

Digital therapeutic improves visual acuity and encourages high adherence in amblyopic children in open-label pilot study

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BACKGROUND

The effectiveness of amblyopia therapy can be limited by poor adherence. Dichoptic therapies are a new approach, but recent trials have demonstrated difficulty maintaining high adherence over extended periods of at-home treatment. We evaluated the efficacy and adherence of Luminopia One—a dichoptic treatment that applies therapeutic modifications to streaming content chosen by the patient.

METHODS

This single-arm, multicenter prospective pilot study enrolled children aged 4-12 with anisometropic, strabismic, or mixed amblyopia at 10 pediatric ophthalmic and optometric practices across the United States. The therapeutic was prescribed for 1 hour/day, 6 days/week for 12 weeks of at-home use. The primary endpoint was best-corrected visual acuity (BCVA) at the 12-week follow-up visit.

RESULTS

In total, 90 participants (mean age, 6.7 ± 2.0 years) were enrolled, and 73/90 participants (81%) had prior treatment beyond refractive correction. For those who completed the 12-week visit, mean amblyopic eye BCVA improved from 0.50 logMAR to 0.35 logMAR (1.5 logMAR lines; 95% CI, 1.2-1.8 lines; $P < 0.0001$). Mean stereoacuity improved by 0.28 log arcsec (95% CI, 0.14-0.42 log arcsec; $P < 0.0001$). Median adherence was 86% (interquartile range, 70%-97%).

CONCLUSIONS

In our study cohort, adherence over the 12-week study period was high, and participants demonstrated clinically and statistically significant improvements in visual acuity and stereoacuity. (J AAPOS 2021; ■:1.e1-6)

The current standard-of-care treatment for amblyopia involves refractive correction followed by patching or penalizing (blurring) the nonamblyopic (fellow) eye.¹ Poor adherence contributes significantly to poor outcomes in amblyopia therapy.²⁻⁵ When adherence is patient reported, only about half of patients complete more than 75% of prescribed patching.⁴ When

objectively monitored, adherence is even lower, with 44% average adherence, and patients skipping 42% of prescribed days.⁶ However, even highly adherent patients may fail to improve,⁷ suggesting underlying deficiencies in the mechanism of action as well.

Dichoptic, or binocular, therapy is a recently introduced amblyopia treatment modality first reported by Baker and

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colleagues.⁸ The approach is predicated on addressing suppression through binocular modifications to visual inputs rather than monocular occlusion and was pioneered by the Hess^{9,10} and Birch labs.^{11,12} Selective reduction of luminance or contrast of images presented to the fellow eye reduces interocular suppression and promotes binocularity. Dichoptic therapies have shown promise in pilot studies as an alternative to patching when delivered as a video game^{13,14} or using video content, first reported by Li and colleagues.¹⁵⁻¹⁷ However, two large, randomized, controlled trials—Amblyopia Treatment Study (ATS) 18 and ATS 20—failed to demonstrate efficacy,^{18,19} partly because of low adherence. We hypothesized that a dichoptic therapy with consistently high adherence over an extended treatment period in an at-home setting would improve outcomes.

To test this hypothesis, we conducted a pilot study of a digital therapeutic for amblyopia. The device applies therapeutic modifications to streaming content and allows patients to choose from popular television shows and movies to watch as treatment. The study was conducted in two phases to obtain feedback on the therapeutic and to evaluate initial efficacy and adherence.

Materials and Methods

We conducted a multicenter, single-arm, two-phase pilot study at 10 academic and community-based clinical sites in the United States (<https://clinicaltrials.gov/ct2/show/NCT02782117>). Nine sites were pediatric ophthalmic practices, and 1 was an optometric practice. The study was approved by the Alpha Institutional Review Board for all sites and carried out in accordance with the principles of the Declaration of Helsinki and the US Health Insurance Portability and Accountability Act of 1996.

A parent or guardian (referred to subsequently as “parent”) of each participant gave written informed consent prior to all study-related procedures, and participants aged 7 or older provided written assent as well. The key inclusion criteria for the study were established prospectively as follows: (1) age 4 to <8 years (phase 1) or age 4 to <13 years (phase 2); (2) monocular amblyopia associated with anisometropia, strabismus, or both; (3) amblyopic eye best-corrected visual acuity (BCVA) 20/40-20/200 inclusive (0.3-1.0 logMAR); (4) fellow eye BCVA 20/25 or better (phase 1) or 20/32 or better (phase 2); (5) interocular BCVA difference ≥ 3 lines (≥ 0.3 logMAR); (6) visual acuity stability in current refractive correction (phase 2) defined as either at least 16 weeks in current correction or ≤ 0.1 logMAR change in amblyopic eye BCVA between two measurements at least 4 weeks apart; and (7) heterotropia of $\leq 5^\Delta$ at distance with correction ($<10^\Delta$, phase 1).

Data from both phases were pooled and reported here. Data from phase 1 participants who completed the 12-week visit have previously been published,²⁰ along with further information on the design and engineering considerations behind the therapeutic.

Treatment

All participants were prescribed the therapeutic for 1 hour/day to be used over their prescribed refractive correction (if applicable)

for 12 weeks. Participants were not permitted to change refractive correction until exiting the study. Participants were instructed to use the therapeutic 7 days/week in phase 1 and 6 days/week in phase 2.

The therapeutic included a smartphone containing the treatment software application and a virtual reality (VR) headset, which allowed images to be presented dichoptically at optical infinity without adjustment in stimulus position. Phase 1 used a custom-designed VR headset,²⁰ and phase 2 used commercially available headsets (Gear VR [Samsung, Seoul, South Korea] and VR One Plus [Zeiss, Oberkochen, Germany]). The smartphone operating system was modified to make it impossible for participants to access other aspects of the smartphone’s functionality. Participants used the therapeutic at home and had access to 758 hours of streaming content licensed from PBS Kids, Dreamworks, Sesame Street, Nelvana, and Nickelodeon. Available content was filtered based on parental guidelines such that participants were only able to select age-appropriate videos.

Therapeutic modifications were applied in real-time to selected video content. The modifications are based on those described by Li and colleagues¹⁵ and Birch and colleagues²¹ and consisted of two components: (1) the total contrast of images presented to the fellow eye was reduced to 15% of that presented to the amblyopic eye, and (2) complementary dichoptic masks were superimposed on the images presented such that binocular viewing was required to fully appreciate the video content (Figure 1). The therapeutic we evaluated is distinguished from previously reported approaches in two ways: the fellow eye contrast remained constant instead of incrementing during treatment, and the dichoptic masks were specifically designed to keep the center of the amblyopic eye view clear. The therapeutic automatically recorded adherence based on the amount of time spent watching videos. Participants were allowed to exceed the prescribed duration of treatment. Parents were given access to an online patient portal where they could review their child’s daily usage (Figure 1E) and curate content for their child.

Study Visits and Procedures

Participants returned for follow-up visits 2, 4, 8, and 12 weeks after the baseline visit. At each visit, BCVA was measured in each eye using an electronic visual acuity system with pre-programmed testing protocols: participants 4-6 years of age were assessed using the ATS-HOTV protocol²¹; participants 7-12 years of age, using the e-ETDRS protocol.²² The primary endpoint was amblyopic eye BCVA after 12 weeks of treatment. At each visit, ocular alignment was measured in current correction using the simultaneous prism and cover test at distance, and stereoacuity was measured in current correction using the Randot Fly and Preschool tests at near.

Participant satisfaction with the therapeutic was assessed at 2 weeks using a net promoter score (NPS), a common tool to gauge customer satisfaction.²³ Parents were asked how likely they would be to recommend the therapeutic to someone else with “lazy eye” and asked to respond on a scale of 0-10, with 0 being not likely at all and 10 being very likely.

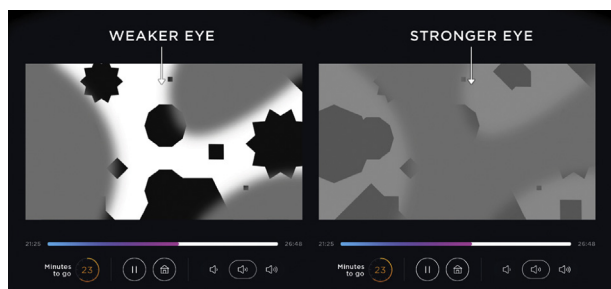


FIG 1. Example video frame with therapeutic modifications applied.

Safety of the therapeutic was assessed by monitoring for new diplopia, new or worsening heterotropia, worsening visual acuity of either eye, adverse symptoms from the device (eg, headaches, nausea, eye strain, and general discomfort), or unanticipated adverse events. Worsening heterotropia was defined as an increase of $\geq 10^\Delta$ from baseline. Worsening visual acuity was defined as a loss of ≥ 2 lines (≥ 0.2 logMAR) from baseline in either eye.

Statistics

For all analyses, the intent-to-treat population was used, which included all participants enrolled in the study, without imputation of missing data. Of the 90 participants enrolled, the 74 who completed the primary endpoint visit were included. Descriptive statistics (mean, standard deviation) and confidence intervals were calculated using Excel for Mac, version 16.38 (Microsoft, Redmond, WA). Other statistical tests were performed using SPSS version 26.0 for Mac (IBM, Armonk, NY).

Changes in BCVA and stereoacuity were assessed using a Wilcoxon signed-rank test. Linear multivariate regression analysis was conducted using the following covariates (baseline unless otherwise stated): age, prior treatment type, prior treatment duration, amblyopic eye BCVA, interocular BCVA difference, stereoacuity (log), horizontal deviation, vertical deviation, NPS at 2 weeks, total treatment received at 12 weeks. Comparisons of treatment responses (change in BCVA and stereoacuity) between subgroups employed the Mann-Whitney test of ranks. Spearman correlation coefficients were calculated for BCVA and stereoacuity. In all cases, two-tailed P values of < 0.05 were considered statistically significant (multivariate regression P values are Bonferroni-corrected, unless otherwise specified).

Results

Between August 2017 and November 2018, 90 participants were enrolled (mean age, 6.7 ± 2.0 years): 12 participants in phase 1 and 78 in phase 2. Males and females were equally represented (45 males), and 73 participants (81%) had prior amblyopia treatment beyond refractive correction. Of the 90, 74 (82%) participants completed 12 weeks of follow-up.

Visual Acuity

At baseline, mean amblyopic-eye BCVA was 0.49 ± 0.16 logMAR (approximately 20/63 Snellen equivalent), and

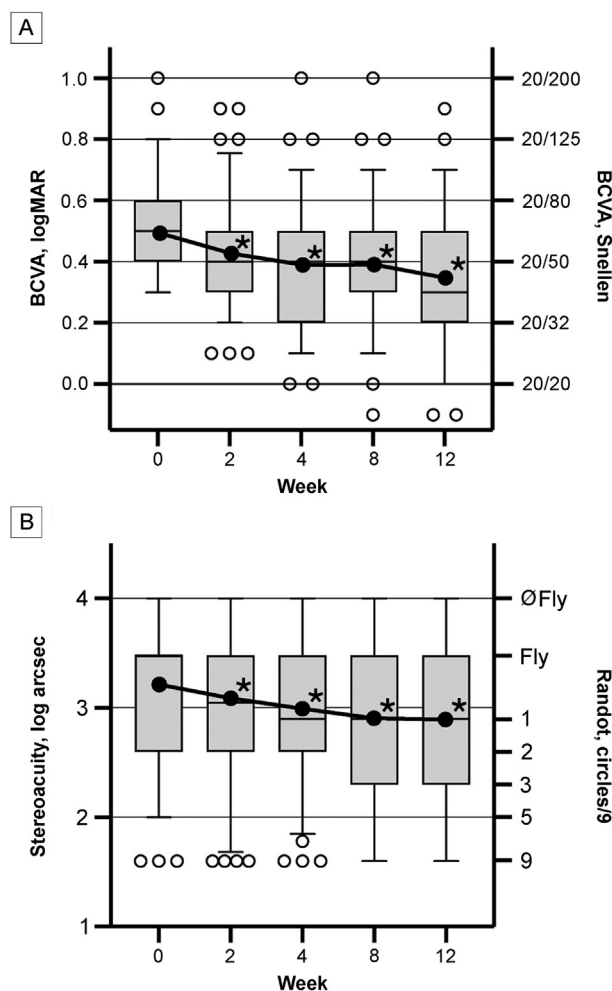


FIG 2. Amblyopic eye visual acuity and stereoacuity outcomes. A, Box plots, with median and 25-75 percentile values, of baseline (week 0) and follow-up (weeks 2, 4, 8, and 12) amblyopic eye best-corrected visual acuity. B, Box plots of baseline (week 0) and follow-up (weeks 2, 4, 8, and 12) stereoacuity measures. Stereoacuity thresholds (log arcsec) are plotted on the left axis and corresponding Randot responses on the right axis. Outliers are individually plotted (open circles); 10%-90% ranges are depicted by whiskers. Means at each timepoint are depicted by the superimposed line plot (filled circles). An asterisk indicates $P < 0.005$ compared with week 0 (baseline).

mean interocular BCVA difference was 0.48 ± 0.17 logMAR (difference of 4.8 logMAR lines). Significant improvement in BCVA was appreciated as early as the 2-week follow-up and continued across the treatment duration (Figure 2A). Of the 74 who completed the 12-week visit, mean BCVA improved from 0.50 ± 0.15 to 0.35 ± 0.21 logMAR (change of 0.15 logMAR; 1.5 logMAR lines; 95% CI, 1.2-1.8 lines; $P < 0.0001$). Thirty-three participants (45%) improved ≥ 0.2 logMAR (2 lines) with 12 weeks of treatment, and 16 participants (22%) had resolution of their amblyopia (final interocular difference ≤ 0.2 logMAR). At baseline, mean fellow-eye BCVA was 0.01 ± 0.10 logMAR and improved to -0.03 ± 0.10

logMAR by the 12-week visit (change of 0.04 logMAR; 0.4 logMAR lines; 95% CI, -0.2 to -0.6 lines, $P < 0.0001$).

Stereoacuity

Mean stereoacuity at baseline was 3.22 ± 0.63 log arcsec (3522 ± 3659 arcsec). Significant improvement in stereoacuity was appreciated as early as the 2-week follow-up visit and continued across the treatment duration (Figure 2B). Of the 74 who completed 12 weeks, stereoacuity improved from 3.18 ± 0.66 log arcsec to 2.90 ± 0.75 log arcsec (change of 0.28 log arcsec, 0.51 octaves; 95% CI, 0.14-0.42 log arcsec; $P < 0.0001$).

Adherence

Adherence was automatically recorded by the therapeutic during the study and calculated as a percentage of the total time prescribed that each participant watched videos. Median adherence over 12 weeks of therapy was 86% (interquartile range, 70%-97%) and was stable over the treatment period (Figure 3). Of the 74 participants who completed 12 weeks, 15 (20%) exceeded their prescribed treatment.

Subgroup Analysis

A linear multivariate regression analysis found no independent factors that influenced gains in amblyopia eye BCVA ($F = 0.25$; $P > 0.9$). Prior treatment duration (coefficient, 0.011 ± 0.003 ; $P = 0.023$) and baseline stereoacuity (coefficient, -0.368 ± 0.116 ; $P = 0.024$) had independent effects on stereoacuity change ($F = 2.44$; $P = 0.02$). See eSupplement 1, available at jaapos.org.

A post hoc subgroup analysis was conducted to further characterize the effects of baseline factors. Whereas multivariate regression did not reveal age to exert an independent effect on amblyopic eye BCVA change, we compared gains in BCVA and stereoacuity between younger and older age groups, given the well-established relationship between age and amblyopia therapeutic response.^{18,25} There was no difference between younger and older participants in BCVA gains (age ≤ 7 [$n = 57$], -0.15 ± 0.14 logMAR; age > 7 [$n = 17$], -0.14 ± 0.11 logMAR; $P > 0.4$) or stereoacuity gains (age ≤ 7 [$n = 57$], -0.35 ± 0.60 log arcsec; age > 7 [$n = 17$], -0.09 ± 0.57 log arcsec; $P > 0.1$).

Prior amblyopia treatment duration was not significantly correlated with change in BCVA ($r = 0.14$; $P > 0.2$). Comparing participants with > 12 months of prior treatment to those with ≤ 12 months revealed no significant difference in BCVA change (> 12 months [$n = 28$], -0.13 ± 0.11 ; ≤ 12 months [$n = 44$], -0.17 ± 0.15 ; $P > 0.1$), although significant gains were made in both subgroups. By contrast, change in stereoacuity was significantly inversely correlated with prior amblyopia treatment duration ($r = 0.28$; $P = 0.02$). Participants with ≤ 12 months of prior treatment showed significantly greater gains in stereoacuity at the 12-week visit than those

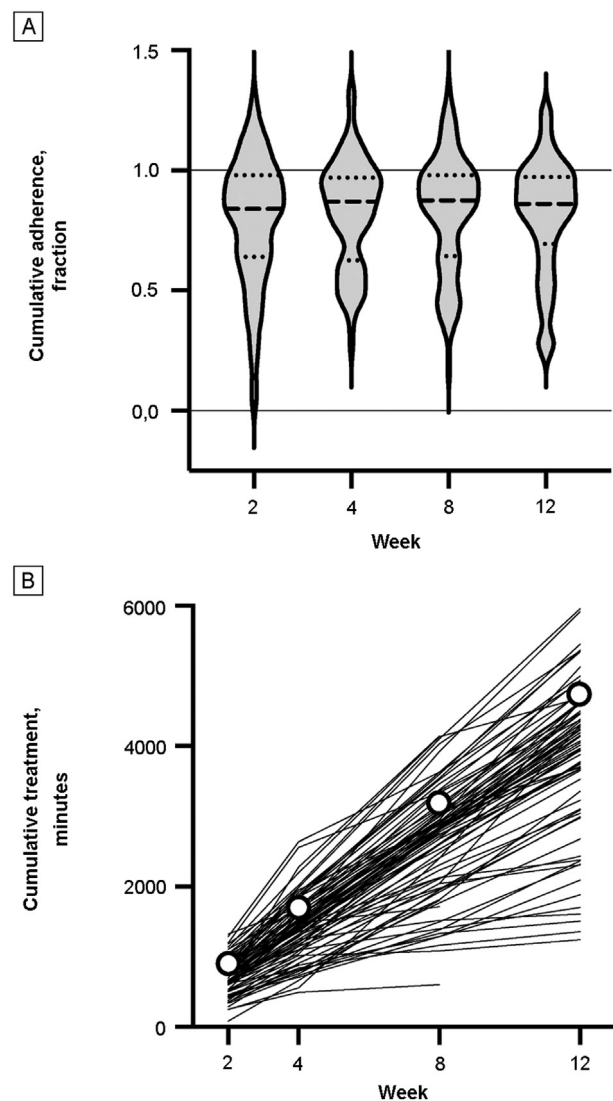


FIG 3. A, Violin plots of cumulative adherence (fraction of prescribed) at each follow-up visit. Median fractional adherence is depicted with dashed lines and 25-75 percentile values are depicted with dotted lines. B, Line plots of cumulative treatment (in minutes) by each patient (lines) at each follow-up visit. Open circles depict mean cumulative prescribed treatment at each follow-up visit.

with more treatment experience (> 12 months, -0.04 ± 0.61 ; ≤ 12 months, -0.46 ± 0.56 ; $P = 0.009$; Figure 4A). Whereas multivariate regression revealed a significant independent effect of baseline stereoacuity on gains in stereoacuity, univariate Spearman correlation of the inverse relationship between these parameters (worse baseline stereoacuity conferring greater gains) did not meet statistical significance ($r = -0.20$; $P = 0.09$; Figure 4B).

Personalization

The ability for parents and patients to choose video content in the therapeutic enabled personalization of treatment. We evaluated the importance of personalization by

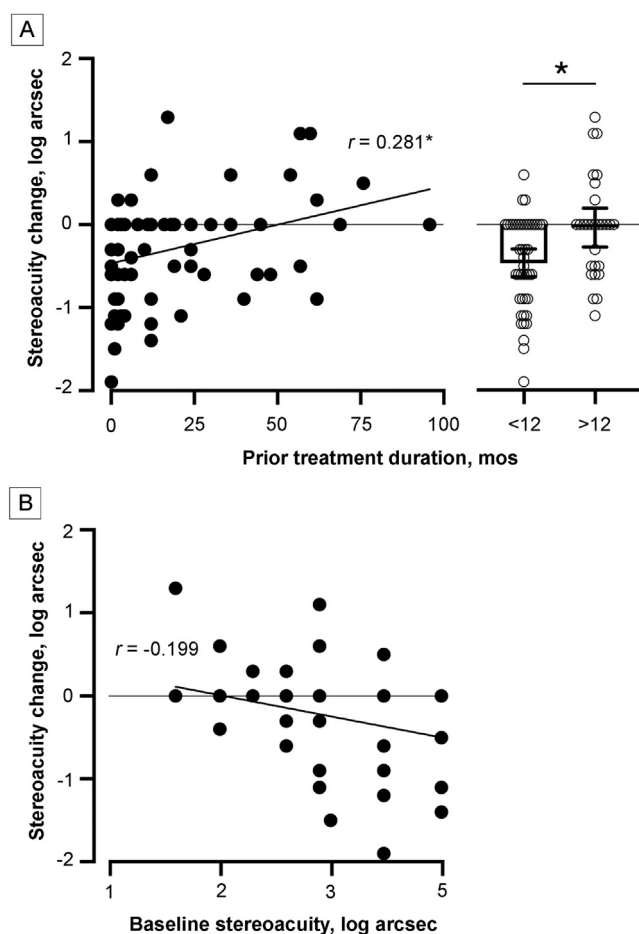


FIG 4. A, Scatterplot depicting the change in stereoacuity (log arcsec) between week 0 (baseline) and week 12 as a function of prior amblyopia treatment duration in months. A linear fit is plotted with the correlation coefficient r depicted. An asterisk indicates $P < 0.05$ Spearman correlation. Bar plot depicting the change in stereoacuity between week 0 (baseline) and week 12 as a function of prior treatment less than or greater than 12 months. Error bars represent 95% confidence interval. The asterisk indicates $P < 0.05$ between groups. B, Scatterplot depicting the change in stereoacuity (log arcsec) between week 0 (baseline) and week 12 as a function of baseline stereoacuity. A linear fit is plotted with the correlation coefficient r depicted.

analyzing the distribution of participant content selections from the library of available content. In total, 172 distinct shows were available to participants; 158 (92%) of available shows were watched at least once.

Participant Satisfaction, Dropout, and Adverse Events

Mean response to the NPS question was 8.9 ± 1.5 , and 49 of 85 patients (58%) responded with a 10 out of 10. Of the 16 participants enrolled who did not complete the 12-week visit, 9 were noncompliant with study procedures (ie, visit schedule, prescribed dosage), and 7 were lost to follow-up.

Twenty adverse events were observed during the study and graded as possibly related to the therapeutic; in 22

cases, there was general discomfort with the therapeutic. All 20 adverse events were mild in severity. The most common adverse events were headaches ($n = 6$), eye strain ($n = 3$), blurry vision ($n = 2$), and worsening visual acuity ($n = 2$). One of 90 patients (1.1%) developed a new heterotropia that did not resolve prior to study exit but did not require discontinuation of the therapeutic (eSupplement 2, available at jaapos.org).

Deidentified individual participant data that underlie our results are provided in eSupplement 3 (available at jaapos.org).

Discussion

In this pilot study, the therapeutic showed promise as a treatment for amblyopia. The 1.5-line improvement in amblyopic eye BCVA from baseline to 12 weeks of treatment exceeds the 1.2-line improvement observed after 12 weeks with patching in a similar age cohort.¹⁸ Of the participants who completed the study, 23% were older (8-12 years), and 81% had prior treatment—two patient subgroups known to be generally less responsive to therapy^{18,25}; both older participants and those with >12 months of prior amblyopia treatment showed significant gains in amblyopic eye visual acuity. The improvements in visual acuity are comparable to those reported by Birch and colleagues²¹ on a similar movie-based dichoptic approach, which yielded a 1.5-line gain after 2 weeks of treatment.

We also observed a significant improvement in stereoacuity after 12 weeks of treatment. No baseline factors were associated with gains in amblyopic eye visual acuity, but patients with less prior treatment and worse baseline stereoacuity were more likely to make gains in stereoacuity. Given that dichoptic therapies are believed to reduce interocular suppression and improve binocularity,¹² gains in stereoacuity may present an important advantage over monocular treatments.

The high median rate of adherence (86%) may have contributed to the robust visual acuity improvement. Digital technology in the therapeutic allowed for adherence to be objectively measured to the nearest minute, avoiding the inaccuracies of self-reporting¹⁸ and imprecision of daily reports.¹⁷ Adherence with the therapeutic was substantially higher than that reported with patching^{6,18,19} and remarkably consistent throughout the study, unlike the drop-off typically seen with patching.⁶ Adherence also exceeded that of dichoptic video games prescribed for similar durations, with median adherences of 46% and 78%.^{18,19} High adherence with the therapeutic may also help to explain the significant gains observed in treatment-resistant subgroups.

Participants' ability to self-select content and personalize their treatment may have contributed to high rates of both adherence and patient satisfaction. The distribution of participant content selections suggests that participants took advantage of the broad library of available

content. Although video games used in other dichoptic therapies may be more engaging than video viewing for the short term, children could lose interest over time if there is only a single game option.

It is important to note key differences between the therapeutic we evaluated and the dichoptic therapies employed in similar movie- and game-based approaches to date. In this therapeutic, the contrast of images presented to the fellow eye remained constant at 15% of the amblyopic eye, whereas in other movie^{15,21} and game-based approaches,^{18,19} the fellow eye contrast was incrementally increased over time. In addition, this therapeutic delivered visual stimuli through a head-mounted display, similar to that reported in Mezzad-Koursh and colleagues,¹⁷ rather than through anaglyphic glasses,^{13,18,19} a stereoscope,¹⁴ a passive 3D display,¹⁵ or shutter glasses.¹⁶ Further research is required to understand how these differences may affect efficacy.

This study is limited by the lack of a comparison group, which prevents our drawing conclusions about relative efficacy. A randomized, controlled trial with a comparison to a conventional treatment would provide the strongest evaluation of efficacy. In addition, this study did not evaluate durability of benefit with the therapeutic. The 1.5 lines of amblyopic eye BCVA improvement found in this extended pilot study is less than the 2.9 lines reported among patients enrolled into phase 1,²⁰ likely owing to a larger sample size and expansion of the study to multiple sites. A randomized, controlled trial on the therapeutic is required to definitively assess its efficacy.

Study Sites

Children's Eye Care of Michigan, Dearborn, MI; Concord Eye Center, Concord, NH; Conestoga Eye, Lancaster, PA; Eye Physicians of Central Florida, Maitland, FL; Houston Eye Associates, Houston, TX; Indiana University, Bloomington, IN; Kids Eye Care of Maryland, Frederick, MD; Virginia Pediatric Eye Center, Virginia Beach, VA; Wheaton Eye Clinic, Chicago, IL.

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