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

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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.

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In addition, participants had to have completed a period of optical treatment, if indicated, and BCVA in the amblyopic eye had to 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.

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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

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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

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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 anisometropic 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-

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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: "(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).
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

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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.

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- 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 Chi^2 test and calculation of I^2 with confidence intervals. We planned to interpret values of I^2 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 I^2 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.

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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 heterogeneity (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).

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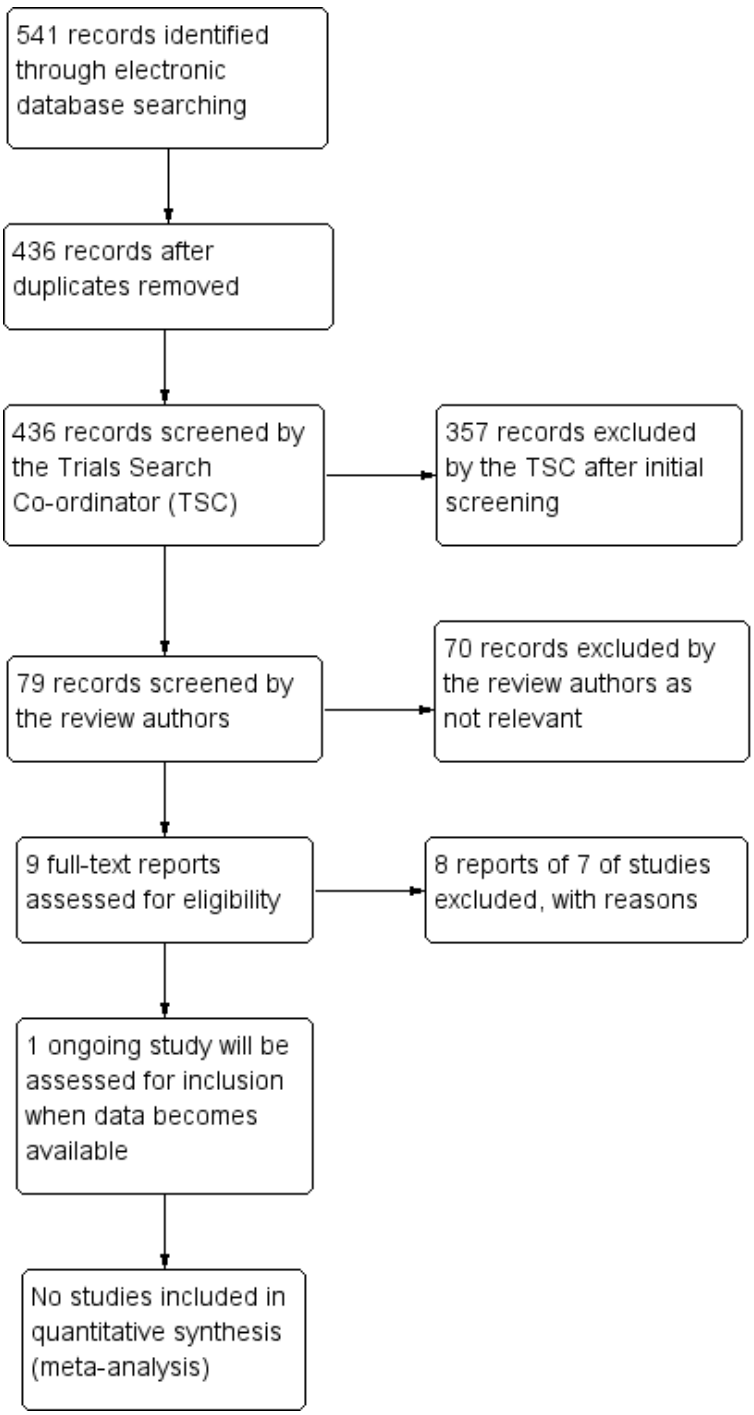
Figure 1. Results of searching for studies for inclusion in the review.



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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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* *Indicates the major publication for the study*

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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: Stereoacuity [Time Frame: 16 weeks] [Designated as safety issue: No] Stereoacuity will be tested at near in current refractive correction using the Randot Butterfly and Randot Preschool stereoacuity tests

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NCT02200211 (*Continued*)

	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	

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DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

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

	Treatment	N	Age range (mean)	Control group	Type of amblyopia	Previous treatment other than glasses	Treatment duration	Total dose received	Daily dose received	Compliance %	Visual acuity gain amblyopic eye in logMAR (SD)	Visual acuity % change in amblyopic eye *	Stereoacuity gain	Recurrence
Hess 2010a; Hess 2010b	**Anti-suppression:** dichoptic coherent motion, via lenticular overlay/ red-green glasses or head-mounted display	9	24-49 (39.6)	No	Strabismic, combined mechanism	5/9 occlusion	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 specified	"significant"	Not specified
Hess 2012	**Anti-suppression:** Tetris with modula-	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)

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

	tion of contrast on iPod													
Knox 2012	**Anti-suppression:** Tetris game using head-mounte 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-suppression:** Binocular games through anaglypl glasses (contrast increment in	45/50 binocular group, 24/25 sham group	4-12	Yes (sham game and +/- occlusion)	All	77% occlusion or atropine for around 1.9 years (n= 58)	4 hours/ week for 4 weeks (+ 4 weeks in 60% binocular, but no gain)	≥ 1 hour per week, 4 weeks (i.e. 25% prescribed dose)	-	34/45 (76%)	**0.08 (0.01)**	Not specified (not individual acuities, also in supp. material)	5/50, not significant	Nil at 3 months

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

	fellow eye)												
Waddingham 2006	**I-BiT:** Videos and modified video games (imbalanced visual scene to favour amblyopic eye)	6	5.42-7.75 (6.25)	No	All	3 occlusion, 3 neither occlusion nor atropie	7 to 15 sessions of 20 minutes each	mean 4.4 hours	1 to 2 sessions of 20 minutes twice a week	-	0.325 in 5 of 6 children	42%	-	Not specified
Herbison 2013	**I-BiT:** Videos and modified video games (imbalanced visual scene to favour amblyopic eye)	10	4-8 (5.4)	No	All	All, occlusion or atropine	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 measured	0.055 at 10 weeks (in 6/9)
Bossi 2014	**Balanced binocular viewing:**	8	6-11 (9.46)	No	Anisometro	None	Around 60 hours (1 hour/	48 hours 18 min	56 min per day	90%	**0.26 (0.28)**	29%	6/7, significant mean gain	0.02 at 14 weeks (in 6/7)

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

	Watching modified movies wearing 3D glasses						day)						of 165 seconds of arc	

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
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**	**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 **Secondary outcomes** • 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

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Table 2. Data extraction form (*Continued*)

	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 (Felius 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 amblyopic eye at 12 months after the cessation of the interventions 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*

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Table 2. Data extraction form (*Continued*)

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)						
Or: improvement of BCVA from baseline						
SECONDARY OUTCOMES: proportion of change in BCVA defined by the equation	Intervention 1			Intervention 2		

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Table 2. Data extraction form (*Continued*)

"(BCVA of amblyopic eye at start - BCVA of ambly-opic eye at end of treatment) /(BCVA of amblyopic eye at start - BCVA of fellow eye at end of treatment)"						
Timepoint	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*
End of treatment						
SECONDARY OUTCOMES: Stereoacuity 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	Standard deviation*
Baseline (note method used to measure stereoacuity)						
12 months after cessation of intervention						
SECONDARY OUTCOMES: Stereoacuity 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						

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Table 2. Data extraction form (*Continued*)

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 timpoint 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*
Second timepoint (please specify)						
SECONDARY OUTCOMES: Pro-	Intervention 1	Intervention 2				

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Table 2. Data extraction form (*Continued*)

portion of participants with improvement in stereoacuity of 2 levels or more 12 months after cessation of treatment						
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 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*
Second timepoint (please specify)						
SECONDARY OUTCOMES: Mean change in stereoacuity in logarcsec defined as "stereoacuity at start - stereoacuity at						

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Table 2. Data extraction form (*Continued*)

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 total dose (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)						

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Table 2. Data extraction form (*Continued*)

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 12 months after start of intervention						
Loss of BCVA in fellow eye > 0.10 logMAR at 12 months after start of intervention						

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Table 2. Data extraction form (*Continued*)

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

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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 anisometropi*
#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/

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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. anisometropi$.tw.
22. ammetropi$.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).

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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/

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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. *meta*Register 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.

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