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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, typically patching or pharmacological blurring, have limited success. Less than two-thirds of children achieve good acuity of 0.20 logMAR in the amblyopic eye, with limited improvement of stereopsis, and poor adherence to treatment. A new approach, based on presentation of movies or computer games separately to each eye, may yield better results and improve adherence. These treatments aim to balance the input of visual information from each eye to the brain.

Objectives

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

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register), MEDLINE, Embase, ISRCTN, ClinicalTrials.gov, and the WHO ICTRP to 19 November 2020, with no language restrictions.

Selection criteria

Two review authors independently screened the results of the search for relevant studies. We included randomised controlled trials (RCTs) that enrolled children between the ages of three and eight years old with unilateral amblyopia. Amblyopia was classed as present when the best-corrected visual acuity (BCVA) was worse than 0.200 logMAR in the amblyopic eye, with BCVA 0.200 logMAR or better in the fellow eye, in the presence of an amblyogenic risk factor, such as anisometropia, strabismus, or both. To be eligible, children needed to have undergone cycloplegic refraction and ophthalmic examination, including fundal examination and optical treatment, if indicated, with stable BCVA in the amblyopic eye despite good adherence with wearing glasses. We included any type of binocular viewing intervention, on any device (e.g. computer monitors viewed with liquid-crystal display shutter glasses; hand-held screens, including mobile phones with lenticular prism overlay; or virtual reality displays). Control groups received standard amblyopia treatment, which could include patching or pharmacological blurring of the better-seeing eye. We included full-time (all waking hours) and part-time (between 1 and 12 hours a day) patching regimens.

We excluded children who had received any treatment other than optical treatment; and studies with less than 8-week follow-up.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. The primary outcome of the review was the change from baseline of distance BCVA in the amblyopic eye after 16 (± 2) weeks of treatment, measured in logMAR units on an age-appropriate acuity test.

Main results

We identified one eligible RCT of conventional patching treatment versus novel binocular treatment, and analysed a subset of 68 children who fulfilled the age criterion of this review. We obtained data for the mean change in amblyopic eye visual acuity, adverse events (diplopia), and adherence to prescribed treatment at 8- and 16-week follow-up intervals, though no data were available for change in BCVA after 52 weeks. Risk of bias for the included study was considered to be low.

The certainty of evidence for the visual acuity outcomes at 8 and 16 weeks of treatment and adherence to the study intervention was rated moderate using the GRADE criteria, downgrading by one level due to imprecision. The certainty of evidence was downgraded by two levels and rated low for the proportion of participants reporting adverse events due to the sample size.

Acuity improved in the amblyopic eye in both the binocular and patching groups following 16 weeks of treatment (improvement of -0.21 logMAR in the binocular group and -0.24 logMAR in the patching group, mean difference (MD) 0.03 logMAR (95% confidence interval (CI) -0.10 to 0.04; 63 children). This difference was non-significant and the improvements in both the binocular and patching groups are also considered clinically similar.

Following 8 weeks of treatment, acuity improved in both the binocular and patching groups (improvement of -0.18 logMAR in the patching group compared to -0.16 logMAR improvement in the binocular-treatment group) (MD 0.02, 95% CI -0.04 to 0.08). Again this difference was statistically non-significant, and the differences observed between the patching and binocular groups are also clinically non-significant. No adverse event of permanent diplopia was reported.

Adherence was higher in the patching group (47% of participants in the iPad group achieved over 75% compliance compared with 90% of the patching group).

Data were not available for changes in stereopsis nor for contrast sensitivity following treatment.

Authors' conclusions

Currently, there is only one RCT that offers evidence of the safety and effectiveness of binocular treatment.

The authors are moderately confident that after 16 weeks of treatment, the gain in amblyopic eye acuity with binocular treatment is likely comparable to that of conventional patching treatment. However, due to the limited sample size and lack of long term (52 week) follow-up data, it is not yet possible to draw robust conclusions regarding the overall safety and sustained effectiveness of binocular treatment.

Further research, using acknowledged methods of visual acuity and stereoacuity assessment with known reproducibility, is required to inform decisions about the implementation of binocular treatments for amblyopia in clinical practice, and should incorporate longer term follow-up to establish the effectiveness of binocular treatment. Randomised controlled trials should also include outcomes reported by users, adherence to prescribed 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 may remain limited in some cases. A new type of *binocular* treatment (with both eyes open) 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.

What did we want to find out?

We wanted to find out if binocular treatments were better than conventional patching or pharmacological blurring treatment in getting better visual outcomes in children, aged three to eight years, with unilateral amblyopia.

What did we do?

We searched for studies that examined 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) - studies comparing the new treatment with a standard treatment, and where children were assigned treatment groups at random (like flipping a coin).

What did we find?

We identified one RCT that met these criteria. The study recruited 385 children of which a subset were analysed; 36 were randomised to a binocular iPad game and 32 children were randomised to conventional patching treatment. The study found, on average that vision improves with both patching and the new computer treatment after 16 weeks, with little-to-no difference in the amount of improvement with either approach, though there were some limitations with the study.

We conclude that more research is needed to allow decisions about the new treatment. We recommend that future research be done in the form of RCTs, and that researchers use acknowledged tests of visual acuity (fine detail) 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.

How up to date is this evidence?

This review updates our previous review. The evidence is up to date to November 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Binocular iPad treatment compared with occlusion therapy for amblyopia

Binocular iPad treatment compared with occlusion therapy for amblyopia						
Patient or population: 5- to 8-year-old children with amblyopia						
Settings: clinical						
Intervention: binocular iPad treatment						
Comparison: occlusion therapy						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk with occlusion therapy	Corresponding risk with binocular iPad treatment				
Change in BCVA amblyopic eye after 16 weeks logMAR (lower logMAR values indicate better visual acuity)	Mean change in acuity for the occlusion group was an improvement of 0.24 logMAR	Mean change in acuity for the binocular iPad groups was 0.03 logMAR higher (worse) (-0.04 to 0.10)		63 (1 study)	⊕⊕⊕⊖ moderate^a	
Change in BCVA amblyopic eye after 8 weeks logMAR (lower logMAR values indicate better visual acuity)	Mean change in acuity for the occlusion group was an improvement of 0.18 logMAR	Mean change in acuity for the binocular iPad groups was 0.02 logMAR higher (worse) (-0.04 to 0.08)		62 (1 study)	⊕⊕⊕⊖ moderate^a	
Change in distance BCVA in the amblyopic eye 12 months after cessation of treatment	–	–	–	–	–	No data recorded for this outcome
Adherence to intervention Proportion of adherence to prescribed intervention across predefined categories	Subjective recording of adherence to treatment: 90.3% of participants achieved over 75% compliance.	Subjective recording of treatment adherence: 46.9% of participants achieved over 75% compliance.	N/A	63 (1 study)	⊕⊕⊕⊖ moderate^a	

<p>Proportion of participants experiencing an adverse event of permanent diplopia (double vision)</p> <p>Reports of diplopia across all measured time points</p>	No reports of permanent diplopia.				63 (1 study)	⊕⊕○○ low^b	
<p>Change in the interocular difference in contrast sensitivity</p> <p>Any validated test, from baseline to 16 (± 2) weeks</p>	–	–	–	–	–	–	No data recorded for this outcome
<p>Measurable change in stereopsis after 8 (± 2) weeks and 16 (± 2) weeks of intervention</p> <p>'Real change' in stereopsis is defined as a change in stereoacuity of two or more octaves.</p>	–	–	–	–	–	–	No data recorded for this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BCVA: best-corrected visual acuity; **CI:** Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence

High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate-certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low-certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect

Very low-certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

^aDowngraded one level due to imprecision

^bDowngraded two levels due to sample size

BACKGROUND

Description of the condition

Unilateral amblyopia is a developmental disorder of vision. With 2% to 5% prevalence, 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 deficits in vision and gaze stability. This includes the definitive reduction in acuity or resolution, as well as 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; anisometric amblyopia produces 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) have also been reported (Ho 2006; Sharma 2000).

If amblyopia persists into adulthood, affected individuals may be unable to take up professions that require depth perception, such as piloting aeroplanes. 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 (Birch 2019; 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 anisometric and strabismic amblyopia are likely to be 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 (ie. high resolution input (Kiorpes 1998; Kiorpes 1999)). On the other hand, in strabismus, 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, however. 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 reduced, 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; Clavagnier 2015; 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', 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 thought to be refined and matched to the input from both eyes at an earlier stage than those of extrastriate areas. Nonetheless, imbalance of visual input could 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 was identical to that of visual development, and that after the end of the critical period, amblyopia could not be induced, nor could 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). 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; Holmes 2011).

Description of the intervention

In the UK, 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 beyond (Cotter 2006; Cotter 2007; Stewart 2004b; Taylor 2014; Wallace 2006). If amblyopia persists, current treatment consists of patching 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 patching treatment is associated with an improvement of visual acuity and stereopsis, both statistically, and

in clinical terms (Stewart 2013; Wallace 2011). Pharmacological blurring of the better-seeing eye, using atropine eye drops, appears to be equivalent to patching treatment in improving visual acuity (Li 2009; PEDIG 2002; Repka 2009; Scheiman 2008). Although the sequential approach to amblyopia treatment (optical treatment followed by patching) is a clinical standard, it is yet to be supported by empirical evidence. A recent clinical trial has examined whether the sequential approach can improve the number of successfully treated children with amblyopia, though published data is not yet available (ISRCTN51712593).

The main drawbacks of patching and pharmacological blurring are poor adherence to treatment, and suboptimal treatment outcomes. Lack of adherence to patching 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 adherence decreasing with both an increase in severity of amblyopia, and an increase in the prescribed daily dose of patching (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 (Feliuss 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 0.20 logMAR or better with patching 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 pre-treatment 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 (where both eyes work together as a pair), several groups have designed methods of simultaneous binocular visual stimulation, i.e. binocular treatment for amblyopia. To date, four systems have been developed.

1. Anti-suppression therapy

Anti-suppression therapy presents the visual scene with reduced contrast to the better-seeing eye and normal contrast to the amblyopic eye (Hess 2010a; Hess 2010b; Hess 2011; Hess 2012; Hess 2013). This approach aims to balance the input to visual cortex, in order 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), lenticular prism overlays on tablet computers or screens of other hand-held devices (To 2011), or red/green anaglyph glasses (Birch 2020; Gao 2018; Li 2014). The

observer then has to carry out a task that requires the 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 combined to form complete lines (Black 2011); other games include DigRush, where children manipulate miners digging for gold (Kelly 2016). In each case, game elements are divided between the two eyes. The training dose for these treatments may be up 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 (Kelly 2016; Knox 2012).

2. Balanced binocular viewing

Balanced binocular viewing (BBV) uses dichoptically presented movies, such that each eye receives an altered version of the same image, with the goal to balance input to the visual cortex (Bossi 2014; Bossi 2017). Children watch movies at home for an hour on a desktop computer, while wearing LCD shutter glasses. Visibility of the content across the two eyes is balanced by applying Gaussian blur to the image seen by the better-seeing eye, with the amount of blur set to reduce its resolution to that of the amblyopic eye. A simple game, interspersed with the movies, allows both compliance and the level of interocular suppression to be monitored throughout the treatment period. BBV has been further developed into a handheld device that uses a parallax barrier to separate the input to each eye without the need for shutter glasses. A phase 2a feasibility randomised controlled trial (RCT) evaluating this handheld system is currently in progress (NCT03754153).

3. I-BiT™

The I-BiT™ system presents different parts of a two-dimensional visual scene to each eye via shutter glasses, combined with a task that requires the 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. As with the other binocular therapies, presentation of the visual scene is dichoptic rather than 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. While initially designed for hospital-based use, the I-BiT™ system has recently been designed for home use, achieved using a desktop computer (Brown 2019). Shutter glasses have typically been used to separate the images for each eye, though red/green anaglyph glasses have also been used with this approach (Rajavi 2019).

4. Dichoptic action video-games

Rather than split the presented image between the two eyes, an alternative approach presents the same image to each eye at different luminance levels. This technique was initially applied to action video-games, presented via mirror haploscope to adults (Vedamurthy 2015a; Vedamurthy 2015b). A Gabor orientation discrimination task is interspersed with gameplay to give continuous measures of resolution and interocular suppression. Binocular fusion is encouraged with nonius fixation lines (where elements of the fixation target are presented to each eye). The approach has recently been adapted with more child-friendly video-games, similarly presented via mirror haploscope and with

intermittent resolution/suppression measurements (Gambacorta 2018).

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 have 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, as considered in this review, are those based on dichoptic stimulus presentation to balance the input to the visual cortex from the right and left eyes, either by reducing the contrast (anti-suppression therapy) or luminance (dichoptic action video-games) of the visual scene viewed with the better-seeing eye, or by blurring it to match the perception with the amblyopic eye (balanced binocular viewing). 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 combination. 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 binocular imbalance is a fundamental component of amblyopia, it is possible that the specific targeting of this deficit will lead to improved outcomes for a range of amblyopic visual deficits.

The role of interocular suppression in these treatments is more controversial. Some have argued that binocular therapies (and anti-suppression therapy in particular) operate by breaking interocular suppression, which in turn allows vision to improve (Hess 2014). Were this to be the case, any gains in acuity should follow reductions in suppression. However, though one study observed both an improvement in acuity and a reduction in suppression following dichoptic action video-game treatment, the two were not correlated (Vedamurthy 2015a). Balanced binocular viewing has further been found to produce improvements in acuity without a measurable change in suppression (Bossi 2017). Therefore, although suppression may play a causal role in the development of amblyopic deficits, it seems that the mechanism underlying these deficits in acuity and stereovision can be altered by binocular therapies without changes in suppression (Li 2011). Instead, improvements in binocular combination could be driven by increases in the number of neurons driven by the amblyopic eye (Kiorpes 1998), a decrease in the positional disorganisation of their receptive fields (Hess 1994), alterations of their spatial properties, or a combination (Clavagnier 2015).

Why it is important to do this review

Binocular treatments aim to 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 treatments may soon enter regular 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 patching or pharmacological blurring treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We only included randomised controlled trials (RCT) in this review. To ensure that these RCTs had allowed for sufficient time to adequately identify the change in best-corrected visual acuity (BCVA) in either treatment arm, we only included RCTs with a minimum of 8 (± 2)-week follow-up intervals.

Types of participants

We included 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 been considered stable, despite reportedly good adherence with wearing glasses. To avoid any potential confounding factors due to the inclusion of pretreated amblyopes (e.g. improvement of BCVA to their previous best-corrected level, rather than new improvement following binocular treatment), participants included in this review would not have received any treatment other than optical treatment prior to enrolment.

Types of interventions

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

Control groups received standard amblyopia treatment; this could have included patching 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) patching regimens.

Types of outcome measures

Primary outcomes

Change in distance best-corrected visual acuity (BCVA) in the amblyopic eye from baseline to 16 (± 2) weeks of treatment, measured in logMAR units on an age-appropriate acuity test. Lower logMAR values indicate better visual acuity, but as we examined change in BCVA, a higher logMAR difference indicates higher levels of improvement in BCVA following treatment (either conventional or binocular).

Secondary outcomes

1. Main secondary outcome: change in BCVA in the amblyopic eye from baseline to 8 (± 2) weeks of treatment, measured in logMAR units on an age-appropriate acuity test.
2. Change in stereopsis from baseline to 8 (± 2) and 16 (± 2) weeks of intervention. 'Real change' in stereopsis was defined as a change in stereoacuity of two or more octaves (Adams 2009).
3. Change in distance BCVA in the amblyopic eye, measured 12 months after cessation of treatment.
4. Adherence to interventions, measured by usage time as a proportion of prescribed time, following 8 (± 2) and 16 (± 2) weeks of treatment.
5. Change in the interocular difference in contrast sensitivity from baseline to 16 (± 2) weeks, using any validated test.
6. Proportion of participants experiencing adverse events, such as permanent diplopia (double vision), at any time point.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials. There were no restrictions to language or year of publication.

- Cochrane Central Register of Controlled Trials, which contains the Cochrane Eyes and Vision Trials Register (CENTRAL; 2020, Issue 11) in the Cochrane Library (searched 19 November 2020; Appendix 1);
- MEDLINE Ovid (1946 to 19 November 2020; Appendix 2);
- Embase Ovid (1980 to 19 November 2020; Appendix 3);
- International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.isrctn.com/editAdvancedSearch; searched 19 November 2020; Appendix 4);

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 19 November 2020; Appendix 5);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.who.int/ictpr; searched 19 November 2020; Appendix 6).

Searching other resources

We manually searched the reference lists of the included trials 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 specifically handsearch journals or conference proceedings for this review.

Data collection and analysis

We planned to follow the guidelines in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* for data analysis (Deeks 2017). We planned to meta-analyse the primary outcome, mean distance BCVA in the amblyopic eye after 16 (± 2) weeks 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. With fewer than three studies, we planned to use a fixed-effect model.

Selection of studies

Two review authors (VT and SL) independently screened the results of the search (titles and abstracts) to identify studies that loosely met the inclusion criteria of the review (Figure 1). Review authors were not masked 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 'definitely include' and '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 when identified, we planned to link them. The review authors independently examined full-text reports for compliance with inclusion criteria. We resolved any disagreements by discussion with the third review author (ADN). We listed studies that we excluded after obtaining the full-text in [Characteristics of excluded studies](#), giving a reason for exclusion.

Figure 1. PRISMA flowchart for study selection (2015 and 2021 literature searches)

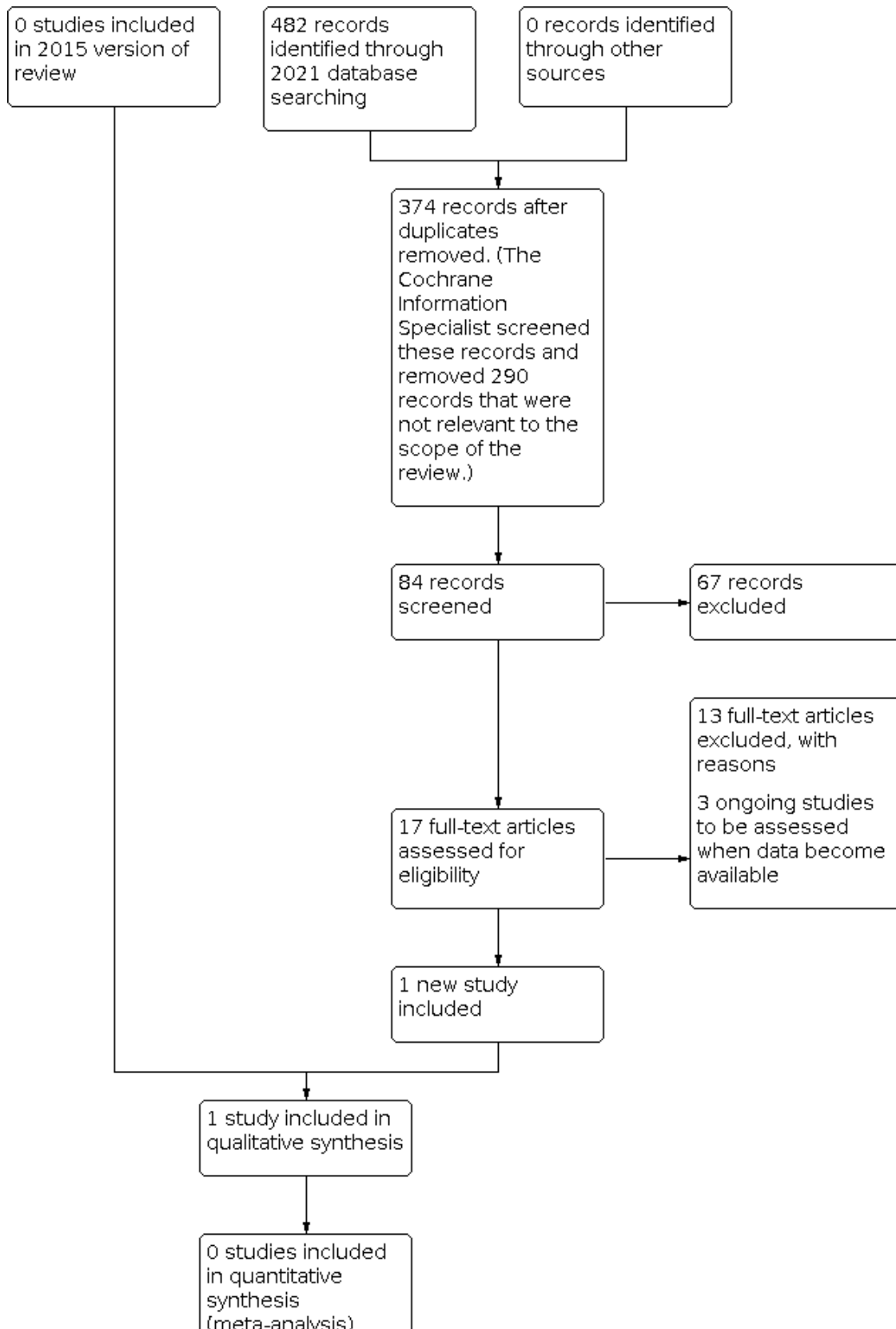


Figure 1. (Continued)

synthesis
 (meta-analysis)

Data extraction and management

Two review authors (VT and SL) independently extracted data, using a data extraction form developed in conjunction with Cochrane Eyes and Vision, using guidance from Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; Table 1). When data were missing or unclear, one review author (SL) attempted to contact the trial authors for unpublished data, or for clarification. We made initial contact via email, sending a second email if there was no response. We planned to enter data into Review Manager 5 (Review Manager 2020); one review author (SL) entered the data, after which a second review author (VT) checked for any errors.

At a minimum, we planned to extract the following data, which we presented in the 'Characteristics of included studies' table.

- Trial registration ID
- 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, we recorded the unit of measurement, or if a scale was used, the upper and lower limits of the scale of measurement, and whether a high or low score was 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

Studies that were identified as meeting the inclusion criteria were independently reviewed by two authors (VT and SL), who assessed for risk of bias, using RoB 1, according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We considered the following domains: generation of the random sequence, allocation concealment, masking (blinding) of examiners, completeness of outcome data, selective reporting, and other biases (such as any conflicts of interest or financial interests).

We graded each domain 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 clearly specified primary and secondary outcomes.

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.

Measures of treatment effect

Our primary outcome was the change in BCVA in the amblyopic eye in logMAR 16 (± 2) weeks after commencing 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 authors assessed symmetry of their data, and which logMAR test they used, as different charts may yield different values.

Our main secondary outcome was a change in BCVA in the amblyopic eye in logMAR after 8 (± 2) weeks of treatment. This is also typically normally distributed, and we aimed to use the mean difference with 95% confidence intervals.

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 (SL) was to retrieve any missing data by contacting the authors of the relevant papers. If we failed to obtain this, but the review authors (SL and VT) 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;

- looking for poor overlap of the confidence intervals on the forest plot;
- 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 2017). 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 planned to generate 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 were relevant to our primary and secondary outcomes.

We intended to meta-analyse outcomes where appropriate.

We planned to use a random-effects model, unless there was a very small number of studies (less than three), in which case we planned to use a fixed-effect model. Had we detected substantial heterogeneity (either by methodological review of studies or by values of I² > 50%), as advised by Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017), we planned not to conduct a meta-analysis, unless effect estimates were in the same direction.

Subgroup analysis and investigation of heterogeneity

As we expected visual outcomes to be similar across studies, at both 8 (± 2) and 16 (± 2) week time points, 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 scored high risk 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.

Summary of findings and assessment of the certainty of the evidence

We prepared a summary of findings table, presenting relative and absolute risks. Two review authors (VT and SL) independently graded the overall certainty of the evidence for each outcome, using the GRADE factors (study limitations, indirectness of evidence, inconsistency of results, imprecision, and publication bias) and GRADEpro GDT software (GRADEpro GDT). We included the following outcomes in the summary of findings table:

- Change in distance best-corrected visual acuity (BCVA) in the amblyopic eye from baseline to 16 (± 2) weeks of treatment
- Change in BCVA in the amblyopic eye from baseline to 8 (± 2) weeks of treatment
- Change in distance BCVA in the amblyopic eye, measured 12 months after cessation of treatment
- Change in stereoacuity after 16 (± 2) and 8 (± 2) weeks of treatment
- Adherence to interventions, measured by usage time as a proportion of prescribed time, following 8 (± 2) and 16 (± 2) weeks of treatment
- Change in the interocular difference in contrast sensitivity from baseline to 16 (± 2) weeks
- Proportion of participants experiencing adverse events, such as permanent diplopia (double vision), at any time point

RESULTS

Description of studies

Results of the search

Our initial (2015) electronic search yielded a total of 541 references. The Cochrane Eyes and Vision Information Specialist (CIS) 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 eight full-text reports of seven studies for possible inclusion in the review. After this assessment, we excluded eight reports of seven studies (see [Characteristics of excluded studies](#) for details). That is, no studies met the inclusion criteria in 2015.

Updated searches run in November 2020 yielded a total of 482 records ([Figure 1](#)). After 108 duplicates were removed, the CIS screened the remaining 374 records, and removed 290 references that were not relevant to the scope of the review. We screened the remaining 84 references and obtained 17 full-text reports for further assessment. We included one new study in the review ([Holmes 2016](#)), and excluded 13 studies (see [Characteristics of excluded studies](#)).

Included studies

[Holmes 2016](#) recruited 385 children aged 5 to 13 years old, 187 of whom were female. Sixty-eight children were aged between three and eight years; we requested, received and analysed their data. Thirty-six children were randomised to a binocular iPad game (implementing anti-suppression therapy) and 32 children were randomised to conventional patching treatment. Please see [Characteristics of included studies](#) for further details.

Excluded studies

In our 2015 review, we excluded eight full-text reports of seven studies; none of the studies met the inclusion criteria. For the 2022 update, we excluded six full-text reports of six studies, this in total is 13 excluded studies. We have listed the reasons for exclusion in the [Characteristics of excluded studies](#) table. Discussion of the results of these studies are included in the [Description of the intervention](#) section.

Ongoing studies

We identified three ongoing studies ([ChiCTR1900022490](#); [NCT03754153](#); [NCT03767985](#)). Because [NCT03767985](#) should have completed recruitment, we contacted the study lead, who informed us that recruitment had finished, but they were awaiting the collection of follow-up data. As data collection is ongoing, we did not include this study in this review; however, we shall assess these data once they becomes available. [NCT03754153](#) and

[ChiCTR1900022490](#) may be included in the next edition of this review, as recruitment is still ongoing.

Risk of bias in included studies

We evaluated the risk of bias according to prespecified criteria in RoB 1 ([Figure 2](#)). Overall, we judged [Holmes 2016](#) to have a low risk of bias, however, some elements were unclear from the available reports ([Figure 3](#)).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

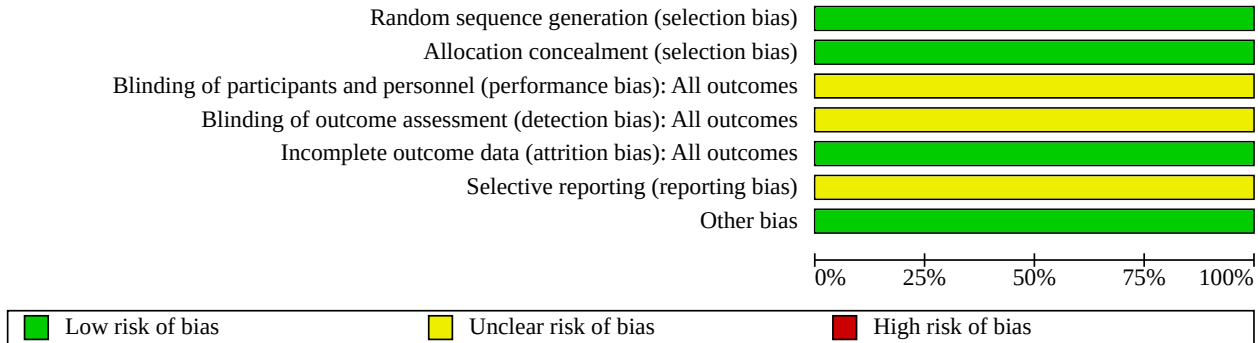
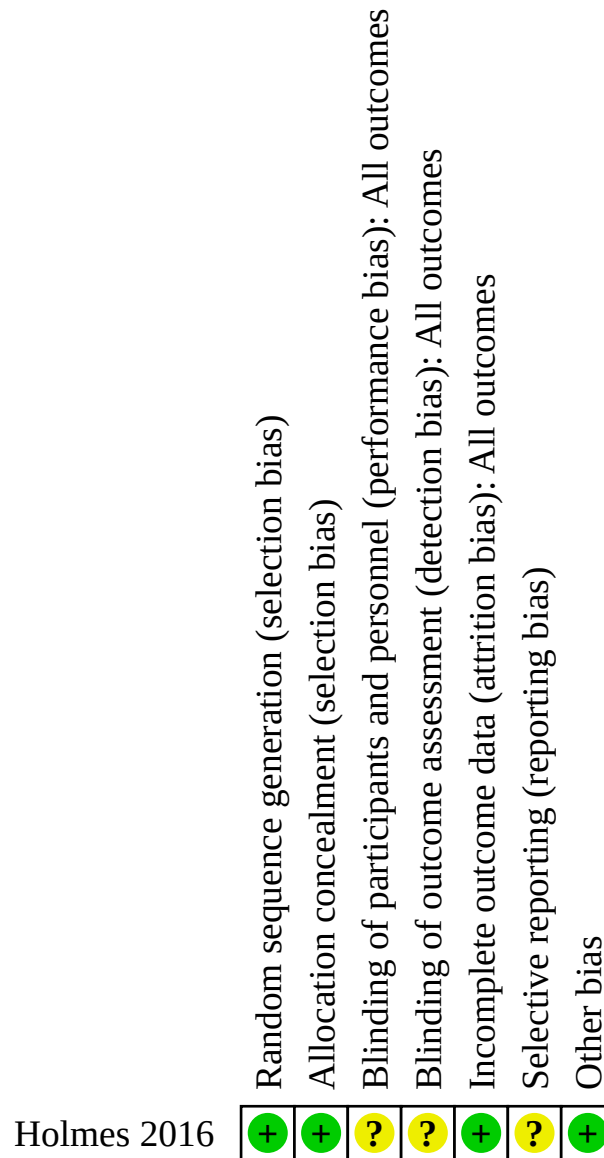


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Holmes 2016 used a computer generated permuted block design randomisation, with 1:1 allocation, stratified by age and site. This was considered an appropriate allocation method, and as such we determined that there was low risk of selection bias. Allocation concealment was also deemed adequate as the examiner was masked.

Blinding

The primary outcome of Holmes 2016 was the change in visual acuity following treatment with either a binocular iPad game (implementing anti-suppression therapy) or patching. Visual acuity and stereoacuity assessment were completed by an examiner masked to the participant's treatment allocation. Investigators unmasked to the participants' treatment allocation carried out the remaining examinations, such as ocular alignment and completion of questionnaires. As the primary outcome was performed by masked observers, detection bias for the primary outcome could

be considered low risk. However, having some investigations completed by team members unmasked to treatment allocation could introduce some bias on any other outcomes reported. Therefore, we judged the overall risk of bias to be unclear. Allocation was not blinded to the participants as they undertook two different tasks. It is not possible to undertake a placebo comparison with two different treatment arms.

Incomplete outcome data

Holmes 2016 data had an attrition rate of 4% in the patching group and 1% in the binocular group at 16 weeks. As mentioned above, the primary study outcome was change in visual acuity after 16 weeks of treatment. One hundred and ninety participants were recruited to each treatment arm; 182 participants in the patching group and 188 in the binocular group completed the 16 week follow-up visit. Therefore, the overall risk of attrition bias was considered to be low.

Selective reporting

We had insufficient evidence to judge reporting bias in Holmes 2016. Although the authors kindly provided subset data, it was unfortunately not possible to interpret this in all cases, due to the format in which the data were supplied. For example, it was not possible to interpret the stereoacuity data because the dataset was supplied in rank change format (i.e. the change from baseline per participant was not supplied). The analysis window for the 16-week follow-up visit was 98 to 140 days; from the supplementary information, seven participants completed the 16-week visit outside of the analysis window (at 147 to 196 days), though these participants were retained in the analysis. While the number completing the primary outcome visit outside the analysis window was small (7/370), the inclusion of participants outside the analysis window led to our assessment of an unclear risk of bias.

Other potential sources of bias

There were no risk of bias in relation to financial interests and no obvious conflict of interest identified.

Effects of interventions

See: [Summary of findings 1 Binocular iPad treatment compared with occlusion therapy for amblyopia](#)

We included one trial in this review (Holmes 2016). As detailed in the [Included studies](#) section and the [Summary of findings 1](#), 68 children from this study satisfied the inclusion criteria, and we therefore included their data in this review. Data were obtained for our primary outcome and the following secondary outcomes:

Primary outcome

Change in distance best-corrected visual acuity (BCVA) in the amblyopic eye from baseline to 16 (± 2) weeks of treatment

At 16 weeks of treatment, mean amblyopic eye BCVA in the patching group improved by 0.24 logMAR from baseline. Mean improvement for the iPad (binocular group) was 0.21 logMAR. Improvements for the patching group were 0.03 logMAR better (95% CI -0.04 worse to 0.10- better) than those of the binocular group, although the overlap of the CI with zero indicates a non-significant difference. Therefore, we cannot exclude the possibility that they are clinically comparable. The certainty of evidence for the visual acuity at 16

weeks of treatment was rated moderate using the GRADE criteria, downgrading by one level due to imprecision.

Secondary outcomes

Change in BCVA in the amblyopic eye from baseline to 8 (± 2) weeks of treatment

Improvement in amblyopic eye acuity was observed in both the patching and binocular groups at the 8-week follow-up interval. Improvement with patching was found to be 0.02 logMAR better (95% CI -0.04 worse to 0.08 better) than the binocular treatment. Again, this difference in improvement between the patching and binocular group is non-significant, suggesting that the tests are clinically comparable. The certainty of evidence for the visual acuity at 8 weeks of treatment was rated moderate using the GRADE criteria, downgrading by one level due to imprecision.

Change in distance BCVA in the amblyopic eye, 12 months after cessation of treatment

The included study did not measure this outcome.

Change in stereoacuity from baseline to 8 (± 2) and 16 (± 2) weeks of treatment

The included study did not measure this outcome.

Adherence to interventions following 8 (± 2) and 16 (± 2) weeks of treatment

Compliance was reported to be high in the patching group (90.3% reported adherence of 75% or more) compared to the iPad group (46.9% reported adherence of 75% or more). The certainty of evidence for the adherence to the interventions at 16 and 8 weeks of treatment was rated moderate using the GRADE criteria, downgrading by one level due to imprecision.

Change in the interocular difference in contrast sensitivity from baseline to 16 (± 2) weeks of treatment

The included study did not measure this outcome.

Proportion of participants experiencing adverse events, such as permanent diplopia (double vision), at any time point

In this small subgroup analysis, no participant was reported to have experienced permanent diplopia. However, it was noted that one participant self-reported episodes of diplopia up to 10 times a day at the 16-week follow-up. As this analysis included a relatively small sample size, the authors cannot be certain that there was adequate power to detect any true risk of permanent diplopia in this study. The certainty of evidence was downgraded by two levels and rated low for the proportion of participants reporting adverse events due to the sample size.

DISCUSSION

Summary of main results

We identified one RCT examining anti-suppression therapy that met our inclusion criteria (Holmes 2016). This study compared a new anti-suppression therapy against the standard patching treatment. We analysed a subset of data that fit our criteria. In this, our findings were that the subset of data, both treatments successfully improved acuity, though the difference between them

was non-significant, and the data was limited by the small sample size and imprecision in the primary and secondary outcomes.

Overall completeness and applicability of evidence

[Holmes 2016](#) examined the efficacy of a binocular treatment (anti-suppression therapy) compared to conventional treatment (patching) in children with amblyopia. The study included children aged 5 to 12 years, making the full published dataset outside the age range of this review. The full published dataset also included children who had previously undergone amblyopia treatment. A subset of participants did fit the remit of this review and following a request, [Holmes 2016](#) kindly obliged by providing the data for the eligible subset in order to complete this update.

We obtained data relating to children aged five to eight years who did not have any prior patching treatment. Participants were randomised to either binocular treatment or conventional patching. Data were available for 16-week and 8-week follow-up visits ([Summary of findings 1](#)). We obtained data for the mean amblyopic eye visual acuity, adverse events (diplopia), and adherence to prescribed treatment at each follow-up point. We were unable to analyse the provided stereoacuity values because the results were presented in a rank format. We subsequently requested further clarification and individual data from the study authors, but unfortunately, received no response. Contrast sensitivity was not evaluated in this study, so we did not seek the data. Final follow-up in this study was 16 weeks; therefore, change in distance BCVA in the amblyopic eye 12 months after cessation of treatment was not available.

Despite all of the relevant studies being identified in this review, the review remains limited by the number of studies available for inclusion. Many studies were excluded as the participant group included children who had had prior amblyopia treatment. Regression of visual acuity over time is possible following conventional amblyopia treatment; therefore, including previously treated amblyopes can confound data, as it is not possible to differentiate between visual acuity gain from the study treatment arms or previous amblyopia treatment. In order to identify real change achieved with binocular amblyopia treatments, it is important to maintain exclusion of previously treated amblyopia.

Quality of the evidence

Only one RCT met the criteria for inclusion ([Holmes 2016](#)), from which only a small subset of the data were applicable to this review. The overall certainty of the included methodology was good. The study was limited in that the protocol included previously treated amblyopic children, though however the subset analysis that we undertook dealt with this issue. There was no inconsistency of results noted, but we do note that the data provided for the 16-week and 8-week timepoints was low. We therefore downgraded its rating due to the resulting imprecision. We graded the certainty of evidence for the proportion of participants experiencing adverse events to low and downgraded this two levels due to the small sample size. There was no notable publication bias. Overall, the available evidence does not therefore allow us to draw robust conclusions regarding the efficacy of binocular amblyopia treatments compared to conventional patching or blurring eye drops.

Potential biases in the review process

Although all relevant studies were identified in this review, the review is obviously limited by the number of studies suitable for inclusion. Information and data was provided by [Holmes 2016](#) on request, however requests for further clarification of the data were not answered. Given our adherence to the protocol set out in our plan, the review presents the best-possible characterisation of the current evidence on the efficacy of these treatments.

Agreements and disagreements with other studies or reviews

The rather muted conclusions of this review differ somewhat from the optimism of reviews discussing exploratory studies on binocular treatments for amblyopia ([Hess 2014](#); [Hess 2015](#); [Levi 2015](#); [Piano 2019](#); [Tailor 2016](#); [Tailor 2017](#)). A range of these exploratory studies have investigated the effectiveness of binocular treatments on individuals with amblyopia ([Black 2012](#); [Bossi 2017](#); [Cleary 2009](#); [Eastgate 2006](#); [Foss 2013](#); [Gambacorta 2018](#); [Gao 2018](#); [Herbison 2013](#); [Herbison 2016](#); [Hess 2010a](#); [Hess 2010b](#); [Hess 2012](#); [Kelly 2016](#); [Knox 2012](#); [Li 2014](#); [Rajavi 2019](#); [Repka 2014](#); [Sauvan 2019](#); [Spiegel 2013a](#); [Spiegel 2013b](#); [To 2011](#); [Vedamurthy 2015b](#); [Waddingham 2006](#)), a summary of which is included in [Table 2](#) and [Table 3](#). While these do give us insight into possible effectiveness of the binocular treatment approach, the results of these published cohort studies are limited by various methodological factors, such as 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. A further systematic review encompassing studies outside the remit of this review may be useful in this regard. However, the variability in treatment outcomes amongst these studies does suggest that their success will depend on the precise nature of the binocular treatment approach, including details such as the treatment duration, daily dose duration, and viewing content. Therefore, it is important that these approaches are examined in further RCTs.

AUTHORS' CONCLUSIONS

Implications for practice

We only included a subset of data from one randomised controlled trial in this review and find the current evidence base is insufficient to recommend binocular treatment for clinical practice at this time. This was due to the downgrading two of the five GRADE domains for imprecision of the data and the small sample size. We are moderately confident in the results of the subset of data for this trial. It seems probable that following four months of treatment, improvement in amblyopic eye acuity obtained with binocular treatment is comparable to that obtained with patching. However, this study lacks longer term follow-up data to indicate whether these gains can be maintained over time. Furthermore, it does not have a sufficient sample size to establish the risk of permanent diplopia following treatment.

Implications for research

The current evidence base for binocular treatments in amblyopia is limited by methodology, in particular by the inclusion of previously treated children with amblyopia, or the reporting of non-controlled cohort studies.

Future research should be conducted in the form of randomised controlled trials (RCT), using acknowledged methods of visual acuity and stereoacuity assessment with known reproducibility in order to reach firm conclusions regarding the applicability and efficacy of binocular treatments in amblyopia. Other important outcome measures include outcomes reported by users, treatment adherence levels, amblyopic eye acuity after prolonged periods (e.g. 12 months), and recurrence rates of amblyopia after cessation of treatment. There are currently a number of RCTs in progress, investigating binocular treatments in amblyopia, the results of which may provide further guidance in this area in the future.

ACKNOWLEDGEMENTS

2022 update

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We thank Ray Kraker, Director, PEDIG coordinating centre for providing the subset data from [Holmes 2016](#) included in this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Holmes 2016
Study characteristics

Methods	Randomised controlled trial
Participants	385; subset 68 to be analysed
Interventions	36 for Binocular iPad game, 32 for conventional treatment
Outcomes	Change in amblyopic-eye VA from baseline to 16 weeks
Notes	<p>Additional information gathered from supplement 1 and 2, as not available and clear in the final published article.</p> <p>Funding source. This study was supported by the National Eye Institute, National Institutes of Health (NIH), Department of Health and Human Services grants EY011751, EY023198, and EY018810. Casey Eye Institute received support from NIH grant EY010572 to fund shared departmental resources for research purposes. Casey Eye Institute, Wilmer Institute, Mayo Clinic, Rainbow Babies and Children's Hospital, and University of Minnesota received support from an unrestricted grant from Research to Prevent Blindness Inc.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permutated block design stratified by age group (5 to < 7 years and 7 to < 13 years) and site
Allocation concealment (selection bias)	Low risk	Computer generated via the PEDIG website, determined by age group and site
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	A masked examiner performed distance visual acuity testing and stereo-acuity testing. Researcher was not masked to randomisation of participant treatment group.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Main outcomes were performed by masked examiner. Other procedures were undertaken by researchers who were not masked to outcome of participant treatment group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The 16-week primary outcome was completed by 182 children (95.8%) in the binocular group and 188 children (96.4%) in the patching group.
Selective reporting (reporting bias)	Unclear risk	CONSORT legend leads us to believe there is an unclear risk of reporting bias due to some participants performing outcome visits outside the specified time-point window

Holmes 2016 *(Continued)*

Other bias	Low risk	There was no evidence demonstrating a conflict of evidence or funding source conflict for this study
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Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Astle 2011	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
Birch 2020	Insufficient follow-up interval (too short)
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
Gambacorta 2018	Insufficient follow-up interval (too short)
Gao 2018	None of the treatment groups received an occlusion or blurring treatment
Herbison 2016	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
Kelly 2016	Study time points not compatible with Cochrane protocol (8 or 16 weeks).
Lennerstrand 1983	Stimulation therapy: grating; full-time occlusion. Better-seeing eye occluded during treatment, so treatment not binocular
Rajavi 2019	Insufficient follow-up interval (too short)

Characteristics of ongoing studies *[ordered by study ID]*
ChiCTR1900022490

Study name	A randomized controlled study for a new binocular game in children with anisometropic amblyopia
Methods	Randomised controlled trial, patching treatment vs binocular game
Participants	92
Interventions	Binocular game
Outcomes	Ongoing

ChiCTR1900022490 (Continued)

Starting date	2019
Contact information	dr_zhaochen@163.com
Notes	Recruitment end date March 2021

NCT03754153

Study name	Binocularly Balanced Viewing Study (BALANCE)
Methods	Randomised controlled trial, novel treatment vs conventional patching or pharmacological blurring
Participants	66
Interventions	Balanced binocular viewing (BBV) - customised movies presented on Nintendo 3DSXL console
Outcomes	Ongoing
Starting date	September 2019
Contact information	res-admin@moorfields.nhs.uk
Notes	Anticipated study conclusion June 2021

NCT03767985

Study name	A randomised clinical trial objectively comparing the effect of patching therapy with video gaming for amblyopia
Methods	Randomised controlled trial, standard patching therapy or the dichoptic video game therapy
Participants	124
Interventions	Dichoptic video game therapy
Outcomes	Ongoing
Starting date	December 2017
Contact information	s.loudon@erasmusmc.nl
Notes	Anticipated study conclusion June 2021

DATA AND ANALYSES

Comparison 1. iPad versus patching

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Change in BCVA amblyopic eye at 16 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2 Change in BCVA amblyopic eye at 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: iPad versus patching, Outcome 1: Change in BCVA amblyopic eye at 16 weeks

Study or Subgroup	iPad			Patching			Mean Difference IV, Fixed, 95% CI [logMAR]	Mean Difference IV, Fixed, 95% CI [logMAR]
	Mean [logMAR]	SD [logMAR]	Total	Mean [logMAR]	SD [logMAR]	Total		
Holmes 2016	-0.21	0.15	32	-0.24	0.12	31	0.03 [-0.04, 0.10]	

Analysis 1.2. Comparison 1: iPad versus patching, Outcome 2: Change in BCVA amblyopic eye at 8 weeks

Study or Subgroup	iPad			Patching			Mean Difference IV, Fixed, 95% CI [logMAR]	Mean Difference IV, Fixed, 95% CI [logMAR]
	Mean [logMAR]	SD [logMAR]	Total	Mean [logMAR]	SD [logMAR]	Total		
Holmes 2016	-0.16	0.13	32	-0.18	0.13	30	0.02 [-0.04, 0.08]	

ADDITIONAL TABLES

Table 1. Data extraction form

Review author	
Trial registration 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)

Table 1. Data extraction form (Continued)

Outcomes (as defined in study)	Primary outcome					
Please specify which	Change in distance BCVA in the amblyopic eye following 16(±2) weeks of intervention, as measured in logMAR units on an age-appropriate acuity test.					
	Secondary outcomes					
	<ul style="list-style-type: none"> • Main secondary outcome: change in BCVA in the amblyopic eye from baseline to 8 (± 2) weeks, as measured in logMAR units on an age-appropriate acuity test • Change in stereoacuity after 16 (± 2) and 8 (± 2) weeks of intervention, measured in octaves (Adams 2009) • Adherence to intervention determined by a ratio of usage/prescribed treatment dosage • Change in contrast sensitivity interocular difference from baseline to 16 (± 2) weeks, measured using any validated test • Proportion of participants experiencing an adverse event of permanent diplopia (double vision) at any time point during intervention 					
Interventions compared	Intervention 1 = standard care (occlusion or pharmacological blurring) Intervention 2 = binocular treatment					
PRIMARY OUTCOME	Intervention 1			Intervention 2		
Change in distance BCVA in the amblyopic eye following 16 (± 2) weeks of intervention, as measured in logMAR units on an age-appropriate acuity test						
Time point	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*
Baseline (note method used to measure BCVA)						
BCVA at 16 (± 2)						
Or: improvement of BCVA from baseline						
SECONDARY OUTCOME	Intervention 1			Intervention 2		
Main secondary outcome: change in BCVA in the amblyopic eye from baseline to 8 (± 2) weeks, as measured in logMAR units on an age-appropriate acuity test						
Time point	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*
Baseline (note method used to measure BCVA)						
BCVA at 8 (± 2)						
Or: improvement of BCVA from baseline						
SECONDARY OUTCOME	Intervention 1			Intervention 2		

Table 1. Data extraction form *(Continued)*

Time point	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*
Baseline stereopsis						
Change in stereopsis after 16 (± 2)						
Change in stereoacuity after 8 (± 2) weeks of intervention, measured in octaves						
Time point						
Baseline stereopsis						
Change in stereopsis after 8 (± 2)						
SECONDARY OUTCOME		Intervention 1		Intervention 2		
Adherence to intervention determined by a ratio of usage/prescribed treatment dosage						
Time point	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*
End of intervention (specify time from start of treatment)						
SECONDARY OUTCOME		Intervention 1	Intervention 2			
Change in contrast sensitivity interocular difference from baseline to 16 (± 2) weeks measured using any validated test						
Time point	Total number of participants	Mean	Standard deviation*	Total number of participants	Mean	Standard deviation*
End of intervention (specify test)						
SECONDARY OUTCOME		Intervention 1		Intervention 2		
Adverse events (Proportion of participants experiencing an adverse event of permanent diplopia (double vision) at any time point during intervention.)						
Time point	Total number of participants	Number of affected participants		Total number of participants	Number of affected participants	

Table 1. Data extraction form *(Continued)*

Permanent diplopia						
Time point						
Other (specify)						
SECONDARY OUTCOME	Intervention 1			Intervention 2		
Change in distance BCVA in the amblyopic eye 12 months after cessation of treatment						
Time point	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 treatment						
Or: improvement of BCVA from baseline to 12 months post-treatment						

ATI: Amblyopia Treatment Index

BCVA: best-corrected visual acuity

CAT-QoL: Child Amblyopia Treatment Questionnaire

QoL: quality of life

RCT: randomised controlled trial

Table 2. Summary of methodologies in published studies of binocular treatment for amblyopia

	Treatment	N	Age range (mean)	Control group	Type of amblyopia	Previous treatment other than glasses	Treatment duration	Daily dose received	Total dose received
Hess 2010a; Hess 2010b	Anti-suppression: dichoptic coherent motion, via lenticular overlay, red-green glasses or head-mounted display	9	24 to 49 (39.6)	No	Strabismic, combined mechanism	5/9 occlusion	Around 60 trials/block (0.5 to 3.7 per week, i.e. 1 to 3 hours in 2 to 3 days for 2 to 6 weeks)	-	8.2 blocks per week (SD 6.3)
Hess 2012	Anti-suppression: Tetris game with modulation of contrast on iPod	10	17 to 51 (33.8)	No	All	4/10 occlusion	0.5 to 2 hours per day for 1 to 9 weeks	45 min to 1 hour	15 sessions (SD 4)
Knox 2012	Anti-suppression: Tetris game using head-mounted display goggles	14	5 to 14 (8.5)	No	All	All occlusion (at least 6 months)	1 hour for 5 days in 1 week	1 hour	5 hours
To 2011	Anti-suppression: Tetris game, interleaved breaks, via lenticular layer	9	18 to 51 (35.5)	No	All	Not specified	10 to 19 sessions	Not specified	15.75 hours (0.88 to 27.42 hours per week)
Li 2014	Anti-suppression: binocular games through anaglyph glasses (contrast increment in fellow eye)	45/50 binocular group; 24/25 sham group	4 to 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)
Kelly 2016	Anti-suppression: binocular iPad adventure game: red/green anaglyphic glasses worn to separate game elements; high contrast elements seen by amblyopic eye with altered contrast to fellow eye relative to visual acuity level	28	4 to 10 (6.78)	Yes	All	None	10 hours total (1 hour a day for 5 days over 2 weeks)	1 hour per day	10 hours

Table 2. Summary of methodologies in published studies of binocular treatment for amblyopia (Continued)

Gao 2018	Anti-suppression: falling blocks game on iPod with dichoptic offset of contrast	115 (11 7 to 8 years of age)	> 7 years (age range not specified)	Yes (placebo)	All	No	1 to 2 hours daily for six weeks	–	>10.5hrs (i.e. 25% of prescribed dose)
Sauvan 2019	Anti-suppression: dichoptic movie design: parts of image seen by one eye and complementary parts by the other with unequal contrast to amblyopic and non amblyopic eye	17	9 to 67 years (34.47)	Yes (sham - treatment and patch for 2 hours prior to treatment)	All	7/17 previous occlusion treatment	6 x 1.5 hour dichoptic movie sessions for both groups; patched group augmented with 2 hours of patching prior to session	–	16/17 participants - 9 hours 1/17 participant – 7.5 hours
Birch 2020	Anti-suppression: binocular iPad adventure game: red/green anaglyphic glasses worn to separate game elements; high contrast elements seen by amblyopic eye with altered contrast to fellow eye relative to visual acuity level	47	4.3 to 10.8 (6.8)	Yes	All	58% previous patching, atropine or both	10 x 1 hour session over 2 weeks	1 hour 5 days a week	10 hours
Vedamurthy 2015a	Dichoptic action video-games	38	39.18 years	Yes (sham - watching movies monocularly with patch on)	All	25/38 previous occlusion treatment	Total treatment time 40 hours	–	1.5 to 2 hours for 2 to 5 times per week
Vedamurthy 2015b	Dichoptic action video-games	23	39.57 (15.74)	No	All	Not stated	Total treatment 40 hours	Not stated	Not stated
Waddingham 2006	I-BiT™: videos and modified video games (imbalanced visual scene to favour amblyopic eye)	6	5.42 to 7.75 (6.25)	No	All	3 occlusion; 3 neither occlusion nor atropine	7 to 15 sessions of 20 minutes each	1 to 2 sessions of 20 minutes twice a week	mean 4.4 hours
Herbison 2013	I-BiT™: videos and modified video games (imbalanced visual scene to favour amblyopic eye)	10	4 to 8 (5.4)	No	All	All, occlusion or atropine	6 weeks, 0 to 10 games + 15 to 30 videos	0 to 10 to 15 to 30 min per day	159.3 min

Table 2. Summary of methodologies in published studies of binocular treatment for amblyopia (Continued)

Herbison 2016	I-BiT™: videos and modified video games (imbalanced visual scene to favour amblyopic eye)	75	4 to 8 (separate means per group)	No	All	All, occlusion or atropine	30 minutes a week for six weeks	–	3 hours
Bossi 2017	Balanced binocular viewing: watching modified movies wearing 3D glasses	22	3.5 to 11.3 (6.6)	No	All	None	Anisometropia – 56 hours Strabismus – 168 hours	56 min per day	Not reported

Table 3. Summary of outcomes in published studies of binocular treatment for amblyopia

	Treatment adherence %	Visual acuity gain amblyopic eye in logMAR (SD)	Visual acuity % change in amblyopic eye *	Stereoacuity gain	Recurrence
Hess 2010a; Hess 2010b	-	0.26	Not specified	“significant”	Not specified
Hess 2012	-	0.19 (0.17)	Not specified	6/10 improved	Nil at 1 to 2 months (in 4/10)
Knox 2012	All	0.09	22%	7/14 (small squint), 4/7 significant	Not specified
To 2011	All	0.16 (0.18)	Not specified (fellow eye acuity not available)	Trend of improvement	Not specified
Li 2014	34/45 (76%)	0.08 (0.01)	Not specified (not individual acuities, also in supp. material)	5/50, not significant	Nil at 3 months
Kelly 2016	82 to 100%				
Gao 2018	64% in treatment group	0.06 (0.12) active group	Not specified	0.23 (0.76) log seconds of arc in active group; no significant change	Not specified
Sauvan 2019	16/17 participants – 9 hours 1/17 participant – 7.5 hours	0.08 in non-patched group	Not specified	Trend of improvement in both groups; no statistically significant improvement	Not specified
Birch 2020	103% in binocular group	0.15	Not specified	No significant improvement reported	Not specified
Vedamurthy 2015a	All	0.14 (0.01) in dichoptic game group	28% (2%)	0.18 (0.05) log arc second improvement	0.12 (0.02) in dichoptic game group at 8 week follow-up
Vedamurthy 2015b	Not stated	0.14	Not specified		
Waddingham 2006	-	0.27	42%	-	Not specified
Herbison 2013	88.5%	0.18 (0.143)	32.3%	Not measured	0.055 at 10 weeks (in 6/9)
Herbison 2016	> 90% (specifics not given)	0.06 to 0.10 (mean 0.08)	Not specified	No significant improvement	Not specified
Bossi 2017	Anisometropia – 87%	0.27 (0.22)	not reported	Anisometropia – 6/7, significant mean gain of 165 seconds of arc Strabismus – not reported	Unclear, as participants went onto conventional treatments after BBV

Table 3. Summary of outcomes in published studies of binocular treatment for amblyopia (Continued)

Strabismus –
 between 84%
 and 90%

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)

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 Ovid 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 2006](#).

Appendix 3. Embase Ovid 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. anisometri\$.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. ISRCTN search strategy

Amblyopia AND participant age range: child

Appendix 5. ClinicalTrials.gov search strategy

Condition = amblyopia AND study type = Interventional studies AND age = children

Appendix 6. WHO ICTRP search strategy

amblyopia = Condition limited to children

WHAT'S NEW

Date	Event	Description
18 February 2021	New citation required and conclusions have changed	One trial included (Holmes 2016); subset data analysed; conclusions updated
18 February 2021	New search has been performed	Searches updated; secondary outcomes updated; addition of a summary of findings table

HISTORY

Protocol first published: Issue 11, 2014

Review first published: Issue 8, 2015

CONTRIBUTIONS OF AUTHORS

2022 update

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

DECLARATIONS OF INTEREST

VT: No relevant interests were disclosed

SL: No relevant interests were disclosed

MB: No relevant interests were disclosed

CB: No relevant interests were disclosed

JG: No relevant interests were disclosed

ADN: received payment from

- Coopervision inc. for speaking at an educational event;
- Novartis for participation in a patient/family/eye care professional forum;
- Santen and SightGlassVision for participating on their Advisory Board.

These activities are unrelated to the topic of this review.

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Internal sources

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The views expressed are those of the review author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

External sources

- National Institute for Health Research (NIHR), UK

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- Public Health Agency, UK

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- Queen's University Belfast, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2022 review update

Following updated Cochrane guidance, we included methods for preparing a summary of findings table, including the use of the GRADE classification to grade the overall certainty of the evidence for each outcome, specified for inclusion in the summary of findings table.

The primary outcome of the previous review was the change in visual acuity 12 months following cessation of treatment. Unfortunately, there are no such trials investigating binocular treatment for amblyopia reporting this data. Many studies investigating binocular treatments report short-term outcomes and it is unlikely at this stage that any trials will be in a position to report such data in the near future, given the early stages of these trials. There is also a paucity of data for this outcome in the conventional occlusion evidence base to facilitate comparison. In view of this, we amended the primary and secondary outcome time points in this review to 8 (± 2) and 16 (± 2) weeks. We undertook this amendment to ensure the maximum inclusion of available randomised controlled trials (RCT) to inform management decisions. While we amended the primary outcome, the outcome of change in amblyopic eye acuity 12 months after the cessation of treatment is still of utmost importance to accurately inform clinical practice. As such, this outcome remains an essential part of this review, and features as a secondary outcome. We have also clarified ambiguity in how the change in amblyopic eye best corrected visual acuity (BCVA) was reported – this is now reported as the change in BCVA of the amblyopic eye from baseline.

We have now simplified secondary outcomes to include the most salient outcomes, with amended secondary outcome time points such that where two timepoints are to be considered these consistently are 8 (± 2) and 16 (± 2) weeks. In order to ensure that any included RCTs provided adequate follow-up time to identify real change in BCVA in both the conventional and binocular treatment arms, we decided to exclude studies where the follow-up time was less than 8 (± 2) weeks. Currently in the UK, children undergoing amblyopia treatment attend between 4 and 10 follow-up visits per annum ([Royal College of Ophthalmologists](#)). Therefore, 8 (± 2)-week follow-up was selected as the minimum time frame, to ensure the maximum inclusion of studies, whilst still ensuring that those included had allowed sufficient follow-up time for treatment in the control and intervention arms to show treatment effect.

Different stereotests may be used across studies; as such, comparisons of any change in stereoacuity during treatment may be confounded by the type(s) of stereotest used. Therefore, we decided to amend how we reported the change in stereoacuity to ensure appropriate comparison. In this update, change in stereoacuity was reported in octaves, to ensure appropriate comparison across stereotests ([Adams 2009](#)).

Trial registration ID was added as a data collection item.

Where previously we had decided to collate rather than meta-analyse data, we amended this in line with current guidance; in this protocol update, we decided to undertake meta-analysis of outcomes where appropriate.

INDEX TERMS

Medical Subject Headings (MeSH)

Amblyopia [*therapy]

MeSH check words

Child; Child, Preschool; Humans