.gov ([Appendix 5](#)), and the ICTRP ([Appendix 6](#)).

Searching other resources

We manually searched the reference lists of the trials included in the review for additional trials. We also used the Science Citation Index to identify reports that had cited the studies included in this review. With both of these strategies, we aimed to identify any relevant reports or trials that we had not identified by the electronic searches. We did not handsearch journals or conference proceedings specifically for this review.

Data collection and analysis

Data analysis would have followed the guidelines in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Deeks 2011](#)). We had planned to meta-analyse the primary outcome, that is mean distance BCVA in the amblyopic eye at 12 months after the cessation of treatment. LogMAR acuities are normally distributed and provided we did not detect heterogeneity, we planned to meta-analyse data using the random-effects model with the mean difference as our treatment effect measure.

Selection of studies

Two review authors (VT and ADN) independently screened the results of the search (titles and abstracts) to identify studies that loosely met the inclusion criteria of the review. Review authors were not masked with respect to study authors, institution, or journal. We divided studies into 'definitely include', 'definitely exclude', and 'possibly include'. We made final judgements on inclusion or exclusion by obtaining the full-text copy of those studies in the 'possibly include' category. We had abstracts and, where necessary, full-text articles translated into English before making a final decision regarding inclusion or exclusion. We took care to identify multiple reports of the same study and, where identified, these were to be linked together. The review authors independently examined full-text reports for compliance with inclusion criteria. We resolved any disagreements over which studies to include by discussion. No consultation with a third review author (CB) was required. We have listed studies that were excluded after obtaining the full text in [Characteristics of excluded studies](#), giving a reason for exclusion.

Data extraction and management

Two review authors (VT and ADN) were to extract data independently using a data extraction form ([Table 2](#)) developed in conjunction with the Cochrane Eyes and Vision Group, using information from Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). Where data were missing or unclear, one review author (VT) was to attempt to contact the authors of the trial for unpublished data or for clarification. We were to make initial contact via email, sending a second email if there was no response. If there was still no response after the second email, we would attempt to reach authors by phone. We intended to document if this was unsuccessful in the review. We planned to enter data into Review Manager (RevMan) ([RevMan 2014](#)); one review author (VT) was to enter the data, after which a second review author (ADN) was to check for any errors. At a minimum, we planned to extract the following data, which we intended to present in a 'Characteristics of included studies' table.

- Methodology: study design, interventions, intervention arms, duration of treatment.

- Participants: number in each group, age, gender, comparability at baseline.
- Outcomes: primary and secondary outcomes collected and reported; for each outcome the unit of measurement would be recorded or, if a scale was used, the upper and lower limits of the scale of measurement and whether a high or low score is good.
 - Results: sample size, missing participants, summary data.
 - Miscellaneous: dates (when study was conducted), funding source, declarations of interest, whether correspondence was required, miscellaneous comments by the review authors.

Assessment of risk of bias in included studies

Had we identified studies meeting the inclusion criteria, two review authors (VT and ADN) would have assessed them for risk of bias according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We were to consider the following parameters: generation of the random sequence, allocation concealment, masking (blinding) of examiners, completeness of outcome data, and selective reporting. We would have graded each parameter of trial quality as low, high, or unclear risk of bias.

Examples of low risk of bias:

- randomisation using computer-generated sequences or random number table;
- central allocation;
- masking of examiners;
- no missing data or missing data are balanced in numbers across intervention groups and similar reasons given across groups;
- study protocol is available with clear primary and secondary outcomes specified.

Examples of high risk of bias:

- randomisation is determined by date of visit or name (an example of quasi-randomisation, which would make study ineligible for inclusion);
- alternate allocation used (as above);
- examiners are aware of the treatment allocation prior to assessing outcomes;
- missing data are excluded and appear to be more common in one treatment arm than the other;
- none of the study's prespecified primary outcomes are reported.

Examples of unclear risk of bias:

- insufficient information in publications to allow us to make a judgement, and attempts to contact authors for clarification are unsuccessful.

Measures of treatment effect

Our primary outcome was visual acuity in the amblyopic eye in logMAR at one year after cessation of treatment. logMAR acuities

tend to be normally distributed, and we aimed to use the mean difference with 95% confidence intervals as our measure of treatment effect. However, we planned to note whether or not authors assessed symmetry of their data and also which logMAR test was used, as different charts may yield different values.

Our main secondary outcome was visual acuity in the amblyopic eye in logMAR at any time point during or after cessation of treatment. This is also typically normally distributed, and we aimed to use the mean difference with 95% confidence intervals.

We planned to collate information on other outcomes but not to meta-analyse these so as to avoid any multiplicity issues.

Unit of analysis issues

Each child would have one amblyopic eye, so there would be a single observation per child. Therefore, the unit of analysis was the child.

Dealing with missing data

We planned to carry out intention-to-treat analysis for each outcome. One review author (VT) was to retrieve any missing data by contacting the authors of the relevant papers. If we failed to obtain this, but the authors had examined reasons for loss to follow-up adequately and found that losses were similar between treatment groups, we may have used available case analysis. We planned to document whether the original studies stated that they compared the characteristics of participants with complete data to those without and whether they provided any information about possible effects of missing data.

Assessment of heterogeneity

We planned to examine studies for sources of methodological and clinical heterogeneity. We intended to then assess statistical heterogeneity by:

1. examining the characteristics of the included studies;
2. looking for poor overlap of the confidence intervals on the forest plot;
3. carrying out a Chi² test and calculation of I² with confidence intervals. We planned to interpret values of I² as advised by Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We did not plan to adopt strict thresholds for I² but would typically be concerned with values of 50% or more.

Assessment of reporting biases

If we had a sufficient number of trials (10 or more), we would have conducted a funnel plot to assess evidence of publication bias, although we acknowledge that asymmetry in such a plot does not always indicate publication bias.

Data synthesis

We planned to collate all data that are relevant to our primary and secondary outcomes.

We intended to only meta-analyse our primary outcome and main secondary outcome. We were to collate data for secondary outcomes, but to avoid any multiplicity issues, and for review clarity, we did not plan to meta-analyse these data, but to report summary statistics in tables.

We had planned to prepare a 'Summary of findings' table presenting relative and absolute risks. Two review authors were to independently grade the overall quality of the evidence for each outcome using the GRADE classification (www.gradeworkinggroup.org/). We planned to include the following outcomes in the 'Summary of findings' table:

- Primary outcome, i.e. mean distance BCVA in the amblyopic eye at 12 months after the cessation of the interventions in logMAR units on an age-appropriate acuity test.
- Proportion of change in BCVA defined by the equation: "(BCVA of amblyopic eye at start minus BCVA of amblyopic eye at end of treatment) divided by (BCVA of amblyopic eye at start minus BCVA of fellow eye at end of treatment)" (Stewart 2003).
- Proportion of participants achieving normal stereoacuity score of 60 seconds of arc or better 12 months after cessation of treatment.
- Compliance or adherence to interventions as total dose, determined by occlusion dose monitors, electronic compliance measures of binocular treatments, or parental treatment diaries (ratio of received dose/prescribed total dose).
- Impact of treatment on quality of life measured by a validated tool such as Child Amblyopia Treatment Questionnaire or Amblyopia Treatment Index (Carlton 2013; Felius 2010).
- Proportion of participants experiencing adverse events such as diplopia (double vision) or loss of BCVA greater than 1 line in either eye.
- Proportion of participants experiencing regression of BCVA in the amblyopic eye to baseline level, Malik 1975, or recurrence defined as a 2 or more logMAR lines (0.2 logMAR) deterioration in amblyopic eye BCVA, Holmes 2004, 12 months after cessation of treatment.

We planned to use a random-effects model unless there was a very small number of studies (less than three), in which case we would have used a fixed-effect model. Had we detected substantial het-

erogeneity (either methodological by review of studies or by large values of I^2), as advised by Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011), we intended not to conduct a meta-analysis.

Subgroup analysis and investigation of heterogeneity

As we expected visual outcomes at 12 months to be similar across studies, we did not plan to carry out subgroup analysis or investigations of heterogeneity.

Sensitivity analysis

We planned sensitivity analysis to assess how robust our review results were and to study the effects of:

- missing data: we planned to consider whether or not data were likely to be missing completely at random or whether there was a possibility that missingness was related to the treatment, which might bias our results;
- excluding studies at high risk of bias, i.e. any study that scores high in any domain;
- the funding source as an indicator of potential conflict of interest, such as studies that are commercially as opposed to charity- or research-council funded.

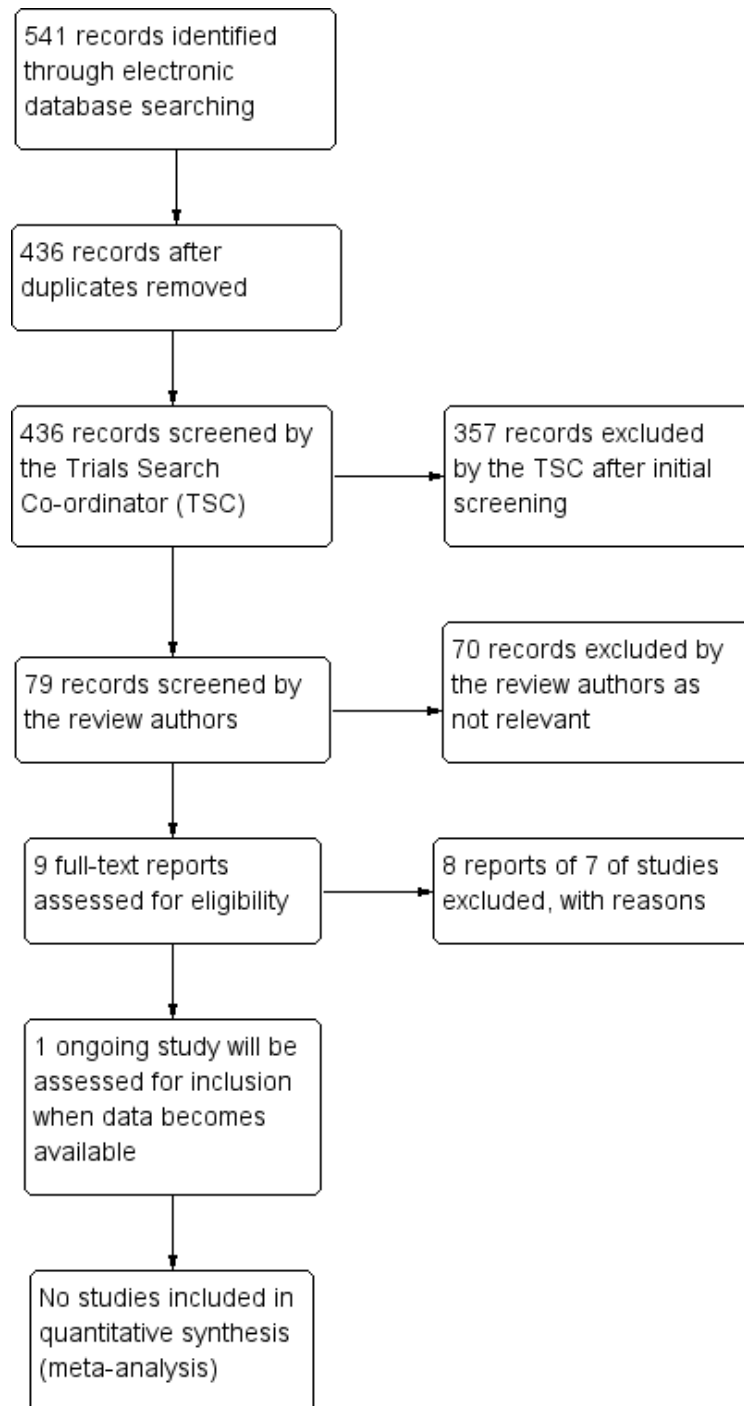
RESULTS

Description of studies

Results of the search

The electronic searches yielded a total of 541 references (Figure 1). The Trials Search Co-ordinator removed 105 duplicate records, screened the remaining 436 records, and removed 357 references that were not relevant to the scope of this review. We screened the remaining 79 references and discarded 70 reports as not relevant. We reviewed nine full-text reports of eight studies for possible inclusion in the review. After this assessment, we excluded eight reports of seven studies (see [Characteristics of excluded studies](#) for details).

Figure 1. Results of searching for studies for inclusion in the review.



We identified one ongoing study, [NCT02200211](#), which is currently recruiting participants and may meet the inclusion criteria once results have been published. In this RCT, children aged 5 to 17 years with amblyopia (either previously treated or untreated) will be randomised to an iPad-based binocular treatment or to conventional occlusion treatment for two hours a day. We may include a subgroup of children aged three to eight years with no previous amblyopia treatment (other than glasses) in future updates of this review. We have assigned this trial to 'ongoing studies' and will report on it in further updates of this review.

Included studies

We did not find any studies that met our inclusion criteria.

Excluded studies

We obtained eight full-text reports of seven studies for further assessment, however none of the studies met the inclusion criteria; see [Characteristics of excluded studies](#) for reasons for exclusion. An RCT of a binocular treatment, [Foss 2013](#), has completed recruitment but not yet published findings (personal communication); however, this trial did not include a control group receiving occlusion treatment. Children with unilateral amblyopia aged four to eight years were eligible for this trial; participants were randomised to three arms: clinic-based binocular treatment using a computer game, clinic-based sham computer game, and home-based binocular treatment.

Risk of bias in included studies

We included no trials in the review.

Effects of interventions

We included no trials in the review.

DISCUSSION

Summary of main results

We did not find any RCTs that met our inclusion criteria. One ongoing RCT, [ATS18 \(NCT02200211\)](#), includes children aged

three to eight years receiving a binocular anti-suppression treatment as first modality after optical treatment. This subgroup will be eligible for inclusion in future updates of this review. The recent I-BiT trial ([NCT01702727 \(Foss 2013\)](#)) does not include an occlusion treatment control arm. There is an obvious need for RCTs to evaluate the safety and efficacy of binocular treatment approaches for childhood amblyopia.

Published work in this area is so far limited to cohort studies, which we have briefly summarised below.

Overall completeness and applicability of evidence

Not applicable.

AUTHORS' CONCLUSIONS

Implications for practice

There are no RCTs to guide clinical practice; further research is required to allow decisions about implementation.

Implications for research

Currently there are no clinical trials offering standardised evidence of the safety and effectiveness of binocular treatments for childhood amblyopia, but results from non-controlled cohort studies are encouraging. Future research should be conducted in the form of RCTs, using acknowledged methods of visual acuity and stereoacuity assessment with known reproducibility. Other important outcome measures include outcomes reported by users, compliance with treatment, and recurrence of amblyopia after cessation of treatment.

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REFERENCES

References to studies excluded from this review

Astle 2011a *{published data only}*

Astle AT, McGraw PV, Webb BS. Can human amblyopia be treated in adulthood?. *Strabismus* 2011;**19**(3):99–109.

Bau 2012 *{published data only}*

Bau V, Rose K, Pollack K, Spoerl E, Pillunat LE. Effectivity of an occlusion-supporting PC-based visual training programme by horizontal drifting sinus gratings in children with amblyopia. *Klinische Monatsblätter für Augenheilkunde* 2012;**229**(10):979–86.

Chen 2008 *{published data only}*

Chen PL, Chen JT, Fu JJ, Chien KH, Lu DW. A pilot study of anisometric amblyopia improved in adults and children by perceptual learning: an alternative treatment to patching. *Ophthalmic and Physiological Optics* 2008;**28**(5): 422–8.

Foss 2013 *{published data only}*

Foss AJ, Gregson RM, MacKeith D, Herbison N, Ash IM, Cobb SV, et al. Evaluation and development of a novel binocular treatment (I-BiT) system using video clips and interactive games to improve vision in children with amblyopia ('lazy eye'): study protocol for a randomised controlled trial. *Trials* 2013;**14**:145.

NCT01702727. Evaluation and development of a novel binocular treatment (I-BiT) system using video clips and interactive games to improve vision in children with amblyopia ('lazy eye'). clinicaltrials.gov/ct2/show/NCT01702727 (accessed 20 November 2014).

Ide 2013 *{published data only}*

Ide T, Ishikawa M, Tsubota K, Miyao M. The effect of 3D visual simulator on children's visual acuity - a pilot study comparing two different modalities. *Open Ophthalmology Journal* 2013;**7**:69–48.

Kampf 2001 *{published data only}*

Kampf U, Muchamedjarow F, Seiler T. Supportive amblyopia treatment by means of computer games with background stimulation; a placebo controlled pilot study of 10 days. *Klinische Monatsblätter für Augenheilkunde* 2001; **218**(4):243–50.

Lennerstrand 1983 *{published data only}*

Lennerstrand G, Samuelsson B. Amblyopia in 4-year-old children treated with grating stimulation and full-time occlusion; a comparative study. *British Journal of Ophthalmology* 1983;**67**(3):181–90.

References to ongoing studies

NCT02200211 *{published data only}*

NCT02200211. Study of binocular computer activities for treatment of amblyopia. clinicaltrials.gov/ct2/show/NCT02200211 (accessed 10 October 2014).

Additional references

Adams 2009

Adams WE, Leske DA, Hatt SR, Holmes JM. Defining real change in measures of stereoacuity. *Ophthalmology* 2009; **116**(2):281–5.

Anderson 2012

Anderson EJ, Dakin SC, Schwarzkopf DS, Rees G, Greenwood JA. The neural correlates of crowding-induced changes in appearance. *Current Biology* 2012;**22**(13): 1199–206.

Assaf 1982

Assaf AA. The sensitive period: transfer of fixation after occlusion for strabismic amblyopia. *British Journal of Ophthalmology* 1982;**66**(1):64–70.

Astle 2011

Astle AT, Webb BS, McGraw PV. The pattern of learned visual improvements in adult amblyopia. *Investigative Ophthalmology and Visual Science* 2011;**52**(10):7195–204.

Awan 2005

Awan M, Proudlock FA, Gottlob I. A randomized controlled trial of unilateral strabismic and mixed amblyopia using occlusion dose monitors to record compliance. *Investigative Ophthalmology and Visual Science* 2005;**46**(4):1435–9.

Baker 2007

Baker DH, Meese TS, Mansouri B, Hess RF. Binocular summation of contrast remains intact in strabismic amblyopia. *Investigative Ophthalmology and Visual Science* 2007;**48**(11):5332–8.

Baker 2008

Baker DH, Meese TS, Hess RF. Contrast masking in strabismic amblyopia: attenuation, noise, interocular suppression and binocular summation. *Vision Research* 2008;**48**(15):1625–40.

Barnes 2001

Barnes GR, Hess RF, Dumoulin SO, Achtman RL, Pike GB. The cortical deficit in humans with strabismic amblyopia. *Journal of Physiology* 2001;**533**(Pt 1):281–97.

Barrett 2003

Barrett BT, Pacey IE, Bradley A, Thibos LN, Morrill P. Nonveridical visual perception in human amblyopia. *Investigative Ophthalmology and Visual Science* 2003;**44**(4): 1555–67.

Barrett 2004

Barrett BT, Bradley A, McGraw PV. Understanding the neural basis of amblyopia. *Neuroscientist* 2004;**10**(2): 106–17.

Birch 2000

Birch EE, Swanson WH. Hyperacuity deficits in anisometric and strabismic amblyopes with known ages of onset. *Vision Research* 2000;**40**(9):1035–40.

Birch 2013

Birch EE. Amblyopia and binocular vision. *Progress in Retinal and Eye Research* 2013;**33**:67–84.

Black 2011

Black JM, Thompson B, Maehara G, Hess RF. A compact clinical instrument for quantifying suppression. *Optometry and Vision Science* 2011;**88**(2):E334–43.

Black 2012

Black JM, Hess RF, Cooperstock JR, To L, Thompson B. The measurement and treatment of suppression in amblyopia. *Journal of Visualized Experiments* 2012;**70**: e3927.

Bossi 2014

Bossi M, Anderson EJ, Taylor V, Bex P, Greenwood JA, Dahlmann-Noor AH, et al. An exploratory study of a novel home-based binocular therapy for childhood amblyopia. *Investigative Ophthalmology and Visual Science* 2014;**55**: ARVO E-Abstract 5981.

Carlton 2008

Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J. The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4-5 years: a systematic review and economic evaluation. *Health Technology Assessment* 2008;**12**(25):iii, xi-194.

Carlton 2013

Carlton, J. Identifying potential themes for the Child Amblyopia Treatment Questionnaire. *Optometry and Vision Science* 2013;**90**(8):867–73.

Cleary 2009

Cleary M, Moody AD, Buchanan A, Stewart H, Dutton GN. Assessment of a computer-based treatment for older amblyopes: the Glasgow Pilot Study. *Eye* 2009;**23**(1): 124–31.

Conner 2007

Conner IP, Odom JV, Schwartz TL, Mendola JD. Monocular activation of V1 and V2 in amblyopic adults measured with functional magnetic resonance imaging. *Journal of AAPOS* 2007;**11**(4):341–50.

Corbetta 1995

Corbetta M, Shulman GL, Miezin FM, Petersen SE. Superior parietal cortex activation during spatial attention shifts and visual feature conjunction. *Science* 1995;**270** (5237):802–5.

Cotter 2006

Cotter SA, Edwards AR, Wallace DK, Beck RW, Arnold RW, Astle WF, et al. Treatment of anisometropic amblyopia in children with refractive correction. *Ophthalmology* 2006; **113**(6):895–903.

Cotter 2007

Cotter SA, Edwards AR, Arnold RW, Astle WF, Barnhardt CN, Beck RW, et al. Treatment of strabismic amblyopia with refractive correction. *American Journal of Ophthalmology* 2007;**143**(6):1060–3.

daCunha 1961

daCunha D, Jenkins EM. Amblyopia in three year olds. *Medical Officer Journal* 1961;**106**:146–8.

Davis 2006

Davis AR, Sloper JJ, Neveu MM, Hogg CR, Morgan MJ, Holder GE. Differential changes of magnocellular and parvocellular visual function in early- and late-onset strabismic amblyopia. *Investigative Ophthalmology and Visual Science* 2006;**47**(11):4836–41.

Daw 1998

Daw NW. Critical periods and amblyopia. *Archives of Ophthalmology* 1998;**116**(4):502–5.

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Dixon-Woods 2006

Dixon-Woods M, Awan M, Gottlob I. A qualitative study. *Archives of Disease in Childhood* 2006;**91**(6):491–4.

Eastgate 2006

Eastgate RM, Griffiths GD, Waddingham PE, Moody AD, Butler TK, Cobb SV, et al. Modified virtual reality technology for treatment of amblyopia. *Eye* 2006;**20**(3): 370–4.

Eibschitz-Tsimhoni 2000

Eibschitz-Tsimhoni M, Friedman T, Naor J, Eibschitz N, Friedman Z. Early screening for amblyogenic risk factors lowers the prevalence and severity of amblyopia. *Journal of AAPOS* 2000;**4**(4):194–9.

Espinosa 2012

Espinosa JS, Stryker MP. Development and plasticity of the primary visual cortex. *Neuron* 2012;**75**(2):230–49.

Evans 2011

Evans BJ, Yu CS, Massa E, Mathews JE. Randomised controlled trial of intermittent photic stimulation for treating amblyopia in older children and adults. *Ophthalmic and Physiological Optics* 2011;**31**(1):56–68.

Felius 2010

Felius J, Chandler DL, Holmes JM, Chu RH, Cole SR, Hill M, et al. Evaluating the burden of amblyopia treatment from the parent and child's perspective. *Journal of AAPOS* 2010;**14**(5):389–95.

Gilbert 2008

Gilbert CE, Ellwein LB. Prevalence and causes of functional low vision in school-age children: results from standardized population surveys in Asia, Africa, and Latin America. *Investigative Ophthalmology and Visual Science* 2008;**49**(3): 877–81.

Glanville 2006

Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association* 2006; **94**(2):130–6.

Goodale 1992

Goodale MA, Milner AD. Separate visual pathways for perception and action. *Trends in Neurosciences* 1992;**15**(1): 20–5.

Grant 2007

Grant S, Melmoth DR, Morgan MJ, Finlay AL. Prehension deficits in amblyopia. *Investigative Ophthalmology and Visual Science* 2007;**48**(3):1139–48.

Grant 2011

Grant S, Moseley MJ. Amblyopia and real-world visuomotor tasks. *Strabismus* 2011;**19**(3):119–28.

Greenwood 2012

Greenwood JA, Tailor VK, Sloper JJ, Simmers AJ, Bex PJ, Dakin SC. Visual acuity, crowding, and stereo-vision are linked in children with and without amblyopia. *Investigative Ophthalmology and Visual Science* 2012;**53**(12):7655–65.

Harwerth 1986

Harwerth RS, Smith EL 3rd, Duncan GC, Crawford ML, von Noorden GK. Multiple sensitive periods in the development of the primate visual system. *Science* 1986;**232**(4747):235–8.

Herbison 2013

Herbison N, Cobb S, Gregson R, Ash I, Eastgate R, Purdy J, et al. Interactive binocular treatment (I-BiT) for amblyopia: results of a pilot study of 3D shutter glasses system. *Eye* 2013;**27**(9):1077–83.

Hertle 2007

Hertle RW, Scheiman MM, Beck RW, Chandler DL, Bacal DA, Birch E, et al. Stability of visual acuity improvement following discontinuation of amblyopia treatment in children aged 7 to 12 years. *Archives of Ophthalmology* 2007;**125**(5):655–9.

Hess 2010a

Hess RF, Mansouri B, Thompson B. A new binocular approach to the treatment of amblyopia in adults well beyond the critical period of visual development. *Restorative Neurology and Neuroscience* 2010;**28**(6):793–802.

Hess 2010b

Hess RF, Mansouri B, Thompson B. A binocular approach to treating amblyopia: antisuppression therapy. *Optometry and Vision Science* 2010;**87**(9):697–704.

Hess 2011

Hess RF, Mansouri B, Thompson B. Restoration of binocular vision in amblyopia. *Strabismus* 2011;**19**(3): 110–8.

Hess 2012

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**(2):87–94.

Hess 2013

Hess RF, Thompson B. New insights into amblyopia: binocular therapy and noninvasive brain stimulation. *Journal of AAPOS* 2013;**17**(1):89–93.

Hess 2014

Hess RF, Thompson B, Baker DH. Binocular vision in amblyopia: structure, suppression and plasticity. *Ophthalmic and Physiological Optics* 2014;**34**(2):146–62.

Higgins 2011a

Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Ho 2006

Ho CS, Paul PS, Asirvatham A, Cavanagh P, Cline R, Giaschi DE. Abnormal spatial selection and tracking in children with amblyopia. *Vision Research* 2006;**46**(19): 3274–83.

Holmes 2003

Holmes JM, Kraker RT, Beck RW, Birch EE, Cotter SA, Everett DF, et al. A randomized trial of prescribed patching regimens for treatment of severe amblyopia in children. *Ophthalmology* 2003;**110**(11):2075–87.

Holmes 2004

Holmes JM, Beck RW, Kraker RT, Astle WF, Birch EE, Cole SR, et al. Risk of amblyopia recurrence after cessation of treatment. *Journal of AAPOS* 2004;**8**(5):420–8.

Holmes 2008

Holmes J, Strauber S, Quinn G, Cole S, Felius J, Kulp M, et al. Further validation of the Amblyopia Treatment Index parental questionnaire. *Journal of AAPOS* 2008;**12**(6):581–4.

Hrisos 2006

Hrisos S, Clarke MP, Kelly T, Henderson J, Wright CM. Unilateral visual impairment and neurodevelopmental performance in preschool children. *British Journal of Ophthalmology* 2006;**90**(7):836–8.

Husk 2012

Husk JS, Farivar R, Hess RF. Amblyopic deficits in processing structure-from-motion. *Journal of Vision* 2012;**12**(4):1–12.

Hussain 2012

Hussain Z, Webb BS, Astle AT, McGraw PV. Perceptual learning reduces crowding in amblyopia and in the normal periphery. *Journal of Neuroscience* 2012;**32**(2):474–80.

Kiorpes 1998

Kiorpes L, Kiper DC, O'Keefe LP, Cavanaugh JR, Movshon JA. Neuronal correlates of amblyopia in the visual cortex of macaque monkeys with experimental strabismus and

- anisometropia. *Journal of Neuroscience* 1998;**18**(16): 6411–24.
- Kiorpes 1999**
Kiorpes L, McKee SP. Neural mechanisms underlying amblyopia. *Current Opinion in Neurobiology* 1999;**9**(4): 480–6.
- Knox 2012**
Knox PJ, Simmers AJ, Gray LS, Cleary M. An exploratory study: prolonged periods of binocular stimulation can provide an effective treatment for childhood amblyopia. *Investigative Ophthalmology and Visual Science* 2012;**53**(2): 817–24.
- Levi 1982**
Levi DM, Klein S. Differences in vernier discrimination for grating between strabismic and anisometropic amblyopes. *Investigative Ophthalmology and Visual Science* 1982;**23**(3): 398–407.
- Levi 1985**
Levi DM, Klein SA. Vernier acuity, crowding and amblyopia. *Vision Research* 1985;**25**(7):979–91.
- Levi 1986**
Levi DM, Klein SA. Sampling in spatial vision. *Nature* 1986;**320**(6060):360–2.
- Levi 2005**
Levi DM. Perceptual learning in adults with amblyopia: a reevaluation of critical periods in human vision. *Developmental Psychobiology* 2005;**46**(3):222–32.
- Levi 2008**
Levi DM. Crowding - an essential bottleneck for object recognition: a mini-review. *Vision Research* 2008;**48**(5): 635–54.
- Levi 2009**
Levi DM, Li RW. Improving the performance of the amblyopic visual system. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 2009; **364**(1515):399–407.
- Li 2007**
Li X, Dumoulin SO, Mansouri B, Hess RF. The fidelity of the cortical retinotopic map in human amblyopia. *European Journal of Neuroscience* 2007;**25**(5):1265–77.
- Li 2009**
Li T, Shotton K. Conventional occlusion versus pharmacologic penalization for amblyopia. *Cochrane Database of Systematic Reviews* 2009, Issue 4. DOI: 10.1002/14651858.CD006460.pub2
- Li 2014**
Li SL, Jost RM, Morale SE, Stager DR, Dao L, Stager D, et al. A binocular iPad treatment for amblyopic children. *Eye* 2014;**28**(10):1246–53.
- Loudon 2006**
Loudon SE, Fronius M, Looman CW, Awan M, Simonsz B, van der Maas PJ, et al. Predictors and a remedy for noncompliance with amblyopia therapy in children measured with the occlusion dose monitor. *Investigative Ophthalmology and Visual Science* 2006;**47**(10):4393–400.
- Malik 1975**
Malik SR, Virdi PS, Goel BK. Follow-up results of occlusion and pleoptic treatment. *Acta Ophthalmologica* 1975;**53**(4): 620–6.
- Mansouri 2008**
Mansouri B, Thompson B, Hess RF. Measurement of suprathreshold binocular interactions in amblyopia. *Vision Research* 2008;**48**(28):2775–84.
- Maus 2010**
Maus GW, Weigelt S, Nijhawan R, Muckli L. Does area V3A predict positions of moving objects?. *Frontiers in Psychology* 2010;**1**:186.
- McKee 2003**
McKee SP, Levi DM, Movshon JA. The pattern of visual deficits in amblyopia. *Journal of Vision* 2003;**3**(5):380–405.
- McNeil 1955**
McNeil J. Patterns of visual deficits in children. *British Medical Journal* 1955;**39**:820-5.
- Mirabella 2011**
Mirabella G, Hay S, Wong AM. Deficits in perception of images of real-world scenes in patients with a history of amblyopia. *Archives of Ophthalmology* 2011;**129**(2): 176–83.
- Mitchell 2009**
Mitchell DE, Sengpiel F. Neural mechanisms of recovery following early visual deprivation. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 2009;**364**(1515):383–98.
- Moseley 1995**
Moseley M, Fielder A. Measurement of compliances with occlusion therapy. *Journal of Pediatric Ophthalmology and Strabismus* 1995;**32**(6):399–400.
- Neri 2006**
Neri P, Levi DM. Spatial resolution for feature binding is impaired in peripheral and amblyopic vision. *Journal of Neurophysiology* 2006;**96**(1):142–53.
- Niechwiej-Szwedo 2011**
Niechwiej-Szwedo E, Goltz HC, Chandrakumar M, Hirji Z, Wong AM. Effects of anisometropic amblyopia on visuomotor behavior, III: Temporal eye-hand coordination during reaching. *Investigative Ophthalmology and Visual Science* 2011;**52**(8):5853–61.
- O'Connor 2010**
O'Connor AR, Birch EE, Anderson S, Draper H. The functional significance of stereopsis. *Investigative Ophthalmology and Visual Science* 2010;**51**(4):2019–23.
- PEDIG 2002**
Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs patching for treatment of moderate amblyopia in children. *Archives of Ophthalmology* 2002;**120**(3):268–78.
- Polat 2004**
Polat U, Ma-Naim T, Belkin M, Sagi D. Improving vision in adult amblyopia by perceptual learning. *Proceedings of the*

- National Academy of Sciences of the United States of America* 2004;**101**(17):6692–7.
- Powell 2009**
Powell C, Hatt SR. Vision screening for amblyopia in childhood. *Cochrane Database of Systematic Reviews* 2009, Issue 3. DOI: 10.1002/14651858.CD005020.pub3
- Rahi 2002**
Rahi J, Logan S, Timms C, Russell-Eggitt I, Taylor D. Risk, causes, and outcomes of visual impairment after loss of vision in the non-amblyopic eye: a population-based study. *The Lancet* 2002;**360**(9333):597–602.
- Rahi 2006**
Rahi JS, Cumberland PM, Peckham CS. Does amblyopia affect educational, health, and social outcomes? Findings from the 1958 British birth cohort. *BMJ* 2006;**332**(7545): 820–5.
- Repka 2003**
Repka MX, Beck RW, Holmes JM, Birch EE, Chandler DL, Cotter SA, et al. A randomized trial of patching regimens for treatment of moderate amblyopia in children. *Archives of Ophthalmology* 2003;**121**(5):603–11.
- Repka 2005**
Repka MX, Wallace DK, Beck RW, Kraker RT, Birch EE, Cotter SA, et al. Two-year follow-up of a 6-month randomized trial of atropine vs patching for treatment of moderate amblyopia in children. *Archives of Ophthalmology* 2005;**132**(2):149–57.
- Repka 2009**
Repka MX, Kraker RT, Beck RW, Birch E, Cotter SA, Holmes JM, et al. Treatment of severe amblyopia with weekend atropine: results from 2 randomized clinical trials. *Journal of AAPOS* 2009;**13**(3):258–63.
- Repka 2014**
Repka MX, Kraker RT, Holmes JM, Summers AI, Glaser SR, Barnhardt CN, et al. Atropine vs patching for treatment of moderate amblyopia: follow-up at 15 years of age of a randomized clinical trial. *JAMA Ophthalmology* 2014;**132**(7):799–805.
- RevMan 2014 [Computer program]**
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
- Sato 2008**
Sato M, Stryker MP. Distinctive features of adult ocular dominance plasticity. *Journal of Neuroscience* 2008;**28**(41): 10278–86.
- Scheiman 2008**
Scheiman MM, Hertle RW, Kraker RT, Beck RW, Birch EE, Felius J, et al. Patching vs atropine to treat amblyopia in children aged 7 to 12 years: a randomized trial. *Archives of Ophthalmology* 2008;**126**(12):1634–42.
- Sengpiel 2006**
Sengpiel F, Jirmann KU, Vorobyov V, Eysel UT. Strabismic suppression is mediated by inhibitory interactions in the primary visual cortex. *Cerebral Cortex* 2006;**16**(12):1750–8.
- Sengpiel 2011**
Sengpiel F. Experimental models of amblyopia: insights for prevention and treatment. *Strabismus* 2011;**19**(3):87–90.
- Sharma 2000**
Sharma V, Levi DM, Klein SA. Undercounting features and missing features: evidence for a high-level deficit in strabismic amblyopia. *Nature Neuroscience* 2000;**3**(5): 496–501.
- Simmers 2003**
Simmers AJ, Ledgey T, Hess RF, McGraw PV. Deficits to global motion processing in human amblyopia. *Vision Research* 2003;**43**(6):729–38.
- Sinha 2008**
Sinha I, Jones L, Smyth RL, Williamson PR. A systematic review of studies that aim to determine which outcomes to measure in clinical trials in children. *PLoS Medicine* 2008;**5**(4):e96.
- Song 2014**
Song S, Levi DM, Pelli DG. A double dissociation of the acuity and crowding limits to letter identification, and the promise of improved visual screening. *Journal of Vision* 2014;**14**(5):3.
- Spiegel 2013a**
Spiegel DP, Byblow WD, Hess RF, Thompson B. Anodal transcranial direct current stimulation transiently improves contrast sensitivity and normalizes visual cortex activation in individuals with amblyopia. *Neurorehabilitation and Neural Repair* 2013;**27**(8):760–9.
- Spiegel 2013b**
Spiegel DP, Li J, Hess RF, Byblow WD, Deng D, Yu M, et al. Transcranial direct current stimulation enhances recovery of stereopsis in adults with amblyopia. *Neurotherapeutics* 2013;**10**(4):831–9.
- Stewart 2002**
Stewart CE, Fielder AR, Stephens DA, Moseley MJ. Design of the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). *British Journal of Ophthalmology* 2002;**86**(8): 915–9.
- Stewart 2003**
Stewart CE, Moseley MJ, Fielder AR. Defining and measuring treatment outcome in unilateral amblyopia. *British Journal of Ophthalmology* 2003;**87**(10):1229–31.
- Stewart 2004a**
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**(9):3048–54.
- Stewart 2004b**
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**(12):1552–6.
- Stewart 2005**
Stewart CE, Fielder AR, Stephens DA, Moseley MJ. Treatment of unilateral amblyopia: factors influencing visual outcome. *Investigative Ophthalmology and Visual Science* 2005;**46**(9):3152–60.
- Stewart 2013**
Stewart CE, Wallace MP, Stephens DA, Fielder AR, Moseley MJ, MOTAS Cooperative. The effect of amblyopia treatment on stereoacuity. *Journal of AAPOS* 2013;**17**(2):166–73.
- Taylor 2014**
Taylor K, Elliott S. Interventions for strabismic amblyopia. *Cochrane Database of Systematic Reviews* 2014, Issue 7. DOI: 10.1002/14651858.CD006461.pub4
- To 2011**
To L, Thompson B, Blum JR, Maehara G, Hess RF, Cooperstock JR. A game platform for treatment of amblyopia. *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 2011;**19**(3):280–9.
- Victor 1994**
Victor JD, Purpura K, Katz E, Mao B. Population encoding of spatial frequency, orientation, and color in macaque V1. *Journal of Neurophysiology* 1994;**72**(5):2151–66.
- Vorobyov 2013**
Vorobyov V, Kwok JC, Fawcett JW, Sengpiel F. Effects of digesting chondroitin sulfate proteoglycans on plasticity in cat primary visual cortex. *Journal of Neuroscience* 2013;**33**(1):234–43.
- Waddingham 2006**
Waddingham PE, Butler TK, Cobb SV, Moody AD, Comaish IF, Haworth SM, et al. Preliminary results from the use of the novel Interactive binocular treatment (I-BiT) system, in the treatment of strabismic and anisometropic amblyopia. *Eye* 2006;**20**(3):375–8.
- Wallace 2006**
Wallace DK, Edwards AR, Cotter SA, Beck RW, Arnold RW, Astle WF, et al. A randomized trial to evaluate 2 hours of daily patching for strabismic and anisometropic amblyopia in children. *Ophthalmology* 2006;**113**(6):904–12.
- Wallace 2011**
Wallace DK, Lazar EL, Melia M, Birch EE, Holmes JM, Hopkins KB, et al. Stereoacuity in children with anisometropic amblyopia. *Journal of AAPOS* 2011;**15**(5):455–61.
- Wallace 2013**
Wallace MP, Stewart CE, Moseley MJ, Stephens DA, Fielder AR. Compliance with occlusion therapy for childhood amblyopia. *Investigative Ophthalmology and Visual Science* 2013;**54**(9):6158–66.
- Webber 2008a**
Webber AL, Wood JM, Gole GA, Brown B. The effect of amblyopia on fine motor skills in children. *Investigative Ophthalmology and Visual Science* 2008;**49**(2):594–603.
- Webber 2008b**
Webber AL, Wood JM, Gole GA, Brown B. Effect of amblyopia on self-esteem in children. *Optometry and Vision Science* 2008;**85**(11):1074–81.
- White 2007**
White LE, Fitzpatrick D. Vision and cortical map development. *Neuron* 2007;**56**(2):327–38.
- Wiesel 1963**
Wiesel TN, Hubel DH. Single-cell responses in striate cortex of kittens deprived of vision in one eye. *Journal of Neurophysiology* 1963;**26**:1003–17.
- Woodruff 1994**
Woodruff G, Hiscox F, Thompson JR, Smith LK. Factors affecting the outcome of children treated for amblyopia. *Eye* 1994;**8**(Pt 6):627–31.
- Xi 2014**
Xi J, Jia WL, Feng LX, Lu ZL, Huang CB. Perceptual learning improves stereoacuity in amblyopia. *Investigative Ophthalmology and Visual Science* 2014;**55**(4):2384–91.
- Zhang 2011**
Zhang B, Tao X, Wensveen JM, Harwerth RS, Smith EL 3rd, Chino YM. Effects of brief daily periods of unrestricted vision during early monocular form deprivation on development of visual area 2. *Investigative Ophthalmology and Visual Science* 2011;**52**(10):7222–31.
- References to other published versions of this review**
- Taylor 2014**
Taylor V, Bossi M, Bunce C, Greenwood JA, Dahlmann-Noor A. Binocular versus standard occlusion or blurring treatment for unilateral amblyopia in children aged three to eight years. *Cochrane Database of Systematic Reviews* 2014, Issue 11. DOI: 10.1002/14651858.CD011347
- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Astle 2011a	Perceptual learning to reduce stereo deficits. Adults; review article; no randomisation
Bau 2012	Stimulation therapy: drifting sinus grating combined with computer games. Better-seeing eye occluded during treatment, so treatment not binocular
Chen 2008	Perceptual learning approach, grey-level gratings, Gabor patch contrast detection task. Better-seeing eye occluded during treatment, so treatment not binocular; no randomisation
Foss 2013	None of the treatment groups received an occlusion or blurring treatment
Ide 2013	Treatment not for amblyopia
Kampf 2001	Stimulation therapy: drifting sinus grating combined with foreground game. Better-seeing eye occluded during treatment, so treatment not binocular
Lennerstrand 1983	Stimulation therapy: grating; full-time occlusion. Better-seeing eye occluded during treatment, so treatment not binocular

Characteristics of ongoing studies *[ordered by study ID]*

[NCT02200211](#)

Trial name or title	
Methods	Parallel-group RCT Masking: single blind (outcomes assessor)
Participants	Children aged 5-17
Interventions	iPad® device Patching 2 hours per day, 7 days per week
Outcomes	Following text taken from clinicaltrials.gov Primary Outcome Measures: Distance Visual Acuity [Time Frame: 16 weeks] [Designated as safety issue: No] Monocular distance visual acuity in current refractive correction (if required) in each eye by a certified examiner using the electronic ATS-HOTV visual acuity protocol for children < 7 years and the E-ETDRS visual acuity protocol for children ≥ 7 years on a study-certified acuity tester displaying single surrounded optotypes Secondary Outcome Measures: Stereoaquity [Time Frame: 16 weeks] [Designated as safety issue: No] Stereoaquity will be tested at near in current refractive correction using the Randot Butterfly and Randot Preschool stereoaquity tests

	Ocular Alignment [Time Frame: 16 weeks] [Designated as safety issue: No] Ocular alignment will be assessed in current refractive correction by the cover/uncover test, simultaneous prism and cover test (SPCT), and prism and alternate cover test (PACT) in primary gaze at distance (3 meters) and at near (1/3 meter) Diplopia Questionnaire [Time Frame: 16 weeks] [Designated as safety issue: Yes] The child and parent(s) will be specifically questioned regarding the presence and frequency of any diplopia since the last study visit using a standardized diplopia assessment
Starting date	2014
Contact information	clinicaltrials.gov/ct2/show/NCT02200211
Notes	

ADDITIONAL TABLES

Table 1. Summary of published non-randomised, uncontrolled studies of binocular treatment for amblyopia

	Treat- ment	N	Age range (mean)	Con- trol group	Type of am- bly- opia	Pre- vious treat- ment other than glasses	Treat- ment dura- tion	Total dose re- ceived	Daily dose re- ceived	Com- pli- ance %	Visual acuity gain am- bly- opic eye in log- MAR (SD)	Visual acuity % change in am- bly- opic eye *	Stereoac- uity gain	Re- cur- rence
Hess 2010a ; Hess 2010b	Anti-sup- pres- sion: di- chop- tic co- herent motion, via lentic- ular over- lay/ red- green glasses or	9	24-49 (39.6)	No	Strab- ismic, com- bined mech- anism	5/9 occlu- sion	Around 60 trials/ block (0.5 to 3. 7 per week, i.e. 1-3 hours in 2- 3 days for 2-6 weeks)	8.2 blocks per week (SD 6. 3)	-	-	0.26	Not speci- fied	“sig- nifi- cant”	Not speci- fied

Table 1. Summary of published non-randomised, uncontrolled studies of binocular treatment for amblyopia (Continued)

	head-mounted display													
Hess 2012	Anti-suppression: Tetris with modulation of contrast on iPod	10	17-51 (33.8)	No	All	4/10 occlusion	0.5-2 hours per day for 1-9 weeks	15 sessions (SD 4)	45 min to 1 hour	-	0.19 (0.17)	Not specified	6/10 improved	Nil at 1-2 months (in 4/10)
Knox 2012	Anti-suppression: Tetris game using head-mounted display goggles	14	5-14 (8.5)	No	All	All occlusion (at least 6 months)	1 hour for 5 days in 1 week	5 hours	1 hour	All	0.09	22%	7/14 (small squint), 4/7 significant	Not specified
To 2011	Anti-suppression: Tetris game, interleaved breaks, via lenticular layer	9	18-51 (35.5)	No	All	Not specified	10-19 sessions	15.75 hours (0.88-27.42 hours per week)	Not specified	All	0.16 (0.18)	Not specified (fellow-eye acuity not available)	Trend of improvement	Not specified
Li 2014	Anti-sup-	45/50 binoc-	4-12	Yes (sham)	All	77% occlu-	4 hours/	≥ 1 hour	-	34/45 (76%)	0.08	Not	5/50,	Nil

Table 1. Summary of published non-randomised, uncontrolled studies of binocular treatment for amblyopia (Continued)

	pres- sion:	ular group, 24/25 sham group		game and +/- occlu- sion)		sion or at- ropine for around 1.9 years (n= 58)	week for 4 weeks (+ 4 weeks in 60% binoc- ular, but no gain)	per week, 4 4 weeks (i.e. 25% pre- scribed dose)				(0.01)	spec- ified (not indi- vidual acuities also in supp. mate- rial)	not signif- icant	at 3 months
Waddi- ham 2006	I-BiT:	6	5.42- 7.75 (6.25)	No	All	3 oc- clu- sion, 3 nei- ther occlu- sion nor at- ropie	7 to 15 ses- sions of 20 min- utes each	mean 4.4 hours	1 to 2 ses- sions of 20 min- utes twice a week	-	0.325 in 5 of 6 chil- dren	42%	-	Not speci- fied	
Her- bison 2013	I-BiT:	10	4-8 (5. 4)	No	All	All, occlu- sion or at- ropine	6 weeks, 0-10 games + 15- 30 videos	159.3 min	0-10 to 15- 30 min per day	88. 5%	0. 18 (0. 143)	32. 3%	Not mea- sured	0.055 at 10 weeks (in 6/ 9)	

Table 1. Summary of published non-randomised, uncontrolled studies of binocular treatment for amblyopia (Continued)

	to favour amblyopic eye)													
Bossi 2014	Bal- anced binoc- ular view- ing; Watch- ing mod- ified movies wear- ing 3D glasses	8	6-11 (9.46)	No	Ani- sometro	None	Around 60 hours (1 hour/ day)	48 hours 18 min	56 min per day	90%	0.26 (0.28)	29%	6/7, signif- icant mean gain of 165 sec- onds of arc	0.02 at 14 weeks (in 6/ 7)

SD: standard deviation

* calculated as $(AEs-AEe)/(AEs-Fee)$, where AEs and AEe are respectively visual acuity values in amblyopic eye at entry (best-corrected visual acuity) and exit, FEe is the acuity in the fellow eye at entry (baseline)

Table 2. Data extraction form

Review author	
Study ID	
Dates when study was conducted	If not available, comment "dates not available"
Funding source (s)	
Declarations of interest by researchers	
Methods	Study design (RCT) Interventions; mean dose prescribed and mean dose received

Table 2. Data extraction form (Continued)

Participants	Total number, number in each group (sample size) Comparability Setting	
Risk of bias	Assessed using risk of bias tool (see Handbook)	
Outcomes (as defined in study) Please specify which	<p>Primary outcome Mean distance (3, 4 or 6 m) BCVA in the amblyopic eye at 12 months after the cessation of the interventions in logMAR units on an age-appropriate acuity test</p> <p>Secondary outcomes</p> <ul style="list-style-type: none"> • main secondary outcome: mean distance (3, 4 or 6 m) BCVA in the amblyopic eye at any timepoint during or after cessation of treatment in logMAR units on an age-appropriate acuity test • proportion of change in BCVA defined as “(BCVA of amblyopic eye at start - BCVA of amblyopic eye at end of treatment)/(BCVA of amblyopic eye at start - BCVA of fellow eye at end of treatment)” (Stewart 2003) • stereopsis 12 months after cessation of treatment in seconds of arc • stereopsis at any timepoint during or after cessation of treatment in seconds of arc • proportion of participants achieving normal stereoacuity score of 60 seconds of arc or better 12 months after cessation of treatment • proportion of participants achieving normal stereoacuity score of 60 seconds of arc or better at any timepoint during or after cessation of treatment • proportion of participants with improvement in stereoacuity of 2 log levels or more (with 2 levels being the test-retest variability for stereoacuity tests) at 12 months after cessation of treatment (Adams 2009; Wallace 2011) • proportion of participants with improvement in stereoacuity of 2 log levels or more at any timepoint during or after cessation of treatment • mean change in stereoacuity in log seconds of arc defined as ”stereoacuity at start - stereoacuity at end of treatment“ • compliance or adherence to interventions as daily dose in hours/day, determined by occlusion dose monitors, electronic compliance measures of binocular treatments, or parental treatment diaries (ratio of received dose/prescribed daily dose) • compliance or adherence to interventions as total dose, determined by occlusion dose monitors, electronic compliance measures of binocular treatments, or parental treatment diaries (ratio of received dose/prescribed total dose) • impact of treatment on quality of life measured by a validated tool such as CAT-QoL (Carlton 2013) or ATI (Feliuss 2010) • proportion of participants experiencing adverse events such as diplopia (double vision) or loss of BCVA > 1 line in either eye • proportion of participants experiencing regression of BCVA in the amblyopic eye to baseline level (Malik 1975) or recurrence defined as a 2 or more logMAR lines (0.2 logMAR) • deterioration in amblyopic eye BCVA (Holmes 2004) 12 months after cessation of treatment • where available, we will include analysis of cost-effectiveness or cost-utility of treatments 	
Interventions compared	Intervention 1 = Standard care (occlusion or pharmacological blurring) Intervention 2 = Binocular treatment	
PRIMARY OUTCOME: Mean distance (3, 4 or 6 m) BCVA in the	Intervention 1	Intervention 2

Table 2. Data extraction form (Continued)

amblyopic eye at 12 months after the cessation of the interventions in logMAR units on an age-appropriate acuity test.						
Timepoint	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*
Baseline (note method used to measure BCVA)						
12 months after cessation of intervention						
Or: improvement of BCVA from baseline						
SECONDARY OUTCOMES: mean distance (3, 4 or 6 m) BCVA in the amblyopic eye at any timepoint during or after cessation of treatment in logMAR units on an age-appropriate acuity test	Intervention 1			Intervention 2		
Timepoint	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*
Baseline (note method used to measure BCVA)						
Second timepoint (please specify)						

Table 2. Data extraction form (Continued)

Or: improvement of BCVA from baseline						
SECONDARY OUTCOMES: proportion of change in BCVA defined by the equation “(BCVA of amblyopic eye at start - BCVA of amblyopic eye at end of treatment) / (BCVA of amblyopic eye at start - BCVA of fellow eye at end of treatment)”	Intervention 1			Intervention 2		
	Timepoint	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean
End of treatment						
SECONDARY OUTCOMES: Stereoaucuity 12 months after cessation of intervention in seconds of arc	Intervention 1			Intervention 2		
	Timepoint	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean
Baseline (note method used to measure stereoaucuity)						
12 months after cessation of intervention						

Table 2. Data extraction form (Continued)

SECONDARY OUTCOMES: Stereoaucuity at any timepoint during or after cessation of intervention	Intervention 2			Intervention 2		
Timepoint	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*
Baseline						
Second timepoint (please specify)						
SECONDARY OUTCOMES: Proportion of participants achieving normal stereoacuity of 60 seconds of arc 12 months after cessation of treatment	Intervention 1	Intervention 2				
Timepoint	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*
12 months after cessation of treatment (note method used to measure stereoacuity)						
SECONDARY OUTCOMES: Proportion of participants achieving normal stereoacuity of 60 seconds of arc at any timepoint during or	Intervention 1	Intervention 2				

Table 2. Data extraction form (Continued)

after cessation of treatment						
Timepoint	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*
Second timepoint (please specify)						
SECONDARY OUTCOMES: Pro-portion of participants with improvement in stereoacuity of 2 levels or more 12 months after cessation of treatment	Intervention 1	Intervention 2				
Timepoint	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*
12 months after cessation of treatment (note method used to measure stereoacuity)						
SECONDARY OUTCOMES: Pro-portion of participants with improvement in stereoacuity of 2 levels or more at any timepoint during or after cessation of treatment	Intervention 1	Intervention 2				
Timepoint	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*

Table 2. Data extraction form (Continued)

Second timepoint (please specify)							
SECONDARY OUTCOMES: Mean change in stereoacuity in logarcsec defined as "stereoacuity at start - stereoacuity at end of treatment"							
Timepoint	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*	
End of treatment (note method used to measure stereoacuity and time from start of treatment)							
SECONDARY OUTCOMES: Compliance or adherence to interventions as daily dose in hours/day (ratio of received/prescribed)	Intervention 1	Intervention 2					
Timepoint	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*	
End of intervention (specify time from start of treatment)							
SECONDARY OUTCOMES: Compliance or adherence to interventions as	Intervention 1	Intervention 2					

Table 2. Data extraction form (Continued)

total dose (ratio of received/prescribed)						
Timepoint	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*
End of intervention (specify time from start of treatment)						
SECONDARY OUTCOMES: Impact on QoL	Intervention 1			Intervention 2		
Timepoint	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*
Last measurement in trial (specify time from start of treatment)						
SECONDARY OUTCOMES: Adverse events (diplopia, loss of BCVA in amblyopic eye > 0.10 logMAR, loss of BCVA in fellow eye > 0.10 logMAR, regression, recurrence, other)	Intervention 1			Intervention 2		
Timepoint	Total number of participants	Number of affected participants		Total number of participants	Number of affected participants	
Diplopia at 12 months after start of intervention						
Loss of BCVA in amblyopic eye > 0.10 logMAR at						

Table 2. Data extraction form (Continued)

12 months after start of intervention				
Loss of BCVA in fellow eye > 0.10 logMAR at 12 months after start of intervention				
Regression of BCVA in amblyopic eye to baseline level at 12 months after start of intervention				
Recurrence: deterioration of BCVA in amblyopic eye of 0.20 logMAR or more at 12 months after start of intervention				
Other (specify)				
SECONDARY OUTCOMES: Cost-effectiveness or cost-utility	Intervention 1		Intervention 2	

ATI: Amblyopia Treatment Index
 BCVA: best-corrected visual acuity
 CAT-QoL: Child Amblyopia Treatment Questionnaire
 QoL: quality of life
 RCT: randomised controlled trial

APPENDICES

Appendix 1. CENTRAL search strategy

#1 [mh amblyopia]
#2 amblyop*
#3 lazy near/3 eye*
#4 [mh strabismus]
#5 strabism* or squint*
#6 astigmati* or meridonal
#7 [mh anisometropia]
#8 [mh "refractive errors"]
#9 anisometripi*
#10 ammetropi*
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 [mh "computer systems"]
#13 [mh software]
#14 [mh "computer simulation"]
#15 [mh "computer graphics"]
#16 [mh "imaging, three-dimensional"]
#17 [mh "photic stimulation"]
#18 [mh "therapy, computer-assisted"]
#19 [mh "play and playthings"]
#20 [mh "video games"]
#21 (computer) near/2 (game* or device* or application*)
#22 handheld near/2 device*
#23 (mobile) near/2 (phone* or app* or device*)
#24 (perceptual) near/2 (learn* or train*)
#25 anti-suppression therap*
#26 mirror haploscope*
#27 head-mounted video*
#28 lenticular near/3 prism
#29 Balanced Binocular Viewing
#30 BBV
#31 Interactive Binocular Treatment
#32 i-bit or I-BiTTM
#33 shutter near/3 (glasses or spectacles)
#34 virtual reality
#35 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
or #30 or #31 or #32 or #33 or #34
#36 #11 and #35

Appendix 2. MEDLINE (OvidSP) search strategy

1. randomized controlled trial.pt.
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\$.tw.
15. (lazy adj3 eye\$).tw.
16. exp strabismus/
17. (strabism\$ or squint\$).tw.
18. (astigmati\$ or meridonal).tw.
19. anisometropia/
20. exp refractive errors/
21. anisometripi\$.tw.
22. ammetropi\$.tw.
23. or/13-22
24. exp computer systems/
25. exp software/
26. exp computer simulation/
27. computer graphics/
28. imaging, three-dimensional/
29. photic stimulation/
30. therapy, computer-assisted/
31. "play and playthings"/
32. video games/
33. (computer adj2 (game\$ or device\$ or application\$)).tw.
34. (handheld adj2 device\$).tw.
35. (mobile adj2 (phone\$ or app\$ or device\$)).tw.
36. (perceptual adj2 (learn\$ or train\$)).tw.
37. anti-suppression therap\$.tw.
38. mirror haploscope\$.tw.
39. head-mounted video\$.tw.
40. (lenticular adj3 prism\$).tw.
41. Balanced Binocular Viewing.tw.
42. BBV.tw.
43. Interactive Binocular Treatment.tw.
44. (i-bit or I-BiTTM).tw.
45. (shutter adj3 (glasses or spectacles)).tw.
46. virtual reality.tw.
47. or/24-46
48. 23 and 47
49. 12 and 48

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al ([Glanville 2006](#)).

Appendix 3. EMBASE (OvidSP) search strategy

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\$.tw.
35. (lazy adj3 eye\$).tw.
36. exp strabismus/
37. (strabism\$ or squint\$).tw.
38. (astigmati\$ or meridonal).tw.
39. anisometropia/
40. exp refractive errors/
41. anisometropi\$.tw.
42. ammetropi\$.tw.
43. or/33-42
44. computer/
45. computer system/
46. computer simulation/
47. computer graphics/
48. photostimulation/
49. computer assisted therapy/
50. virtual reality/
51. recreation/

52. play/
53. psychomotor performance/
54. (computer adj2 (game\$ or device\$ or application\$)).tw.
55. (handheld adj2 device\$).tw.
56. (mobile adj2 (phone\$ or app\$ or device\$)).tw.
57. (perceptual adj2 (learn\$ or train\$)).tw.
58. anti-suppression therap\$.tw.
59. mirror haploscope\$.tw.
60. head-mounted video\$.tw.
61. (lenticular adj3 prism\$).tw.
62. Balanced Binocular Viewing.tw.
63. BBV.tw.
64. Interactive Binocular Treatment.tw.
65. (i-bit or I-BiTtM).tw.
66. (shutter adj3 (glasses or spectacles)).tw.
67. virtual reality.tw.
68. or/44-67
69. 43 and 68
70. 32 and 69

Appendix 4. metaRegister of Controlled Trials search strategy

amblyopia AND (computer OR video OR Interactive Binocular Treatment OR i-bit OR I-BiTtM OR shutter)

Appendix 5. ClinicalTrials.gov search strategy

amblyopia AND (computer OR video OR Interactive Binocular Treatment OR i-bit OR I-BiTtM OR shutter)

Appendix 6. ICTRP search strategy

amblyopia = Condition AND computer OR video OR Interactive Binocular Treatment OR i-bit OR I-BiTtM OR shutter = Intervention

CONTRIBUTIONS OF AUTHORS

VT, MB, JG, and ADN developed the background, objectives, and methods with CB's support in writing the methods section. VT and ADN reviewed the results of the search. MB and ADN drafted the results and discussion, and all review authors contributed critically to the final version.

DECLARATIONS OF INTEREST

No financial interests to declare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

At the review stage, we decided to include methods for preparing a Summary of findings table including the use of the GRADE classification to grade the overall quality of the evidence for each specified outcome in the [Data synthesis](#) section.

INDEX TERMS

Medical Subject Headings (MeSH)

Amblyopia [*therapy]

MeSH check words

Child; Child, Preschool; Humans