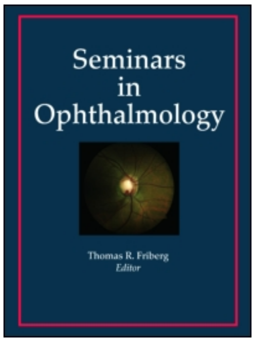

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REVIEW

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Emerging therapies for amblyopia

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ABSTRACT
Traditional therapies to treat amblyopia, such as optical correction or occlusion/penalization of the non-amblyopic eye, are efficacious but are not without limitations such as poor adherence and decreased success with increasing age. Recently, there has been an interest in new amblyopia therapies, some using binocular techniques, through a variety of platforms including video games, movies, and virtual reality. Overall, available efficacy results for these treatments are highly variable.

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INTRODUCTION

Amblyopia is the leading cause of monocular vision impairment in children and adults.[1] It is defined as a reduction of best-corrected visual acuity that results from abnormal processing of visual images early in life that cannot be attributed to structural abnormalities of the eye or visual pathway.[2] It is most commonly unilateral, though it can be bilateral.[3] Though the prevalence of amblyopia in individuall a studies varies based on definition, the pooled prevalence was recently estimated to be around 1.5%.[4,5] Amblyopia is classified according to the underlying cause and can be strabismic, refractive, or deprivational.[2]

If recognized and treated early, vision loss secondary to amblyopia can be reversible. Traditional therapies for amblyopia include correction of refractive errors, patching, and atropine penalization. In children with deprivational amblyopia, surgery and refractive rehabilitation are also necessary.[2] While these traditional therapies have been well studied and are efficacious, their limitations include poor adherence and decreased treatment success with increasing age.[6] In this article, we will review traditional amblyopia therapies and discuss new therapies being used to treat amblyopia, particularly binocular treatments.

TRADITIONAL AMBLYOPIA THERAPIES

Traditional amblyopia therapies include optical treatment and penalization of the sound eye.[7,8] Correcting refractive error alone can improve visual acuity in both refractive and strabismic amblyopia.[9–11] The Pediatric Eye Disease Investigator Group (PEDIG) found that in previously untreated children 3 to <7 years old who were treated with optical correction alone, anisometropic amblyopia improved by 2 or more lines in 77% of patients and resolved in 27%, and strabismic amblyopia improved by 2 or more lines in 88% and resolved in 40%.[9,11] Overall, resolution of amblyopia with optical treatment alone occurs in 32% of patients, and the remaining patients require additional therapy with penalization of the sound eye either in conjunction with spectacle correction or sequentially with incomplete resolution after optical treatment.[2,11,12]

Occlusion and penalization of the sound eye has been the gold standard treatment for unilateral amblyopia since 1743.[7] In children <7 years old, patching 2 hours per day compared to 6 hours per day results in similar improvements in visual acuity in moderate amblyopia, and patching 6 hours per day compared to full-time patching leads to similar improvement in visual acuity in severe amblyopia.[13,14] In children 13 to 17 years old with treatment-naïve amblyopia, patching may improve visual acuity.[15] One of the barriers to successful patching is treatment adherence. Young children, children with developmental delays, or children with severe amblyopia may not tolerate patching. Children who use a cloth patch over spectacles may find a way to peek around it. Patching carries a stigma and consequential psychosocial impact that may dissuade older children from adhering to their prescribed treatment.

Optical penalization of the non-amblyopic eye with atropine drops via its cycloplegic effect has been used as an alternative to patching.[2] In a PEDIG study of children <7 years with strabismic or anisometropic amblyopia randomized to receive either patching or atropine, visual acuity improved substantially in both groups and at 6 months, there was no difference in visual acuity outcomes between treatment groups; however, the patching group improved more rapidly.[16] Though atropine penalization may be particularly useful in cases where there is poor adherence to patching, it carries a risk of ocular side effects such as light sensitivity.[16] It also carries a higher risk of reverse amblyopia, particularly in highly hyperopic children under 4 years old with dense strabismic amblyopia,[17] and a risk of systemic side effects.

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EMERGING AMBLYOPIA THERAPIES

In recent years, there has been an interest in new amblyopia treatments, particularly for children who fail or are non-adherent to traditional therapies.[18] There has also been a push to develop therapies effective in older children or adults with amblyopia, particularly given growing evidence that suggests plasticity in the visual system beyond the period of critical visual development.[7] Many of these new therapeutic techniques are based on the idea that binocular approaches may be superior to monocular methods for treating amblyopia through targeting of interocular suppression and promoting binocularity and stereopsis.[18–20] We will discuss emerging amblyopia therapies including perceptual learning, video game play, and dichoptic training and review studies that have tested these approaches.

PERCEPTUAL LEARNING

Perceptual learning (PL) is based on the principle that performance of sensory tasks can be improved with practice.[7] As it applies to the visual system, PL involves practicing challenging visual tasks to promote long-lasting visual improvements[21] through the strengthening of neural pathways engaged by the same tasks. PL training can be monocular or binocular and requires a rigorous, supervised visual experience with feedback.[7] During PL, the patient is asked to make fine discriminations with the amblyopic eye under difficult conditions.[7] There is a wide variety of visual tasks that the patient may be asked to perform, such as Vernier acuity, contrast detection, letter identification, position discrimination, spatial frequency discrimination, or motion coherence.[21] *Levi et al.* performed a systematic review of 14 studies where perceptual learning was used as a treatment for amblyopia.[22] The patients included in these studies ranged from 7 to 60 years, and age did not account for the variance in success among studies.[22] Based on the results of these small case series, the authors concluded that PL appears to be effective for improving task performance and visual acuity in amblyopia. Thus, PL may represent an opportunity to treat adults with amblyopia, who traditionally are thought to be treatment-resistant. Despite this success, PL has not yet gained widespread support likely due to the small number of participants in these studies, the strict supervision requirement, and the lack of long-term follow-up.[18] Larger randomized, control trials are needed to determine which tasks, under what conditions, and for what durations PL is most effective. Additionally, many PL tasks are non-engaging and can become monotonous, which raises concerns for difficulty with adherence.

VIDEO GAME PLAY

Video game play, particularly with commercial video games, might serve as a more entertaining alternative to traditional PL activities for use as a visual training tool.[21] Action video games may have an added advantage over PL since they present a variety of visual demands and experiences.[7] Playing action video games has also been associated with release of dopamine which may promote neuroplasticity and could therefore promote recovery.[21]

Li et al. studied the effect of video game play in 20 adults (ages 15 to 61 years) with amblyopia.[23] The patients were divided into three groups – action video game (n = 10, *Medal of Honor: Pacific Assault* first-person shooter game), non-action video game (n = 3, *SimCity Societies* game), and cross-over controls who received patching therapy initially (20 hours of total patching) followed by video game therapy (n = 7). Video games were played with the non-amblyopic eye patched for 40–80 hours (2 hours per day). For both video game groups, there was improvement in visual acuity in the amblyopic eye (average 1.6 lines on a logMAR letter chart for the action game group and 1.5 letter-lines for the non-action game group). Those who were in the crossover control group showed no significant improvement in visual acuity after patching alone, and in those who went on to play both action and non-action video games for another 40 hours (n = 5), all had significant improvement in visual acuity of the amblyopic eye (average 1.7 letter-lines). Despite the monocular nature of the treatment, stereopsis improved in all 5 patients with anisometropic amblyopia who were tested, with a mean improvement of 53.6% ± 8.4%.[23]

Monocular video game play has also been studied as an adjunct to occlusion therapy in patients with anisometropic amblyopia. *Singh et al.* randomized 68 children ages 6 to 14 years with anisometropic amblyopia to receive either 6 hours of occlusion therapy per day alone (n = 34) or 6 hours of occlusion therapy per day with 1 hour per day of video game play (n = 34).[24] There was significantly greater improvement in visual acuity in the amblyopic eye in the video game group compared to the patching-only control group at both 1 month (mean improvement 1 line vs. 0.5 lines) and 3 months (mean improvement 2.1 lines vs. 1.7 lines from baseline).[24] The results suggest that monocular video game play may be useful in conjunction with patching, though the relative additional improvement is quite small (less than one additional line after 3 months of treatment).

BINOCULAR THERAPY USING DICHOPTIC STIMULI

Dichoptic amblyopia treatments employ use of both eyes together in order to target reduction of interocular suppression.[19] There are three different techniques that utilize dichoptic presentation, where eye-selective modified visual stimuli are presented to achieve this goal.[20] In anti-suppression therapy, the fellow, non-amblyopic eye is exposed to images with significantly reduced contrast compared to that of the amblyopic eye. Balanced binocular viewing employs blurring of images seen by the non-amblyopic eye. Interactive binocular treatment presents different parts of a visual scene to each eye as the patient watches a video or plays a game that requires binocular summation.[20] Each of these techniques can be used alone or in combination. Binocular amblyopia therapy has been applied through different platforms which we will discuss here (Table 1).

Table 1. Binocular amblyopia therapy using dichoptic stimuli.

Category	Platform	Relevant Studies	Description of activity	Dichoptic technique
Video game	Falling blocks iPad game	*Holmes et al.*[25] *Manh et al.*[26] *Gao et al.*[27]	Game where points are scored by moving falling blocks to form complete lines of blocks	Red-green anaglyphic glasses; high-contrast elements seen by the amblyopic eye and reduced-contrast by the fellow eye
	Dig rush iPad game	*Kelly et al.*[28] *Holmes et al.*[29] *Holmes et al.*[30]	Action adventure game with miners digging for gold	
Video	viewing Glasses with polarized lenses; a patterned image mask made of irregularly shaped blobs is applied to the images seen by the amblyopic eye (high contrast) and the inverse mask is applied to the images seen by the fellow eye (reduced contrast)	Dichoptic movie	*Birch et al.*[19] *Sauvan et al.*[31]	Movies shown on a passive 3D display
	Dichoptic movie with interactive tasks	*Bossi et al.*[32]	Movies shown on a 3D-capable computer monitor and interrupted by interactive tasks to measure suppression	Shutter glasses mounted in a customized ski mask; blurred image presented to the non-amblyopic eye
	BinoVision home system	*Mezad-Koursh et al.*[33]	Video or movie shown on custom, head-mounted goggles; customizable content	Contrast and brightness levels reduced for the non-amblyopic eye; superimposed moving objects and momentary repetitive bright video frame stimuli shown only to the amblyopic eye
	Luminopia One	*Xiao et al.*[34]	Video shown via a smartphone on a head-mounted display; streaming of wide variety of licensed content	Contrast levels reduced for the non-amblyopic eye; dichoptic masks superimposed so that parts of the video are only visible to the amblyopic eye
Virtual reality (VR)	Interactive Binocular Treatment (I-BiT) system[35]	*Waddingham et al.*[36] *Cleary et al.*[37] *Rajavi et al.*[38] *Herbison et al.*[39]	Interactive games and movies on a 3D VR based computer system	Red-green filter or shutter glasses; enriched image presented to the amblyopic eye; for games, key elements only visible to the amblyopic eye
	Diplopia game in Oculus Rift OC DK2	*Žiak et al.*[40]	Games played in a 3D setting in a VR head mounted display connected to a computer	Dichoptic setting in which the central part of the picture is shown differently to each eye; images from both eyes needed to successfully play the games

DICHOPTIC VIDEO GAMES

A number of recent studies have focused on dichoptic video game therapy in amblyopia, including several randomized, controlled trials. These studies combine dichoptic approaches by presenting essential game elements to each eye separately with high contrast to the amblyopic eye and low to the fellow eye. Thus, binocular viewing is required to complement the tasks in these games. Given the novelty of dichoptic therapy, initial trials have primarily targeted older children and/or patients with residual amblyopia after prior treatment, possibly limiting their potential to demonstrate efficacy.

PEDIG has published the results of 4 randomized, controlled trials across two protocols (Amblyopia Treatment Studies [ATS] 18 and 20) designed to assess the efficacy of binocular video game therapy in amblyopia. The first study (ATS18) compared a binocular iPad game to part-time patching in 385 children ages 5 to 12 years with amblyopia from anisometropia, strabismus, or both (77% having received prior treatment).[25] Participants were randomized to receive either 16 weeks of the binocular falling blocks iPad game for 1 hour per day or patching of the non-amblyopic eye for 2 hours per day. At 16 weeks, visual acuity in the amblyopic eye improved from baseline by a mean of 1.1 lines in the binocular game group compared to 1.4 lines in the patching group. The lack of treatment effect was at least partially attributed to low adherence (only 22% of children in the game group played the game for ≥75% of the prescribed time), with many participants reporting loss of interest in the game. No treatment dose–response relationships for visual acuity or stereoacuity were appreciated.[25]

An older cohort of 100 patients ages 13 to <17 years with anisometropic, strabismic, or mixed amblyopia was treated using the same PEDIG ATS18 protocol.[26] Amblyopic eye visual acuity improved by 3.5 letters in the binocular game group vs. 6.5 letters in the patching group. Adherence with the binocular video game was also poor with the older cohort; only 13% of participants completed >75% of the treatment. This arm of ATS18 was stopped early due to an interim analysis showing results favoring the patching group and poor adherence to binocular therapy. Again, no treatment dose–response relationships for visual acuity or stereoacuity were appreciated.[26]

To address the problems with low adherence, a more engaging binocular iPad (Apple, Inc.) video game, "*Dig Rush*," was tested in ATS20. Dig Rush was previously evaluated in a smaller cohort by *Kelly et al*.[28] This pilot study compared the effectiveness of Dig Rush with patching in 28 patients ages 4 to 10 in a cross-over study. At the 2-week visit, a 1.5-line improvement in the amblyopic eye visual acuity in the binocular game group surpassed the 0.7-line improvement in the patching group. Participants in the patching group who crossed over to the binocular game group caught up to the binocular game group at the 4-week visit with mean improvement of 1.7 lines for the binocular game group and 1.2 lines for the patching crossover group. Neither group showed improvement in stereoacuity. Near perfect adherence was noted during the first 2 weeks of therapy (100% for game play and 99% for patching).[28] The promising results from this approach were carried forward into ATS20, in which Dig Rush was compared with optical therapy alone in 138 children ages 7 to 12 years, 96% of whom had prior treatment.[29] Enrollees were required to have at least 16 weeks of optimal optical treatment or show no improvement in amblyopic eye visual acuity after 8 weeks of optical treatment prior to participating. Participants were randomized to receive either 8 weeks of treatment with binocular Dig Rush play for 1 hour per day for 5 days per week with spectacle wear or spectacle wear alone. Again, there was no difference in mean improvement in visual acuity between the groups (2.3 letters for the binocular group vs 2.4 letters for the spectacle group). Adherence, as measured by the device, was better than in ATS18 but still low, with only 56% of those in the video game group completing >75% of the treatment at the 8-week visit.[29]

Recently, data from the younger cohort from the ATS20 protocol were presented at the American Academy of Ophthalmology annual meeting.[30] Children ages 4 to 6 years with anisometropic, strabismic, or combined amblyopia were included. After 169 children underwent 4 weeks of therapy, mean visual acuity improvement was greater in the binocular treatment group compared to the spectacle group (1.1 vs 0.6 lines). However, for the 164 children who completed 8 weeks of therapy, this difference did not remain statistically significant.[30] Thus, none of the 4 PEDIG studies have shown an advantage of binocular video game therapy over conventional therapy.[25,26,29,30] Though the high rate of nonadherence may have affected the results of these studies, it is important to note that ATS18 (younger and older cohort) and the ATS20 older cohort showed no dose–response relationship. The dose–response data for the ATS20 younger cohort are not yet available.

The binocular treatment of amblyopia using video games (BRAVO) study group conducted a trial involving 115 participants ages 7 to 55 years with monocular anisometropic, strabismic, or combined type amblyopia.[27] Participants were randomized to undergo treatment with a falling blocks dichoptic video game or with a placebo video game where identical images were presented to both eyes for 1 hour per day for 6 weeks. Mean visual acuity improvement in the amblyopic eye in the treatment group was 3 letters and similarly modest at 3.5 letters in the placebo group. A secondary analysis separating pediatric and adult patients also showed no significant difference in visual acuity improvement between the groups. Any potential treatment effect may have been masked by the high percentage of enrolled patients included who had previously failed traditional amblyopia therapy.[27]

PASSIVE BINOCULAR VIDEO VIEWING

Several studies have asked whether passive dichoptic movie viewing might have the same effect as active video game play. These studies have primarily consisted of pilot and small open-label and/or single-arm studies. *Birch et al*. evaluated 27 children with anisometropic, strabismic, or combined amblyopia ages 4 to 10 years who wore polarized glasses to watch 6 contrast-rebalanced movies on a 3D display.[19] They found improvement of 1.5 lines with treatment over a 2 week period. Younger children (3–6 years) had significantly greater improvement than older children (7–10 years), and children with worse amblyopic eye visual acuity at baseline had greater improvement.[19] In another study, the effect of binocular movie viewing was evaluated in 22 treatment-naïve (except for spectacle correction) children ages 3 to 11 years with anisometropic, strabismic, or combined mechanism amblyopia.[32] Subjects were instructed to view movies for 1 hour per day while wearing 3D shutter glasses to control the image presented to each eye for 8 to 24 weeks. The movie was interrupted every minute by an interactive game used to measure suppression. Participants exhibited significant improvement in visual acuity in the amblyopic eye (mean gain of 2.7 ± 2.2 lines). In contrast to other studies with binocular therapy, there was no change in suppression after treatment.[32]

There has been one study to evaluate the efficacy of the BinoVision home system, which utilizes binocular dichoptic video content by incorporating elements of different contrast and luminance levels, amblyopic eye tracking training, and amblyopic eye flicker stimuli in a head-mounted device.[33] All children had either failed or did not comply with traditional amblyopia treatment. Of the 27 children (ages 4–8 years) included in the study, 19 received dichoptic treatment and 8 received sham treatment with an altered BinoVision device for the first 4 weeks. After 4 weeks, mean visual acuity improved significantly in the treatment group (2.0 lines) compared to no change in the sham group. After 8 weeks, mean improvement in visual acuity was 2.6 lines in the treatment group compared to baseline. Adherence was high at 88% on average, which the authors attributed to the home video system and customizable video content.[33]

Xiao et al. conducted a pilot study of 10 children ages 4 to 7 years using the Luminopia One therapeutic that utilizes dichoptic video viewing via a head-mounted device.[34] Treatment consisted of viewing video content 1 hour per day. Nine of the 10 children had previously been treated for amblyopia with either patching or atropine. The authors claim that allowing children to choose from a wide selection of licensed view content that directly streamed to the head-mounted device facilitated high adherence rates (mean 78%) and improvement in amblyopic eye visual acuity of 2.9 lines over 12 weeks of therapy.[34]

Dichoptic video therapy has also been studied as a treatment for children beyond the period of critical visual development and adults with amblyopia. *Sauvan et al.* conducted a study with 17 patients with stable, residual anisometropic or strabismic amblyopia ages 9 to 67 years (mean 34 years).[31] Ten participants underwent 6 sessions of 1.5 hours of dichoptic movie viewing and 7 underwent the same regimen but had 2 hours of patching over the amblyopic eye prior to each session. The protocol was structured in this manner due to a shift in dominance that is known to occur after about 1 hour of occlusion in adults. Both groups showed improvement in amblyopic eye visual acuity after completing treatment (0.8 lines in the non-patched group and 1.9 lines for the patched group) with no significant difference between the two groups immediately after treatment. However, at 1 month post treatment, the patched group retained a statistically significant improvement in visual acuity compared to baseline whereas the non-patched group did not. This study suggests that dichoptic movie viewing aided by short-term monocular occlusion of the amblyopic eye may be helpful as a treatment for amblyopia in older children and adults; however, further study is needed given the small sample size, wide age range of participants, and short follow-up period.[31]

VIRTUAL REALITY

Virtual reality (VR) has become a new tool for neurorehabilitation of many different pathologies.[41,42] Unlike 2-dimensional binocular therapy, VR presents content in a 3D environment in which the user is immersed. This therapeutic approach allows researchers to leverage the sensory-motor adaptive capabilities of the nervous system to manipulate sensory feedback thereby providing patient-specific graduated rehabilitation.[41] The interactive binocular treatment (I-BiT) group was one of the first to apply this method in amblyopia treatment through their development of a VR-based binocular system with interactive games and 3D videos with red-green filter or shutter glasses.[35,41]

In a case series of 6 children with anisometropic or strabismic amblyopia ages 3 to 7 years who had previously failed traditional amblyopia treatment (3 treatment failures and 3 non-compliant), *Waddingham et al.* showed that 5 children improved visual acuity in their amblyopic eye with an average increase of 10 letters (2 lines) after a mean of 4.4 hours with the I-BiT system.[36] Another pilot study using the I-BiT system included 12 children with strabismic or mixed anisometropic-strabismic amblyopia who had not complied with or failed occlusion therapy. There was sustained improvement in high-contrast visual acuity in 58% of children, and in low-contrast visual acuity in 67% including 2 patients in which amblyopia had resolved.[37] *Rajavi et al.* conducted a randomized clinical trial to compare I-BiT games to patching with placebo games in 38 children with unilateral amblyopia ages 3 to 10 years.[38] Visual acuity improved significantly in both groups after 1 month of treatment (mean improvement 0.8 ± 0.9 lines in the I-BiT group and 0.9 ± 0.9 lines in the patching with placebo game group), but there was no difference in the amount of improvement between the two groups.[38]

In a larger study, 75 amblyopic children ages 4 to 8 years were randomized to 3 treatment groups: I-BiT game, I-BiT DVD, and non-I-BiT game (control where both eyes received identical stimulation).[39] All three groups showed a modest yet statistically significant improvement in visual acuity at 6 weeks (mean improvement 0.6 ± 0.2 lines for I-BIT game, 1.0 ± 0.2 for I-BIT DVD, and 0.3 ± 0.2 for control game). There was no significant difference in visual acuity improvement between those receiving I-BiT games and those receiving non-I-BIT control games at 6 weeks, and the authors did not statistically compare the two treated groups with the control group. Stereopsis did not improve in any of the groups. Most patients had prior treatment (67/75) and/or manifest strabismus (70/75), and treatment in the study was limited to 30 minutes per week, which may have limited potential gains.[39]

A pilot study evaluated dichoptic visual training using the beta version of the computer game, "*Diplopia Game*" (Vivid Vision, San Francisco, USA), provided via a VR head-mounted display (Oculus Rift OC DK2, Irvine, CA, USA).[40] Two games were available, and both used dichoptic therapy where the central part of the picture varied in color between the two eyes. Seventeen adults with anisometropic amblyopia (average age 31.2 years, range 17–69 years) participated. After eight 40-minute sessions, there were significant improvements in mean amblyopic eye visual acuity (mean improvement 1.5 lines) and stereopsis (mean 263.3 ± 135.1 arcseconds baseline to 176.7 ± 152.4 after training).[40]

While some of these studies offer promising preliminary results, there is no consistent evidence yet that amblyopia treatment with dichoptic VR is superior to conventional therapies or non-VR-based dichoptic therapy. There are many variables that differ between these small pilot studies that may have affected the results including 1) age, 2) type and amount of time spent participating in the VR amblyopia therapy, and 3) number of patients who failed previous treatment. Larger randomized controlled trials are needed to ascertain the role of VR systems in managing amblyopia.

CONCLUSION

Much of the current research in amblyopia therapy is focused on the utility of binocular treatment in both children and adults. The results of the studies summarized herein are highly variable due to the diversity of interventions and study designs. The American Academy of Ophthalmology Ophthalmic Technology Assessment Committee concluded that, based on the more rigorously designed studies, there is currently no consistent evidence to support the use of binocular therapy over standard treatments.[42] This is largely supported by 4 large PEDIG randomized controlled trials (protocols ATS18 and ATS20), which showed no superiority of binocular therapy over conventional therapy.[25,26,29,30] Alternative approaches, including PL and VR treatments, show promise in pilot trials, though this was also the case for the treatments that eventually were shown by PEDIG to be ineffective. Adherence continues to be a challenge in amblyopia therapy, even with these emerging therapies that would intuitively seem to circumvent the challenges of patching. Small pilot trials suggest that provision of choice and allowance for passive viewing of content may enhance engagement and promote adherence. Continued research with large randomized, controlled trials of these new technologies are needed to further assess their efficacy and potential superiority over traditional approaches.

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