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Ophthalmic Technology Assessment

Binocular Treatment of Amblyopia

A Report by the American Academy of Ophthalmology

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Purpose: To review the published literature assessing the efficacy of binocular therapy for the treatment of amblyopia compared with standard treatments.

Methods: Literature searches with no date restrictions and limited to the English language were conducted in January 2018 and updated in April 2019 in the PubMed database and the Cochrane Library database with no restrictions. The search yielded 286 citations, and the full text of 50 articles was reviewed. Twenty articles met the inclusion criteria for this assessment and were assigned a level of evidence rating by the panel methodologist. Six studies were rated level I, 1 study was rated level II, and 13 studies were rated level III because of the impact on the development and popularization of this technology.

Results: Two of the level I and II studies reviewed described a significant improvement in visual acuity in the binocular group versus standard patching standard treatment (the total number of patients in these 2 studies was 147). However, the 5 studies that failed to show a visual improvement from binocular therapy compared with standard treatments were larger and more rigorously designed (the total number of patients in these 5 studies was 813). Level I and II studies also failed to show a significant improvement over baseline in sensory status, including depth of suppression and stereopsis of those treated with binocular therapy. Several smaller level III case series (total number of patients in these 13 studies was 163) revealed more promising results than the binocular treatments studied in the level I and II studies, especially using treatments that are more engaging and are associated with better compliance.

Conclusions: There is no level I evidence to support the use of binocular treatment as a substitute for current therapies for amblyopia (including patching and optical treatment). Furthermore, 2 large randomized controlled trials showed inferior performance compared with standard patching treatment. On the basis of this review of the published literature, binocular therapy cannot be recommended as a replacement for standard amblyopia therapy. However, more research is needed to determine the potential benefits of proposed binocular treatments in the future. *Ophthalmology 2019;■:1–12 © 2019 by the American Academy of Ophthalmology*

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to systematically review the available research for clinical efficacy, effectiveness, and safety. After review by members of the Ophthalmic Technology Assessment Committee, other assessments by Academy committees, relevant subspecialty societies, and legal counsel are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee Pediatric Ophthalmology/Strabismus Panel was to review the published literature assessing the efficacy of binocular treatment for amblyopia.

Binocular treatment of amblyopia involves any treatment whereby both eyes are being used, but the amblyopic eye is the primary eye performing a given visual task. Dichoptic therapies are a specific type of binocular treatment that use dichoptic contrast balance, whereby contrast level of the dominant eye is reduced to negate suppression to a level where the contrast sensitivity of the 2 eyes is equal and balanced in pursuit of the given visual task.

Background

Amblyopia is the most common cause of monocular vision loss and occurs in 2% to 4% of children.[1] Untreated or undertreated unilateral amblyopia has been shown to result in reduced reading speed, abnormal fine-motor skills, and reduced stereoacuity.[2,3] Although amblyopia is common, it is successfully treated using standard penalization when initiated during the critical period of visual development.

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Historically, patching or other means of penalization has been the main treatment for amblyopia. The Pediatric Eye Disease Investigator Group (PEDIG) produced a series of randomized, controlled amblyopia treatment studies that have helped to define current standards of care. In children ages 3 to 7 years with amblyopia, treatment is typically initiated with optical correction only, followed by penalization or occlusion therapy if the child fails to improve with optical therapy alone.[4] The PEDIG studies have also demonstrated that patching and atropine penalization are both reasonable choices for children with unilateral mild or moderate amblyopia. For children with moderate amblyopia (20/40−20/80) and severe amblyopia (20/100−20/400), patching for 2 hours or 6 hours per day is equivalent overall.[5,6] Atropine penalization has been shown to be a reasonable first-line therapy as an alternative to occlusive patching, and twice-weekly administration has been demonstrated to be effective.[7-10] These results have also been shown in other studies on older populations, and patching or atropine has resulted in successful treatment of amblyopia in cohorts of patients aged 7 to 12 years.[10] Despite these advances in treatment recommendations, there are still patients who are treatment resistant, have difficulty with compliance, or are diagnosed later in life.

Treatment of adult amblyopia has garnered interest in recent years, with reports of improved visual acuity (VA) in adults undergoing various treatments, especially with an active treatment component (as opposed to passive occlusion).[11-15] Because of the potential ability to improve VA in older patients who have amblyopia as well as to treat the population of children who are treatment resistant or poorly compliant, many novel active amblyopia therapies have been introduced in the past decade.[13-16] Binocular amblyopia therapy was developed as a more functional treatment approach that had the potential benefit of improved compliance. Although binocular therapy was historically used during the 1960s with the synoptophore, technological developments have allowed for more novel modes of delivery. Several groups have published results of studies that used binocular treatments to improve VA in the amblyopic eye. Dichoptic contrast balancing was first introduced by Hess et al[13] in 2010. The goal was to strengthen the amblyopic eye primarily by improving fusion and stereopsis using complementary dichoptic stimuli (stimuli that balanced contrast between the amblyopic and fellow eye) that require binocular integration to complete a visual task. Unlike previous binocular therapies, this technique uses contrast balancing to improve stereopsis and binocularity, with a secondary effect of improving VA in the amblyopic eye. Binocular viewing occurs when the amblyopic eye is the primary eye performing the visual task.[17-19] To achieve dichoptic contrast balance, the contrast level of the dominant eye is reduced to negate suppression to a level where the contrast level of the 2 eyes is rebalanced and made equal in pursuit of the given visual task. The potential benefit of dichoptic contrast balancing and binocular therapies is to minimize suppression of the amblyopic eye, thereby improving not only VA but also binocular function.

Description of the Treatment

Various methods of binocular amblyopia treatments for children or adults were studied, including versions of visual tasks such as playing video games or watching movies that are presented binocularly and that differ in terms of the amount of time prescribed. The binocular amblyopia therapy may include presentation of a different visual stimulus to each eye or may include dichoptic contrast balance.

Questions for Assessment

The focus of this assessment is to address the following questions: (1) Is the VA improvement resulting from binocular treatment of amblyopia equivalent to standard treatments in children such as patching and optical treatment? (2) Are there sensory benefits, such as improved stereoacuity or reduced suppression to dichoptic treatment of amblyopia, compared with traditional penalization treatment?

Description of Evidence

Literature searches limited to English language studies and with no date restrictions were conducted in January 2018 in the PubMed database and updated in April 2019, and in the Cochrane Library database with no restrictions. The following terms were used, along with publication and language filters: *Amblyopia*[mh], *amblyop**, "*lazy eye,*" "*lazy eyes,*" *amblyopia, amblyopic, strabismic, anisometropic, binocular, dichoptic. Therapy, therapies, treat, treatment, train, training, "amblyopia prevention and control"* OR "*video games*"[mh],"*Oculus rift,*" *ipad, i-bit, plasticity*, "*computers, handheld*"[mh], *BRAVO, "video clips*," "*interactive games,*" "*perceptual learning,*" "*amblyopia/therapy*"[mh].

A total of 286 unique citations were identified for review. Articles were excluded if they were editorials or review articles, or if they consisted of research that was unrelated to this assessment. The remaining 50 articles were reviewed in full text by the primary author (S.L.P.) to select those that met the following inclusion criteria: (1) The study primarily evaluated VA outcomes after binocular treatment for amblyopia; (2) the study reported at least 1 of the following outcomes: VA or improvement in VA; (3) the study included at least 4 weeks of follow-up; and (4) the study included a minimum of 5 subjects. Of these articles, 30 were excluded because of insufficient patient numbers or follow-up duration. The 20 articles that met the inclusion criteria were subsequently assigned a level of evidence rating by the methodologist (V.K.A.) using a rating scale developed by the Oxford Centre for Evidence-Based Medicine.[20] A level I rating was assigned to well-designed and well-conducted randomized clinical trials; a level II rating was assigned to well-designed case-control and cohort studies and lower-quality randomized studies; and a level III rating was assigned to case series, case reports, and lower-quality cohort and case-control studies. Six studies were rated

level I, 1 study was rated level II, and 13 studies were rated level III.

Published Results

Tables 1 and 2 show a summary of the results and details of the studies. The reviewed articles examined the effect of dichoptic amblyopia therapy on several different metrics, including the VA of the amblyopic eye, binocularity and sensory outcomes such as stereopsis, the persistence of VA changes after a treatment washout period, and the reporting of adverse events.

Amblyopic Eye Visual Acuity

In 2006, Waddingham et al[21] reported their results using a novel Interactive Binocular Treatment (I-BiT) system. The I-BiT is an in-office, computer-based, virtual-reality treatment that combines active games and passive visualization of movie clips using binocular technology. The subject watches the screen as shutter glass lenses lighten and darken in synchrony at a rate faster than the viewer can perceive, allowing a common background to be presented to both eyes and an "enriched" image to be presented only to the amblyopic eye.[22] This pilot study (level III) included 6 children ages 5 to 8 years (mean, 6.3 years) treated in 20-minute sessions once or twice a week for a total of 7 to 15 sessions. The results revealed a mean improvement in the amblyopic eye VA from 0.7 to 0.35 logarithm of the minimum angle of resolution (logMAR) (~20/70−20/40). No statistical analysis was performed because of the small sample size in this study. A follow-up level III study assessed the I-BiT in 12 older amblyopes ages 6 to 11 years (median, 8 years) who underwent 8 weeks of treatment consisting of one 25-minute session per week (20 minutes of binocular movie watching and 5 minutes of game play).[17] After 10 weeks of treatment, the VA had improved in 75% of the subjects (range pretreatment, 0.35−0.875 logMAR [~20/40−20/150] improving to 0.125−0.35 logMAR [20/25−20/40], $P = 0.002$). In addition, low-contrast VA was evaluated and found to have improved in 67% of subjects. On the basis of these results, a level I randomized controlled trial was organized and reported in 2016 by Herbison et al.[23] In this study, 75 children (ages 4−8 years) were randomized to an active I-BiT game (n = 26), an I-BiT movie (n = 24), or a sham game (n = 25). Treatment consisted of 30-minute weekly sessions over 6 weeks. At the 6-week follow-up, there was no statistically significant difference in the improvement in VA among the groups (mean, 0.1 logMAR, 0.06 logMAR, and 0.03 logMAR improvement in VA in the I-BiT movie, I-BiT game, and sham game groups, respectively). The authors of this study acknowledged that the total treatment time may have been too short to see an effect. Also in 2016, Rajavi et al[24] reported the results of another randomized controlled trial (level I) to evaluate the role of I-BiT therapy as an adjunct to patching. In this study, 50 subjects aged 3 to 10 years were randomized to patching for 2 hours per day with or without the addition of I-BiT 5 times per week in 20-minute sessions for a total of 4 weeks. After 4 weeks, both groups had significant improvement in VA of the amblyopic eye. The I-BiT plus patching group improved by 0.17 logMAR from 0.34 logMAR (~20/40) to 0.17 logMAR (~20/30) ($P < 0.001$) from pretreatment to posttreatment, and the patching group improved by 0.07 logMAR from 0.33 logMAR to 0.26 logMAR ($P = 0.024$) from pretreatment to posttreatment. The improvement in the VA after the I-BiT plus patching was significantly better than that of patching alone ($P < 0.001$).

In 2012, Hess et al[25] described an adaptation to their groups' laboratory-based dichoptic system as a handheld treatment using an Apple iPad device (Apple Inc, Cupertino, CA). This device used a lenticular approach to provide dichoptic stimulation with reduced contrast to the elements seen by the fixing eye while playing a falling-blocks−style video game. Their level III study included 10 adult subjects who were aged 17 to 51 years and who played the dichoptic game for 0.5 to 2 hours per day for 1 to 9 weeks. The mean pretreatment VA was 0.48 logMAR (~20/60), which improved by a mean of 0.19 logMAR ($P < 0.008$). This study was followed in 2014 by a study of 14 older amblyopes (ages 13−50 years) who underwent treatment using the dichoptic game at home for 1 hour per day over a period of 22 to 108 days. The game was adjusted to include an anaglyph method of dichoptic stimulation, allowing patients to play the game using red/green glasses instead of the lenticular overlay used in the prior study. In this level III study, the results revealed an improvement in VA from 0.36 logMAR (~20/45) before treatment to 0.25 logMAR (~20/35) after treatment ($P < 0.001$).

After these preliminary level III studies were published, a controlled trial was published in 2014 by Li et al.[26] This study enrolled 69 children ages 5 to 13 years who were placed into treatment groups 2:1 to undergo treatment with a dichoptic game (falling blocks, balloon, or labyrinth) or a sham game for 4 hours per week for 4 weeks. The groups were not matched and were chosen on the basis of the time of their presentation to the study (i.e., the first 25 subjects received the sham game, and the remaining subjects received the active dichoptic therapy). In this study, there was a significant improvement in VA in the active treatment group (from mean 0.47 logMAR [~20/60] to 0.39 logMAR [~20/50] after 4 weeks [$P < 0.001$]) but not in the sham control group. Several subjects in this study continued to patch their fellow eye during the study, and a secondary analysis revealed that patching plus the active binocular game was associated with significantly more improvements in VA than patching with the sham game. The authors also performed a secondary analysis to evaluate the impact of compliance. They found that the amount of VA improvement did not correlate with the number of hours of game play, but that overall the 11 children who were noncompliant (<25% compliance) had poorer outcomes than the 34 subjects with good compliance (>25%). In 2015, the same group[27] published a similar study (level III) evaluating 50 preschool age children (3−7 years) who played a sham game (first 5 children) or a binocular game (subsequent 45 children) for at least 4 hours per week for a total of 4 weeks. In this younger population of children, the findings

Table 1. Results and Details of Level I and II Studies

Authors, Year	Level of Evidence, Design	Premise	Total Patients	Age Range (yrs)	Pretreatment Mean VA (logMAR)	Post-treatment VA (logMAR)	Difference in Mean Improvement (logMAR)	Grouping	Cause of Amblyopia (n)	Length of Treatment, Follow-up	Comments
Binocular Treatment vs. Sham Games											
Herbison et al, 2016[23]	I, RCT	I-BiT game 1 hr/day for 6 wks vs. I-BiT video or non-I-BiT sham game	75	4–8	I-BiT movie 0.53 I-BiT game 0.49 Sham game 0.5	I-BiT movie: 0.1 logMAR improvement I-BiT game: 0.06 logMAR improvement Sham game: 0.03 logMAR improvement Final follow-up: I-BiT movie: 0.07 logMAR improvement I-BiT game: 0.07 logMAR improvement Sham game: 0.06 logMAR improvement	I-BiT game/sham game: 0.02 logMAR (95% CI, −0.07 to 0.03, $P = 0.429$)	24 I-BiT movie 26 I-BiT game 25 sham game	S (24) A (5) A/S (36)	10 wks Final follow-up 4 wks after treatment	Diplopia in 2 patients with I-BiT treatment
Gao et al, 2018[36]	I, RCT	Falling blocks dichoptic game on iPad (Microsoft Corp, Redmond, WA) for 1 hr/day for 6 wks. Control group played a sham video game	115	7–55	Dichoptic therapy: 0.53 Control group: 0.51	0.06 logMAR improvement in treatment vs. 0.07 logMAR in sham	Dichoptic game/sham game: −0.02 (95% CI, −0.06 to 0.02, $P = 0.25$)	56 active 59 sham	Dichoptic therapy: A (17) S (9) A/S (30) Control group: A (25) S (3) A/S (31)	10 wks Final follow-up 4 wks after treatment	Significant loss of patients due to protocol violations
Binocular Treatment vs. Optical Treatment											
Holmes et al, 2019[31]	I, RCT	Dig Rush dichoptic game on iPad for 1 hr/day, 5 days/wk for 8 wks vs. spectacles only	138	7–12	Dichoptic therapy: 60 letters Control group: 59 letters	Improved from baseline by 2.3 letters (2-sided 95% CI, 0.7–3.9 letters) with dichoptic therapy and 2.4 letters (2-sided 95% CI, 0.8–4.0) with spectacles only	Dichoptic game/control: −0.1 letters, (98% CI, −2.4 to 2.1 letters, $P = 0.71$)	69 dichoptic 69 spectacles only	Dichoptic therapy: A (27) S (15) A/S (27) Control group: A (39) S (19) A/S (11)	8 wks	

Table 1. (Continued.)

Authors, Year	Level of Evidence, Design	Premise	Total Patients	Age Range (yrs)	Pretreatment Mean VA (logMAR)	Post-treatment VA (logMAR)	Difference in Mean Improvement (logMAR)	Grouping	Cause of Amblyopia (n)	Length of Treatment, Follow-up	Comments
Binocular Treatment vs. Patching											
Holmes et al, 2016[29]	II, RCT	Dichoptic iPad game for 1 hr/day vs. patching 2 hrs/day	385	5–12	Dichoptic therapy: 0.51 Patching: 0.48	Dichoptic therapy: 0.41 Patching: 0.35	Patching/dichoptic game: 0.31 lines (95% CI, 0.04–0.58 lines)	190 dichoptic therapy 195 patching	S (12% dichoptic, 23% patching), A (56% dichoptic, 47% patching), A/S (32% dichoptic, 30% patching)	16 wks	Significant issues with compliance and loss of outcome data (22% of binocular treatment patients completed >75% of the intervention)
Kelly et al, 2016[28]	I, RCT	Dichoptic action adventure game (Dig Rush) for 1 hr/day for 5 days/wk for 2 wks vs. patching 2 hrs/day	28	4.9–9.5	Dichoptic therapy: 0.48 Patching: 0.5	Dichoptic therapy: 0.15 logMAR improvement (P = 0.02 compared with patching improvement) Patching: 0.07 logMAR improvement	Patching/dichoptic game: 0.07 logMAR (0.7 lines), 95% CI, 0.01–0.14 logMAR (0.1–1.4 lines, P = 0.02)		S (9) A (14) A/S (5)	2 wks	
Rajavi et al, 2016[24]	I, RCT	I-BiT game 20 min/session for 5 sessions/wk vs. patching 2 hrs/day	50	3–10	Dichoptic therapy: 0.34 logMAR Patching: 0.33 logMAR	(0.17 logMAR improvement, $P < 0.001$) Patching: 0.26 (0.07 logMAR improvement, P = 0.0024) 1 mo after cessation of I-BiT, BCVA difference between the 2 groups was not statistically significant (0.16 logMAR vs. 0.18 logMAR, P = 0.246)	Not reported		A	4 wks Final follow-up 4 wks after treatment	
Manh et al, 2018[30]	I, RCT	Dichoptic falling blocks game for 1 hr/day vs. patching 2 hrs/day for 16 wks	100	13–17	Dichoptic therapy: 58.8 letters Patching: 56.1 letters	Dichoptic therapy: 3.5 letters improvement Patching: 6.5 letters improvement	Patching/dichoptic game: 0.5 lines/2.7 letters (95% CI, −5.7 to 0.3 letters, P = 0.082)	40 dichoptic 60 patching	Dichoptic group: S (5), A (22) A/S (13) Patching group: S (9) A (29) A/S (22)	16 wks	

A = anisometropic amblyopia; A/S = combined amblyopic and strabismic amblyopia; BCVA = best-corrected visual acuity; CI = confidence interval; I-BiT = Interactive Binocular Treatment; logMAR = logarithm of the minimum angle of resolution; RCT = randomized controlled trial; S = strabismic amblyopia; VA = visual acuity.

Table 2. Results and Details of Level III Studies

Author(s), Year	Level of Evidence, Design	Premise	Total Patients	Age Range (yrs)	Pretreatment Mean VA (logMAR)	Post-treatment VA (logMAR)	Grouping	Cause of Amblyopia (n)	Length of Treatment, Follow-up	Comments
Uncontrolled Studies										
Waddingham et al, 2006[21]	III, case series	I-BiT video 20- min session 1: 2/wk vs. virtual reality game	6	3–7	0.7	0.35		A (2) S (2) A/S (2)	11–22 mos	
Cleary et al, 2009[17]	III, case series	I-BiT virtual reality images (20-min movie and 5-min game) for 25 min/ week for 8 wks	12	6.1–11.4	0.56	Improved in 9/12 subjects (range of improvement of 0.125–0.35 logMAR) After washout period, 7/12 (58%) maintained VA improvements		A/S (7) S (5)	1 wk Final follow-up 3–18 mos after treatment	3 children withdrew because of suppression density reduction
Hess et al, 2012[25]	III, case series	Dichoptic falling blocks game for 0.5 –2 hrs/day for 1–9 wks	10	17–51	0.48	0.22 (0.19 logMAR improvement, $P = 0.008$)		A (5) S (1) A/S (4)	1–9 wks	Calculated mean VA for pretreatment and post-treatment and difference is not the same as reported difference of 0.19 (calculate difference is 0.26 logMAR)
Hess et al, 2014[39]	III, case series	Dichoptic falling blocks game on iPad for 1 hr/day for 22–108 days	14	13–50	0.36	0.25 (0.11 logMAR improvement, $P < 0.001$)		S (6) A (6) A/S (2)	22–108 days	
Mansouri et al, 2014[40]	III, case series	Dichoptic motion task for 2-hr sessions 2 –3 times/wk. Each patient's baseline VA served as their own control.	22	5–73	0.82	0.48 logMAR (0.34 logMAR improvement, $P < 0.05$) Mean improvement maintained at 6 mos		A (7) S (22)	6 wks Final follow-up at 6 mos after treatment	
Bossi et al, 2017[33]	III, case series	3-dimensional computer system watching movies and using shutter glasses with BBV for 1 hr/day for 8 wks	22	3.5–11.3	0.78	0.51 (0.27 logMAR improvement) After washout period in 11 subjects, no significant change from end of treatment		A (7) S (6) A/S (9)	8 wks (A) 24 wks (S and A/S) Final follow-up 47±10 wks for 11 subjects	
Hamm et al, 2017[38]	III, case series	Falling blocks dichoptic game on iPad for 1 hr/day for 6 wks	18	5–14	Deprivation: 0.94 A/S: 0.57	Deprivation: 0.85 (0.09 logMAR improvement, $P = 0.004$) A/S: 0.42 (0.15 logMAR improvement, $P = 0.014$)		Deprivation (18) A (8) Mixed mechanism (2)	6 wks	
Ziak et al, 2017[34]	III, case series	Virtual reality head-mounted display with games 40 min/ session, 2 times/wk	17	17–69	0.58	0.43 (0.15 logMAR improvement, $P < 0.001$)		A (all)	4 wks	

Table 2. (Continued.)

Author(s), Year	Level of Evidence, Design	Premise	Total Patients	Age Range (yrs)	Pretreatment Mean VA (logMAR)	Post-treatment VA (logMAR)	Grouping	Cause of Amblyopia (n)	Length of Treatment, Follow-up	Comments
Bao et al, 2018[35]	III, case series	Altered reality headset for 3 hrs/day for 7 days. Each patient's baseline VA served as their own control.	18	14–35	0.567	0.418 (0.149 logMAR improvement, $P < 0.001$)		A (13) A/S (4) A/ Deprivation (1)	4 wks	
Controlled Studies										
Li et al, 2014[26]	III	Dichoptic game on iPad (falling blocks, balloon, labyrinth) 4 hrs/wk for 4 wks vs. sham game	69	4.5–12.7	Dichoptic therapy: 0.47 Sham: 0.45	Dichoptic therapy: 0.39 (0.08 logMAR improvement, $P < 0.001$) Sham: no significant change Final follow-up: maintained post-treatment VA in 21 subjects from dichoptic group 3 mos after treatment cessation	50 dichoptic treatment 25 sham	Dichoptic group: S (10) A (11) A/S (24) Sham group: S (5) A (11) A/S (8)	4 wks Final follow-up 3 mos after treatment	No matching done or randomization; simply enrolled first 25 subjects in sham and remainder in dichoptic therapy
Birch et al, 2015[27]	III, nonrandomized clinical trial	iPad dichoptic game with red/green glasses 4 hr/week for 4 wks	50	3.8–6.9	Treatment: 0.43 Sham: 0.4	Treatment: 0.34 (0.09 logMAR improvement, $P < 0.0001$) Sham: 0.38 (no significant improvement)	5 sham 45 treatment	A (44) S (6)	4 wks	Numerous confounders (patching in differential portions of group, limited matching)
Vedamurthy et al, 2015[16]	III, nonrandomized clinical trial	Dichoptic game for 2-hr sessions 2–5 times/wk vs. patching and movie. Total treatment 40 hrs	38	19–66	Dichoptic therapy: 0.58 Movie/ patching: 0.49	Dichoptic therapy: 0.14 logMAR improvement Movie/patching: 0.07 logMAR improvement	23 dichoptic 15 patching/ movie	S (23) A (15)	2 mos	
Mezad-Koursh et al, 2018[37]	III, clinical trial	Dichoptic BinoVision movies for 1 hr/day, 6 days/wk for up to 12 wks vs. 4-wk sham movies	27	4–8	BinoVision treatment: 0.66 (range, 0.4–1.18) logMAR, sham 0.62 (range, 0.4 –0.88) logMAR	Dichoptic BinoVision treatment: 0.39 logMAR, mean change: 0.26 logMAR, $P = 0.001$ Sham: 0.61 logMAR, mean change: 0.009 logMAR, $P = 0.285$ after 4 wks	8 sham 19 dichoptic	S (9) A (3) S/A (7)	12 wks	

A = anisometropic amblyopia; A/S = combined amblyopic and strabismic amblyopia; BBV = balanced binocular viewing; I-BiT = Interactive Binocular Treatment; logMAR = logarithm of the minimum angle of resolution; RCT = randomized controlled trial; S = strabismic amblyopia; VA = visual acuity.

were similar to the results of their older cohort, with a mean improvement from 0.43 to 0.34 logMAR ($P = 0.09$) in the active treatment group but no significant improvement in the control subjects. Overall compliance for the dichoptic game was poor (<25% compliance) in 38% of subjects. Like the previous study, this study was flawed, without controls, and included varying levels of patching in both groups. The authors again performed a secondary analysis to evaluate the impact of compliance and found that in this population there was a modest correlation between number of hours of game play and change in VA.

Given the poor compliance for the dichoptic game play in the studies by Li et al[26] and Birch et al,[27] a trial with a potentially more engaging game was reported in 2016 by Kelly et al.[28] A randomized controlled trial (level I) enrolled 28 children ages 5 to 10 years and randomized them to a dichoptic action adventure game (Dig Rush) for 1 hour per day or patching for 2 hours per day for 2 weeks. After 2 weeks, the groups underwent a crossover in treatment. Compliance was markedly better in this study, with 100% compliance for the game play and 99% compliance for the patching groups for the first 2 weeks. At the end of 2 weeks, there was a significant difference ($P = 0.02$) in the level of VA improvement in the dichoptic game group (0.15 logMAR) compared with the improvement in the patching group (0.07 logMAR). After the crossover period (4 weeks from enrollment), the children who were initially patched and were crossed over to dichoptic game play caught up with the children originally randomized to the binocular game, for a mean standard deviation (SD) improvement of 0.17 (0.10) logMAR (mean [SD], 1.7 [1.0] lines) for the binocular game versus a mean SD improvement of 0.16 (0.12) logMAR (mean [SD], 1.6 [1.2] lines) for the patching crossover ($P = 0.73$).

In 2016, a level II, randomized controlled trial of 385 participants ages 5 to 13 years was reported by the Pediatric Eye Disease Investigator Group (PEDIG).[29] This study was designed as a noninferiority study and randomized children to 1 hour per day of dichoptic game play (falling blocks) or 2 hours of patching per day for 16 weeks. After 16 weeks, the mean VA improved in the dichoptic game group by 1.05 lines compared with 1.35 lines in the patching group. The upper limit of the 95% confidence interval (CI) exceeded the prespecified noninferiority limit of 0.5 lines; however, there were significant difficulties with adherence in the game play group, with only 22% of participants performing greater than 75% of the prescribed treatment based on automatic recording of game play duration by the iPad tablet (Microsoft Corp., Redmond, WA). A post hoc analysis revealed that the 2-sided 95% CI for the adjusted treatment group difference was 0.04 to 0.58 lines, favoring patching. A secondary analysis that included compliance data did not reveal a correlation between improvements in VA and number of hours of game play.

This study was followed by another report by PEDIG in 2017 that reported the results of a level I randomized controlled trial of 100 older participants ages 13 to 17 years who were randomized to 1 hour of daily dichoptic game play (falling blocks, n = 40) or patching 2 hours per day (n = 60) for 16 weeks. The results of this study were similar to PEDIG's previous study of the younger cohort, showing a mean improvement of 3.5 letters in the dichoptic game group and 6.5 letters in the patching group after 16 weeks.[30] After adjusting for baseline VA, the authors reported that the difference between the groups was 0.5 lines (2.7 letters) with a 95% CI of −5.7 to 0.3 letters ($P = 0.082$), favoring patching. Adherence was again a limitation in the study. Only 13% of the subjects in the binocular game group were found to have been adherent with more than 75% of the prescribed treatment; however, post hoc analysis revealed that improvement in VA was not associated with total hours of treatment. Most recently, in 2019, PEDIG published the results of its study of Dig Rush, which was found to be a more engaging game for children.[31] This report detailed the results of an older cohort, ages 7 to 13 years, who were randomized to 1 hour of daily dichoptic game play (Dig Rush, n = 69) or continued spectacle wear (n = 69) for 8 weeks. The VA results were similar to PEDIG's previous studies; after adjusting for baseline VA, the mean amblyopic eye letter score at 8 weeks improved by 2.3 letters (95% CI, 0.7−3.9 letters) for the dichoptic group and 2.4 letters (95% CI, 0.8−4.0 letters) for the control group. This difference was not statistically significant: The adjusted mean was −0.1 letters with a 95% CI of −2.4 to 2.1 letters. Adherence in this study was better than in the falling blocks game; 56% of subjects completed more than 75% of prescribed game play according to the automatic recording by the patient's device over the 8-week study (median, 80%; range, 1%−133%).

A different group of investigators in Australia and New Zealand led by Guo et al[32] evaluated the dichoptic falling blocks game in the Binocular Treatment of Amblyopia Using Videogames randomized controlled trial. This study enrolled 115 subjects aged 7 to 55 years and randomized them to daily 1-hour game play of the dichoptic therapy (n = 56) or a sham game (n = 59) for 6 weeks. Subjects were stratified into 3 age groups, including child (7−12 years), teenager (13−17 years), and adult (>17 years). Of note, 77% of the subjects had prior occlusion therapy. After 6 weeks, there was no significant difference in the changes in VA among groups regardless of age; subjects in the dichoptic therapy group showed 0.06 logMAR improvement compared with 0.07 logMAR improvement in the sham group. The mean treatment difference between groups, adjusted for baseline VA and age, was −0.02 logMAR (95% CI, −0.06 to 0.02, $P = 0.25$).

A different form of dichoptic treatment was reported by Vedamurthy et al[16] in 2015 that combined perceptual learning, video game play, and dichoptic techniques. In this study, 38 adults (ages 19−66 years) were assigned to a dichoptic treatment group (n = 23) or a monocular movie-watching group (n = 15). Both groups underwent treatment for 2-hour sessions 2 to 5 times per week for a total of 40 hours of treatment. After treatment, the dichoptic therapy group had a mean improvement of 0.14 logMAR (SD, 0.01 logMAR) compared with the monocular movie-watching group that

improved by 0.07 logMAR (SD, 0.03 logMAR [95% CIs were not presented]).

Bossi et al[33] reported another form of dichoptic therapy in 2017 that they described as balanced binocular viewing (BBV) treatment. This therapy uses a computer and shutter glasses to present dichoptic movies that are matched in visibility across the eyes. Movies were interrupted each minute with an interactive game used to measure suppression. The BBV treatment consisted of daily movie viewing for 1 hour per day for 8 weeks total. Twenty-four children (ages 4−11 years) were enrolled in this level III case series, and 22 completed the study. Overall, the mean VA improved from 0.78 logMAR to 0.51 logMAR ($P < 0.001$), with a mean improvement of 0.27 logMAR (SD, 0.22 logMAR). The authors of this study claimed that in their cases the improvement in VA and stereoacuity exceeded reports for other binocular therapies. However, this study was not randomized and had no control group, so it is difficult to draw strong conclusions.

A dichoptic visual training therapy using an oculus rift virtual reality headset was developed and reported in 2017 by Ziak et al.[34] In their level III study, they enrolled 17 adults (ages 17−69 years) with anisometropic amblyopia who were prescribed twice-weekly 40-minute sessions of game play for 4 weeks. The mean amblyopic eye VA improved from 0.58 logMAR to 0.43 logMAR ($P < 0.01$). The authors hypothesized that their results may have been bolstered by the ability of virtual reality headsets to reduce the misperception of 3-dimensional movement, and they suggested further studies using this modality. In 2018, Bao et al[35] reported preliminary results of their head-mounted altered reality system that allowed patients to experience ambient world images captured by a camera in real-time. Subjects were asked to wear the altered-reality headset for 3 hours per day for 7 days. In this level III case series, 18 subjects ages 14 to 35 years underwent therapy for 1 week and were followed for 4 additional weeks. The authors reported an improvement in amblyopic eye VA of 0.145 logMAR ($P < 0.001$) but acknowledged the small sample size and uncontrolled nature of their study.

In 2018, preliminary results were reported of a level III study of BinoVision, a binocular, head-mounted video goggle system designed for dichoptic stimulation connected to a personal computer that stored children's television shows and movies.[37] This study enrolled children aged 4 to 8 years and assigned them to the dichoptic study group (n = 19) for 8 to 12 weeks or a sham group (n = 8) for 4 weeks. All patients were instructed to watch animated programs at home for 60 minutes per day, 6 days per week. After a 2-week washout period, the 5 children originally assigned to the sham group were offered treatment using the dichoptic device. After 8 weeks of treatment, mean amblyopic eye VA improved from 0.66±0.2 logMAR (range, 0.4−1.18 to 0.39±0.16 logMAR; range, 0.1−0.65 logMAR; $P = 0.0002$). In the sham group, the mean amblyopic VA did not significantly change (0.62±0.2 to 0.61±0.17 logMAR). Compliance rates in this study were good, with an average compliance of 88% (percent of patients completing all of the assigned treatment based on automatic device recordings).

Binocularity and Sensory Outcomes Such as Stereopsis

Sensory outcome was addressed in all of the level I and II studies included in this assessment. Overall, there was no convincing evidence of improvements in sensory status among these studies.

In the level III study by Li et al[26] using the dichoptic falling blocks game, there was no significant change in the mean severity of suppression or stereoacuity in the treatment or control groups. In their similarly designed level III study of younger subjects, no significant improvement in stereopsis was found in the treatment or control group.[27] In the PEDIG studies reported by Holmes et al[29] and Manh et al,[30] there were no significant differences in stereoacuity outcomes between the dichoptic therapy and patching groups. In a similar study by Gao et al,[36] there was no significant difference between the active therapy and placebo game groups. In the most recent PEDIG study of the Dig Rush game, there was also no significant change in stereoacuity in either treatment group.[30]

In the 2016 level I study of the I-BiT treatment by Herbison et al,[23] there was no significant improvement in stereoacuity among the 3 study arms (I-BiT game, I-BiT movie, sham game). In the level III study of the I-BiT by Cleary et al,[17] stereoacuity outcomes were improved. Of their 8 of 12 subjects with pretreatment binocularity, there was an overall improvement from a median of 400 arc seconds (range, 1980−110) to a median of 200 arc seconds (range, 1980−110). Likewise, in other level III studies, there were improvements noted in stereoacuity. In the 2012 Hess et al[25] study of their falling blocks game, 6 of the 10 adult subjects showed improvements in stereoacuity, 4 of whom transitioned from a complete lack of stereopsis to some measurable amount. In their follow-up study, stereoacuity improved on average by 0.61 log units (mean values of 1388 arc seconds improving to 344 arc seconds, $P < 0.001$). In the level III study by Vedamurthy et al[16] that used a combination of perceptual learning and dichoptic therapy, stereoacuity improved by a mean of 0.18 log arc seconds (SD, 0.05 log arc seconds) in the active game group and 0.08 log arc seconds (SD, 0.04 log arc seconds) for the monocular movie-viewing group ($P < 0.005$). In the 2017 level III study of BBV reported by Bossi et al,[33] the number of children with measurable stereoacuity increased from 1 of 7 of the anisometropic amblyopes pretreatment to 6 of 7 post-treatment. In these 7 subjects, the median stereoacuity improved from 170 arc seconds (interquartile 230 arc seconds) to 85 arc seconds (interquartile 30 arc seconds) ($P = 0.0215$). In the level III study of BinoVision by Mezad-Koursh et al,[37] the 2 patients with stereoacuity present at enrollment maintained stereopsis and 3 additional patients obtained stereoacuity of 400 arc seconds or better.

Persistence of Visual Acuity Changes after Treatment Cessation

Visual acuity after treatment cessation was addressed in 3 of the level I and II studies. Overall, there was minimal change in the VA improvements reported in these studies.

In the study by Li et al[26] of the falling blocks dichoptic therapy, 21 of the 34 children who were compliant with treatment were followed for 3 months posttreatment. Of these 21 subjects, there was no significant change from the VA measured immediately after the treatment ended (paired, $t = 1.07$, $P = 0.30$). In the level I study by Herbison et al[22] of I-BiT games and movies, there was a nonsignificant mild decline in vision over the 4-week washout period in all 3 groups. Rajavi et al[24] evaluated the addition of I-BiT to patching, and the 4-week post-treatment cessation period that included patching treatment for both groups revealed further improvement of the patients originally randomized to patching (a mean improvement of -0.08 ± 0.09 logMAR, $P = 0.003$) only, but no improvement in the group originally randomized to I-BiT plus patching (a mean improvement of -0.01 ± 0.07 logMAR, $P > 0.99$).[24] At the end of the washout/patching period, there was no significant difference in the VA between the 2 groups (0.16 ± 0.15 vs. 0.18 ± 0.19 logMAR for the iBiT and control groups, respectively; $P = 0.246$).

In the level III study of the I-BiT by Cleary et al,[17] a washout period of 4 weeks was reported in the 12 older amblyopic children. The authors' findings showed minimal regression overall; 1 child demonstrated a reduction of VA after 4 weeks without treatment, but late improvement was noted in 1 child. In the 2012 level III study by Hess et al,[25] 4 subjects were followed for 1 to 2 months after cessation of treatment. Stereoacuity and VA improved in 3 of these subjects, and these improvements were reportedly maintained at the last follow-up. In the study that combined perceptual learning and dichoptic therapy by Vedamurthy et al,[16] improvements in VA were maintained after a washout period of 2 months. In the 8-week study of BBV, 11 children were followed for 16 additional weeks after completing 8 weeks of therapy. In this subgroup, there was no significant decrement in VA after the cessation period (0.39 ± 0.25 logMAR at completion of BBV treatment and 0.34 ± 0.30 logMAR after an additional mean follow-up time of 47 ± 10 weeks).[33]

Adverse Events

In the studies evaluating dichoptic game play, there were few adverse events. In the PEDIG study of the falling blocks game by Holmes et al[29] (younger cohort ages 5−12 years), a new tropia or worsening of pre-existing deviation was reported in 9% and 11% of patients in the binocular and patching groups, respectively. There were 6 patients in the binocular treatment group and 2 patients in the patching group with positive responses at the 16-week visit for the parent-reported diplopia ($P = 0.17$); however, for the participant-reported diplopia, there were 16 patients in the binocular treatment group and 7 patients in the patching group with positive responses ($P = 0.05$). In the PEDIG study evaluating the older cohort ages 13 to less than 17 years, a new tropia or worsening of pre-existing deviation was reported in 8% and 5% of patients in the binocular and patching groups, respectively. Only 2 participants in each group reported diplopia. In the PEDIG study of Dig Rush with subjects ages 7 to 13 years, a new tropia or worsening of pre-existing deviation was reported in 13% of patients in both groups. In the Binocular Treatment of Amblyopia Using Videogames study, no diplopia was reported.[32] In the study of the I-BiT by Cleary et al,[17] 3 subjects were found to have diminished depth of suppression that was found to be temporary and not associated with diplopia. In the Herbison et al[22] study of the I-BiT, there were 2 cases of diplopia in the I-BiT groups (1 each in the movie and game groups) that resolved after treatment cessation.

Impact of Age of Treatment

Few studies compared results among age groups. In the study by Li et al,[26] patients ages 5 to 13 years were enrolled, and there was no significant difference in the amount of VA improvement in younger (<7 years) versus older (≥7 years) subjects. In the study by Gao et al[36] that enrolled both adults and children, there was no difference in the treatment effect detected based on age group of the participants (mean between group difference in amblyopic eye VA from baseline to 6 weeks of treatment was −0.06 logMAR (95% CI, −0.14 to 0.02), 0.02 logMAR (95% CI, −0.06 to 0.10), and −0.004 (95% CI, −0.05 to 0.04), for children aged 7 to 12 years, 13 to 17 years, and adults, respectively, $P = 0.39$).[36] Of the studies that enrolled adults, all were level III except for 1 (Gao et al[36]), so it is difficult to draw any strong conclusions about these treatments in adult populations.

Impact of Amblyopia Subtype and Inclusion of Deprivation Amblyopia

In the level III study by Birch et al,[27] there was no significant difference among VA improvement of anisometropic, strabismic, or mixed mechanism etiologies of amblyopia (0.10 ± 0.04, 0.07 ± 0.03, and 0.09 ± 0.02 logMAR improvement, respectively).[27] In the level III study by Vedamurthy et al,[16] the investigators found that anisometropic amblyopes improved equally, whether they underwent active dichoptic therapy or monocular movie viewing; however, strabismic anisometropia subjects only improved after game play.

In 2017, a level III study by Hamm et al[38] sought to evaluate the dichoptic falling blocks game (first described in 2012 by Hess et al[25] in a population of patients with deprivation amblyopia), because prior studies had largely excluded patients with deprivation amblyopia in favor of enrolling anisometropic and strabismic amblyopes. This study enrolled 18 subjects ages 5 to 14 years, 8 of whom had deprivation amblyopia (the remaining 10 subjects had anisometropia [n = 8] or mixed mechanism [n = 2]). The patients were all prescribed dichoptic game play for 1 hour per day for a period of 6 weeks. The results revealed a significant improvement in both groups. The deprivation group improved from 0.94 ± 0.12 to 0.85 ± 0.12 logMAR ($P = 0.004$), and the anisometropia/strabismus group improved from 0.57 ± 0.13 to 0.42 ± 0.09 logMAR ($P = 0.014$). The authors suggested that dichoptic therapy could be evaluated further and may be especially useful in the groups that fared well in their study, specifically those with early bilateral deprivation.

Conclusions

This assessment suggests that despite promising results from early level III case series, the more rigorously designed level I and II studies have not yielded consistent evidence of efficacy for binocular treatments of amblyopia. Furthermore, 2 large randomized controlled trials have shown inferior performance of binocular treatment relative to standard treatment (patching).[29,30] One potential difficulty in obtaining positive results may be a lack of engaging games in the largest studies, especially compared with video game units that are currently available. There is sufficient evidence to advocate for well-designed studies using more engaging technologies; however, should such studies yield beneficial results, cost and availability may limit the use of these technologies, especially when compared with the proven efficacy, low cost, and high availability of patching and atropine 1% eye drops.

Future Research

At this time, although binocular therapy cannot be recommended as a replacement for standard amblyopia therapy, further research and more rigorous study of newer, more engaging therapies would be useful to continue to determine whether they have a role as an adjunct to or replacement of the current standard treatment options. In addition, optimal timing and treatment duration require more in-depth study for all of these technologies.

References

1. Friedman DS, Repka MX, Katz J, et al. Prevalence of amblyopia and strabismus in white and African American children aged 6 through 71 months the Baltimore Pediatric Eye Disease Study. *Ophthalmology*. 2009;116:2128−2134. e2121-2122.
2. O'Connor AR, Birch EE, Anderson S, Draper H. Relationship between binocular vision, visual acuity, and fine motor skills. *Optom Vis Sci*. 2010;87:942−947.
3. Stifter E, Burggasser G, Hirmann E, et al. Monocular and binocular reading performance in children with microstrabismic amblyopia. *Br J Ophthalmol*. 2005;89:1324−1329.
4. Cotter SA, Pediatric Eye Disease Investigator Group, Edwards AR, et al. Treatment of anisometropic amblyopia in children with refractive correction. *Ophthalmology*. 2006;113:895−903.
5. Pediatric Eye Disease Investigator Group. A comparison of atropine and patching treatments for moderate amblyopia by patient age, cause of amblyopia, depth of amblyopia, and other factors. *Ophthalmology*. 2003;110:1632−1637. discussion 1637−1638.
6. Pediatric Eye Disease Investigator Group. A randomized trial of near versus distance activities while patching for amblyopia in children aged 3 to less than 7 years. *Ophthalmology*. 2008;115:2071−2078.
7. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. *Arch Ophthalmol*. 2002;120:268−278.
8. Pediatric Eye Disease Investigator Group. Pharmacological plus optical penalization treatment for amblyopia: results of a randomized trial. *Arch Ophthalmol*. 2009;127:22−30.
9. Repka MX, Kraker RT, Beck RW, et al. Treatment of severe amblyopia with weekend atropine: results from 2 randomized clinical trials. *J AAPOS*. 2009;13:258−263.
10. 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.
11. Astle AT, McGraw PV, Webb BS. Can human amblyopia be treated in adulthood? *Strabismus*. 2011;19:99−109.
12. 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.
13. 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.
14. Levi DM, Li RW. Perceptual learning as a potential treatment for amblyopia: a mini-review. *Vision Res*. 2009;49:2535−2549.
15. Polat U, Ma-Naim T, Belkin M, Sagi D. Improving vision in adult amblyopia by perceptual learning. *Proc Natl Acad Sci U S A*. 2004;101:6692−6697.
16. 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.
17. Cleary M, Moody AD, Buchanan A, et al. Assessment of a computer-based treatment for older amblyopes: the Glasgow Pilot Study. *Eye (Lond)*. 2009;23:124−131.
18. Noah SB, Bayliss J, Vedamurthy I, et al. Comparing dichoptic action video game play to patching in adults with amblyopia. *J Vision*. 2014;14:691.
19. Ooi TL, Su YR, Natale DM, He ZJ. A push-pull treatment for strengthening the 'lazy eye' in amblyopia. *Curr Biol*. 2013;23:R309−R310.
20. Oxford Centre for Evidence-Based Medicine. Levels of evidence (March 2009). http://www.cebm.net/index.aspx?o=1025. Accessed August 19, 2016.
21. Waddingham PE, Butler TK, Cobb SV, et al. Preliminary results from the use of the novel Interactive binocular treatment (I-BiT) system, in the treatment of strabismic and anisometropic amblyopia. *Eye (Lond)*. 2006;20:375−378.
22. Herbison N, Cobb S, Gregson R, et al. Interactive binocular treatment (I-BiT) for amblyopia: results of a pilot study of 3D shutter glasses system. *Eye (Lond)*. 2013;27:1077−1083.
23. Herbison N, MacKeith D, Vivian A, et al. Randomised controlled trial of video clips and interactive games to improve vision in children with amblyopia using the I-BiT system. *Br J Ophthalmol*. 2016;100:1511−1516.
24. Rajavi Z, Sabbaghi H, Amini Sharifi E, et al. The role of Interactive Binocular Treatment system in amblyopia therapy. *J Curr Ophthalmol*. 2016;28:217−222.
25. Hess RF, Thompson B, Black JM, et al. An iPod treatment of amblyopia: an updated binocular approach. *Optometry*. 2012;83:87−94.
26. Li SL, Jost RM, Morale SE, et al. A binocular iPad treatment for amblyopic children. *Eye (Lond)*. 2014;28:1246−1253.
27. Birch EE, Li SL, Jost RM, et al. Binocular iPad treatment for amblyopia in preschool children. *J AAPOS*. 2015;19:6−11.
28. Kelly KR, Jost RM, Dao L, et al. Binocular iPad game vs patching for treatment of amblyopia in children: a randomized clinical trial. *JAMA Ophthalmol*. 2016;134:1402−1408.

29. 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.
30. Manh VM, Holmes JM, Lazar EL, et al. A randomized trial of a binocular iPad game versus part-time patching in children aged 13 to 16 years with amblyopia. *Am J Ophthalmol*. 2018;186:104−115.
31. Pediatric Eye Disease Investigator Group, Holmes JM, Manny RE, et al. A randomized trial of binocular dig rush game treatment for amblyopia in children aged 7 to 12 years. *Ophthalmology*. 2019;126:456−466.
32. 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.
33. Bossi M, Tailor VK, Anderson EJ, et al. Binocular therapy for childhood amblyopia improves vision without breaking interocular suppression. *Invest Ophthalmol Vis Sci*. 2017;58:3031−3043.
34. Ziak P, Holm A, Halicka J, et al. Amblyopia treatment of adults with dichoptic training using the virtual reality oculus rift head mounted display: preliminary results. *BMC Ophthalmol*. 2017;17:105.
35. Bao M, Dong B, Liu L, et al. The best of both worlds: adaptation during natural tasks produces long-lasting plasticity in perceptual ocular dominance. *Psychol Sci*. 2018;29:14−33.
36. 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*. 2018;136:172−181.
37. Mezad-Koursh D, Rosenblatt A, Newman H, Stolovitch C. Home use of binocular dichoptic video content device for treatment of amblyopia: a pilot study. *J AAPOS*. 2018;22:134−138.e134.
38. Hamm LM, Chen Z, Li J, et al. Contrast-balanced binocular treatment in children with deprivation amblyopia. *Clin Exp Optom*. 2018;101:541−552.
39. Hess RF, Babu RJ, Clavagnier S, et al. The iPod binocular home-based treatment for amblyopia in adults: efficacy and compliance. *Clin Exp Optom*. 2014;97:389−398.
40. Mansouri B, Singh P, Globa A, Pearson P. Binocular training reduces amblyopic visual acuity impairment. *Strabismus*. 2014;22:1−6.

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Abbreviations and Acronyms:
BBV = balanced binocular viewing; **CI** = confidence interval; **I-BiT** = Interactive Binocular Treatment; **logMAR** = logarithm of the minimum angle of resolution; **PEDIG** = Pediatric Eye Disease Investigator Group; **SD** = standard deviation; **VA** = visual acuity.

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