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Optical treatment of amblyopia in older children and adults is essential prior to enrolment in a clinical trial

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Abstract

Purpose: Optical treatment alone can improve visual acuity (VA) in children with amblyopia, thus clinical trials investigating additional amblyopia therapies (such as patching or videogames) for children require a preceding optical treatment phase. Emerging therapies for adult patients are entering clinical trials. It is unknown whether optical treatment is effective for adults with amblyopia and whether an optical correction phase is required for trials involving adults.

Methods: We examined participants who underwent optical treatment in the Binocular Treatment for Amblyopia using Videogames (BRAVO) clinical trial (ANZCTR ID: ACTRN12613001004752). Participants were recruited in three age groups (7 to 12, 13 to 17, or ≥18 years), and had unilateral amblyopia due to anisometropia and/or strabismus, with amblyopic eye VA of 0.30–1.00 logMAR (6/12 to 6/60, 20/40 to 20/200). Corrective lenses were prescribed based on cycloplegic refraction to fully correct any anisometropia. VA was assessed using the electronic visual acuity testing algorithm (e-ETDRS) test and near stereoacuity was assessed using the Randot Preschool Test. Participants were assessed every four weeks up to 16 weeks, until either VA was stable or until amblyopic eye VA improved to better than 0.30 logMAR, rendering the participant ineligible for the trial.

Results: Eighty participants (mean age 24.6 years, range 7.6–55.5 years) completed four to 16 weeks of optical treatment. A small but statistically significant mean improvement in amblyopic eye VA of 0.05 logMAR was observed (S.D. 0.08 logMAR; paired *t*-test $p < 0.0001$). Twenty-five participants (31%) improved by ≥1 logMAR line and of these, seven (9%) improved by ≥2 logMAR lines. Stereoacuity improved in 15 participants (19%). Visual improvements were not associated with age, presence of strabismus, or prior occlusion treatment. Two adult participants withdrew due to intolerance to anisometropic correction.

Sixteen out of 80 participants (20%) achieved better than 0.30 logMAR VA in the amblyopic eye after optical treatment. Nine of these participants attended additional follow-up and four (44%) showed further VA improvements.
Conclusions: Improvements from optical treatment resulted in one-fifth of participants becoming ineligible for the main clinical trial. Studies investigating additional amblyopia therapies must include an appropriate optical treatment only phase and/or parallel treatment group regardless of patient age. Optical treatment of amblyopia in adult patients warrants further investigation.

Introduction

Amblyopia is a neurodevelopmental vision disorder caused by early abnormal visual experience, most commonly due to anisometropia, strabismus, or both (mixed mechanism amblyopia). Unilateral amblyopia affects 1% to 3% of children[1–3] and is the second most common cause of visual impairment in children[4, 5] and adults less than 60 years of age[6] after uncorrected refractive error. While significant effort has been made to diagnose and treat amblyopia in early childhood, most children who undergo conventional therapies do not achieve equal visual acuity in the two eyes[7, 8] or reach normal stereoacuity.[9, 10] Regression of visual gains after stopping treatment is also common.[11, 12] Conventional treatment is sometimes not offered to patients with late diagnoses due to an assumed lack of neuroplasticity for visual recovery. As a result, there are many older patients with residual amblyopia who may benefit from treatment.

Full-time wear of refractive correction ('optical treatment') can produce delayed improvements in visual functions, in addition to the immediate effects of ameliorating refractive error. For children 3 to 7 years of age with no prior treatment, 70–80% experience significant improvement of two or more logMAR lines in amblyopic eye visual acuity after 15–30 weeks of spectacle wear, and 25–45% achieve equal visual acuity between eyes, requiring no further treatment.[13–16] A previous clinical trial conducted by the Paediatric Eye Disease Investigator Group (PEDIG) found that up to 24 weeks of wearing optical correction alone significantly improved visual acuity for 23–25% of 7 to 17 year old patients with mixed treatment history.[17] The effectiveness of this simple intervention has led to optical treatment becoming the first step in conventional treatment for amblyopia[18–21] as well as a standard prerequisite phase for studies investigating additional therapies (such as patching, atropine eye drops, or videogame treatments) in children.[22]

Optical treatment alone in adults has not been comprehensively evaluated. However, a number of studies have demonstrated that adults can improve from combination therapies involving spectacle correction plus part-time occlusion,[23–25] occlusion augmented by videogame play,[26, 27] perceptual learning,[28, 29] and binocular treatments.[30, 31] One study of dichoptic videogame treatment performed by Vedamurthy, Nahum & Huang *et al.*[30] noted three adults who improved to near-normal visual acuity 6–8 weeks after updating refractive correction, but no clinical details were reported.

Given the effectiveness of optical treatment in younger patients and potential neuroplasticity in adults, we may expect some proportion of adults to also improve from optical treatment alone. This possibility led us to apply the same standard optical treatment protocol to all participants in the Binocular treatment for amblyopia using videogames (BRAVO) clinical trial (Australian New Zealand Clinical Trails Registry, ID: ACTRN12613001004752). We have previously reported the case of a 48-year-old participant with anisometropic amblyopia in this study who demonstrated significant improvements after four weeks of spectacle wear.[32] Building on this work, we present here the completed pre-randomisation dataset from this clinical trial to evaluate the effects of age, prior treatment history, and type of amblyopia on visual outcomes from optical treatment.

Methods

Participants

The BRAVO study was a placebo-controlled, double-masked randomised clinical trial of an iPod-based binocular videogame treatment for amblyopia in older children and adults (see Guo, Babu & Black *et al.*[33] for the full study protocol and Gao, Guo, Babu et al.[34] for the trial results). The trial included participants with unilateral amblyopia due to anisometropia and/or strabismus who were not currently undergoing any amblyopia therapy apart from wearing refractive correction. Anisometropia was defined as a difference in spherical equivalent refraction of ≥0.50 D or a difference in astigmatism of ≥1.50 D between eyes in any meridian. Strabismus was defined as presence of heterotropia at any viewing distance, or history of strabismus corrected by surgery or refractive correction. Participants were recruited to three pre-specified age groups: children aged 7–12 years (n = 55), teenagers aged 13–17 years (n = 20), and adults aged 18 years or older with no upper age limit (n = 62). Inclusion criteria for distance visual acuity

(DVA) were 0.30–1.00 logMAR (6/12–6/60, 20/40–20/200) for the amblyopic eye and 0.10 logMAR (6/7.5, 20/25) or better for the fellow eye, measured at study entry using the electronic Early Treatment of Diabetic Retinopathy Study (e-ETDRS) protocol.[35, 36] Measurements were taken through habitual lenses if these met the study prescribing criteria (Appendix S1), otherwise trial lenses were used. Participants also had to align a dichoptic nonius cross on an iPod device within ±1.0 cm tolerances (±1.4° at 40 cm) so that sufficient screen space remained to display the active binocular videogame.[37] This test excluded those with large-angle strabismus who would not be able to play the treatment videogame on an iPod screen if randomised. Participants who met all other inclusion criteria but had not worn appropriate refractive correction full time for at least four months before study entry underwent optical treatment for confirmation of eligibility.

Participants were recruited at clinical- and university-based study sites in Auckland (New Zealand), Melbourne (Australia), Hong Kong (China), and Waterloo and Montreal (Canada). All adult participants and parents/guardians of younger participants gave informed consent to take part in this study. The consent included the optical treatment phase and a provision for data to be analysed even if participants became ineligible for randomisation. All study procedures were approved by institutional ethics review boards at each study site and adhered to the tenets of the Declaration of Helsinki.

Optical treatment

Participants who did not have corrective lenses meeting the study prescribing criteria were prescribed new lenses based on a cycloplegic refraction conducted at study entry. The study protocol recommended cyclopentolate 1.0% for all child and pre-presbyopic adult participants. However, the drug and dosage varied depending on local clinical standards and participant characteristics such as age and iris pigment. Study prescribing criteria were based on established amblyopia clinical trial protocols published by PEDIG.[13, 38–40] Myopia and astigmatism were fully corrected for each eye, hyperopia could be under-corrected by up to 1.50 DS from the cycloplegic refraction but the reduction in plus sphere was symmetrical so that anisometropia was fully corrected, and presbyopia (if present) was corrected with near addition lenses (see Appendix S1). Clinicians could prescribe standard spectacle lenses, lenses designed to reduce aniseikonia, and/or soft contact lenses at their discretion.

Where new lenses were prescribed, baseline vision measurements were taken through new lenses on the day of dispensing after at least 10 min of wear. These new baseline measurements superseded measurements through trial lenses made at study entry, and removed from our analysis any potential effects from optical differences between trial lenses and prescribed spectacles or contact lenses. For participants who had habitual correction meeting the study prescribing criteria but worn for less than four months full time or on a part-time basis prior to study entry, optical treatment baseline measurements were taken through habitual lenses at study entry.

Participants began wearing lenses full time after their baseline visit. Full-time wear was defined as more than 50% of waking hours, although participants were encouraged to wear lenses as much as practical. Compliance was assessed by self-report. Participants were specifically instructed not to attempt patching or any other amblyopia therapy.

Participants attended follow-up assessments every four weeks (±1 week) for up to 16 weeks maximum. Optical treatment was continued until eligibility for the clinical trial was confirmed, at which point participants exited the main optical treatment phase. Participants became eligible for randomisation if they could wear lenses meeting the study prescribing criteria comfortably full time and DVA became stable (≤0.10 logMAR [1 line] change for each eye and binocularly at two consecutive visits ≥4 weeks apart, through the same prescription) within the BRAVO study inclusion range. If participants required a prescription change or had poor compliance with full-time lens wear, then they continued optical treatment until they could wear lenses full time and meet all DVA criteria. Once randomised, participants exited the optical treatment phase and began videogame treatment in the main clinical trial. If a participant's amblyopic eye DVA became better than 0.30 logMAR (6/12 or 20/40) during optical treatment, they were ineligible for randomisation and also exited the optical treatment phase. Vision data from the follow-up visit at which participants exited the optical treatment phase of the clinical trial due to randomisation or ineligibility were used as the outcome time-point for the main statistical analyses.

The subset of participants who became ineligible for the clinical trial due to amblyopic eye DVA becoming better than 0.30 logMAR could choose to attend additional follow-up visits outside of the clinical trial protocol, to assess visual improvements up to 16 weeks from the optical treatment baseline. Data obtained during additional follow-up measurements were analysed separately and were not included in the main statistical analyses.

Vision measurements

Vision measurements at baseline and follow-up visits were taken through the same prescription spectacles or contact lenses worn during optical treatment. The primary outcome was DVA, tested at 3 m using the e-ETDRS protocol on an Electronic Visual Acuity Tester.[35, 36] This test presented single Sloan letter optotypes with crowding bars,

with an initial screening staircase to gauge the testing range, and a threshold phase based on the method of constant stimuli. Like the standard ETDRS chart, five letters were shown at each logMAR size during the threshold phase and each correctly answered letter was scored −0.02 logMAR. Participants were instructed to make only one guess per letter shown. Clinicians provided encouragement to continue the test but gave no feedback on whether responses were correct or incorrect. Near visual acuity (NVA) was assessed at 40 cm using the Sloan Letter Near Vision Card (www.goodlite.com), which contained Sloan letter optotypes in an ETDRS logMAR format. DVA and NVA testing both used the same termination rule, whereby participants continued until they failed to correctly report any of the five letters on a line. Acuity tests were performed monocularly and binocularly for stability assessment, but only monocular measurements were used for statistical analyses. NVA testing was performed with the amblyopic eye first, followed by the fellow eye on the same side of the card, and then binocular NVA was tested using the opposite side of the card. This was to minimise the risk of memorisation. For DVA, the e-ETDRS test produced a new sequence of letters on each run and memorisation was impossible, so testing order was left to clinician preference.

Stereoacuity was assessed at 40 cm using the three booklet version of the Randot Preschool Stereoacuity Test (www.stereooptical.com), which has reasonable test–retest reliability and no monocular cues.[41, 42] Stereoacuity and Lichtenstein Fixation Box Worth 4-dot test (www.good lite.com) results at 6 m were combined into a Binocular Function Score for analysis using the method described in Webber, Wood & Thompson.[43] For participants with measureable stereopsis, the Binocular Function Score was the log-transformation of their stereoacuity threshold. For participants with no detectable stereopsis, a value of 4.00 log seconds of arc was assigned if fusion or diplopia was found on the Worth 4-dot test, and a value of 5.00 log seconds of arc was assigned if suppression was found.

Interocular suppression was assessed using a portable version of the Dichoptic Global Motion Test described in Black, Thompson, Maehara & Hess[44] and implemented on an iPod Touch (www.apple.com) device placed inside a stereoscopic 3D viewer. The test involved a binocular measurement of global motion perception followed by a dichoptic presentation whereby the threshold number of signal dots was shown to the amblyopic eye at high contrast and the remaining noise dots were shown to the fellow eye with variable contrast. Participants swiped the iPod screen to indicate the direction of coherently moving signal dots interspersed with randomly moving noise dots. The test measured suppression through a dichoptic contrast ratio (fellow eye contrast/amblyopic eye contrast), where 1.0 represented perfect balance between eyes and lower values indicated suppression of the amblyopic eye. Because global motion coherence thresholds may not reach maturity until teenage years,[45, 46] we expected some younger participants to have difficulty. Participants who had high (worse) binocular thresholds during the first calibration step of the test would not see a sufficient number of noise dots with their fellow eye in the second step to produce reliable results. We estimated that 15% was the minimum proportion of noise dots needed during the second step for a meaningful measurement of suppression, so we excluded data from participants who could not complete the first calibration step or who produced an average binocular threshold of >85% during this step.

Statistical analyses

Paired *t*-tests were used to compare baseline and outcome measures of DVA and NVA (amblyopic eyes, fellow eyes, and interocular difference in acuity), Binocular Function Score, and interocular suppression. Results are reported as mean and standard deviation (S.D.). The effects of age, type of amblyopia, and prior treatment history on changes in visual measures from baseline were assessed using linear regression models with controls for baseline values. Pearson's correlations were used to test for relationships amongst the magnitude of changes in amblyopic eye DVA, amblyopic eye NVA, Binocular Function Score, and interocular suppression. A post-hoc one-way analysis of variance (ANOVA) was conducted to examine potential differences in change in amblyopic eye DVA between the subgroup of participants wearing existing lenses ($n = 16$) and participants who received new lenses ($n = 64$) during optical treatment. Statistical analyses were performed using IBM SPSS Statistics Version 23 (www.ibm.com). All analyses were two-tailed at the 5% significance level, with no adjustment for multiple comparisons.

Results

Baseline characteristics

In the BRAVO clinical trial, 137 recruited participants either met all eligibility criteria or met all eligibility criteria except for refractive correction status. *Figure 1* shows their habitual refractive correction at study entry. Fifty-one participants (37%) were emmetropic or had worn lenses meeting study prescribing criteria full-time for at least four months prior and were eligible for immediate randomisation (*Figure 1*, white numbers). The remaining 86 participants (63%) entered the optical treatment phase (*Figure 1*, black numbers). Participants were classified as wearing "full correction" if their existing refractive correction met study prescribing criteria. If refractive error in the fellow eye was corrected but the anisometropic difference was not corrected, then this was classified as "balance lens for the

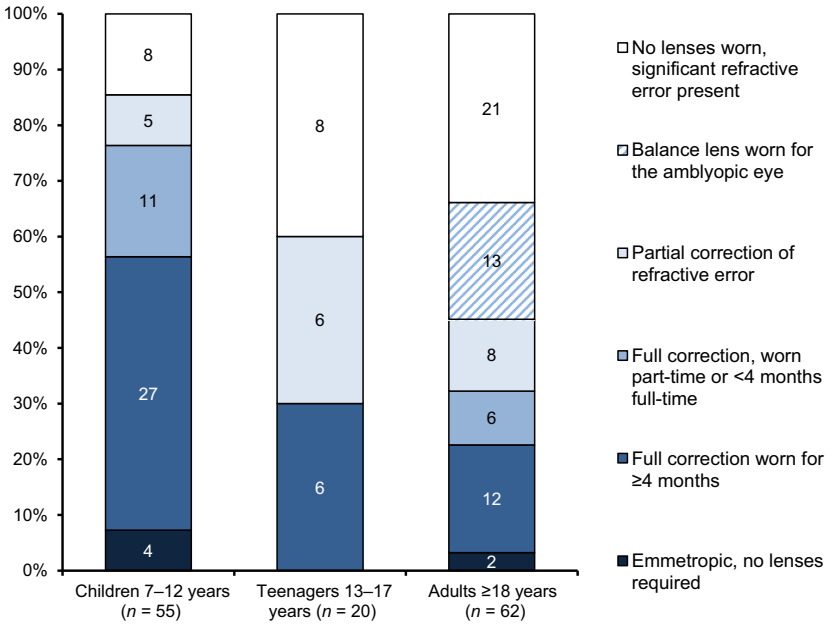

Figure 1. Habitual refractive correction at study entry for 137 eligible or potentially eligible clinical trial participants. Labels on bar segments show the number of participants in each category. White numbers (total n = 51) indicate participants who met all criteria and were eligible for immediate randomisation at study entry. Black numbers (total n = 86) indicate participants who met all eligibility criteria except for refractive correction status, requiring optical treatment before confirmation of eligibility.

amblyopic eye". "Partial correction" was used where some of the anisometropic difference was corrected but existing lenses did not meet study prescribing criteria. A higher proportion of participants in the teenage 13–17 years (70%) and adult ≥18 years (77%) age groups required optical treatment compared to children 7–12 years of age (44%) (*Figure 1*). Baseline characteristics of the 86 participants that entered optical treatment are shown in *Table* 1.

Main optical treatment outcomes

Numbers of participants assessed and analysed for optical treatment outcomes are shown in *Figure 2*. Eighty (93%) of the 86 participants that entered optical treatment were included in the main analyses. Two children were excluded from analyses because DVAs in their amblyopic eyes were 0.16 and 0.14 logMAR (6/7.5−2 and 6/9.5+2) when tested in newly dispensed spectacles (*Figure 2*), compared to 0.30 and 0.40 logMAR (6/12 and 6/15) respectively when tested through trial lenses at study entry. Four participants were excluded as they did not complete optical treatment: two adults withdrew due to spectacle intolerance (see adverse events), one adult could not be contacted after collecting spectacles, and one child entered this phase for observation after stopping patching therapy, but withdrew four weeks later due to regression of acuity and returned to patching.

Duration of optical treatment varied between participants (*Figure 2*). Of the 80 participants included in the main analyses, 73 (91%) received eight weeks or less of optical treatment. Only six (8%) participants had no prior optical treatment (*Table* 1), so our pre-planned analyses for this factor could not be reliably conducted. Instead, comparisons were made between participants with prior occlusion treatment (n = 57) and participants without (n = 23). Only three participants (4%) had strabismic amblyopia (*Table* 1). Those with strabismic amblyopia and those with mixed mechanism amblyopia were combined into a single "with strabismus" group (n = 37) and compared with participants with anisometropic amblyopia (n = 43). Though 28 (35%) out of 80 participants analysed had astigmatism ≥1.50 D, we did not specifically analyse outcomes with respect to astigmatism due to the relatively small contribution of cylinder prescription change compared to change in spherical equivalent (*Table* 1, difference between spherical equivalent and vector difference prescription changes).

Overall visual outcomes are shown in *Table* 2. The distributions of visual improvements in each age group are shown in *Figure 3*.

Distance visual acuity

After 4–16 weeks of optical treatment, amblyopic eye DVA showed a small but statistically significant mean improvement of 0.05 logMAR (S.D. 0.08, *Table* 2: $t_{79} = 5.29$, $p < 0.0001$). Fellow eye DVA did not significantly change

Table 1. Baseline characteristics of optical treatment participants.

Age group		Children 7–12 years	Teenagers 13–17 years	Adults ≥18 years	Overall
		n = 24	*n* = 14	*n* = 48	*n* = 86
Gender					
Female	*n* (%)	13 (54)	3 (21)	26 (54)	42 (49)
Age at study entry					
Age (years)	Mean (S.D.)	10.6 (1.7)	14.6 (1.4)	34.2 (10.4)	24.4 (13.6)
Age range (years)	Min–Max	7.2–12.9	13.2 - 17.4	18.7 - 55.5	7.2 - 55.5
Study site					
Auckland, New Zealand	*n* (%)	11 (46)	7 (50)	23 (48)	41 (48)
Waterloo, Canada	*n* (%)	8 (33)	3 (21)	12 (25)	23 (27)
Montreal, Canada	*n* (%)	0 (0)	0 (0)	2 (4)	2 (2)
Melbourne, Australia	*n* (%)	1 (4)	2 (14)	0 (0)	3 (3)
Hong Kong, China	*n* (%)	4 (17)	2 (14)	11 (23)	17 (20)
Prior amblyopia treatment†					
Optical (glasses and/or contact lenses)	*n* (%)	24 (100)	12 (86)	44 (92)	80 (93)
Occlusion (patching and/or atropine)	*n* (%)	21 (88)	12 (86)	29 (60)	62 (72)
Type of Amblyopia					
Anisometropic	*n* (%)	14 (58)	11 (79)	23 (48)	48 (56)
Mixed mechanism	*n* (%)	9 (38)	2 (14)	24 (50)	35 (41)
Strabismic	*n* (%)	1 (4)	1 (7)	1 (2)	3 (3)
Baseline DVA (logMAR)					
Amblyopic eye	Mean (S.D.)	0.48 (0.22)	0.57 (0.27)	0.49 (0.18)	0.49 (0.21)
Fellow eye	Mean (S.D.)	−0.06 (0.08)	−0.11 (0.06)	−0.13 (0.09)	−0.11 (0.09)
Interocular difference	Mean (S.D.)	0.54 (0.23)	0.69 (0.30)	0.63 (0.21)	0.61 (0.23)
Baseline NVA (logMAR)					
Amblyopic eye	Mean (S.D.)	0.58 (0.20)	0.59 (0.20)	0.57 (0.21)	0.58 (0.20)
Fellow eye	Mean (S.D.)	0.02 (0.10)	−0.04 (0.07)	−0.04 (0.12)	−0.03 (0.09)
Interocular difference	Mean (S.D.)	0.56 (0.23)	0.62 (0.24)	0.61 (0.24)	0.61 (0.22)
Baseline stereoacuity					
Binocular Function score (log seconds of arc)‡	Mean (S.D.)	3.80 (0.93)	3.57 (0.83)	3.41 (0.95)	3.74 (1.06)
Nil detectable stereopsis on Randot Preschool Test	*n* (%)	19 (79)	9 (64)	29 (60)	57 (66)
Baseline interocular suppression					
Able to complete the Dichoptic Global Motion test	*n* (%)	17 (71)	14 (100)	42 (88)	73 (85)
Dichoptic contrast ratio (fellow eye contrast/amblyopic eye contrast)	Mean (S.D.)	0.385 (0.353)	0.521 (0.264)	0.468 (0.326)	0.457 (0.319)
Cycloplegic refraction					
Degree of anisometropia, spherical equivalent difference between eyes (Dioptres)	Mean (S.D.)	2.86 (1.71)	3.81 (1.79)	3.06 (1.74)	3.13 (1.75)
Astigmatism ≥1.50 D in amblyopic eye	*n* (%)	10 (42)	5 (36)	14 (29)	29 (34)
Angle of strabismus at distance§					
Orthotropic	*n* (%)	16 (67)	10 (71)	32 (67)	58 (67)
1–9 Δ	*n* (%)	6 (25)	4 (29)	11 (23)	21 (24)
≥10 Δ	*n* (%)	2 (8)	0 (0)	5 (10)	7 (8)
Angle of strabismus at near§					
Orthotropic	*n* (%)	17 (71)	11 (79)	33 (69)	61 (71)
1–9 Δ	*n* (%)	6 (25)	3 (21)	12 (25)	21 (24)
≥10 Δ	*n* (%)	1 (4)	0 (0)	3 (6)	4 (5)
Optical treatment procedure					
Prescribed new lenses	*n* (%)	13 (54)	14 (100)	42 (88)	69 (80)
Continued wearing existing lenses	*n* (%)	11 (46)	0 (0)	6 (13)	17 (20)
Prescription change for new lenses (*n* = 69)					
Amblyopic eye, spherical equivalent (Dioptres)	Mean (S.D.)	2.04 (1.56)	2.46 (1.69)	2.63 (1.81)	2.48 (1.74)
Amblyopic eye, vector distance (Dioptres)¶	Mean (S.D.)	2.10 (1.54)	2.62 (1.57)	2.75 (1.76)	2.60 (1.68)
Fellow eye, spherical equivalent (Dioptres)	Mean (S.D.)	0.37 (0.42)	0.37 (0.58)	0.40 (0.57)	0.38 (0.54)
Fellow eye, vector distance (Dioptres)¶	Mean (S.D.)	0.39 (0.42)	0.39 (0.59)	0.44 (0.59)	0.42 (0.54)

(continued)

Table 1 (continued)

Age group		Children 7–12 years	Teenagers 13–17 years	Adults ≥18 years	Overall
Lenses worn during optical treatment					
Standard spectacles	*n* (%)	23 (96)	11 (79)	34 (71)	68 (79)
Aniseikonia-reducing spectacle lenses	*n* (%)	0 (0)	1 (7)	4 (8)	5 (6)
Contact lenses	*n* (%)	0 (0)	1 (7)	4 (8)	5 (6)
Both spectacles and contact lenses (mainly spectacles)	*n* (%)	0 (0)	0 (0)	3 (6)	3 (3)
Both spectacles and contact lenses (mainly contact lenses)	*n* (%)	1 (4)	1 (7)	3 (6)	5 (6)
Optical treatment phase outcome					
Randomised into videogame treatment	*n* (%)	16 (67)	9 (64)	39 (81)	64 (74)
Ineligible due to DVA improvement to better than 0.30 logMAR (6/12) after optical treatment	*n* (%)	5 (21)	5 (36)	6 (13)	16 (21)
DVA better than 0.30 logMAR (6/12) when tested in new spectacles at baseline	*n* (%)	2 (8)	0 (0)	0 (0)	2 (2)
Withdrew due to intolerance to anisometropic correction	*n* (%)	0 (0)	0 (0)	2 (4)	2 (2)
Withdrew for other reason/Unable to contact	*n* (%)	1 (4)	0 (0)	1 (2)	2 (2)

DVA, distance visual acuity at 3 m; NVA, near visual acuity at 40 cm; logMAR, logarithm of the minimum angle of resolution; *n*, number of participants; %, percentage; S.D., standard deviation; Min, minimum; Max, maximum. Percentages may not always add to 100 within columns due to rounding.

[†]Where treatments were prescribed but the participant (and parent/guardian where applicable) could not recall performing the treatment, this was counted as no prior treatment. All participants in this study who had atropine therapy for amblyopia also had patching either prior to or in conjunction with atropine.

[‡]The Binocular Function Score includes results from the Randot Preschool Test at 40 cm and the Worth 4-Dot test at 6 m, please see Methods – Vision Measurements for the calculation method.

[§]Maximum angle of strabismus in any direction (eso, exo, hyper or hypo), measured with prism alternate cover test through the spectacles or contact lenses worn during optical treatment.

[¶]Vector distance changes were calculated by decomposing old and new prescriptions into M, J_0 and J_{45} components and then calculating the magnitude of the difference vector.[47] This combines changes in spherical and astigmatic components of the prescription.

from baseline (mean change 0.01 logMAR, S.D. 0.05, *Table* 2: $t_{79} = 1.65$, $p = 0.10$). While the majority of participants did not exhibit a clinically significant change in amblyopic eye DVA, 25 out of 80 participants (31%) improved by at least one logMAR line, and of these, seven (9%) improved by two or more lines (*Figure 3a*).

Post-hoc comparison between the 16 participants who wore existing lenses and the 64 who received new lenses during optical treatment using one-way ANOVA revealed no significant difference in amblyopic eye DVA improvement (existing lenses: mean 0.06 logMAR, S.D. 0.08; new lenses: mean 0.05 logMAR, S.D. 0.08; $F_{1,78} = 0.26$, $p = 0.61$).

Near visual acuity

Amblyopic eye NVA also showed a small but statistically significant mean improvement of 0.04 logMAR (S.D. 0.09, *Table* 2: $t_{79} = 3.37$, $p = 0.0011$). Fellow eye NVA showed no significant change from baseline (mean change 0.01 logMAR, S.D. 0.07, *Table* 2: $t_{79} = 0.82$, $p = 0.41$). Like DVA, clinically significant improvements in amblyopic eye NVA occurred in a subset of participants, with 21 (26%) improving by at least one logMAR line and five (6%) improving by two or more lines (*Figure 3b*).

Binocular Function Score

Mean Binocular Function Score improved significantly from 3.58 log seconds of arc (S.D. 0.90) at baseline to 3.37 log seconds of arc (S.D. 0.88) after optical treatment (*Table* 2: $t_{79} = 2.82$, $p = 0.0060$). Median Binocular Function Score remained at 4.00 log seconds of arc (nil detectable stereoacuity, fusion or diplopia on Worth 4-Dot) after optical treatment, however the number of participants with nil stereopsis reduced from 53 (66%) at baseline to 46 (58%) after optical treatment. A higher proportion of teenagers (29%) and adults (20%) compared to children (9%) showed clinically significant improvements in stereoacuity threshold (an improvement of at least 2-octaves[48] or crossing from nil detectable stereopsis to measurable stereoacuity).[a] One teenager (7%) and four adults (9%) showed worsening of stereoacuity based on the same criterion (*Figure 3c*). Post-hoc analysis found that none of the participants wearing their existing lenses during optical treatment met the 2-octaves criterion for improvement.

[a]Eight participants had stereoacuity of 100 seconds of arc or better at baseline and could not have met the 2-octaves criterion for improvement as the lowest testable threshold on the Randot Preschool Test was 40 seconds of arc. However, inspection of data revealed that these eight participants did not change from their baseline stereoacuity.

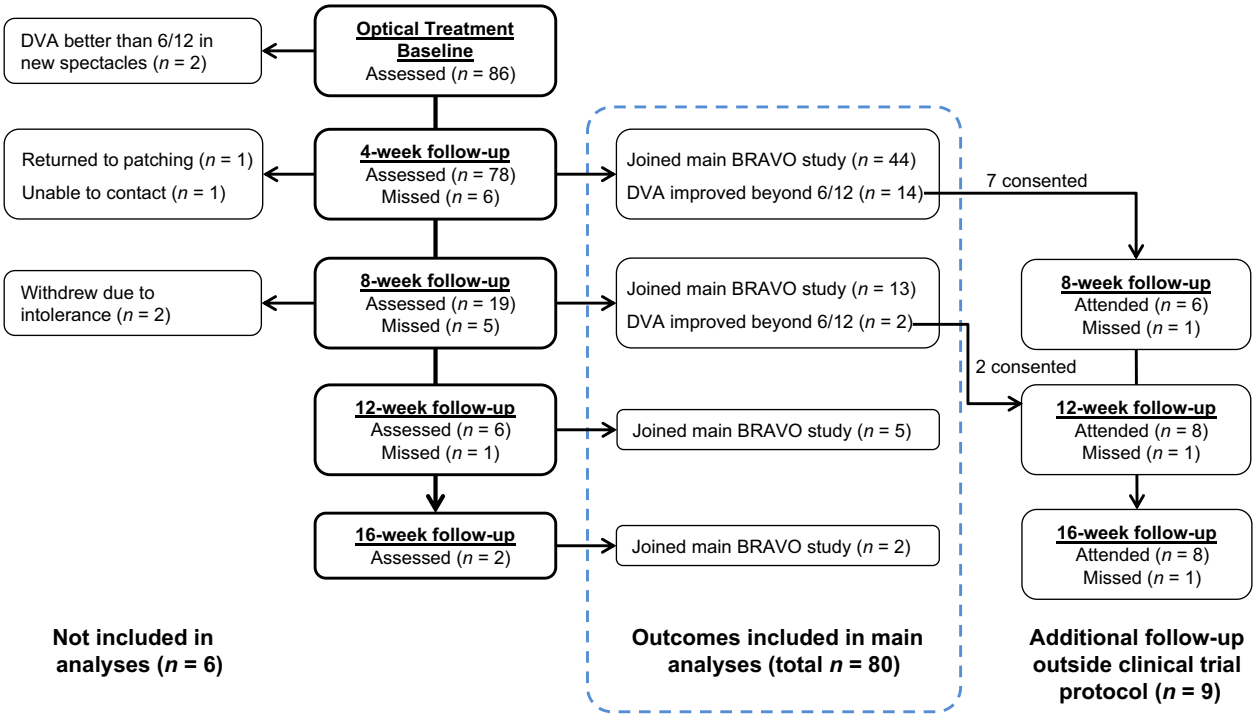

Figure 2. Flow diagram of optical treatment visits and outcome time-points. Visual outcomes for the main analyses were taken from the visit at which participants became either eligible or ineligible for randomisation into the main BRAVO clinical trial (dashed blue box). Participants joined the main BRAVO study if their DVA stabilised (≤0.10 logMAR change across two visits) within the inclusion range (amblyopic eye DVA 0.30–1.00 logMAR, 6/12–6/60, 20/40–20/200) and they were able to wear refractive correction comfortably full-time. Participants became ineligible if their amblyopic eye DVA became better than 0.30 logMAR (6/12 or 20/40). Confirmation of eligibility/ineligibility was sometimes delayed if participants missed follow-up visits, if adjustments were made to prescriptions, or if participants did not comply with full-time lens wear.

Interocular suppression

Only 13 children (62%) out of 21 completed the Dichoptic Global Motion Test at both baseline and outcome visits, compared to all 14 teenagers and 42 out of 45 adults (93%). Children who did not complete the test were unable to achieve a binocular threshold of ≤85% in the calibration step. Two adults did not complete the test at baseline due to inability to maintain fusion in the stereoscopic viewer, but they successfully completed the test at subsequent visits. The remaining adult had a wrist injury from before study entry and could not manipulate the iPod. For the 69 participants who completed the test, there was no significant change in mean dichoptic contrast ratio after optical treatment (*Table* 2: $t_{68} = -0.88$, $p = 0.38$).

Factors influencing visual outcomes

Linear regression analyses conducted on changes in amblyopic eye DVA, amblyopic eye NVA, Binocular Function Score, and interocular suppression while controlling for baseline values found no significant effects of age, presence of strabismus, or prior occlusion/penalisation treatment (*Table* 3: all $p > 0.22$). Baseline values were statistically significant within all models ($p < 0.037$) except the change in NVA model ($p = 0.050$). Regression models were also re-run with optical treatment duration and study site as additional independent variables. Treatment duration was not found to be statistically significant in any model (all $p > 0.072$). Small differences in baseline characteristics and visual improvements were found between some study sites, but these differences may have arisen by chance due to small numbers at some sites (*Table* 1). Inclusion of study site and treatment duration in regression models did not change conclusions regarding the null effects for age, strabismus, and prior occlusion/penalisation treatment.

Change in amblyopic eye DVA was significantly correlated with change in amblyopic eye NVA (Pearson's $r = 0.47$, $p < 0.0001$). All other outcome measures were not significantly correlated (all Pearson's $r < 0.19$, $p > 0.095$).

Additional follow-up in a subgroup of participants who improved beyond 0.30 logMAR

Sixteen (20%) out of the 80 participants who completed optical treatment showed improvements in amblyopic eye

Table 2. Overall visual outcomes for participants who completed optical treatment.

Total $n = 80$	Baseline Mean (S.D.)	Outcome Mean (S.D.)	Change Mean (S.D.)	Comparison of baseline and outcome	
				Test statistic	*p*-Value
DVA of the amblyopic eye (logMAR)	0.49 (0.20)	0.45 (0.20)	0.05 (0.08)	$t_{79} = 5.29$	**<0.0001**
DVA of the fellow eye (logMAR)	−0.11 (0.09)	−0.12 (0.09)	0.01 (0.05)	$t_{79} = 1.65$	0.10
Interocular difference in DVA (logMAR)	0.61 (0.23)	0.57 (0.22)	0.04 (0.09)	$t_{79} = 4.21$	**<0.0001**
NVA of the amblyopic eye (logMAR)	0.58 (0.21)	0.54 (0.21)	0.04 (0.09)	$t_{79} = 3.38$	**0.0011**
NVA of the fellow eye (logMAR)	−0.03 (0.09)	−0.04 (0.10)	0.01 (0.07)	$t_{79} = 0.82$	0.41
Interocular difference in NVA (logMAR)	0.61 (0.23)	0.58 (0.24)	0.03 (0.13)	$t_{79} = 2.02$	**0.047**
Binocular Function Score (log seconds of arc)	3.59 (0.90)	3.37 (0.88)	0.22 (0.69)	$t_{79} = 2.82$	**0.006**
Dichoptic contrast ratio (interocular suppression) - completed by $n = 69$ participants	0.475 (0.320)	0.499 (0.310)	−0.024 (0.223)	$t_{68} = -0.88$	0.38

Paired *t*-tests were used to compare the baseline and outcome measurements for all variables. The bolded p-values indicate statistical significance ($p \leq 0.05$).

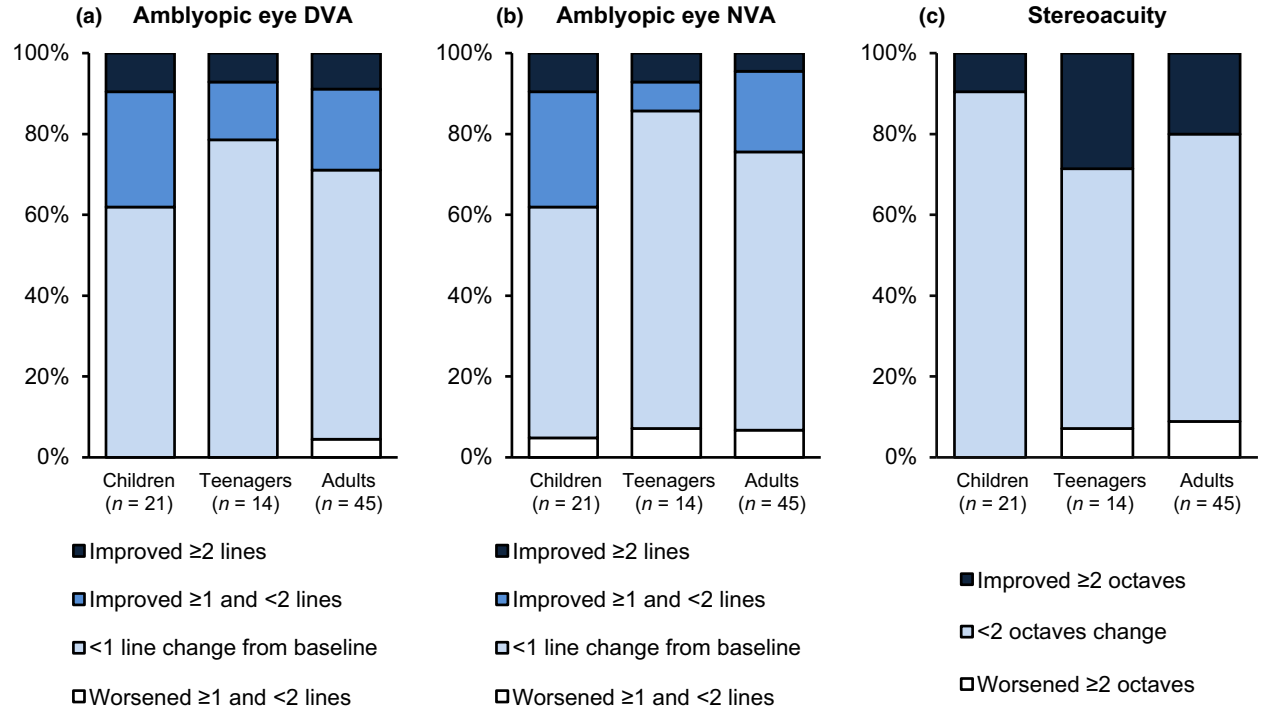

Figure 3. Distribution of visual improvements from optical treatment by age group. (a) Change in distance visual acuity of the amblyopic eye. (b) Change in near visual acuity of the amblyopic eye. For (a) and (b), no participants worsened by ≥0.20 logMAR. (c) Change in stereoacuity on the Randot Preschool Test. A 2-octaves (4-fold) decrease in threshold or a change from no detectable stereopsis at baseline to a measureable threshold at the outcome visit was counted as significant improvement. The reverse was counted as worsening.

DVA to better than 0.30 logMAR (6/12) and became ineligible for randomisation into the main clinical trial (*Table* 1; *Figure 2*). A subgroup of nine (one child, four teenagers, and four adults) ineligible participants consented to attend additional follow-up visits outside the clinical trial protocol, including one adult previously described.[32] Our aim was to assess possible further improvements after DVA had improved beyond 0.30 logMAR not captured by the main study analyses.

All nine participants in this subgroup received new spectacles at the optical treatment baseline, and one adult also wore contact lenses once per week. These participants crossed the 0.30 logMAR eligibility threshold after four to eight weeks of optical treatment within the main study (*Figure 2*). During

Table 3. Results of linear regression analyses for key visual outcomes

Model	Factors	Coefficient B	(95% CI)	*p*-Value	Adjusted Model R^2
Change in DVA of the amblyopic eye (n = 80)					0.019
	Baseline amblyopic eye DVA	0.10	(0.01, 0.20)	**0.037**	
	Age	−0.0004	(−0.002, 0.001)	0.66	
	Strabismus	−0.02	(−0.06, 0.02)	0.36	
	Prior occlusion	0.002	(−0.05, 0.05)	0.93	
Change in NVA of the amblyopic eye (n = 80)					0.012
	Baseline amblyopic eye NVA	0.10	(−0.001, 0.21)	0.050	
	Age	−0.0002	(−0.002, 0.002)	0.84	
	Strabismus	−0.03	(−0.07, 0.02)	0.22	
	Prior occlusion	−0.02	(−0.07, 0.04)	0.50	
Change in Binocular Function Score (n = 80)					0.161
	Baseline Binocular Function Score	0.32	(0.16, 0.48)	**0.00018**	
	Age	−0.004	(−0.017, 0.009)	0.54	
	Strabismus	−0.16	(−0.45, 0.13)	0.29	
	Prior occlusion	−0.21	(−0.58, 0.15)	0.25	
Change in interocular suppression on the Dichoptic Global Motion Test (n = 69)					0.114
	Baseline interocular suppression	0.265	(0.097, 0.433)	**0.0025**	
	Age	−0.001	(−0.006, 0.004)	0.66	
	Strabismus	−0.026	(−0.136, 0.085)	0.65	
	Prior occlusion	−0.005	(−0.146, 0.135)	0.94	

DVA, distance visual acuity; NVA, near visual acuity.
Each regression model included the corresponding baseline value, participant age at optical treatment baseline (in years), presence of strabismus (Yes/No), and prior occlusion/penalisation treatment (Yes/No) as independent variables. *P*-values indicate the statistical significance of each factor when all other factors in the model were held constant. The bolded p-values indicate statistical significance ($p \leq 0.05$).

additional follow-up (to 16 weeks for eight participants and to 12 weeks for one participant), four out of nine (44%) participants showed a further amblyopic eye DVA improvement of at least one logMAR line, and two out of nine (22%) participants showed ≥2-octaves of stereoacuity improvement.

These further improvements with longer follow-up were not included in the main analyses detailed in previous sections because assessment of ineligible participants was outside of our clinical trial protocol. Results from this subgroup indicate that further improvements were possible even after achieving an amblyopic eye DVA of 0.30 logMAR (6/12 or 20/40), and that our main analyses (Table 2 and Table 3, *Figure 3*) did not capture the full extent of possible improvements from optical treatment.

Time required to reach stable distance visual acuity

To examine the time required to reach stable DVA, we analysed data from all participants who met the stability criterion, including available additional follow-up data from participants who improved beyond 0.30 logMAR in the amblyopic eye. A total of 77 participants met the ≤0.10 logMAR change criterion (*Figure 4*). Overall, 70 (91%) participants met this stability criterion by the 8-week visit and 75 (97%) by the 12-week visit, with only two children requiring 16 weeks. The three age groups exhibited similar trajectories.

Adverse events

Possible negative effects of optical treatment include diplopia and spectacle intolerance. No participants developed persistent diplopia in this study. Two adults withdrew from optical treatment due to spectacle intolerance. The first participant had 7.13 D of anisometropia (difference in spherical equivalent between eyes) and could not adapt to the prismatic effects of standard spectacles. The second had 3.13 D of anisometropia and presbyopia, and requested progressive spectacle lenses due to work requirements but could not adapt to lens-related distortions. Contact lenses resolved visual discomfort for both participants but fitting was unsuccessful due to ocular surface and lens handling issues. Both adults stopped wearing their anisometropic prescription and withdrew, with no ongoing issues.

Discussion

There is currently significant interest in developing or enhancing amblyopia therapies for older patients with amblyopia.[29, 49–51] Approximately 70–90% of amblyopic children have significant refractive error in one or both eyes,[3, 40, 52] which may not fully emmetropise with age.[53, 54] As such, most adult patients require refractive correction when undertaking additional therapies, making optical

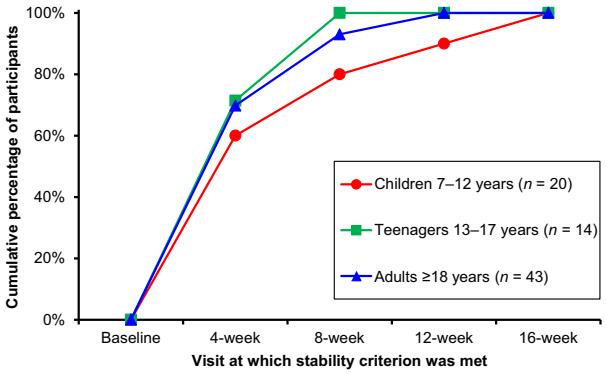

Figure 4. Follow-up visit at which participants met the clinical trial stability criterion of ≤0.10 logMAR change in e-ETDRS visual acuity of the amblyopic eye, fellow eye, and binocularly between two visits at least four weeks apart, measured through the same prescription.

treatment effects important to consider. In this study, we applied standard amblyopia clinical trial procedures to older children and adults with amblyopia and found that one-fifth of participants who entered the optical treatment phase became ineligible for randomisation to the videogame trial due to visual acuity improvement, including 13% of the adults (*Table* 1). Nearly one-third of participants showed improvement in amblyopic eye DVA of one or more logMAR lines after relatively short periods of optical treatment (91% of participants had only 4–8 weeks). While we cannot completely rule out influences from regression to the mean, we do note that fellow eye DVA and NVA did not significantly improve despite undergoing the same repeated testing procedures as amblyopic eyes. Previous studies of the e-ETDRS protocol in children and adults indicated uniform test-retest variability across a wide range of acuities.[35, 36] Our fellow eye DVA data closely match this previously reported test-retest variability while a subset of amblyopic eyes exhibited improvements which exceeded the expected variability (*Figure 3*), leading to decreases in interocular acuity difference (*Table* 2). The mean improvements found in this study were modest (*Table* 2) and likely an underestimate of true optical treatment effects. However, even this modest effect is sufficient to bias studies of additional amblyopia therapies (such as patching or videogame training) towards a positive outcome. Therefore, an appropriate optical treatment only phase prior to starting additional therapy and/or a parallel control group is needed for all amblyopia treatment studies regardless of patient age or other characteristics.

Though we expected some adult participants to show substantial visual improvements from optical treatment, we initially hypothesised that improvements would reduce in magnitude with age. However, our regression analyses showed no significant effect of age on any visual outcome for our participants, ranging in age from 7-55 years old (*Figure 3* and *Table* 3). We also hypothesised that participants with no prior optical treatment history would be more likely to improve, but this could not be tested due to insufficient sample size. Based on previous prospective studies in children,[13–15] we expected and confirmed that strabismus was not a significant factor for DVA or NVA improvements from optical treatment. Strabismus is a known limitation for fine stereoacuity,[55] but we did not find a significant difference in Binocular Function Score change between participants with and without strabismus. This was likely because the BRAVO trial definition of strabismus included participants with previous deviations aligned by surgery or refractive correction, as well as those with misalignment only at some viewing distances. Our inclusion criteria for dichoptic videogame play also limited the range of strabismus angles in our sample (*Table* 1). Including patients with larger angles of manifest strabismus in future optical treatment studies may produce a greater contrast with anisometropic amblyopia for stereoacuity outcomes.

Sixteen participants wore their existing lenses during optical treatment, which were worn for less than four months full time (n = 12) or on a part-time basis (n = 4) prior to study entry. Because optical treatment works gradually,[13–16] these participants may have already experienced some improvements prior to study entry and may be expected to improve less during our study than participants who received new lenses at baseline. However, some participants who received new lenses required only small prescription updates, and thus may also have already experienced partial optical treatment effects before study entry. Previous studies in children <7 years suggested that visual improvements from optical treatment may continue for up to 30 weeks,[13] so we chose to include all optical treatment participants in the initial main analyses. Post-hoc analyses showed that none of the participants wearing existing lenses met the criteria for improvement in stereoacuity, but no significant differences were found for mean DVA improvements between participants wearing new lenses or existing lenses. Though we only had 16 participants wearing existing lenses, our result indicates that continued improvements may still be possible in older children and adults who have already worn appropriate refractive correction part time or for less than four months full time, and that optical treatment controls are still needed in amblyopia treatment studies that include these types of participants.

Nearly half of our 7–12 years age group wore existing lenses, a much higher proportion than the two older age groups (*Table* 1). This baseline difference likely explains why a smaller proportion of children (9%) improved in stereoacuity compared to teenagers (29%) and adults (20%) (*Figure 3c*). Previous studies of optical treatment reported mainly visual acuity outcomes,[13–16] and we did

not find any significant correlations between changes in visual acuity and Binocular Function Score, so it is uncertain whether stereoacuity improvements follow the same pattern and time-course as visual acuity.

The low proportion of untreated amblyopia in this study reflects well-established childhood vision screening and amblyopia treatment programs in the countries in which the BRAVO clinical trial recruited. However, even though 86–100% of participants in each age group had prior optical treatment, only one-third of teenagers and adults were wearing appropriate refractive correction at study entry, compared to 69% of children (*Figure 1*). Most children entered this study within a few years of completing conventional amblyopia therapy and were often still wearing spectacles prescribed according to best-practice guidelines. Most teenage and adult participants wore anisometropic correction in childhood but a significant proportion discontinued wear. Self-reported mean age of discontinuation was 10.9 years (S.D. 4.3 years, range 5.0–25.0 years). Reasons for discontinuing included cosmesis, cost, and the assumption that correction was no longer necessary. At study entry, some adults wore correction for their fellow eye but were not given their full anisometropic prescription (*Figure 1*, balance lenses). While our sample of clinical trial patients is not necessarily representative of the general population, it appears teenage and adult patients with anisometropic or mixed mechanism amblyopia are less likely to be prescribed their full correction than children, perhaps because clinicians expect no benefits or are concerned that correction will not be tolerated. This is despite the previous PEDIG clinical trial evidence showing positive optical treatment effects for teenage patients.[17]

In our study, full-time wear of anisometropic correction was well tolerated by all 14 teenagers and 40 (95%) of the 42 adults who were prescribed new lenses. Measurable visual improvements were found in a subset of participants after 4–16 weeks of optical treatment, indicating there may be additional benefits to simply correcting refractive error. To inform evidence-based clinical practice, optical treatment in adults should be investigated in a future study which includes a larger sample size to evaluate potential effects of prior optical treatment, aniseikonia, and strabismus angle, and a longer follow-up duration with no cut-off thresholds to measure the full extent of visual improvements.

Study limitations

Our study was the pre-randomisation phase of a clinical trial evaluating videogame therapy, and was not designed to measure maximum visual improvements from optical treatment alone. Additional improvements in DVA and stereoacuity outside the main analyses were found for some ineligible participants when follow-up was extended, indicating that our 0.30 logMAR eligibility cut-off prevented measurement of maximum possible improvements. In addition, our stability criterion of ≤0.10 logMAR change per four weeks, which was based on known test–retest variability of the e-ETDRS test[35, 36] and clinical trial protocols for children,[22,38,39] may miss improvements slower than one logMAR line per four weeks. The criterion also did not account for other visual outcomes that potentially may follow a different time-course, such as stereoacuity. Participants who were randomised began videogame treatment, so we do not have further optical treatment follow-up data to ascertain whether slower improvements occurred. These design limitations are likely why only 8% of participants aged 7–17 years in our study improved by two or more logMAR lines in amblyopic eye DVA compared to 23–25% in a previous PEDIG clinical trial which followed patients in this age group for up to 24 weeks.[17] Additionally, we did not collect long-term follow-up data, so we do not know if visual gains from optical treatment were sustained after completion of participation.

For DVA and Binocular Function Score, we found an association between worse baseline visual function and greater improvements (Table 3). This association has been previously reported for optical treatment in children 3–6 years old,[14] but in our study we cannot exclude the influence of the eligibility cut-off at 0.30 logMAR. Participants with better baseline amblyopic eye DVA could become ineligible from small improvements, after which they exited the main study follow-up. This meant we were less likely to measure the full improvements of participants with milder amblyopia, which may have created an artefactual effect of baseline amblyopia severity.

Zhou, Feng, Lin & Hess[56] hypothesised that optical treatment improves visual function by reducing interocular suppression. In our study, we did not find any significant change in suppression after 4–16 weeks of optical treatment (*Table* 2). However, the portable version of the Dichoptic Global Motion Test we used could not compensate for ocular misalignments, and the intermittent loss of image fusion introduced measurement errors. The test was also difficult for younger children. An improved testing method is needed to investigate potential relationships between interocular suppression and optical treatment, for example the dichoptic letter chart described in Birch, Morale & Jost *et al.*[57]

Conclusion

Optical treatment is low risk, convenient, and can produce improvements in a subset of older patients with amblyopia. We did not find age, prior occlusion history, or strabismus to be significant factors for predicting visual improvement.

The effects of refractive correction alone should be accounted for in all studies investigating additional amblyopia treatments, for example through a pre-treatment phase of appropriate length and/or a parallel group with refractive correction alone. In clinical practice, optical treatment may prove beneficial for a subset of older patients. Formal study with clinical trials in adults is warranted.

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Benjamin Thompson and Robert Hess are named inventors on two patents which cover the binocular videogame treatment used in the BRAVO clinical trial (patents US 12528934 and US 8006372 B2).

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References

1. Williams C, Northstone K, Howard M, Harvey I, Harrad RA & Sparrow JM. Prevalence and risk factors for common vision problems in children: data from the ALSPAC study. *Br J Ophthalmol* 2008; 92: 959–964.
2. Groenewoud JH, Tjiam AM, Lantau VK *et al.* Rotterdam Amblyopia screening effectiveness study: detection and causes of amblyopia in a large birth cohort. *Invest Ophthalmol Vis Sci* 2010; 51: 3476–3484.
3. Robaei D, Rose KA, Ojaimi E, Kifley A, Martin FJ & Mitchell P. Causes and associations of amblyopia in a population-based sample of 6-year-old Australian children. *Arch Ophthalmol* 2006a; 124: 878–884.
4. Robaei D, Huynh SC, Kifley A & Mitchell P. Correctable and non-correctable visual impairment in a population-based sample of 12-year-old Australian children. *Am J Ophthalmol* 2006b; 142: 112–118.e111.
5. Robaei D, Rose K, Ojaimi E, Kifley A, Huynh S & Mitchell P. Visual acuity and the causes of visual loss in a population-based sample of 6-year-old Australian children. *Ophthalmology* 2005; 112: 1275–1282.
6. Wang JJ, Foran S & Mitchell P. Age-specific prevalence and causes of bilateral and unilateral visual impairment in older Australians: the Blue Mountains Eye Study. *Clin Exp Ophthalmol* 2000; 28: 268–273.
7. Stewart CE, Stephens DA, Fielder AR, Moseley MJ & ROTAS Cooperative. Objectively monitored patching regimens for treatment of amblyopia: randomised trial. *BMJ* 2007; 335: 707.
8. Repka MX, Wallace DK, Beck RW *et al.* Two-year follow-up of a 6-month randomized trial of atropine vs patching for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2005; 123: 149–157.
9. Wallace DK, Lazar EL, Melia M *et al.* Stereoacuity in children with anisometropic amblyopia. *J AAPOS* 2011; 15: 455–461.
10. Stewart CE, Wallace MP, Stephens DA, Fielder AR, Moseley MJ & MOTAS Cooperative. The effect of amblyopia treatment on stereoacuity. *J AAPOS* 2013; 17: 166–173.
11. Hertle RW, Scheiman MM, Beck RW *et al.* Stability of visual acuity improvement following discontinuation of amblyopia treatment in children aged 7 to 12 years. *Arch Ophthalmol* 2007; 125: 655–659.
12. Bhola R, Keech RV, Kutschke P, Pfeifer W & Scott WE. Recurrence of amblyopia after occlusion therapy. *Ophthalmology* 2006; 113: 2097–2100.
13. Cotter SA, Edwards AR, Wallace DK *et al.* Treatment of anisometropic amblyopia in children with refractive correction. *Ophthalmology* 2006; 113: 895–903.
14. Cotter SA, Foster NC, Holmes JM *et al.* Optical treatment of strabismic and combined strabismic-anisometropic amblyopia. *Ophthalmology* 2012; 119: 150–158.
15. Stewart CE, Moseley MJ, Fielder AR, Stephens DA & MOTAS Cooperative. Refractive adaptation in amblyopia: quantification of effect and implications for practice. *Br J Ophthalmol* 2004; 88: 1552–1556.
16. Chen PL, Chen JT, Tai MC, Fu JJ, Chang CC & Lu DW. Anisometropic amblyopia treated with spectacle correction

alone: possible factors predicting success and time to start patching. *Am J Ophthalmol* 2007; 143: 54–60.
17. Scheiman MM, Hertle RW, Beck RW *et al.* Randomized trial of treatment of amblyopia in children aged 7 to 17 years. *Arch Ophthalmol* 2005; 123: 437–447.
18. Tailor VK, Bossi M, Greenwood JA & Dahlmann-Noor A. Childhood amblyopia: current management and new trends. *Br Med Bull* 2016; 119: 75–86.
19. The Royal College of Ophthalmologists. *Guidelines for the Management of Strabismus in Childhood*, March 2012. The Royal College of Ophthalmologists; https://www.rcophth.ac.uk/standards-publications-research/clinical-guidelines/, accessed: 14 March.
20. Repka MX & Holmes JM. Lessons from the amblyopia treatment studies. *Ophthalmology* 2012; 119: 657–658.
21. American Academy of Ophthalmology Pediatric Ophthalmology/Strabismus Panel. Preferred Practice Pattern Guidelines - Amblyopia, September 2012. American Academy of Ophthalmology; http://www.aao.org/preferred-practice-pattern/amblyopia-ppp–september-2012, accessed: 14 March.
22. Holmes JM. Designing clinical trials for amblyopia. *Vision Res* 2015; 114: 41–47.
23. Simmers AJ & Gray LS. Improvement of visual function in an adult amblyope. *Optom Vis Sci* 1999; 76: 82–87.
24. Kishimoto F, Fujii C, Shira Y, Hasebe K, Hamasaki I & Ohtsuki H. Outcome of conventional treatment for adult amblyopia. *Jpn J Ophthalmol* 2014; 58: 26–32.
25. Megbelayin E, Ekpenyong SM, Azunobi J & Ejiro G. Reversal of myopic anisometropic amblyopia with occlusion therapy in a 25 year old. *Ghana Med J* 2014; 48: 54–56.
26. Li RW, Ngo C, Nguyen J & Levi DM. Video-game play induces plasticity in the visual system of adults with amblyopia. *PLoS Biol* 2011; 9: e1001135.
27. Hussain Z, Astle AT, Webb BS & McGraw PV. The challenges of developing a contrast-based video game for treatment of amblyopia. *Front Psychol* 2014; 5: 1210.
28. Astle AT, Webb BS & McGraw PV. Can perceptual learning be used to treat amblyopia beyond the critical period of visual development? *Ophthalmic Physiol Opt* 2011; 31: 564–573.
29. Levi DM & Li RW. Perceptual learning as a potential treatment for amblyopia: a mini-review. *Vision Res* 2009; 49: 2535–2549.
30. Vedamurthy I, Nahum M, Huang SJ *et al.* A dichoptic custom-made action video game as a treatment for adult amblyopia. *Vision Res* 2015; 114: 173–187.
31. Hess RF, Thompson B & Baker DH. Binocular vision in amblyopia: structure, suppression and plasticity. *Ophthalmic Physiol Opt* 2014; 34: 146–162.
32. Gao TY, Guo CX, South J *et al.* Resolution of anisometropic amblyopia in a 48-year-old with refractive correction alone. *Clin Exp Optom* 2016; 100: 392–395.
33. Guo CX, Babu RJ, Black JM *et al.* Binocular treatment of amblyopia using videogames (BRAVO): study protocol for a randomised controlled trial. *Trials* 2016; 17: 504.
34. Gao TY, Guo CX, Babu RJ *et al.* Effectiveness of a Binocular Video Game vs Placebo Video Game for Improving Visual Functions in Older Children, Teenagers, and Adults With Amblyopia: A Randomized Clinical Trial. *JAMA Ophthalmol.* Published online January 04, 2018. doi:10.1001/jamaophthalmol.2017.6090
35. Beck RW, Moke PS, Turpin AH *et al.* A computerized method of visual acuity testing: adaptation of the early treatment of diabetic retinopathy study testing protocol. *Am J Ophthalmol* 2003; 135: 194–205.
36. Cotter SA, Chu RH, Chandler DL *et al.* Reliability of the electronic early treatment diabetic retinopathy study testing protocol in children 7 to <13 years old. *Am J Ophthalmol* 2003; 136: 655–661.
37. Hess RF, Babu RJ, Clavagnier S, Black J, Bobier W & Thompson B. The iPod binocular home-based treatment for amblyopia in adults: efficacy and compliance. *Clin Exp Optom* 2014; 97: 389–398.
38. Holmes JM, Manh VM, Lazar EL *et al.* Effect of a binocular iPad Game vs part-time patching in children aged 5 to 12 years with amblyopia: a randomized clinical trial. *JAMA Ophthalmol* 2016; 134: 1391–1400.
39. Scheiman MM, Hertle RW, Kraker RT *et al.* Patching vs atropine to treat amblyopia in children aged 7 to 12 years: a randomized trial. *Arch Ophthalmol* 2008; 126: 1634–1642.
40. Repka MX, Beck RW, Kraker RT *et al.* The clinical profile of moderate amblyopia in children younger than 7 years. *Arch Ophthalmol* 2002; 120: 281–287.
41. Fawcett SL & Birch EE. Interobserver test-retest reliability of the Randot preschool stereoacuity test. *J AAPOS* 2000; 4: 354–358.
42. Birch EE, Williams C, James D, Fu VLN, Cheng C & Northstone K. Randot Preschool Stereoacuity test: normative data and validity. *J AAPOS* 2008; 12: 23–26.
43. Webber AL, Wood JM & Thompson B. Fine motor skills of children with amblyopia improve following binocular treatment. *Invest Ophthalmol Vis Sci* 2016; 57: 4713–4720.
44. Black JM, Thompson B, Maehara G & Hess RF. A compact clinical instrument for quantifying suppression. *Optom Vis Sci* 2011; 88: E334–E343.
45. Hadad BS, Schwartz S, Maurer D & Lewis TL. Motion perception: a review of developmental changes and the role of early visual experience. *Front Integr Neurosci* 2015; 9: 49.
46. Hadad BS, Maurer D & Lewis TL. Long trajectory for the development of sensitivity to global and biological motion. *Dev Sci* 2011; 14: 1330–1339.
47. Thibos LN, Wheeler W & Horner D. Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. *Optom Vis Sci* 1997; 74: 367–375.
48. Adams WE, Leske DA, Hatt SR & Holmes JM. Defining real change in measures of stereoacuity. *Ophthalmology* 2009; 116: 281–285.

49. Hess RF, Mansouri B & Thompson B. A new binocular approach to the treatment of amblyopia in adults well beyond the critical period of visual development. *Restor Neurol Neurosci* 2010; 28: 793–802.
50. Astle AT, McGraw PV & Webb BS. Can human amblyopia be treated in adulthood? *Strabismus* 2011; 19: 99–109.
51. Sengpiel F. Plasticity of the visual cortex and treatment of amblyopia. *Curr Biol* 2014; 24: R936–R940.
52. Jamali P, Fotouhi A, Hashemi H, Younesian M & Jafari A. Refractive errors and amblyopia in children entering school: Shahrood, Iran. *Optom Vis Sci* 2009; 86: 364–369.
53. Lepard CW. Comparative changes in the error of refraction between fixing and amblyopic eyes during growth and development. *Am J Ophthalmol* 1975; 80: 485–490.
54. Rutstein RP & Corliss DA. Long-term changes in visual acuity and refractive error in amblyopes. *Optom Vis Sci* 2004; 81: 510–515.
55. Leske DA & Holmes JM. Maximum angle of horizontal strabismus consistent with true stereopsis. *J AAPOS* 2004; 8: 28–34.
56. Zhou J, Feng L, Lin H & Hess RF. On the maintenance of normal ocular dominance and a possible mechanism underlying refractive adaptation. *Invest Ophthalmol Vis Sci* 2016; 57: 5181–5185.
57. Birch EE, Morale SE, Jost RM *et al.* Assessing suppression in amblyopic children with a dichoptic eye chart. *Invest Ophthalmol Vis Sci* 2016; 57: 5649–5654.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. BRAVO study prescribing criteria.

