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A Randomized Trial of a binocular iPad Game Versus Part-Time Patching in Children Aged 13 to 16 Years with Amblyopia

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Abstract

Purpose: To compare visual acuity (VA) improvement in teenagers with amblyopia treated with a binocular iPad game versus part-time patching.

Methods: One hundred participants aged 13 to <17 years (mean 14.3 years) with amblyopia (20/40 to 20/200, mean ~20/63) resulting from strabismus, anisometropia, or both were enrolled into a randomized clinical trial. Participants were randomly assigned to treatment for 16 weeks of either a binocular iPad game prescribed for 1 hour per day (N=40) or patching of the fellow eye prescribed for 2 hours per day (N=60). The main outcome measure was change in amblyopic eye VA from baseline to 16 weeks.

Results: Mean amblyopic eye VA improved from baseline by 3.5 letters (2-sided 95% confidence interval (CI): 1.3 to 5.7 letters) in the binocular group and by 6.5 letters (2-sided 95% CI: 4.4 to 8.5 letters) in the patching group. After adjusting for baseline VA, the difference between the binocular and patching groups was -2.7 letters (95% CI: -5.7 to 0.3 letters, $p = 0.082$) or 0.5 lines, favoring patching. In the binocular group, treatment adherence data from the iPad device indicated only 13% of participants completed >75% of prescribed treatment.

Conclusions: In teenagers aged 13 to <17 years, improvement in amblyopic eye VA with the binocular iPad game used in this study was not found to be better than patching, and was possibly

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worse. Nevertheless, it remains unclear whether the minimal treatment response to binocular treatment was due to poor treatment adherence or lack of treatment effect.

Introduction

Amblyopia treatment has been historically considered less effective in older children and adults,^{1–5} but there is now emerging evidence that a binocular approach to the treatment of amblyopia can improve amblyopic eye visual acuity (VA) for adults with strabismic, anisometropic, and mixed mechanism amblyopia,⁶ and possibly at a greater rate than patching treatment.⁷ To achieve a binocular percept, dichoptic displays have been used to present high contrast images to the amblyopic eye and low contrast images to the fellow eye in order to overcome binocular suppression commonly found in amblyopia.⁸ This type of binocular treatment has recently been adapted to an iPad (Apple Inc.) device such that the treatment can be prescribed for home use.

The purpose of this randomized clinical trial was to compare the improvement in amblyopic eye VA after 16 weeks of home-based treatment with binocular game play on an iPad device prescribed for 1 hour a day versus patching prescribed for 2 hours a day, in teenagers aged 13 to <17 years with amblyopic eye visual acuities of 20/40 to 20/200.

Methods

The study was conducted at 52 institution- or community-based clinical sites (28 and 24, respectively) and approved by the respective institutional review boards (IRB). A parent or guardian (referred to subsequently as “parent”) of each study participant gave written informed consent, and each participant assented to participation as required. The study is listed on www.clinicaltrials.gov, under identifier NCT02200211, accessed 9/5/17. The complete study protocol is available on the PEDIG website (www.pedig.net, accessed 9/5/17). Eligibility criteria are listed in Table 1 including a required period of preceding optical treatment of amblyopia,⁹ which some authors call “refractive adaptation.”¹⁰

Study Visits and Testing Procedures

After randomization (± 1 week), follow-up visits were planned at 4, 8, 12, and 16 weeks (± 1 week), with the primary outcome visit at 16 weeks. At each visit, VA was measured in each eye with optimal refractive correction (if applicable), and without cycloplegia by a study-certified examiner using the Electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS©) protocol.^{11, 12} Ocular alignment was measured with a simultaneous prism and cover test (SPCT) and a prism and alternate cover test (PACT), and stereoacuity was measured using the Randot Butterfly and Randot Preschool stereoacuity tests (Stereo Optical Co., Chicago IL). VA and stereoacuity testing were performed by an examiner masked to the participant’s randomized treatment at follow-up. Additionally, at each follow-up visit, a standardized questionnaire was administered to participants and their parents to assess the presence and frequency of diplopia.

Randomization and Treatment

Participants were randomly assigned via the PEDIG website with equal probability, using a permuted block design stratified by baseline amblyopic eye VA (53 to 72 letters, 33 to 52 letters) and site, to receive either binocular treatment or patching treatment (subsequently referred to as the “binocular” and “patching” treatment groups, respectively).

Treatment was prescribed for 16 weeks. The patching group was prescribed 2 hours of daily patching with an adhesive style patch (i.e., Coverlet, 3M Opticlude, Ortopad). The binocular group was prescribed 1 hour of the binocular falling blocks iPad game (Figure 1). Both treatment groups were allowed to divide the total treatment time per day into shorter sessions. The differing treatment durations per day (2 hours of patching versus 1 hour of binocular treatment) were chosen to reflect commonly used regimens with each treatment. Adherence was calculated based on an intended treatment of 7 days a week for 16 weeks.

The game was played on a study-supplied iPad device at the participant’s habitual reading distance while wearing red/green anaglyphic glasses (over the spectacles, if applicable) with the green filter placed over the amblyopic eye. Green elements were seen by the amblyopic eye, red elements were seen by the fellow eye, and brown elements were seen by both eyes. All participants were asked to align a red/green Nonius cross before the start of each game session such that the image components of the game could be aligned, to compensate for small angles of ocular misalignment (no more than 10° by PACT at near) and thereby allow binocular game play (Figure 1). Participants scored points in the game by moving the falling blocks to form complete lines of blocks (Figure 1), with the level of difficulty (i.e. easy, medium, or hard) set at the participant’s discretion. Investigators and site coordinators had been instructed to encourage participants to advance the difficulty level as tolerated during the 16-week study.

While the contrast of the falling blocks for the amblyopic eye was always 100%, the contrast for the fellow eye was initially set to 20% and automatically increased/decreased by 10% increments (with a lowest level of 10%), or left unchanged from the last contrast level, based on game play duration and performance of the previous day. The contrast only changed if 30 minutes of game play occurred on the previous day, increasing if ≥ 1000 points were scored or decreasing otherwise.

Parents and/or participants recorded the number of hours the participant played the game or wore the patch each day using study-provided log calendars. The iPad device automatically recorded the duration of game play, contrast, and performance. Data from the iPad device was uploaded to the PEDIG server at each follow-up visit and/or at the end of the study when the device was returned to the coordinating center.

Statistical Analyses

The sample size of 166 participants was computed to have 90% power with a 2-sided type I error of 5% to detect a treatment group difference if the true difference in mean VA change was 5 letters (1.0 line), assuming a standard deviation of change of 9.0 letters (1.8 lines) based on a prior PEDIG study,¹³ no more than 10% loss to follow-up and a 5% adjustment for interim futility monitoring. At a regularly scheduled Data and Safety Monitoring

Committee (DSMC) meeting in April 2016, the DSMC recommended stopping the study early for two separate but related reasons. First, the pre-planned interim analysis of 71 participants with 16-week outcomes yielded a difference of 2.33 letters favoring patching (standard error = 1.81 letters), corresponding to a Z-statistic of +1.29, which fell just outside the pre-specified 2-sided stopping region (lower and upper boundaries of -1.28 to +1.28). The probability of a type II error at the interim analysis under this plan, i.e. of stopping for futility when a 5-letter difference actually existed, was 7%. The second reason for the early stopping recommendation was poor adherence. Objectively monitored adherence data revealed that only 13% of participants assigned to binocular treatment completed more than 75% of the prescribed treatment (1 hour per day, 7 days per week) at 16 weeks, despite demonstrating the ability to play the game prior to enrollment. There was no interest in continuing the study to demonstrate potential superiority of patching given that adherence with the binocular treatment was poor.

The primary outcome measure was the change in amblyopic eye VA from baseline to 16 weeks (14 to < 20 weeks). A modified intent-to-treat analysis of covariance (ANCOVA), only including participants completing the 16-week outcome, was performed to estimate the treatment group difference in mean change in VA at 16 weeks with computation of a 2-sided 95% confidence interval on the group difference, adjusted for baseline VA. Alternative approaches to the primary analysis are specified in eTable 1.

Statistical methods for additional analyses are described in the relevant tables and figures (including online tables and figures). Reported 95% confidence intervals were two-sided. Analyses were conducted using SAS version 9.4 (SAS Inc., Cary, NC).

Results

Baseline Characteristics

Between September 2014 and April 2016, 100 participants were randomly assigned to the binocular group (n=40) or to the patching group (n=60). Baseline characteristics were similar in the two groups (Table 2). Two participants were subsequently found to be ineligible post-randomization but were included in the analyses (reasons listed in Table 2).

Visit Completion

The 16-week primary outcome was completed by 39 (98%) in the binocular group and 58 (97%) in the patching group (Figure 2). Masking of the visual acuity/stereoacuity testers was maintained at 100% and 97% of visits for the binocular group and patching groups, respectively.

Adherence

During the 16-week follow-up period, 24 (62%) in the binocular group and 42 (75%) in the patching group reported completing >75% of prescribed treatment using the log calendars provided by the study. However, for the binocular group, objectively recorded adherence data from the iPad device (available from 97% of participants) indicated that only 13% of participants completed >75% of the prescribed treatment (median percentage of prescribed

treatment completed 21%, interquartile range 13% to 38%). Median percentage of prescribed treatment completed was 25% during the initial 4 weeks and remained low throughout the 16 weeks. No participant in either treatment group was prescribed non-randomized protocol alternative treatment during the study.

Regarding the difficulty level of the game, 97% of the participants began the study playing the falling blocks game at the “easy” setting. At 16 weeks, 39% were playing at the medium level and 13% at the hard level.

Contrast Change in the Binocular Treatment Group

To create a binocular percept, the contrast of the falling blocks on the iPad screen was increased or decreased according to a programmed algorithm built into the falling blocks game. In the binocular group, contrast increased from 20% to 100% in the fellow eye for 6 participants (17%) by 4 weeks and for 23 participants (61%) by 16 weeks. Three (8%) participants had 20% contrast or less in the fellow eye at 16 weeks.

Amblyopic Eye Visual Acuity

At 16 weeks, after adjusting for baseline VA, mean amblyopic eye VA improved from baseline by 3.7 letters or 0.74 lines (95% CI: 1.3 to 6.0 letters) in the binocular group and 6.3 letters or 1.26 lines (95% CI: 4.4 to 8.3 letters) in the patching group. The difference between binocular and patching treatment was -2.7 letters or 0.52 lines (95% CI: -5.7 to 0.3 letters, $p = 0.082$), favoring patching (Figure 3, Table 3). Results were consistent between binocular treatment and patching across baseline characteristic subgroups (eTable 2).

At 16 weeks, amblyopic eye VA improved 2 lines from baseline for 6 (15%) and 17 (30%) participants in the binocular and patching groups, respectively (adjusted difference: -15%, 2-sided 95% CI: -31% to 2%). No participant achieved amblyopia resolution (VA of 20/25 or better or 78 letters and within 1 logMAR line or 5 letters of the fellow eye).

For the binocular group, improvement in amblyopic eye VA was not associated with either total hours of treatment or change in fellow eye contrast at 4 or 16 weeks, as objectively-recorded on the iPad device (Figure 4–5).

Stereoacuity

The median change in stereoacuity from baseline to 16 weeks was 0 in both groups. Change in stereoacuity did not differ significantly between treatment groups for the overall cohort ($P = 0.83$) or for participants with no history of strabismus at baseline ($P = 0.69$) (eTable 3).

For the binocular group, improvement in stereoacuity was not associated with either total hours of treatment or change in fellow eye contrast at 4 or 16 weeks, as objectively-recorded on the iPad device (Figure 4–5).

Adverse Events

After adjusting for baseline VA, the mean fellow eye VA was found to improve similarly in both the binocular treatment (2.2 letters, 95% CI: 1.2 to 3.1 letters) and patching groups (2.0 letters, 95% CI: 1.3 to 2.8 letters) (eTable 4).

The number of participants with a new heterotropia and/or worsening of a pre-existing deviation of 10 was 3 (8%) and 3 (5%) in the binocular and patching groups, respectively (Fisher exact test: $P = 0.68$). These rates of new heterophoria and/or worsening of a pre-existing deviation are not dissimilar to rates reported in other amblyopia treatment studies.¹⁴ Only 2 participants in each group reported diplopia at the 16-week exam; no participant in the binocular group and 1 participant in the patching group reported diplopia frequency greater than once per week (eTable 5).

One participant in the patching group reported moderate/severe skin irritation from patching, which resolved by the 16-week visit.

Discussion

In teenagers aged 13 to <17 years with amblyopia, VA improved minimally with the 16-week binocular treatment used in this study and was not found to be more effective than patching treatment. The study was stopped by the Data Safety and Monitoring Committee before the planned sample size was recruited because the accrued data favored the patching group, narrowly missing a pre-specified futility stopping boundary; furthermore, the poor adherence to the binocular intervention precluded an assessment of the actual efficacy of binocular therapy for amblyopia. A subsequent conditional power analysis found the probability of finding a difference favoring binocular therapy by the end of the study, assuming a true 5-letter difference in that direction, was <1%. In view of the poor adherence, we cannot say whether the lack of meaningful improvement with the binocular treatment was due to lack of efficacy of the actual treatment or due to poor adherence, nor can we completely exclude the possibility that the minimal improvement we are attributing to binocular treatment in the present study might be due to continued improvement from concurrent optical treatment of amblyopia^{9, 10, 15} or a learning effect.

In contrast to the current study, binocular treatment has been shown to yield more robust VA improvements in adults with amblyopia. In combining data from four small, laboratory-based pilot studies of 52 adults (aged 17 to 51 years) treated for 5 to 52 hours, Hess and Thompson reported an average improvement of 0.24 logMAR or 2.4 lines (95% CI: ± 0.04 logMAR).¹⁶ In a home-based binocular treatment study involving 13 adults and 1 child (aged 13 to 50 years), VA improvement was 0.11 logMAR or 1.1 lines (95% CI: ± 0.08 logMAR), with an average treatment adherence of 64% for a total of 10 to 30 treatment hours.¹⁷ In our current study, total number of binocular treatment hours ranged from 1 to 114 hours (median of 23 hours over 16 weeks), which is within the range of doses found to be effective in previous studies of adults with amblyopia. Therefore, despite the low adherence with binocular treatment in the teenagers enrolled in our study, it is unclear why we did not find greater improvement with binocular treatment in these teenagers. On the one hand, many of our subjects adhered with as much treatment as found effective in pilot studies of adults (total hours), but, on the other hand, they fell far short of the total number of hours of planned treatment. We also found no precipitous drop in adherence at some point during the 16 weeks of the treatment course. Further work is needed to determine if there is any relationship between duration of treatment and response.

We concurrently conducted a parallel study of binocular treatment in younger children aged 5 to 12 years,¹⁸ which also showed greater VA improvement than the current study. At 16 weeks, adjusted mean VA improved by 1.1 lines (95% CI: 0.8 to 1.2 lines) in the younger cohort compared with 0.7 lines (95% CI: 0.3 to 1.2 lines) in the current study of teenagers. Somewhat similar to the teenagers, adherence was also poor in the younger children with only 22% completing >75% of the prescribed binocular treatment. However, the younger cohort did have a higher median proportion of treatment hours completed (46%) compared with the older cohort (21%) in the current study at 16 weeks and so, in addition to the effect of age, this better treatment adherence could explain the greater treatment effect that was found in the younger children. We speculate, based on anecdotal reports during our current study of teenagers, that teenagers found this particular binocular game uninteresting, and further studies are therefore needed with more compelling binocular games.

It is noteworthy that in the current study of teenagers, most of whom had prior treatment (88%), patching resulted in a mean improvement of more than 1 line of VA. This finding is consistent with prior studies of patching in teenagers.¹³ When other research groups have used objective monitoring of adherence with occlusion dose monitors,^{19–21} they found much worse adherence than that reported by parental diaries, and we did not use such monitoring, so our reported adherence of 75% subjects performing >75% prescribed treatment almost certainly overstates the actual adherence. Nevertheless, our study provided further evidence that 2 hours of prescribed patching is somewhat effective in teenagers with amblyopia with or without prior treatment.

The major limitation of our study was poor treatment adherence, which reduced our ability to determine if binocular treatment for amblyopia is actually more effective than was found in this study. We are currently planning another randomized clinical trial using a more engaging home-based binocular game that has been found to have better treatment adherence.²² Using this new binocular game, Kelly and associates²² reported adherence of 100% in the first 2 weeks of treatment, and 82% adherence in the second two weeks. A larger randomized clinical trial using this new game will more definitively answer the question of whether binocular modalities of treatment are truly effective in treating amblyopia.

Refer to Web version on PubMed Central for supplementary material.

Supplementary Material

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No funding organization had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Appendix

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Clinical Sites

Sites are listed in order by number of participants enrolled. Personnel are listed as (I) for Investigator, (C) for Coordinator or (E) for Examiner.

Fullerton, CA - Southern California College of Optometry at Marshall B. Ketchum University (9)

Susan A. Cotter (I); Angela M. Chen (I); Raymond H. Chu (I); Silvia Han (I); Catherine L Heyman (I); Kristine Huang (I); Reena A Patel (I); Maureen Plaumann (I); Carlee Y Young (I) Sue M. Parker (C)

Norfolk, VA - Virginia Pediatric Eye Center (7)

Earl R. Crouch, Jr. (I); Earl R. Crouch III (I); Stacy R. Martinson (I); Gaylord G. Ventura (C); Candice C. Brown (E); Cynthia M. Carlton (E); Carolina A. Escala (E)

Poland, OH - Eye Care Associates, Inc. (6)

S. Ayse Erzurum (I); Beth J. Colon (C); Diana McOwen (C); Guy C. Barrett (E); Zainab Dinani (E)

Erie, PA - Pediatric Ophthalmology of Erie (5)

Nicholas A. Sala (I); Allyson Sala (C); Catherine Johnson (E); V. Lori Zeto (E)

Columbus, OH - The Ohio State University (4)

Marjean T. Kulp (I); Freda D. Dallas (C); Nancy Stevens (C); Jennifer S. Fogt (E); Tamara S. Oechslin (E); Emmanuel Owusu (E); Andrew J. Toole (E)

Cranberry TWP, PA - Everett and Hurite Ophthalmic Association (3)

Darren L. Hoover (I); Pamela A. Huston (C); Christine J. Deifel (E); Jody L. Desiderio (E); Pamela M. Racan (E); Kari E. Soros (E)

Lisle, IL - Progressive Eye Care (3)

Patricia L. Davis (I); Indre M. Rudaitis (C); Carrie S. Bloomquist (E); Jackie M. Twite (E)

Rio Rancho, NM - City of Vision Eye Care (3)

Lisa M. Edwards (I); Carolyn S. Marquez (C); Jessica N. Marquez (E); Tristan L. Martinez (E)

The Woodlands, TX - Houston Eye Associates (3)

Aaron M. Miller (I); Jorie L. Jackson (C); Kathleen M. Curtin (E); Maria N. Olvera (E);
Starla J. Skaggs (E)

Waterbury, CT - Eye Care Group, P.C. (3)

Tara H. Cronin (I); Andrew J. Levada (I); Susan H. Heaton (C); Jesse M. Bendler (E);
Cheryl Capobianco (E); Lindsay Gill (E)

Atlanta, GA - The Emory Eye Center (2)

Amy K. Hutchinson (I); Scott R. Lambert (I); Judy L. Brower (C); Jayne M. Brown (E);
Linda T. Curtis (E); Melanie K. Fowler (E); Phoebe D. Lenhart (E); Marla J. Shainberg (E)

Boise, ID - St Luke's Hospital (2)

Katherine A. Lee (I); Bonita R. Schweinler (C); Daniel R. Brooks (E); Lori L. McDaniel
(E); Larry W. Plum (E)

Boston, MA - Boston Medical Center (2)

Stephen P. Christiansen (I); Jean E. Ramsey (I); Jenna R. Titelbaum (I); Marissa G. Fiorello
(C); Kelly M. Castle (E); Jennifer E. Lambert (E); Kate Hutton McConnell (E)

Chattanooga, TN - Pediatric Eye Specialists (2)

Edward A. Peterson (I); Zachary S. McCarty (I); Charla H. Peterson (C); Amie Jenkins (E)

Chicago Ridge, IL - The Eye Specialists Center, L.L.C. (2)

Benjamin H. Ticho (I); Birva K. Shah (I); Deborah A. Clausius (C); Megan Allen (E);
Sharon L. Giers (E); Micaela N. Quebbemann (E)

Chicago, IL - Illinois College of Optometry (ICO) (2)

Yi Pang (I); Elyse Nylin (C); Huizi Yin (E)

Gainesville, FL - Accent Physicians (2)

Nausheen Khuddus (I); Tammy Toskes Price (C); Kathleen Lorraine Bryan (E)

Glendale, AZ - Midwestern University Eye Institute (2)

Alicia E. Feis (I); Christina A. Esposito (I); Paula A. Handford (I); Tracy A. Bland (C)

Houston, TX - University of Texas- Robert Cizik Eye Clinic (2)

Kartik S. Kumar (I); Ephrem K. Melese (C); Laura A. Baker (E)

Hurricane, WV - Marshall University (2)

Deborah L. Klimek (I); Ginger Peters (C); Amanda C. Conley (E); Sara E. Miramontes (E); Sonya G. Walls (E)

New Haven, CT - Yale University Medical School, Department of Ophthalmology and Visual Science (2)

Jennifer A. Galvin (I); Margaret B. Therriault (C); Jaime Harrison (E); Christine C. Medina (E)

Rochester, MN - Mayo Clinic (2)

Jonathan M. Holmes (I); Suzanne M. Wernimont (C); Matthew W. Heiderscheit (E); Anita R. Hermanson (E); Julie A. Holmquist (E); Jordan J. Huisman (E); Melissa J Hunemuller (E); Lindsay D. Klaehn (E); Marna L. Levisen (E); Laura Liebermann (E); Rebecca A. Nielsen (E); Debbie M. Priebe (E); Casandra M. Turri (E)

Aberdeen, NC - Family Eye Care of the Carolinas (1)

Michael J. Bartiss (I); Tennille F. McGaw (C); Leah M. Kelly (E); Lauren E. Simmons (E)

Birmingham, AL - University of Alabama at Birmingham School of Optometry (1)

Katherine K. Weise (I); Jenifer Montejo (C); Marcela Frazier (E); Kristine T. Hopkins (E); Sarah D. Lee (E)

Boston, MA - Harvard Vanguard Medical Associates (1)

Mei L. Mellott (I); Troy L. Kieser (C); Flor M. Flores (E); Linette Miranda (E)

Calgary, AB, Canada - Alberta Children's Hospital (1)

William F. Astle (I); Emi N. Sanders (C); Zuzana Ecerova (E); Charlene D. Gillis (E); Catriona I. Kerr (E); Shannon L. Steeves (E)

Charleston, SC - Medical University of South Carolina, Storm Eye Institute (1)

Edward W. Cheeseman (I); Carol U. Bradham (C); Carole M. Lemieux (E)

Chicago, IL - Ann & Robert H. Lurie Children's Hospital of Chicago (1)

Bahram Rahmani (I); Sudhi P. Kurup (I); Magdalena Stec (I); Hantamalala Ralay Ranaivo (C); Kristyn M. Magwire (E); Erika A. Talip (E); Vivian Tzanetakos (E)

Cincinnati, OH - Cincinnati Children's Hospital (1)

Michael E. Gray (I); Corey Suzanne Bowman (C); Shemeka Rochelle Butler (E); Kaylie M. Davidson (E); Amanda R. Johnson (E); Melissa L. Rice (E); Daniele P. Saltarelli (E); Erica M. Setser (E); Miqua Lynn Thomas (E); Felicia Jean Timmermann (E)

Columbus, OH - Pediatric Ophthalmology Associates (1)

Don L. Bremer (I); Richard P Golden (I); Mary Lou McGregor (I); Meghan C. McMillin (C); Sara Ann Oravec (C); Andrea N. Gearhart (E); Benita Nechell Mansperger (E)

Concord, NH - Concord Ophthalmologic Associates (1)

Christie L. Morse (I); Melanie L. Christian (C); Caroline C. Fang (E)

Durham, NC - Duke University Eye Center (1)

Laura B. Enyedi (I); David K. Wallace (I); Sarah K. Jones (C); Courtney E. Fuller (E); Namita Kashyap (E)

Fall River, MA - Center for Eye Health, Inc. (1)

John P. Donahue (I); Samantha J Pape (C); Danielle K Berry (E); Linda M. Cabeceiras (E); Mary E. Silvia (E); Samantha Teixeira (E)

Grand Rapids, MI - Pediatric Ophthalmology, P.C. (1)

Patrick J. Droste (I); Jan Hilbrands (C); Leslie J. Bileth (E); Andrew P. Droste (E); Jennifer L. Mooney (E); Robert J. Peters (E)

Iowa City, IA - University of Iowa Hospitals and Clinics (1)

Scott A. Larson (I); Xiaoyan Shan (C); Tara L. Bragg (E); Miriam Di Menna (E)

Jacksonville, FL - Nemours Children's Clinic (1)

John W. Erickson (I); Charlotte Reaser (C); Gracie Sylvester (E)

Kansas City, MO – Children's Mercy Hospitals and Clinics (1)

Amy L. Waters (I); Christina M. Twardowski (I); Rebecca J. Dent (C); Lori L. Soske (C); Lezlie L. Bond (E); Cindy J. Cline (E)

Kingston, ON, Canada - Children's Eye Research Center (1)

Brian W. Arthur (I); Lesley E. MacSween (E)

La Jolla, CA - Abraham Ratner Children's Eye Center, University of California San Diego (1)

Shira L. Robbins (I); Erika C. Acera (C); Michael Kinori (E)

Marlton, NJ - Michael F. Gallaway, O.D., P.C. (1)

Michael F. Gallaway (I); Debbie L. Killion (C); Tammy L. Thomas (E); Beth Zlock (E)

Miami, FL - Bascom Palmer Eye Institute (1)

Susanna M. Tamkins (I); Kara M. Cavuoto (E); Isaura Crespo (E); Maria D. Martinez (E); Eva M. Olivares (E); Oriel Spierer (E); Erin Yanowitch (E)

New York, NY - State University of New York, College of Optometry (1)

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Omaha, NE - University of Nebraska Medical Center (1)

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Mitchell M. Scheiman (E); Ruth Y. Shoge (E)

Pomona, CA – Western University College of Optometry (1)

Ida Chung (I); Jennifer Kurtz (C); Chunming Liu (E)

Portland, OR - Casey Eye Institute (1)

Allison I. Summers (I); Paula K. Rauch (C); Yelena M. Bubnov (E); Grant A. Casey (E);
Rhea N. Nelson (E); Kevin M. Woodruff (E)

Schaumburg, IL - Advanced Vision Center (1)

Ingryd J. Lorenzana (I); Angelyque L. Lorenzana (C); Yesenia Meza (E); Beata Wajs (E)

Seattle, WA - Virginia Mason Medical Center (1)

Hee-Jung S Park (I); Neil Avila (C); Michael J. Sato (E)

Spokane, WA - Spokane Eye Clinical Research (1)

Jeffrey D. Colburn (I); Eileen Dittman (C); Dylan C. Waidelich (E); Marilyn M. Westerman
(E)

St. Louis, MO - Saint Louis University Institute (1)

Rafif Ghadban (I); Dawn M. Govreau (C); Lisa L. Breeding (E)

Toms River, NJ - Ocean Eye Institute (1)

Michael J. Spedick (I); Dena Mitchell (C); Emily Guyer (E); Katelyn Karausky (E); Mary A.
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Figure 1.

(top) Nonius cross: This red/green Nonius cross is aligned by the participant at the start of each session to allow game elements to be adjusted to compensate for small ocular misalignments. **(bottom)** Falling blocks game: The falling blocks game on the “hard” level of difficulty.

Figure 2. Visit Completion by Treatment Group

* The numbers in the parenthesis indicate the number of participants who completed the visit outside of the pre-specific analysis window. Two participants in the patching group completed the 16-week visit outside of the analysis window (14 to <20 weeks after randomization) at approximately 25 to 27 weeks after randomization

Figure 2.

Visit completion by treatment group: Flowchart showing study completion in each treatment group.

Mean Treatment Group Improvement in Amblyopic-Eye Visual Acuity at Follow-up Visits

Treatment Group:	4-Week Visit	8-Week Visit	12-Week Visit	16-Week Visit
Binocular Group	2.1 Letters	3.3 Letters	3.9 Letters	3.5 Letters
Patching Group	2.0 Letters	4.8 Letters	5.4 Letters	6.5 Letters

Figure 3.

Change in Amblyopic-eye Visual Acuity (VA) from Baseline across Follow-up Visits: At each time point, the box on the left is the distribution of change (letters) in amblyopic eye VA from baseline for the binocular group and that on the right represents the patching group. Positive values for VA change indicate improvement. The bottom and top of each box represents the 25th and 75th percentiles of the data and the line in the box is the median. The treatment group means are represented by a dot and are connected across the visits with either a solid line (binocular group) or a dashed line (patching group). The bars extending above and below each box extend to the closest observed data point inside 1.5 times the interquartile range (difference between the 25th and 75th percentiles). The open circles represent near statistical outliers and the asterisks indicate far outliers.

Figure 4.

Relationship between Change in 4-Week Outcomes and Objective Adherence Measures in the Binocular Group: Relationship between change in 4-week outcomes and objective adherence measures (total hours of game play, change in fellow-eye contrast from baseline) in the binocular group were evaluated in a post hoc analysis using descriptive statistics and scatterplots. The scatterplots on the top row represent the relationship between the change in 4-week amblyopic-eye visual acuity (VA) from baseline and (1) cumulative hours of binocular treatment at 4 weeks (top left) and (2) change in fellow-eye contrast from baseline to 4 weeks (top right). The scatterplots on the bottom row represent the relationship between the change in 4-week stereoacuity from baseline and (1) cumulative hours of binocular treatment at 4 weeks (bottom left) and (2) change in fellow-eye contrast from baseline to 4 weeks (bottom right). Positive values for change in VA and stereoacuity indicate improvement. Analyses were limited to participants who completed the 4-week visit within the pre-defined analysis window (3 to <6 weeks after randomization).

Figure 5.

Relationship between Change in 16-Week Outcomes and Objective Adherence Measures in the Binocular Group: Relationship between change in 16-week outcomes and objective adherence measures (total hours of game play, change in fellow-eye contrast from baseline) in the binocular group were evaluated using descriptive statistics and scatterplots. The scatterplots on the top row represent the relationship between the change in 16-week amblyopic-eye visual acuity (VA) from baseline and (1) cumulative hours of binocular treatment at 16 weeks (top left) and (2) change in fellow-eye contrast from baseline to 16 weeks (top right). The scatterplots on the bottom row represent the relationship between the change in 16-week stereoacuity from baseline and (1) cumulative hours of binocular treatment at 16 weeks (bottom left) and (2) change in fellow-eye contrast from baseline to 16 weeks (bottom right). Positive values for change in VA and stereoacuity indicate improvement. Analyses were limited to participants who completed the 16-week visit within the pre-defined analysis window (14 to <20 weeks after randomization).

Table 1.**Study Inclusion and Exclusion Criteria****ELIGIBILITY CRITERIA**

The following criteria must be met for the patient to be enrolled in the study:

- 1 Age 13 to <17 years
- 2 Amblyopia associated with strabismus, anisometropia, or both (previously treated or untreated)
 - a. Criteria for strabismus: At least one of the following must be met:
 - Presence of a heterotropia on examination at distance or near fixation (with or without spectacles)
 - Documented history of strabismus which is no longer present (which in the judgment of the investigator could have caused amblyopia)
 - b. Criteria for anisometropia: At least one of the following criteria must be met:
 - 0.50 D difference between eyes in spherical equivalent
 - 1.50 D difference between eyes in astigmatism in any meridian
 - c. Criteria for combined-mechanism amblyopia: Both of the following criteria must be met:
 - Criteria for strabismus are met (see above)
 - 1.00 D difference between eyes in spherical equivalent OR 1.50 D difference between eyes in astigmatism in any meridian
 - Note: the spherical equivalent requirement differs from that in the definition for refractive/anisometropic amblyopia
- 3 No amblyopia treatment in the past 2 weeks (patching, atropine, Bangerter, vision therapy)
- 4 Requirements for refractive error correction (based on a cycloplegic refraction that is not more than 7 months old):
 - Hypermetropia of 3.00D or more by spherical equivalent (SE)
 - Myopia of amblyopic eye of 0.50D or more SE
 - Astigmatism of 1.50D or more
 - Anisometropia of more than 0.50D SE
 - *Note: Subjects with cycloplegic refractive errors that do not fall within the requirements above for spectacle correction may be given spectacles at investigator discretion but must follow the study-specified prescribing guidelines, as detailed below.*
 - a. Refractive error correction prescribing instructions:
 - SE must be within 0.50D of fully correcting the anisometropia.
 - SE must not be under corrected by more than 1.50D SE, and reduction in plus sphere must be symmetric in the two eyes.
 - Cylinder power in both eyes must be within 0.50D of fully correcting the astigmatism.
 - Cylinder axis must be within ± 10 degrees if cylinder power is $\leq 1.00D$, and within ± 5 degrees if cylinder power is $>1.00D$. This criterion does not apply for dry over-refractions performed for subjects with contact lens correction.
 - Myopia must not be undercorrected by more than 0.25D or over corrected by more than 0.50D SE, and any change must be symmetrical in the two eyes.
 - b. Refractive error correction meeting the above criteria must be worn:
 - 16 weeks **OR** until visual acuity stability is documented (defined as <0.1 logMAR change by the same testing method measured on 2 consecutive exams at least 4 weeks apart).
 - c. For determining visual acuity stability (non-improvement):
 - The first of two measurements may be made 1) in current correction, or 2) in trial frames with or without cycloplegia or 3) without correction (if new correction is prescribed),
 - The second measurement must be made without cycloplegia in the correct spectacles that have been worn for at least 4 weeks.
 - *Note: since this determination is a pre-study procedure, the method of measuring visual acuity is not mandated.*

ELIGIBILITY CRITERIA

The following criteria must be met for the patient to be enrolled in the study:

- The same form of correction must be worn throughout the entire study (i.e., no changing between contacts and spectacles). Monocular or binocular contact lens wear is allowed provided that the over refraction with the contact lenses meets the above requirements. Safety glasses are not required for patients wearing contact lenses, but investigators are encouraged to suggest safety glasses be worn over contact lenses.
- 5 Visual acuity, measured in each eye without cycloplegia in current refractive correction (if applicable) within 7 days prior to randomization using the E-ETDRS® visual acuity protocol on a study-approved device displaying single surrounded optotypes, as follows:
 - Visual acuity in the amblyopic eye of 33 to 72 letters
 - Visual acuity in the fellow eye of 78 letters
 - Interocular difference 15 letters (i.e., amblyopic-eye acuity at least 15 logMAR lines worse than fellow-eye acuity)
 - 6 Heterotropia or heterophoria with a total near deviation of 10 (measured by PACT).
 - 7 Ability to align the Nonius cross on the binocular game system (angles of ocular deviation >10 would require the Nonius cross to be adjusted to such an extent that playing of the game would be compromised).
 - 8 Subject is able to play the special game on the study iPad® (on easy setting) under binocular conditions (with red-green glasses), as demonstrated by scoring at least 1 line in the office.
 - 9 Investigator is willing to prescribe computer game play or patching per protocol.
 - 10 Parent understands the protocol and is willing to accept randomization.
 - 11 Parent has phone (or access to phone) and is willing to be contacted by Jaeb Center staff.
 - 12 Relocation outside of area of an active PEDIG site for this study within the next 16 weeks is not anticipated.

EXCLUSION CRITERIA

- 1 Prism in the refractive correction at time of enrollment (eligible only if prism is discontinued 2 weeks prior to enrollment).
- 2 Myopia greater than -6.00D spherical equivalent in either eye.
- 3 Previous intraocular or refractive surgery.
- 4 Known skin reactions to patch or bandage adhesives
- 5 Any treatment for amblyopia (patching, atropine, Bangerter filter, or vision therapy) during the past 2 weeks. Previous amblyopia therapy is allowed regardless of type, but must be discontinued at least 2 weeks immediately prior to enrollment.
- 6 Ocular co-morbidity that may reduce visual acuity determined by an ocular examination performed within the past 7 months (*Note: nystagmus per se does not exclude the subject if the above visual acuity criteria are met*).
- 7 No Down syndrome or cerebral palsy
- 8 No severe developmental delay that would interfere with treatment or evaluation (in the opinion of the investigator). Subjects with mild speech delay or reading and/or learning disabilities are not excluded.
- 9 Heterotropia or heterophoria with a total ocular deviation >10 (phoria plus tropia >10) at near (measured by PACT).

Table 2.Baseline Characteristics for Randomized Participants according to Treatment Group^a

	Binocular Group (n=40)		Patching Group (n=60) ^b	
	N	%	N	%
Gender				
Female	16	40	26	43
Race/Ethnicity				
White	30	75	43	72
Black/African American	2	5	4	7
Hispanic	8	20	11	18
Asian	0	0	1	2
More than one race	0	0	1	2
Age at Enrollment (Years) ^c				
Mean (SD)	14.3 (1.1)		14.3 (1.1)	
Prior Amblyopia Treatment				
None	9	23	7	12
Patching	17	43	35	58
Other d	0	0	1	2
Patching/Other ^d	14	35	17	28
Distance Amblyopic-Eye Visual Acuity				
20/200 (33–37 Letters)	0	0	2	3
20/160 (38–42 Letters)	2	5	5	8
20/125 (43–47 Letters)	4	10	8	13
20/100 (48–52 Letters)	3	8	4	7
20/80 (53–57 Letters)	7	18	12	20
20/63 (58–62 Letters)	6	15	10	17
20/50 (63–67 Letters)	12	30	14	23
20/40 (68–72 Letters)	6	15	5	8
Mean (SD) Letters	58.8 (9.1)		56.1 (9.7)	
Distance Fellow-Eye Visual Acuity				
Mean (SD) Letters (Approximate Snellen equivalent)	87.9 (4.6) (20/16–2)		88.6 (4.7) (20/16–1)	
Interocular Difference				
Mean (SD) Letters	29.1 (8.9)		32.5 (10.9)	
Baseline Stereoacuity (Seconds of Arc) ^e				
Nil	16	40	29	48
2000	3	8	7	12
800	5	13	4	7
400	7	18	7	12

	Binocular Group (n=40)		Patching Group (n=60) ^b	
	N	%	N	%
200	2	5	4	7
100	6	15	6	10
60	1	3	1	2
40	0	0	2	3
Median (Range)	800 (60 to Nil)		2000 (40 to Nil)	
Amblyopia cause				
Strabismus	5	13	9	15
Anisometropia	22	55	29	48
Strabismus/Anisometropia combined	13	33	22	37
Maximum Magnitude of Tropia Deviation at Distance Measured by SPCT ()				
Orthotropic	26	65	35	58
1 to <10	12	30	22	37
10	2	5	3	5
Maximum Magnitude of Tropia Deviation at Near Measured by SPCT ()				
Orthotropic	25	63	38	63
1 to <10	13	33	22	37
10	2	5	0	0
Amblyopic-Eye Spherical Equivalent (Diopters)				
Mean (SD) Letters	+3.94 (2.39)		+3.90 (2.50)	
Fellow-Eye Spherical Equivalent (Diopters)				
Mean (SD) Letters	+1.22 (1.88)		+1.22 (2.15)	
Spherical Equivalent Anisometropia (Diopters)				
Mean (SD) Letters	+2.76 (1.98)		+2.60 (1.98)	

SD = standard deviation, SPCT = simultaneous prism and cover test, = prism diopters

^a Of the 18 participants who wore contact lens(s) during the study, an over-refraction was not performed for 2 participants. An over-refraction was not initially required for study eligibility but later added as an amendment to the protocol.

^b Two participants in the patching group were later found to be ineligible for the study due to failure to meet visual acuity stability criteria.

^c The protocol co-chairs pre-approved study enrollment of one participant who had just turned 17 years old by the enrollment visit.

^d Other treatment includes atropine, plano (or reduced plus) lens wear, fogging (Bangerter filter, tape, optical), vision therapy (home or office), orthoptics/binocular therapy, flicker glasses or levodopa treatment for amblyopia.

^e Results of the Randot Butterfly stereoacuity test were analyzed as 2000 seconds of arc (if correct response). Nil was defined as an incorrect response on the butterfly (n=16 and n=29 in binocular and patching groups, respectively), or on the 800 seconds of arc level of the Randot Preschool stereoacuity test if the butterfly was not attempted (0 participants).

Table 3.Amblyopic-eye Visual Acuity Outcomes at 16 Weeks by Treatment Group^a

	Binocular Group (N=39)		Patching Group (N=56)	
	N	%	N	%
Distribution of Amblyopic-eye Visual Acuity				
20/200 (33–37 Letters)	1	3	1	2
20/160 (38–42 Letters)	0	0	1	2
20/125 (43–47 Letters)	2	5	4	7
20/100 (48–52 Letters)	4	10	7	13
20/80 (53–57 Letters)	5	13	8	14
20/63 (58–62 Letters)	5	13	4	7
20/50 (63–67 Letters)	11	28	9	16
20/40 (68–72 Letters)	6	15	7	13
20/32 (73–77 Letters)	4	10	11	20
20/25 (78–82 Letters)	0	0	3	5
20/20 (83–87 Letters)	1	3	1	2
Mean (SD) Letters	62.0 (9.7)		62.5 (11.6)	
Distribution of Amblyopic-eye Visual Acuity Change				
3 lines (15 letters) better	2	5	7	13
2 lines (10–14 letters) better	4	10	10	18
1 line (5–9 letters) better	9	23	19	34
0 line (within 4 letters)	22	56	18	32
1 line (5–9 letters) worse	1	3	1	2
2 lines (10–14 letters) worse	0	0	0	0
3 lines (15 letters) worse	1	3	1	2
Unadjusted Mean (95% CI) Letters	3.5 (1.3 to 5.7)		6.5 (4.4 to 8.5)	
Adjusted Mean (95% CI) Letters ^b	3.7 (1.3 to 6.0)		6.3 (4.4 to 8.3)	
Adjusted Treatment Group Difference (95% CI) Letters ^b	-2.7 (–5.7 to 0.3)			
Participants with Amblyopic-eye Improvement of 2 Lines (10 Letters) from Baseline	6	15	17	30
Treatment Group Difference (95% CI) ^c	-15% (–31% to 2%)			
Participants with Amblyopia Resolution ^d	0	0	0	0

SD = standard deviation, CI = confidence interval

^aVisual acuity analyses only included data from participants who completed the 16-week visit within the pre-defined analysis window (14 to <20 weeks after randomization).^bChange in amblyopic-eye visual acuity from baseline to 16 weeks, adjusted for baseline acuity. Negative values for the treatment group difference in mean change in amblyopic-eye visual acuity favor patching treatment.^cBinomial regression was used to compute the treatment group difference, which was adjusted for baseline visual acuity. Negative values favor the patching group.

^d Amblyopia resolution was defined as having an amblyopic-eye visual acuity of 20/25 or better (78 letters) and an interocular difference within 1 line (5 letters).

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