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TECHNOLOGY REVIEW (MINI-HTA)

VIRTUAL REALITY (VR) TREATMENT FOR AMBLYOPIA (LAZY EYES)

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
08/2021

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DISCLAIMER

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EXECUTIVE SUMMARY

Background

Amblyopia is a reversible deficit of vision that has to be treated within the sensitive period for visual development. Screening programmes have been set up to detect this largely asymptomatic condition and refer children for treatment while an improvement in vision is still possible. The value of such programmes and the optimum protocol for administering them remain controversial. Amblyopia commonly known as “lazy eye” is an abnormal binocular experience due to a mismatch between the images perceived with each eye. This situation may be caused by visual deprivation due to congenital cataract, unequal refractive errors or strabismus. This is known as the 'critical period'. In some situations, the critical period may be extended. The developing visual system relies on good quality visual images. Amblyopia can develop when the image coming into one or both eyes is either blurred or obscured. It develops through an abnormal binocular cortical interaction and results in a loss of acuity, contrast sensitivity, and/or positional disorder. The aetiology is often a high refractive error, anisometropia, strabismus or a combination of these factors.

Amblyopia is the leading cause of monocular visual impairment in children, affecting 2-3% in the United States. Amblyopia has traditionally been viewed as a monocular disorder that can be treated by patching the fellow eye to force use of the amblyopic eye. Patching can improve visual acuity for 73% to 90% of children with amblyopia, but 15% to 50% may never achieve normal visual acuity after a lengthy course of treatment. Amblyopia recurs after successful treatment in 25% to 50% of children, and normal binocularity is rarely restored after patching treatment.

In recent years, virtual reality (VR) has emerged as a new tool for neuro rehabilitation of different childhood and adulthood conditions. Virtual reality-based therapies can induce cortical reorganization and promote the activation of different neuronal connections over a wide range of ages, leading to contrasted improvements in motor and functional skills.

In this context, the use of VR technology as a potential treatment for improving vision in amblyopia is recently attracting considerable interest because of the possibility of training each eye independently without the need of occlusion or penalization. This dichoptic stimulation approach has the potential of eliminating one of the major causes of amblyopia treatment failure especially among the paediatric population, which is poor compliance to patching due to social stigma or long treatment duration or the physical properties of the patch itself (design, heat, irritation, poor adhesive material). The VR games are expertly constructed and claimed to improve visual clarity for amblyopic patients, improve depth perception, and other visual problems by selecting the visual information that each eye receives. This stimulates the brain to use both eyes together as a team and strengthen binocular vision.

In Malaysia, children with amblyopia is treated mainly with patch as no virtual reality yet available within the Ministry of Health (MOH) facility. Hence, this technology review is conducted to review the effectiveness/efficacy, safety, cost/cost-effectiveness and organisational issues related to this virtual reality in the management of amblyopia. This review was conducted upon request by our MOH National Head Advisor (Ophthalmology) from Hospital Shah Alam to review the best current scientific evidence on VR for amblyopia.

Objective / Aim
To review the best current scientific evidence on effectiveness/efficacy, safety, cost/cost-effectiveness and organisational issues related to this virtual reality in the management of amblyopia.

Results and conclusions
From a total of 67 titles identified through the Ovid and PubMed interface, four studies were included in this review which consisted of two randomised controlled trials, one single arm study and one pre- and post- intervention study. The included articles were published between 2016 and 2020. Most studies were conducted in United States of America, United Kingdom, Spain and Slovakia.

Effectiveness:
There was very limited fair level of retrievable evidence to suggest the use of VIVID® Vision VR was associated with best corrected visual acuity (BCVA) and stereoacuity for treating amblyopia.

- at the 2- and 4- week, a larger improvement in amblyopic eye BCVA was found with the binocular game compared with patching, with a mean (SD) improvement of 0.15 (0.08) logMAR (mean [SD], 1.5 [0.8] lines) versus 0.07 (0.08) logMAR (mean [SD]], 0.7 [0.8] line improvement); (mean difference, 0.07 logMAR [0.7 line]; 95% CI, 0.01 to 0.14 logMAR [0.1-1.4 lines]; $p = 0.02$).
- mean stereoacuity changed from a value of 263.3 ± 135.1 before dichoptic training to a value of 176.7 ± 152.4 s of arc after training ($p < 0.01$).
- the visual acuity improved in all three groups at weeks 3, 6 and 10 with the average improvement of vision at week 6 of 0.07 logMAR which was sustained at week 10. This improvement was significant at all three time points ($p< 0.001$)

Safety:
There was no retrievable evidence on use of VR reported in the included studies. Virtual reality from VIVID® Vision was registered with USFDA in 2018.

Cost/Cost-effectiveness:
There was no retrievable evidence on the cost or cost-effectiveness of VIVID® Vision VR treatment for amblyopia (lazy eye). However, various price or fees of VR devices of the treatment for lazy eye/amblyopia. Ranging price from USD 129 to USD 399 (~RM1800). Costs estimation of VR therapy is around USD2,000 – USD6,000 (MYR 8 400 - MYR 25 100) for all evaluations, therapy, progress examinations, and follow-up post-therapy visits per patient.

Organisational:
There was no guideline retrieved which specifically addressed the use of virtual reality reported.

Methods

Electronic databases were searched through the Ovid interface; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to 1 September 2021, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to 1 September, 2021, Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations 1946 to 1 September 2021, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 2017 to 1 September 2021, Ovid MEDLINE(R) 1946 to September Week 1 2021, Ovid MEDLINE(R) 1996 to September Week 1, Ovid MEDLINE(R) Epub Ahead of Print 1 September 2021, Ovid MEDLINE(R) Daily Update 1 September 2021 and Ovid MEDLINE(R) 2017 to September Week 1 2021. Searches were also run in PubMed, INAHTA, Cochrane Library and US Food and Drug Administration. Google was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 1 September 2021.

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ABBREVIATION

2D	2 Dimensions
3D	3 Dimensions
BCVA	best corrected visual acuity
CASP	Critical Appraisal Skills Programme
fMRI	functional magnetic resonance imaging
HCVA	high-contrast visual acuity
HMDs	head mounted displays
HTA	health technology assesssment
IEC	International Electrotechnical Commission
IQR	Interquartile range
LCVA	low-contrast visual acuity
MOH	Ministry of Health
NCVD	National Cardiovascular Disease Database
PSF	point spread function
ROB	Risk of bias
RCTs	Randomised Control Trials
ROI	Return on investment
RSA	Radiostereometric analysis
SD	Standard deviation
SR MA	Systematic review with meta-analysis
US	United States
VA	visual acuity
VR	Virtual reality

1.0 BACKGROUND

Amblyopia commonly known as “lazy eye” is a reduction of the best corrected visual acuity of the eye without organic cause. In this condition, there is an abnormal binocular experience due to a mismatch between the images perceived with each eye. This situation may be caused by visual deprivation due to congenital cataract, unequal refractive errors or strabismus[1] This is known as the 'critical period'. In some situations, the critical period may be extended. The developing visual system relies on good quality visual images. Amblyopia can develop when the image coming into one or both eyes is either blurred or obscured. It develops through an abnormal binocular cortical interaction and results in a loss of acuity, contrast sensitivity, and/or positional disorder.[2] The aetiology is often a high refractive error, anisometropia, strabismus or a combination of these factors.[3]

Amblyopia is the leading cause of monocular visual impairment in children, affecting 2-3% in the United States. Amblyopia has traditionally been viewed as a monocular disorder that can be treated by patching the fellow eye to force use of the amblyopic eye. Patching can improve visual acuity for 73% to 90% of children with amblyopia, but 15% to 50% may never achieve normal visual acuity after a lengthy course of treatment. Amblyopia recurs after successful treatment in 25% to 50% of children, and normal binocularity is rarely restored after patching treatment.[4]

Active vision therapy using perceptual learning and/or dichoptic or binocular environments has shown its potential effectiveness in amblyopia, but some doubts remain about the type of stimuli and the mode and sequence of presentation that should be used. Over the last few years, vision therapy has been suggested to be an effective option to promote visual rehabilitation and even to accelerate recovery when combined with patching. New trends in computer-based active vision therapy have been developed for amblyopia treatment, such as the use of perceptual learning environments, dichoptic stimulation and binocular training. These video games use visual and perceptual tasks, such as orientation discrimination or letter recognition, among others, to cause a response in neuro-modulatory pathways and the enhancement of attentional skills, according to neurophysiological studies.[5] Virtual reality (VR) systems typically offer a stereo image of a 3D virtual environment by presenting an image separately to each eye.[6]

Amblyopia is usually classified by cause:.[7]

- strabismic when it is due to the presence of a squint;
- anisometropic where the refractive error is significantly greater for one eye than the other (a difference of more than or equal to 0.75 dioptre is generally thought to be significant);
- meridional where there is a significant degree of astigmatism (more than or equal to 1.00 dioptre);
- stimulus deprivation where, for example, a cataract or ptosis (droopy lid) obscures the visual axis;
- ametropic where the refractive error is such that neither eye receives a good quality image.jadi

It is not uncommon for the types to co-exist.

Among the more recent products resulting from the evolution of digital technology, VR has become increasingly entrenched in the field of visual training, emerging as a safe, effective and very attractive tool that promotes treatment compliance[6]. VR consists of the presentation of computer-generated 3D environments, enabling users to become fully immersed in a simulated world in which they can interact via multiple sensory channels: visual, auditory or haptic.[7,8]

Using VR, visual stimuli can be presented to the user in two ways: on a monitor screen or in a fully immersive environment generated using technological equipment such as head mounted displays (HMDs) and motion capture systems. Treating amblyopia with a combination of different serious games based on perceptual learning environments for distinct VR interfaces has shown to be a useful therapeutic approach for enhancing visual impairments that occur in amblyopia even after the critical period of visual development.[9] **(see Table 1)**

Table 1: Summary of the clinical studies conducted to this date to evaluate the use of virtual reality technologies for the treatment of amblyopia.

Author (year)	Patients/ groups	age	Amblyopia type	Technology (intervention)	Results	Follow -up
Waddingham et al.(2006)	7 children	3 to 7 yrs	residual amblyopia (anisometropic or strabismic with previous failed treatments	I-BiT system (games & movie clips) Dichoptic	VA improvement from 6/12=6/12-pretreatment to 6/7.5-6/24 - posttreatment Total treatment time: 4.4 hours VA (+) un 5/7	7 to 15 sessions
Cleary et al (2009)	12 children	6.1 to 11.4 years	5 strabismic or mixed 7 anisometropic	I-BiT system (driving games and video clip) Dichoptic 8 session, (25 min/session)	58% sustained improvements in HCVA 67% improvement in LCVA Amblyopia eliminated in 2 patients 5 children with VA 6/12 or better at 6 months after stopping treatment HCVA improvement: 4 sessions LCVA improvement: 7 sessions	18 weeks
Herbison et al. (2013)	10 children	Mean: 5.4 years	3 strabismic, 4 anisometropic and 3 mixed	I-BiT system (Nux game and video clip) Dichoptic 6 weekly sessions, 30 min/ session	78% showed VA improvement 67% demonstrated a clinically significant increase in VA of ≥0.125 (0.175 to 0.300 LogMAR) Mean change from baseline to follow-up was 0.13 ± 0.14 logMAR	10 weeks
Herbison et al. (2016)	75 children	4 to 8 years	67 were residual amblyopes and 70 had an associated strabismus	RCT with three arms: (i) DVD footage shown to the amblyopic eye and common background to both (I-BiT DVD) (ii) Modified shooter game, Nux, with sprite and targets presented to the amblyopic eye (I-BiT game) (iii) Both background & foreground presented to both eyes (non-I-BiT) games)	VA improvement in all three arms by approx. 0.07 logMAR No difference between IBiT DVD and non-I-BiT games compared with IBiT games in terms of gain in vision	10 weeks
Cepeda-Zapata et al. (2019)	45 students	17 to 28 years	Nonamblyopes	Conventional visual therapies implemented in virtual reality: brock cord, approach technique, and eccentric circles	Evaluation of simplicity and versatility for both clinician and infant patients Pragmatic quality above average (1.73) Attractiveness (2.03) and hedonic qualities (1.90) above average	N/A
Ziak et al. (2017)	17 adults	17 to 69	Anisometropic	Diplopia game + Oculus Rift OC DK2	Mean BCVA in amblyopic eye improved from 0.58 ± 0.35 before	1 month

		years		head mounted display 8 sessions, 40 min/session, twice per week Dichoptic	training to a posttraining value of 0.43 ± 0.38 ($p < 0.01$) Mean stereoacuity changed from 263.3 ± 135.1'' before dichoptic training to a value of 176.7 ± 152.4'' after training $p < 0.01$ 47.1% before dichoptic treatment had unmeasurable stereoacuity while this only occurred in 11.8% after training	
VA, visual acuity; HCVA, high-contrast visual acuity; LCVA, low-contrast visual acuity						

Source: adapted from Coco-Martin MB, Piñero DP, Leal-Vega L, Hernández-Rodríguez CJ, Adiego J, Molina-Martín A, de Fez D, Arenillas JF. The Potential of Virtual Reality for Inducing Neuroplasticity in Children with Amblyopia. J Ophthalmol. 2020 Jun 29;2020:7067846

Hence, this technology review was selected during the Priority Setting exercise for 2021-2022 HTA Unit, Malaysian Health Technology Assessment Section (MaHTAS) and was conducted upon request by Senior Consultant Specialist (Ophthalmology) from Hospital Shah Alam to review the best current scientific evidence on virtual reality vision for treating amblyopias.

2.0 OBJECTIVE / AIM

The objective of this technology review is to evaluate and assess the efficacy, safety, cost-effectiveness and organisational issues related to the virtual reality vision for treating amblyopia, particularly the VIVID® Vision VR.

3.0 TECHNICAL FEATURES

Virtual reality is a system allowing for dichoptic and stereoscopic training. Its offers a virtual reality based treatment for lazy eye disorders. Optometrists have been able to use the company's treatment in their practice since 2015. The treatment, which pairs VR headsets with special software to help patient's eyes learn how to work correctly together. Virtual reality Vivid Vision® claims their treatment is effective for amblyopia, strabismus, and convergence insufficiency. It works by increasing visual stimulation to the weak eye, while decreasing stimulation in the dominant eye (this is achieved with relative ease in a VR headset thanks to the device naturally showing separate images to each eye). This is done under the guise of immersive VR games where the player sees important game cues in their weak eye, leading their brain to lean more heavily on the information coming from that eye. **(Figure 1)**

Figure 1: Vivid® Vision Virtual Reality

3.1 VISUAL TRAINING

For an appropriate treatment, the stimuli used for visual training should be scientific-based and adapted to the specific characteristics of the amblyopic visual system. Thus, a good comprehension of the neural mechanisms and visual deficits of amblyopia is needed.

3.1.1 Crowding, Flankers and Masking

Crowding is one of the most important visual deficits in amblyopia described as a “deleterious influence of nearby contours of visual discrimination, is a form of inhibitory interaction which is ubiquitous in spatial vision”. Crowding is also present in the normal population when the target is surrounded by other stimuli called flankers, with the consequent impairment of the recognition of an object in a clutter. In the peripheral vision of non-amblyope subjects, a letter becomes unrecognisable when there are other stimuli around it, despite both target and flankers being clearly separated in the retinal point spread function (PSF), this being dependent on target eccentricity. In addition, in the foveal vision of the non-amblyope subject, crowding can occur when the target–flankers distance is less than 4–6 min of arc. In amblyopes, crowding occurs with larger distances between targets and flankers, and is related to spatial frequency and target size. Crowding affects many visual tasks such as letter recognition, orientation discrimination, vernier visual acuity and stereoacuity tasks. Furthermore, crowding seems to be the result of a global visual deficit in amblyopia, although the values of visual acuity (VA), contrast sensitivity and stereoacuity may not have a large impact on it. Flankers are the objects located around the target that impair the target perception due to crowding. In strabismic and mixed amblyopia, which present both anisometropia and strabismus, flankers reduce VA. According to previous authors, when the flankers are complex stimuli, such as letters, the correct term is crowding, but when flankers are sidebars, the term contour interaction should be used. Finally, masking is the impairment of target perception due to an overlapped element called a mask. For people with amblyopia, obtaining the information of the target from an array of stimuli is harder than it is for normal subjects. Repeated practice of a masking task leads to improvements in target detection time

in non-amblyopic subjects, as well as in crowded and uncrowded visual acuity in amblyopes. Therefore, adding masking tasks to vision therapy might be interesting for future research. From a neuronal perspective, cortical neuron insufficiency, elevated cortical noise, and abnormal lateral interactions in V1 seem to be related with spatial processing deficits in amblyopic eyes.[11]

3.1.2. Contrast Sensitivity Reduction

Contrast sensitivity is the ability to detect differences in contrast luminance at different spatial frequencies of a grating. Amblyopic eyes can present decreased contrast sensitivity at high spatial frequencies or even at all the spatial frequencies, which is the consequence of alterations in the lateral geniculate nucleus and visual striate cortex. Specifically, there are some differences according to its etiology. In anisometropic amblyopia, a significant decrease in global contrast sensitivity compared with normal subjects is commonly reported, while strabismic amblyopes can show normal or increased low frequency contrast sensitivity. It is interesting that a loss in contrast sensitivity could persist despite the recovery of the visual acuity after amblyopia treatment. However, several authors reported improvements in contrast sensitivity after vision training with perceptual learning in amblyopic subjects. Thus, amblyopia management should involve contrast sensitivity tasks for a global approach, with the aim of obtaining similar values in both eyes and facilitating binocular vision.[11]

3.1.3. Stereopsis Impairment

Stereopsis or stereoacuity is the perception of three-dimensionality because of the cortical combination between the images from each eye. For obtaining correct stereoscopic perception, both eyes should have an adequate and similar visual acuity and contrast sensitivity in the presence of ocular alignment. Therefore, stereopsis is one of the main features that should be assessed in the clinical management of amblyopia, since it usually is decreased or absent due to the differences in the perceived images between the amblyopic and the fellow eye. In anisometropic amblyopia, stereopsis is reduced, although it depends on the degree of anisometropia and the loss of visual acuity in the amblyopic eye. In strabismic or mixed amblyopia with constant deviation greater than 12 prism diopters, subjects are stereoblind due to the lack of bifoveal fixation. Stereopsis is important for appropriate performance in activities such as driving, sports or hand-to-eye coordination tasks, although further research is needed to understand more about how different values of stereopsis interfere with daily activities. In accordance with the aim of this review, it is relevant to note that during the treatment of amblyopia, stereopsis should be assessed and trained, since some authors suggested that vision therapy can also improve stereoacuity. Thus, designing exercises with specific stimuli for stereopsis training assumes great significance as part of the treatment in amblyopic subjects. Recent evidence from functional magnetic resonance imaging (fMRI) studies on the cortical processing of vision in amblyopia shows that, during amblyopic eye stimulation, not only do primary and secondary visual areas present reduced activation when compared to fellow-fixing eye stimulation, but so too do higher-level visual areas, such as the parieto-occipital and temporal cortex. These findings could explain binocular vision deficits in amblyopic patients.[11]

3.2. Visual Stimuli Used for Vision Training in Amblyopia

There are many types of stimuli which are used in vision training for amblyopia. For example, video games or films are usually used in published studies, commonly in dichoptic training. Despite the fact that they seem to be effective, they also have some features which could be a limitation. Some of these treatments are based on dichoptic training or monocular stimulation,

and use eye–hand coordination games and popular films which are not specifically designed for treating amblyopia, or do not adjust the difficulty of the training to the patient's progress. However, there are four types of stimuli which have shown to be effective in clinical research that can be easily added to the amblyopia training software, with the possibility of modification according to the patient's evolution, and these are:[11]

- letter optotypes

  Letter recognition is affected by crowding and interaction contours in amblyopia, but its use in visual training using perceptual learning approaches can be useful, since many of the parameters of these optotypes can be modified, such as size, contrast sensitivity, presence or absence of flankers, orientation, or motion **(Figure 2).** For this reason, visual training based on letter optotypes has been used in several scientific articles.

Figure 2: Letter optotype: Snellen E

- **Gabor's patches**

  These are sinusoidal gratings with a Gaussian envelope, which also are commonly used in amblyopia studies, since experimental research demonstrated that gratings with a neutral background can cause selective cortical responses for orientation and contrast, which additionally correlates with fMRI findings **(Figure 3).** Amblyopia affects high spatial frequency, contrast sensitivity and orientation discrimination, among others visual deficits. Therefore, Gabor´s patches also can be used in perceptual learning, since they allow clinicians to apply many visual tasks, adapting contrast, spatial frequency, size, and other parameters according to each individual case.

Figure 3: Gabor's patch

- **Vernier's stimuli**

  Vernier's stimuli are based on the perception of the continuity of a lineal stimulus, and are related with the concept of visual hyperacuity, which also is decreased in amblyopia. The less separate the lineal stimuli are, the more difficult it is to perceive discontinuity for amblyopic subjects **(Figure 4).**

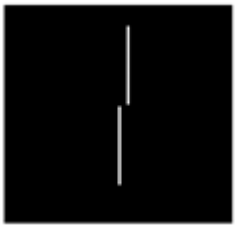

Figure 4: Vernier's stimulus

- **Random-dot Stereograms**

  This stimulus consists of an array of dots randomly presented to the subjects for specific stereoscopic perception stimulation **(Figure 5).** Usually, random-dot stimuli are used for stereoacuity assessment in clinical practice, but recent published works showed their application also in improving stereopsis values in amblyopia. The use of a random-dot stereogram entails a cortical activation in the early visual cortex, particularly with mixed-polarity stimulus, and a small but significant activation of the pupil and accommodation responses. Additionally, the optimal size of the dots should be considered for well-designed random-dot stimuli, since the literature suggests that larger dots implicate better stereo-perception.

Figure 5: Example of a random-dot stimulus, the dark "E" represents the section of the image that is perceived in depth

3.3. Parameters That Can Be Modified in the Visual Stimuli

There are many parameters that should be considered when performing visual training to treat amblyopia. For such purposes, the characteristics of stimuli that are described below should be considered due to their relationship with the neural mechanism of amblyopic subjects**. (see Table 2)**

- spatial–temporal frequency
- contrast sensitivity and luminance
- first- and second-order stimulus
- colour and achromatic stimuli
- figure–ground segregation
- signal–noise

Table 2: Summary of the recommendations for the selection of visual tasks and the initial parameters of the stimulus that should be used in vision training for amblyopia according to the scientific evidence revised.

Stimulus	Initial parameters	Visual Tasks
LETTER OPTOTYPES	1. Low spatial frequency & prolonged exposure 2. Maximum contrast 3. First order achromatic & steady stimulus without noise or masking	Letter recognition with & without crowding Orientation discrimination
GABOR'S PATCH	1. Low spatial frequency & prolonged exposure 2. Maximum contrast 3. Achromatic and steady stimulus without noise nor masking	Orientation discrimination
VERNIER'S STIMULUS	1.Prolonged exposure 2. Maximum contrast 3. Achromatic and steady stimulus without noise nor masking	Continuity discrimination
RANDOM-DOT STEREOGRAM	1. Decreased luminance in fellow eye for allowing binocular vision 2. First order achromatic and steady stimulus 3. Neither masking nor noise	Objects recognition in stereoscopic conditions

To sum up, vision therapy with perceptual learning, dichoptic training and virtual reality head-mounted displays (VR-HMD) seems to be a promising option for promoting visual recovery and rehabilitation in amblyopia, or accelerating the treatment period when combining it with patching. However, it is essential to adapt the stimuli to the patient's individual baseline features according to the spatio-temporal frequency, contrast sensitivity, luminance, first- or second-order, color, figure–ground segregation, signal–noise ratio, and motion. Furthermore, stimuli can be used in both monocular and binocular training using a computer or VR-HMD.

4.0 METHODS

4.1 Searching

Electronic databases were searched through the Ovid interface:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to 20 August 2021
- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to August 20, 2021
- Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations 1946 to August 20, 2021
- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 2017 to August 20, 2021
- Ovid MEDLINE(R) 1946 to September Week 1 2021
- Ovid MEDLINE(R) 1996 to September Week 1 2021
- Ovid MEDLINE(R) Epub Ahead of Print September 1 20, 2021

- Ovid MEDLINE(R) Daily Update September 1, 2021
- Ovid MEDLINE(R) 2017 to September Week 1 2021

Searches were also run in PubMed, INAHTA, Cochrane Library and US Food and Drug Administration. Google was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 1 September 2021.
Appendix 1 shows the detailed search strategies.

4.2 SELECTION

Two reviewers screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria:

Population	Amblyopia
Interventions	virtual reality(VR) including VIVID® Vision
Comparators	Patching Dry cupping, conventional therapy, medicines, placebo
Outcomes	Efficacy: Best corrected vision acuity (BCVA), improved visual acuity, stereoacquity Adverse events: common side effects
Study design	Health Technology Assessment (HTA) reports, Systematic Review (SR) and Meta-Analysis, Randomised Control Trial (RCT), Non-randomised Control Trial (RCT), cohort studies, cross-sectional studies, case studies
Type of publication	English, full text articles

Exclusion criteria:

Study design	Studies conducted in animals, narrative reviews, anecdotal, case report, survey
Type of publication	Non-English full text articles

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) checklist and evidence graded according to the US/Canadian Preventive Services Task Force (See Appendix 2). Data were extracted from included studies using a pre-designed data extraction form (evidence table as shown in **Appendix 3**) and presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review.

5.0 RESULTS

5.1 Selection of the included studies

A total of 67 titles were identified through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2021), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2021), EBM Reviews-Database of Abstracts of Review of Effects (1st Quarter 2021), EBM Reviews-Health Technology Assessment (1st Quarter 2020), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2020) and PubMed. The last search was run on 1 September 2021. Additional articles were identified from reviewing the references of retrieved articles. After removing duplicates, applying inclusion and exclusion criteria, finally four was included in this review consisted of two RCTs, one cross sectional study and one before and after trial (pre- and post- trial. There is only one study using the VIVID® Vision VR and was conducted in Slovakia 2017 which was presented in preliminary results of pre- and post- test trial. **(as seen in Figure 1)** Other studies were conducted in United State of America (USA), Spain and United Kingdom (UK).

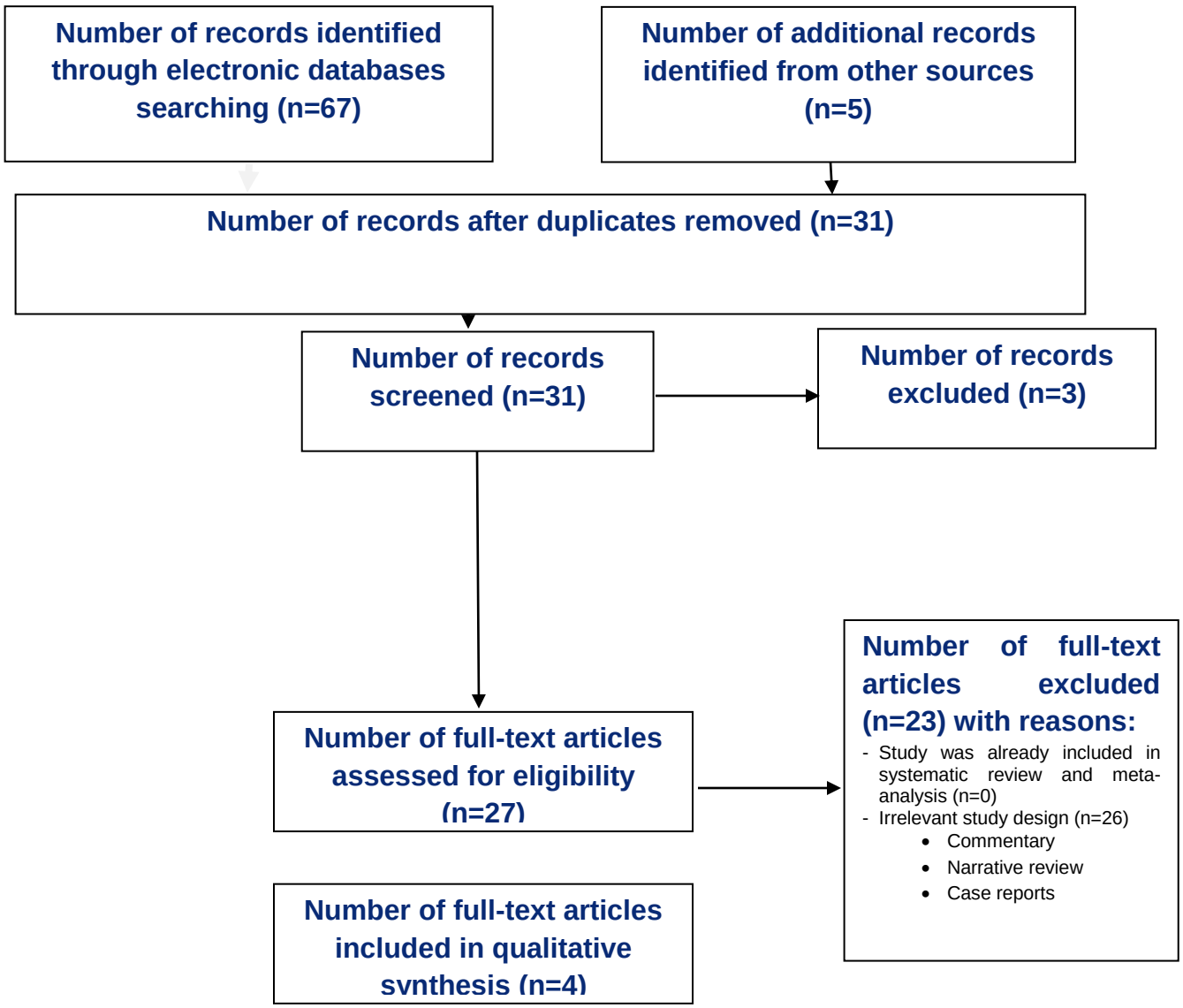

Figure 1: Flow chart of study selection

5.2 RISK OF BIAS / QUALITY ASSESSMENT OF INCLUDED STUDIES

The methodological quality of all the relevant full text articles retrieved was assessed using the relevant checklist of Cochrane Collaboration Assessment tools, Critical Appraisal Skills Programme (CASP) and NIH Quality Assessment Tool depending on the type of the study design. It is done by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

+	Indicates low risk of bias
?	indicates unclear risk of bias / some concerns
-	Indicates high risk of bias

Assessment of Randomised Controlled Trial (RCT) using Cochrane Risk-of-Bias Tool for Randomised Trials (RoB 2)

The risk of bias of RCTs included in this review was assessed using Cochrane Risk-of-Bias Tool for Randomised Trials (RoB 2)[19] checklist. Two RCTs[20-25,33] were included in this assessment. The risk of bias is shown in **Figure 2.**

Assessment of Cohort Study using Critical Appraisal Skills Programme (CASP) Checklist

Figure 3 shows the risk of bias of one retrospective cohort study by Guler O et al. (2015)[26] based on the CASP checklist. The study was at low risk of bias for all five domains assessed.

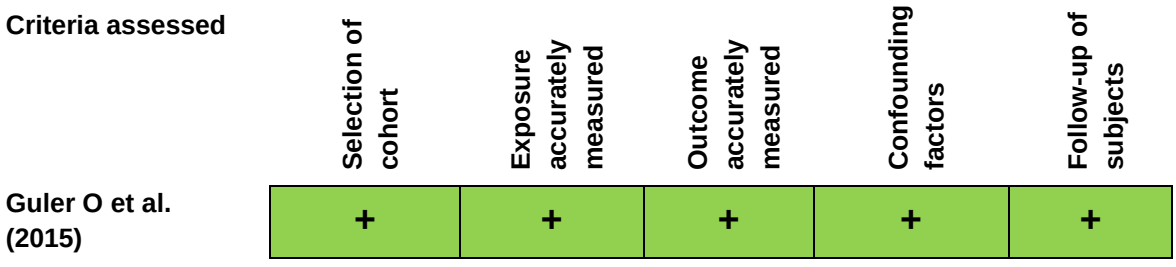

Figure 3: Quality assessment of cohort studies (CASP)

5.3 Efficacy/ Effectiveness

Kelly KR et al. conducted a randomised controlled trials crossover (RCTs) at a single centre of a non-profit eye research institute in Texas specialised in ophthalmology in children (Retina Foundation of the Southwest) to assessed the effectiveness of a binocular iPad adventure game as amblyopia treatment in children and compared this binocular treatment with patching, the current standard of care. The study took place between February 20, 2015, and January 4, 2016.

In this trial study, eligible children four to 10 years old were diagnosed as having amblyopia due to strabismus, anisometropia, or both and were referred to the Retina Foundation of the Southwest by nine paediatric ophthalmologists in the Dallas/FortWorth area. All the eligible children had amblyopic eye best-corrected visual acuity (BCVA) of 0.3 to 0.8 logMAR (20/40 to 20/125) and 0.1 logMAR (20/25) or better fellow eye BCVA (0.2 logMAR or better for 4-yearolds), with an interocular difference of at least 0.3 logMAR (≥3 lines). Children with strabismus were initially diagnosed as having esotropia but were aligned with surgery or spectacle correction to within four prism diopters of orthotropia at distance and near vision. Meanwhile, none of the children were born at less than 32 weeks' postgestational age or had coexisting ocular or systemic disease, congenital infections or malformations, or developmental delay.

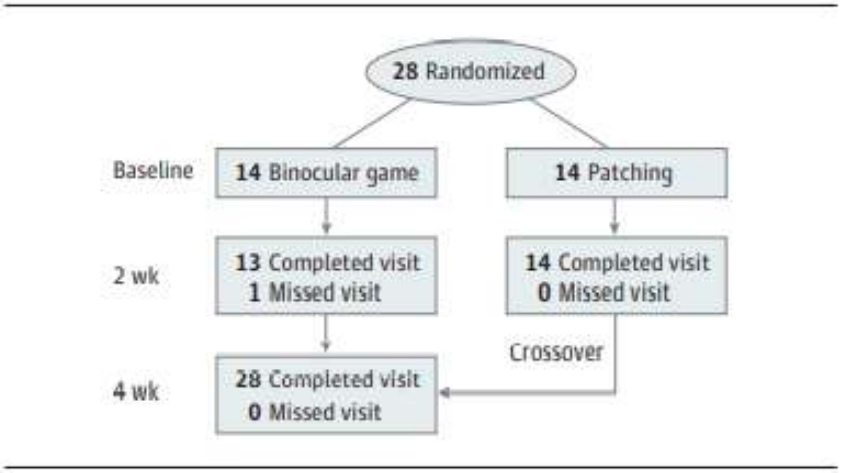

Figure 4: Consolidated Standards of Reporting Trials (CONSORT) Diagram

Randomisation was performed by a statistician who provided individual sealed sequentially numbered envelopes. Two randomization schedules were created using a random number generator function, one for children with prior amblyopia treatment (patching or atropine) and another for children with no prior treatment. Randomisation (1:1) was prepared in permuted blocks with block sizes of 4 or 6. After confirming eligibility and obtaining written informed consent, one of reviewers will opened a sealed envelope, enrolled the child, and assigned him or her to the appropriate treatment.

Treatment Protocol

Treatment groups followed the same protocol timeline and were administered the same vision assessments. At the baseline visit, eligibility for enrolment was ascertained, and vision assessments were conducted. Children were randomised to binocular game treatment or patching treatment for two weeks. At the 2-week visit (11-17 days after baseline), vision was reassessed. Patching children crossed over to the binocular game, and both groups continued treatment for an additional two weeks. At the 4-week visit (25-31 days after baseline), vision was reassessed. Four weeks marked the end of our study, but children had the option to continue game treatment with two more follow-up visits (eight and 12 weeks from baseline). (Figure 4) The primary outcome was change in amblyopic eye BCVA at the 2-week visit. Secondary outcomes were change in stereoacuity and suppression at the 2-week visit and change in amblyopic eye BCVA at the 4-week visit.

Binocular Game Protocol

Children randomised to binocular game treatment were loaned an iPad with an action-oriented adventure game (Dig Rush; developed in collaboration with Robert Hess, PhD, DSc, at McGill University [Montréal, Québec, Canada], and Amblyotech [Atlanta, Georgia] and UbiSoft [Montréal]) that consists of miners digging for gold. Using a finger, the child must manipulate the miners and their surroundings to dig and return gold to a cart as quickly as possible while avoiding obstacles (e.g. fire, lava, and monsters). Children were familiarised with the game and practiced until one of the reviewer was confident in their ability to understand and play it. Children were asked to play the game at home for 1 hour a day 5 days a week for 2 weeks (10 hours total).

During game play, children wore red-green anaglyphic glasses that separate game elements seen by each eye so that reduced-contrast elements (e.g. gold and fire) are seen by the fellow eye, high-contrast elements (e.g. miners and monsters) are seen by the amblyopic eye, and high-contrast background elements (e.g. ground and rocks) are seen by both eyes. For successful game play, both eyes must see their respective game components. Amblyopic eye contrast remained at 100% contrast, while fellow eye contrast started at 20% but increased with game success (a star earned), requiring the amblyopic eye to work harder in tandem with the fellow eye. At least 18 hours of game play were required to reach 100% contrast. If game play was unsuccessful for 30 minutes (no star earned), fellow eye contrast was reduced. At the 2-week visit, children were asked to play the game for an additional 2 weeks.

Patching Protocol

The patching protocol was designed to be similar to the current standard of care for amblyopia treatment. Children were provided with eye patches (Ortopad; Ortopad USA) and were asked to patch their fellow eye 2 hours a day 7 days a week for two weeks (28 hours' total treatment). At the 2-week visit, children assigned to the patching protocol crossed over to the binocular game**.**

Vision Assessment

Vision assessments were conducted at baseline, the 2-week visit, and the 4-week visit and included 4 components. First was crowded monocular BCVA using the electronic Early Treatment Diabetic Retinopathy Study protocol for children at least seven years old or the Amblyopia Treatment Study HOTV protocol for children younger than seven years. Second was a stereoacuity component (Randot Preschool Stereoacuity and Stereo Butterfly Tests; Stereo Optical, Inc). Third was extent of suppression scotoma using the Worth 4-dot test at

seven different distances. Fourth was depth of suppression for children younger than seven years using a dichoptic motion coherence test that determines the maximum contrast of randomly moving dots in the fellow eye that still allows the child to discriminate the direction of coherent motion dots in the amblyopic eye, or for children at least seven years old using a dichoptic eye chart adapted from work by Kwon et al that determines the contrast ratio at which the child reports letters presented to each eye with equal likelihood.

Adherence to Protocol

Parents or legal guardians were provided a personalized calendar to record the minutes per day their child played the game or patched their fellow eye. A log file was also obtained from the iPad that contained the minutes played and fellow eye contrast for each play session.

Results:

A total of 28 patients were enrolled in the study, with 14 randomized to binocular game treatment and 14 to patching treatment. The 2-week outcome visit was completed by all children except for one child randomised to the binocular game who had a scheduling conflict but who attended the 4-week visit. All 28 children completed the 4-week visit. There were no study dropouts. Nine children (32%) had strabismic amblyopia, 14 (50%) had anisometropic amblyopia, and 5 (18%) had combined mechanism amblyopia. Their mean (SD) age was 6.7 (1.4) years (age range, 4.6-9.5 years), and 7 (25%) were female. The mean (SD) amblyopic eye BCVA at enrollment was 0.48 (0.14) logMAR (approximately 20/63; range, 0.3-0.8 logMAR [20/40 to 20/125]). Moderate amblyopia (range, 0.3-0.6 logMAR [20/40 to 20/80]) was present in 23 children (82%), and severe amblyopia (range, 0.7-0.8 logMAR [20/100 to 20/125]) was present in 5 (18%). Twenty children (71%) had received prior amblyopia treatment.

Adherence to Protocol

Compliance for iPad game play using the personalised calendar was similar to that using the iPad log; therefore, the latter was used. Compliance for patching was tabulated using the personalised calendar. For the first two weeks, children assigned to the binocular game completed a mean (SD) of 10.0 (2.3) hours (100% prescribed treatment time). The mean (SD) fellow eye contrast was 46% (15%) at the 2-week visit (iPad contrast logs were available for 11 to 14 children). Children assigned to patching completed a mean (SD) of 27.7 (3.0) hours (99% prescribed treatment time). For the second two weeks, all children were assigned to the binocular game, and they completed a mean (SD) of 8.2 (3.4) hours (82% prescribed treatment time). The mean (SD) fellow eye contrast at the 4-week visit was 71%.

Primary Outcome

At the 2-week primary outcome visit, a larger improvement in amblyopic eye BCVA was found with the binocular game compared with patching, with a mean (SD) improvement of 0.15 (0.08) logMAR (mean [SD], 1.5 [0.8] lines) vs 0.07 (0.08)
logMAR (mean [SD], 0.7 [0.8] line improvement) (mean difference, 0.07 logMAR [0.7 line]; 95% CI, 0.01-0.14 logMAR [0.1-1.4 lines];t25 = 2.42, P = .02). For the binocular game, improvement ranged from 0.0 to 0.2 logMAR (0-2 lines): 11 children (85%; 95% CI, 58%-96%) improved by at least 0.1 logMAR (8 of whom improved by 0.2 logMAR [2 lines], and 3 of whom improved by 0.1 logMAR [1 line]), and 2 (15%; 95%
CI, 3%-46%) did not improve. For patching, improvement ranged from 0.0 to 0.2 logMAR (0-2 lines): 7 children (50%; 95% CI, 27% to 73%) improved by at least 0.1 logMAR (3 of whom

improved by 0.2 logMAR [2 lines], and 4 of whom improved by 0.1 logMAR [1 line]), and 7 (50%; 95% CI, 27%-73%) did not improve.

Secondary Outcomes

Amblyopic eye BCVA had improved at the 2-week visit with the binocular game (mean [SD] improvement, 1.5 [0.8] lines; t12 = 6.79, P < .001) and with patching (mean [SD] improvement, 0.7 [0.8] line; t13 = 3.24, P = .006). At the 4-week visit, amblyopic eye BCVA had improved for children who crossed over to the binocular game, resulting in their catching up with children who started with the binocular game,with a mean (SD) improvement of 0.17 (0.10) logMAR (mean [SD], 1.7 [1.0] lines) for the binocular game vs a mean (SD) improvement of 0.16 (0.12) logMAR (mean [SD], 1.6 [1.2] lines) for patching crossover (mean difference, 0.01 logMAR; 95% CI, −0.07 to 0.01 logMAR;t26 = 0.35, *p* =0.73) (Figure 3). Overall, 23 children (82%) improved by at least 0.1 logMAR (1 line).

The author concluded that the binocular iPad game was a successful treatment for childhood amblyopia and was more effective than patching at the 2-week visit. Although this study only include a small sample size and treatment lasted only two to four weeks, binocular games that rebalance contrast to overcome suppression are a promising additional option for treating amblyopia**.**

Herbison et al. conducted a RCTs at two test sites (Queen's Medical Centre, Nottingham and Addenbrooke's Hospital, Cambridge, United Kingdom using a VR-based system to treat amblyopia using dichoptic stimulation in the context of either playing special video games or watching DVDs. The study with an interactive binocular treatment (I-BiT) was aimed to ensure that the treatment (i-BIT) was safe, acceptable and to get an improved indication of its efficacy.

The study was a randomised parallel group design with the intention to recruit 75 patients. The eligible patients were randomised to one of three treatments:

- I-BiT game
- Non-I-BiT game
- I-BiT DVD.

Each group will have received their randomised treatment weekly for six weeks, for a 30 min period. At baseline their logMAR visual acuity, with glasses if required, was recorded along with the results of their cover test, oculomotility assessment, binocular vision assessment, visuo-scope and Sbisa bar results. Visual acuity was assessed pre-treatment (week 1), after three treatments (week 3), after six treatments (week 6) and four weeks after their final treatment (week 10). Visual acuity was assessed with either the logMAR crowded test (formally Glasgow acuity cards, manufactured by Keeler) or the crowded Kay's picture test. Choice of visual acuity (VA) test was dependent on the participant's ability and remained consistent throughout the trial.

Children aged 4–8 years with strabismic, anisometropic or mixed amblyopia were recruited from two test sites (Queen's Medical Centre, Nottingham and Addenbrooke's Hospital, Cambridge), from January 2012 to November 2013. Stimulus deprivation amblyopia was excluded. Children who had prior treatment with either patching **or atropine penalisation**

were eligible for recruitment providing they had a 0.20 logMAR intraocular acuity difference and no current improvement with patching.

Interventions

I-BiT shutter glasses system

The I-BiT system hardware is designed for use under supervision and consists of a desktop PC with two monitors, one for the clinician and one for the patient. The clinician monitor is used to control the treatment the patient receives and the patient monitor displays the visual stimuli. The patient monitor is a flat-screen 22-inch 3D monitor with a refresh rate of 120 Hz and this allows separate images to be presented to each eye with the use of shutter glasses. The shutter glass lenses lighten and darken in synchrony with the monitor but faster than the user can perceive and this allows a common background to be presented to both eyes and an 'enriched' image to be presented only to the amblyopic eye (dichoptic stimulation). The I-BiT system can display video footage and interactive games. A gaming control pad is used for the games.

DVD stimulus

The I-BiT DVD stimulus is divided into two zones. There is an outer 'border' termed a locking stimulus which is presented to both eyes while the inner part of the screen presents the video footage predominately to the amblyopic eye.

Game stimulus

An interactive game called 'Nux' was used to provide the game play. Through the I BiT system, the player and the background are shown to both eyes but the obstacles, enemies and coins are shown only to the amblyopic eye. Therefore, in order for the child to play the game successfully, they must use their amblyopi**c eye.**

Control stimulus

In the non-I-BiT game version (control arm) both eyes receive identical stimulation**.**

Results:

The visual acuity improved in all three groups at weeks 3, 6 and 10 with the average improvement of vision at week 6 of 0.07 logMAR which was sustained at week 10. This improvement was significant at all three time points (using paired t tests, $p<0.001$ at all three time points). **(Table 3)**

Table 3: Improvement in vision for all the patients in the trial

	Improvement in logMAR vision	CIs	p Value
Baseline and week 3	−0.04	−0.63 to −0.20	<0.001
Baseline and week 6	−0.07	−0.11 to −0.047	<0.0001
Baseline and week 10	−0.067	−0.097 to 0.038	<0.0001

Significance testing was performed using a paired t test and probability values calculated on the basis of two-tailed.

The difference in visual acuity (VA) improvement between the three arms at week six with I-BiT games as the comparison arm. The change in visual acuity from baseline to the end of treatment (week 6) is shown in table 4. There was no difference in the change from baseline between those having I-BiT games and those having non-I-BiT games (mean 0.02 logMAR units 95% CI (−0.07 to 0.03)). The improvement in vision from baseline at 6 weeks differed between the tw0 games treatment groups and the DVD group, with a mean of change in the i-BiT DVD group of −0.1 compared with −0.06 in the i-BiT games group and −0.03 in the non-i-BiT games group.

Table 4: Summary of outcomes

	I-BiT DVD	I-BiT games	Non-I-BiT games
Number randomised	24	26	25
Primary outcome			
Change from baseline to week 6 in visual acuity (logMAR)			
N	21	25	22
Mean (SD)	−0.1 (0.02)	−0.06 (0.02)	−0.03 (0.02)
Median (range)	−0.1 (−0.15, 0.05)	−0.05 (−0.13, 0)	−0.04 (−0.1, 0.04)
Difference from I-BiT games			
Mean (SE)	0.05 (0.03)		0.02 (0.03)
95% CI	−0.004 to 0.10		−0.07 to 0.03
p Value (from ANCOVA with baseline VA as covariate)	0.067		0.429
Secondary outcomes			
Change in VA from baseline to week 10			
Change from baseline to week 10 in visual acuity (logMAR)			
N	23	26	24
Mean (SE)	−0.07 (0.03)	−0.07 (0.03)	−0.06 (0.02)
Median (IQR)	−0.08 (−0.18, −0.02)	−0.09 (−0.16, −0.07)	−0.05 (−0.15, 0)
Difference from I-BiT games			
Mean (SE)	0.003 (0.04)		−0.01 (0.04)
95% CI	−0.07 to 0.07		−0.08 to 0.06
Change in VA from baseline to week 3			
Change from baseline to week 3 in visual acuity (logMAR)			
N	24	26	24
Mean (SD)	−0.05 (0.02)	−0.05 (0.02)	−0.02 (0.02)
Median (IQR)	0.07 (−0.12, −0.005)	−0.04 (−0.1, 0.008)	−0.03 (−0.08, 0.02)
Difference from I-BiT games			
Mean (SE)	0.002 (0.03)		−0.03 (0.02)
95% CI	−0.06 to 0.06		−0.08 to 0.01
Proportion (%) of patients showing a clinically important change in VA (≥1.25 logMAR)			
Week 3	6 (25%)	4 (15%)	1 (4%)
Week 6	6 (25%)	6 (23%)	4 (16%)
Week 10	10 (42%)	11 (42%)	8 (32%)

There were no significant improvements in stereoacuity (Frisby) in the three. The i-BiT DVD and non-I-BiT game improved vision to week six then declined slightly after treatment finished (week 10). The i-BiT games group increased from weeks 3–6 and then a decrease to week 10. The mean VA at week 10 was less than baseline for all three groups. Compliance with each of the treatments was excellent with the majority of participants playing the game/watching the DVD for 30 min at each session.

Martin S et al. conducted an observational study (cross sectional) for all volunteers which were recruited at the same Optometry Clinic in Spain. The data was obtained in their first visit to the clinic, after signing the Consent Agreement (minors signed the agreement together with their parents).

The purpose of this study was:

1. to implement a test for binocular imbalance in a Virtual Reality headset
2. to assess its testability, reliability and outcomes in a population of clinical patients and
3. to evaluate the relationships of interocular acuity difference, stereoacuity and binocular imbalance to amblyogenic risk factors

In this study, they enrolled 100 volunteers (ages six to 70 years old, mean 21.2 ± 16.2 years). Of those patients, 21 volunteers had no amblyogenic factor (control group). Seventy-nine (n=79) have amblyopia or a history of amblyopia (24 anisometropic, 25 strabismic and 30 mixed), most of whom had received previous treatments:

- all of them refractive correction
- 59 occlusion
- 35 perceptual learning using Gabor patches to improve contrast sensitivity
- 24 perceptual learning using random dot stimuli to improve stereoacuity
- six subjects' strabismus surgery.

All 55 participants with strabismus had esotropia. Exotropia is less prevalent than esotropia and is much more likely to be intermittent exotropia. In intermittent exotropia, binocular inhibition is low and the deviation angle at near is generally lower than at far distances. As a result, stereoacuity is likely to be preserved, and amblyopia is uncommon. This may explain why in our strabismus sample we find only participants with esotropia.

Participants were also classified according to their response to optical correction:

- 16 were classified as accommodative (the deviations disappears at near and far distance with full optical correction condition) and
- 39 as non-accommodative (residual esotropia at near and/or far distance despite wearing full optical correction)

Amblyopia was defined as ≥0.10 logMAR BCVA in the amblyopic eye and interocular difference of ≥0.2 logMAR. Anisometropia was defined as an amblyogenic factor due to a spherical equivalent interocular difference of ≥1.0 D. The spherical equivalent was calculated as the sum of sphere plus half the cylinder. Strabismus was defined as an amblyogenic risk factor based on the presence of heterotropia at near or far distance, measured with the Unilateral Cover Test (UCT), with full optical correction condition and an accommodative stimulus. Mixed amblyogenic risk factor was defined as the presence of both strabismus and anisometropia. Exclusion criteria were congenital malformation, ocular pathology, concurrent treatment with atropine penalization, presence of diplopia in daily life conditions, prematurity ≥8 weeks, developmental delay, and coexisting ocular or systemic disease. Due to Virtual Reality headset limitations, volunteers with an interpupillary distance less than 55 mm and/or lower head circumference less than 500 mm were also excluded.

Binocular imbalance test in VR

Binocular imbalance was assessed using a modified version of the dichoptic eye chart proposed by Kwon et al. implemented in VR device (Vive by HTC Co.). Letters are normalised

to device mean luminance and root-mean square (RMS) contrast of 0.1. The size of the letter determines the frequency to be tested in the VR headset. The test starts with a dichoptic eight squares pattern inside a high contrast frame subtending 20˚, which remains visible during the test to facilitate fusion. The participant has to confirm seeing the pattern stable before starting each trial. On each trial, two randomly selected dichoptic letters are presented to the observer (one to each eye) for 200 msec., and the participant is instructed to report the letter seen (or the dominant letter in case of both are perceived simultaneously), following which both previous letters are presented side-by-side, enhanced in contrast and size, and the observer must reaffirm the one that was seen.

Results:

All 100 volunteers, including 18 between the ages of 6 and 8, were able to complete the binocular imbalance test. No one reported dizziness or fatigue due to helmet weight. All participants appear to have understood the test procedure after a short explanation. The binocular imbalance test is highly reliable. Test-retest repeatability (Wilcoxon signed rank test), gave a p-value of 0.831, showing no significant difference between first and second test. The mean of differences is equal to -0.033, which means that first measurements are 1.033 times bigger than second results. Differences follow a normal distribution (Shapiro test, p = 0.001).

To assess whether the binocular imbalance test results were consistent with standard clinical measures of suppression, we evaluated its correlation with the Worth 4 dots test. The Worth test provides patient's responses (fusion, suppression or diplopia) at two visual angles (1.5˚ and 5.0˚). These responses were ordered according to the extent of suppression scotoma, considering diplopia as an intermediate stage between fusion and suppression, obtaining a novel scale of six categories.

Binocular imbalance showed high test-retest reliability (no significant difference between test and retest in a subgroup, n = 20, p = 0.831); was correlated with Worth 4 dots test (r = 0.538, p<0.0001); and correlated with both interocular acuity difference (r = 0.575, p<0.0001) and stereoacuity (r = 0.675, p<0.0001). The mean values of each variable of the triplet differed depending on group classification. Mixed and non-accommodative groups showed the worst mean values compared with the other groups. Among participants with strabismus, strabismic versus mixed subgroups did not show significant differences in any variable of the triplet, whereas the accommodative vs non-accommodative subgroups showed significant differences in all of them.

The author concluded that the binocular imbalance test, using a VR device, is easy for patients to understand, fast, repeatable and valid. Virtual reality is a promising technique in amblyopia treatment. Adjusting contrast to rebalance binocular vision within a VR headset opens the possibility of new treatments based on this technology.
From this study also stress the importance of monitoring amblyopia in clinical practice not only taking into account visual acuity, but also stereoacuity and interocular imbalance. Patching and visual therapy outcomes should be tracked using this triplet.

Žiak, P. et al. conducted a pre-and post- trial training and presented the preliminary results of using the virtual reality oculus rift head mounted display (HMD) in a sample of anisometropic amblyopic adults. The study aims to evaluate the effect of dichoptic visual training using a virtual reality head mounted and evaluate the potential usefulness of this option of treatment.

In this study a total of 17 amblyopic subjects (10 men, 7 women) with a mean age of 31.2 years (range, 17–69 year) were enrolled in this study. Inclusion criteria were subjects with anisometropic amblyopia, age of 17 years old or more and willing to perform the visual training. Exclusion criteria were patients with strabismus, previous ocular surgery, corneal irregularity, opacification of ocular media including cataracts and active ocular disease. The study was conducted in Medical School, Commenius University in Martin, Slovakia.

All patients underwent a baseline ophthalmological examination including visual testing, manifest and cycloplegic refraction, cover test, four dot Worth test, anterior segment examination with the slit lamp, corneal topography, and funduscopy. Best corrected visual acuity (BCVA) was measured using a calibrated liquid crystal display (LCD) optotype with Snellen charts (CC-X10, Topcon, Japan). The stereoacuity was measured using the Stereo Randot graded circle test (Stereo Optical, IL, USA). The BCVA and stereoacuity were measured before and after the program of dichoptic training. Dichoptic visual training was performed using the beta version of the computer game Diplopia Game (Vivid ® Vision, San Francisco, USA) which was run in the Oculus Gear.

5.4 SAFETY

Adverse events
From Herbison et al. there were two cases of double vision which were assumed to be adverse device effects and they both resolved spontaneously following cessation of treatment. All other adverse events are assumed to be not device related. **(Table 5)**

Table 5: Summary of adverse events in the trial

	I-BiT DVD N=24	I-BiT game N=26	Non-I-BiT game N=25
Adverse events leading to withdraw from trial			
Double vision	1	1	0
Drop in vision	2	0	2
Adverse events not leading to withdraw			
Flu or cough	2	2	2
Tonsillitis	1	0	1
Conjunctivitis	1	0	
Diarrhoea and/or vomiting	0	6	2
Other infection	0	1	0
Eczema	1	0	1
Trauma	1	0	1
Eye feeling funny	1	0	0

The author concluded that there was a modest vision improvement in all three arms. Treatment was well tolerated and safe. There was no difference between the three treatments in terms of primary stated outcomes but treatment duration was short and the high proportion of previously treated amblyopia and strabismic amblyopia disadvantaged dichoptic stimulation treatment.

5.5 Cost analysis and cost-effectiveness

There was no retrievable evidence on the cost or cost-effectiveness of VIVID® Vision VR treatment for amblyopia (lazy eyes). However, various price or fees of VR devices of the treatment for lazy eye/amblyopia. Ranging price from USD 129 (~RM 590) plus the cost of a phone for the Gear VR®, USD 199 (~RM 900) for the Oculus Go®, and USD399 (~RM1800) each for the Quest and RiftS®.

5.6 Organisational Issue

There was no retrievable study on organisational issue regarding to VR treatment for amblyopia (lazy eyes). However, the process of visual rehabilitation of the strabismus promote a postural improvement due to postural habits resulting from deviations in the eye. There is a lower risk index in the rehabilitation of strabismus because it is a non -invasive method. This is because the patient does not undergo surgery, is not exposed to surgical and post-surgical infections, does not require hospitalisation and does not undergo cuts. Furthermore, the technique does not cause necrosis. The use of HMD can provide mild nausea, motion

sickness and headaches due to the technology of virtual reality glasses. No matter how advanced it is, the technology has not yet overcome the obstacle of unease to some users, which occurs in these situations due to the differences between the movement perceived by the eyes and the movement perceived by the body. There is a delay between the movement of the head in virtual reality, and when the image in front of the user's eyes changes, there is a mismatch between the sensed movements (with the inner ears) and the observed image (with the eyes). In real life, this delay is zero, and the sensory and motor systems are tightly coupled. In summary, if there is movement in the individual's vision without movement in the vestibular system, a set of organs that regulates balance, the user will feel discomfort.

5.7 Limitations

This technology review has a limitation. Our review has several limitations and these should be considered when interpreting the results. Although there was no restriction in language during the search, only the full text articles in English published in peer-reviewed journals were included in the review, which may have excluded some relevant articles and further limited the study numbers

6.0 CONCLUSION

6.1 Effectiveness

Best corrected visual acquity (BCVA)

There was very fair level of retrievable evidence to suggest that virtual reality was associated with improving BCVA. BCVA improved significantly from a mean logMAR BCVA value of before and after of test conducted. At 2-week primary outcome visit, a larger improvement in amblyopic eye, BCVA was found with the binocular game compared with patching.

Stereoacuity

Stereoacuity was measured using the Stereo Randot graded circle test, with the ability of measuring stereoacuities from 400 to 20 s of arc. Mean stereoacuity changed statistically significant from a value before dichoptic training and after training. However, no differences between the binocular game versus patching treatments were found at the 2-week visit for change in stereoacuity, extent of suppression, and depth of suppression.

Binocular imbalance test

Using a VR device, is easy for patients to understand, fast, repeatable and valid. Virtual reality is a promising technique in amblyopia treatment. Adjusting contrast to rebalance binocular vision within a VR headset opens the possibility of new treatments based on this technology.

6.2 Safety

There was very limited fair level of retrievable evidence to suggest that virtual reality in treating amblyopia. There was no serious adverse event related and the treatment was well tolerated and safe.

6.3 Cost/Cost-Effectiveness

There was no retrievable evidence on the cost-effectiveness of virtual reality in treating amblyopia. However, various price or fees of VR devices of the treatment for lazy eye/amblyopia. Ranging price from USD 129 (~RM 590) plus the cost of a phone for the Gear VR®, USD 199 (~RM 900) for the Oculus Go®, and USD399 (~RM1800) each for the Quest and Rift S®.

6.4 Organisational

There was no guideline retrieved which specifically addressed the use of VR in treating patients with amblyopia

7.0 REFERENCE

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2. Coco-Martin MB, Piñero DP, Leal-Vega L, et al. The Potential of Virtual Reality for Inducing Neuroplasticity in Children with Amblyopia. J Ophthalmol. 2020 Jun 29;2020:7067846

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13. Virtual reality. At https://www.britannica.com/technology/virtual-reality; assessed on 3 August 2021

14. Virtual Reality Concept. At https://www.sciencedirect.com/topics/computer-science/virtual-reality-technology; assessed on 3 August 2021

15. Virtual Reality by VIVID VR. At https://www.seevividly.com/info/Virtual_Reality; Assessed on 29 July 2021

8.0 APPENDIX

8.1 Appendix 1: Search strategy

Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® 1946 to 27 July 2021
1 AMBLYOPIA/
2 amblyopia*.tw.
3 (amblyopia* adj1 (anisometropic or developmental)).tw.
4 lazy eye*.tw.
5 stimulus deprivation induced amblyopia.tw.
6 stimulus deprivation-induced amblyopia*.tw.
7 suppression amblyopia*.tw.
8 AMBLYOPIA/
9 anisometropic amblyopia*.tw.
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 IMAGING, THREE-DIMENSIONAL/
12 3-d imag*.tw.
13 computer generated 3d imaging*.tw.
14 computer-generated 3d imaging*.tw.
15 computer-assisted three-dimensional imaging*.tw.
16 computer assisted three dimensional imaging.tw.
17 three dimensional image.tw.
18 three-dimensional imag*.tw.
19 COMPUTER SIMULATION/
20 (computer adj1 (model* or simulation*)).tw.
21 computerized model*.tw.
22 in silico*.tw.
23 VIRTUAL REALITY/
24 (virtual realit* adj2 (educational or instructional)).tw.
25 virtual realit*.tw.
21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (333803)
22 8 and 21 (67)

OTHER DATABASES	
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to July 27, 2021	
Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations 1946 to July 27, 2021	
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 2017 to July 27, 2021	
Ovid MEDLINE(R) 1946 to July Week 3 2021	
Ovid MEDLINE(R) 1996 to July Week 3 2021	
Ovid MEDLINE(R) Epub Ahead of Print July 27, 2021	
Ovid MEDLINE(R) Daily Update July 27, 2021	
Ovid MEDLINE(R) 2017 to July Week 3 2021	
Cochrane Library	

PubMeD

(((((((AMBLYOPIA/[MeSH Terms]) OR (amblyopia*.tw.[Title/Abstract])) OR (lazy eye*.tw.[Title/Abstract])) OR (stimulus deprivation induced amblyopia.tw.[Title/Abstract])) OR (stimulus deprivation-induced amblyopia*.tw[Title/Abstract])) OR (suppression amblyopia*.tw.[Title/Abstract])) OR (anisometropic amblyopia*.tw.[Title/Abstract])) AND ((((((((((((((IMAGING, THREE-DIMENSIONAL/[MeSH Terms]) OR (3-d imag*.tw[Title/Abstract])) OR (3-d imag*.tw[Title/Abstract])) OR (3-d imag*.tw.[Title/Abstract])) OR (computer generated 3d imaging*.tw.[Title/Abstract])) OR (computer-generated 3d imaging*.tw.[Title/Abstract])) OR (computer-assisted three-dimensional imaging*.tw.[Title/Abstract])) OR (computer assisted three dimensional imaging.tw.[Title/Abstract])) OR (three dimensional image.tw.[Title/Abstract])) OR (three-dimensional imag*.tw.[Title/Abstract])) OR (COMPUTER SIMULATION/[MeSH Terms])) OR (computerized model*.tw.[Title/Abstract])) OR (in silico*.tw.[Title/Abstract])) OR (virtual realit*.tw.[Title/Abstract])) OR (VIRTUAL REALITY/[MeSH Terms]))

8.2 Appendix 2: Hierarchy of evidence for effectiveness/ diagnostic

I Evidence obtained from at least one properly designed randomised controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

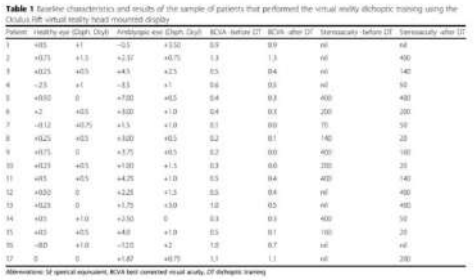
II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

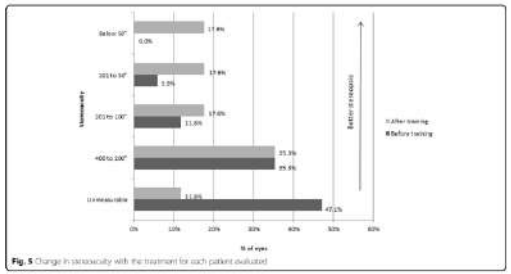
III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

8.3 APPENDIX 3: EVIDENCE TABLES

Evidence Table : **Effectiveness/Safety**
Question : **What is the effectiveness of virtual reality Vision for treating amblyopia?**

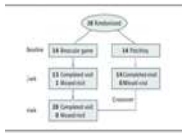
Bibliographic/ citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Žiak, P. et al. Amblyopia treatment of adults with dichoptic training using the virtual reality oculus rift head mounted display: preliminary results. BMC Ophthalmol 17, 105 (2017) Slovakia	Pre-and post Trial Aim/Objectives: to evaluate the effect of dichoptic visual training using a virtual reality head mounted display in a sample of amblyopic adults in order to evaluate the potential usefulness of this option of treatment. Inclusion criteria: subjects with anisometropic amblyopia, age of 17 years old or more and willing to perform the visual training.	II-3	N=17 (10 men, 7 women) Mean age: 31.2 (age range: 17-69 years)	Vivid® Vision -beta version of the computer game Diplopia Game (Vivid Vision, San Francisco, USA) which was run in the Oculus Rift OC DK2 virtual reality head mounted display-HMD (Oculus VR, LLC, Irvine, California, USA). Virtual	Patching		Results: 1. BCVA 2. Stereoacuity Table 1: includes BCVA of the amblyopic eye and stereoacuity data before and after the 8 dichoptic training sessions  BCVA improved significantly from a mean logMAR BCVA value of before: 0.58 ± 0.35 after: 0.43 ± 0.38 ($p < 0.01$, Student t test) Snellen BCVA: Amblyopic eyes: before : from 20/400 to 20/25 and after: from 20/400 to 20/20 after training A total of 29.41% and 47.06% of eyes achieved a BCVA of 20/40 or better before and after training, respectively	Small sample size

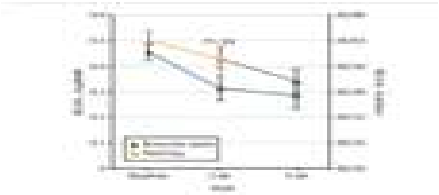
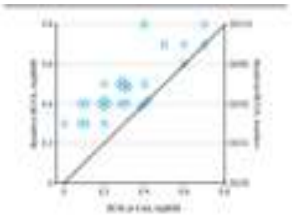
	Exclusion criteria: strabismus, previous ocular surgery, corneal irregularity, opacification of ocular media including cataracts and active ocular disease Methods: All patients underwent a baseline ophthalmological examination including visual testing, manifest and cycloplegic refraction, cover test, four dot Worth test, anterior segment examination with the slit lamp, corneal topography, and funduscopy. Best corrected visual acuity (BCVA) was measured using a calibrated liquid crystal display (LCD) optotype with Snellen charts (CC-X10, Topcon, Japan).			reality HMD Oculus Rift was connected to a PC and 2 games were available, a space game in which subjects were flying spaceship through a system of rings and a breaker game which is a typical block breaker game, but played in a virtual reality 3D setting.			Most of the patients gained lines (1.5 logMAR line on average) of BCVA except those three with the lowest BCVA (1.30, 1.10 and 0.9 logMAR) and one patient with 0.30 logMAR BCVA. In these 4 cases, no change in BCVA was observed. Stereoacuity was measured using the Stereo Randot graded circle test, with the ability of measuring stereoacuities from 400 to 20 s of arc. Mean stereoacuity changed from a value before dichoptic training: 263.3 ± 135.1 after training: 176.7 ± 152.4 s of arc This change was statistically significant ($p < 0.01$, Wilcoxon signed-rank Test). A total of 8 patients (47.1%) before dichoptic treatment had unmeasurable stereoacuity with the method used while this only occurred in 2 patients (11.8%) after training.  Author's Conclusion: In our sample, stereoacuity improved in 7 out of 10 patients, whereas in other studies evaluating other modalities of binocular	

	The stereoacuity was measured using the Stereo Randot graded circle test (Stereo Optical, IL, USA). BCVA and stereoacuity were measured before and after the program of dichoptic training. Each subject underwent 8 training sessions, being performed twice a week. Each session included 40 min of training with 2 different games (20 min per game). Optometric tests that were available in the beta version of the software were performed directly in the HMD before each training (ocular dominance and suppression).						treatment have reported improvement rates of 50% to 60%. Possibly, the use of virtual reality may play a role in this enhanced stereoacuity after dichoptic training in Oculus Rift. The preliminary results of our study indicate the potential for a new treatment for adulthood amblyopia. It is still necessary to perform a controlled clinical trial evaluating this potential treatment option for amblyopia, not only in adults, but also in children. Our results suggest that suppression of the amblyopic eye gates plasticity within the adult amblyopic visual cortex and therefore some degree of residual cortical plasticity can be unmasked in the adult brain. It should be also considered that motivational effects associated with video game plays may play also an important role in neuronal plasticity of the central nervous system.	

	BCVA was tested before first and after last training session. Patient did not perform any other visual training during the period of dichoptic training. Ten patients were treated with patching when they were child, but they did not remember for how long. Data analysis was performed using the software SPSS for Windows version 19.0 (IBM, Armonk, NY, USA). The status of normality of the data was determined using the Kolmogorov-Smirnov test.							

Evidence Table : Effectiveness/Safety
Question : What is the effectiveness of virtual reality Vision for treating amblyopia?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Kelly KR, et al. Binocular iPad Game vs Patching for Treatment of Amblyopia in Children: A Randomized Clinical Trial. JAMA Ophthalmol. 2016 Dec 1;134(12):1402-1408 **2017** **USA**	RCT with crossover single centre Objective: To assess the effectiveness of a binocular iPad adventure game as amblyopia treatment and compare with patching (standard of care) Method: The trial was carried out between Feb 20, 2015 to Jan 4, 2016 at a nonprofit eye research institute in Texas specialised in ophthalmology in children (Retina Foundation of the Southwest) Inclusion criteria: aged 4 -10 years old (diagnosed-amblyopia due to strabismus, anisometropia or both)	I	Total px:(N=28) 14 in binocular game and 14 patching 	Binocular iPad game	Patching	2-weeks - 4 weeks follow up	Primary outcome: change in amblyopic eye best-corrected visual acuity (BCVA) at the 2-week visit. Secondary outcomes: change in stereoacuity and suppression at the 2-week visit and change in BCVA at the 4-week visit. Results: Baseline characteristics (Supplement 1) 9 children (32%) had strabismic amblyopia, 14 (50%) had anisometropic amblyopia, and 5 (18%) had combined mechanism amblyopia. Mean (SD) age: 6.7 (1.4) years (age range, 4.6-9.5 years), and 7 (25%) were female Mean (SD) amblyopic eye BCVA at enrollment was 0.48 (0.14) logMAR (approximately 20/63; range, 0.3-0.8 logMAR [20/40 to 20/125]); Moderate amblyopia (range, 0.3-0.6 logMAR [20/40 to 20/80]) was present in 23 children (82%), and severe amblyopia (range, 0.7-0.8 logMAR [20/100 to 20/125]) was present in 5 (18%). 20 children (71%) had received prior amblyopia treatment. Adherence to protocol for iPad game play	small sample size

	The eligible children had amblyopic eye best-corrected visual acuity (BCVA) of 0.3 to 0.8 logMAR (20/40 to 20/125) and 0.1 logMAR (20/25) or better fellow eye BCVA (0.2 logMAR or better for 4-year olds), with an interocular difference of at least 0.3 logMAR (≥3 lines). Children with strabismus were initially diagnosed as having esotropia but were aligned with surgery or spectacle correction to within 4 prism diopters of orthotropia at distance and near vision. Exclusion criteria: None of the children were born at <32 weeks' post gestational age or had coexisting ocular or systemic disease, congenital infections or malformations, or developmental delay. English was the primary language for all children. Randomisation:						was similar to the using of iPad log and compliance for patching was tabulated using personalised calendar. For the first 2 weeks, children assigned to the binocular game completed a mean (SD) of 10.0 (2.3) hours (100% prescribed treatment time). Mean (SD) fellow eye contrast was 46% (15%) at the 2-week visit (iPad contrast logs were available for 11 to 14 children). Children assigned to patching completed a mean (SD) of 27.7 (3.0) hours (99% prescribed treatment time). For the second 2 weeks, all children were assigned to the binocular game, and they completed a mean (SD) of 8.2 (3.4) hours (82% prescribed treatment time). The mean (SD) fellow eye contrast at the 4-week visit was 71%.  BCVA at baseline, the 2-week visit and the 4-week visit  BCVA improvement from baseline at 4 weeks	

	Randomisation was performed by a statistician who provided individual sealed sequentially numbered envelopes. Two randomization schedules were created using a random number generator function, one for children with prior amblyopia treatment (patching or atropine) and another for children with no prior treatment. Randomization (1:1) was prepared in permuted blocks with block sizes of 4 or 6.						<u>Primary Outcome:</u> At 2-week primary outcome visit, a larger improvement in amblyopic eye BCVA was found with the binocular game compared with patching, with a mean (SD) improvement of 0.15 (0.08) logMAR (mean [SD], 1.5 [0.8] lines) vs 0.07 (0.08) logMAR (mean [SD], 0.7 [0.8] line improvement) (mean difference, 0.07 logMAR [0.7 line]; 95% CI, 0.01-0.14 logMAR [0.1-1.4 lines];t25 = 2.42, P = .02). For the binocular game, improvement ranged from 0.0 to 0.2 logMAR (0-2 lines): 11 children (85%; 95% CI, 58%-96%) improved by at least 0.1 logMAR (8 of whom improved by 0.2 logMAR [2 lines], and 3 of whom improved by 0.1 logMAR [1 line]), and 2 (15%; 95% CI, 3%-46%) did not improve. For patching, improvement ranged from 0.0 to 0.2 logMAR (0-2 lines): 7 children (50%; 95% CI, 27%-73%) improved by at least 0.1 logMAR (3 of whom improved by 0.2 logMAR [2 lines], and 4 of whom improved by 0.1 logMAR [1 line]), and 7 (50%; 95% CI, 27%-73%) did not improve. <u>Secondary Outcomes:</u> Amblyopic eye BCVA had improved at the 2-week visit with the binocular game (mean [SD] improvement, 1.5 [0.8] lines; t12 = 6.79, P < .001) and with patching (mean [SD] improvement, 0.7 [0.8] line; t13 = 3.24, P = .006). At the 4-week visit, amblyopic eye BCVA had improved for children who crossed	

							over to the binocular game, resulting in their catching up with children who started with the binocular game,with a mean (SD) improvement of 0.17 (0.10) logMAR (mean [SD], 1.7 [1.0] lines) for the binocular game vs a mean (SD) improvement of 0.16 (0.12) logMAR (mean [SD], 1.6 [1.2] lines) for patching crossover (mean difference, 0.01 logMAR; 95% CI, −0.07 to 0.01 logMAR;t26 = 0.35, P = .73 Overall, 23 children (82%) improved by at least 0.1 logMAR (1 line). At baseline, 1 child had normal stereoacuity, 10 children had reduced (subnormal but measurable) stereoacuity, and 17 children had nil stereoacuity (assigned a value of 4). No change in stereoacuity was seen at the 2-week visit with the binocular game (median [interquartile range], 4.00 [2.85-4.00] vs 4.00 [2.60-4.00] log arcsec; z = 0.71, P = .48) or with patching (median [interquartile range], 4.00 [2.60-4.00] vs 4.00 [2.60-4.00] log arcsec; z = 0.71, P = .48). Extent of suppression scotoma (Worth 4-dot test) had not changed from baseline at the 2-week visit with the binocular game (mean [SD], 7.16 [8.91] degrees vs 4.95 [7.07] degrees; t12 = 1.32, P = 0.21) or with patching (mean [SD], 3.27 [3.02] degrees vs 5.31 [8.89] degrees;t13 = 1.17, P = 0.26). However, depth of suppression measured by the contrast ratio showed improvement from baseline at the 2-week visit with the binocular game (mean [SD],	

							4.82 [2.82] vs 3.24 [2.87]; t12 = 2.46, P = .03) and with patching (mean [SD], 4.77 [3.10] vs 2.57 [1.67]; t13 = 3.41, P = 0.005) No differences between the binocular game vs patching treatments were found at the 2-week visit for change in stereoacuity, extent of suppression, and depth of suppression. Author's conclusion: The Binocular iPad game was a successful treatment for childhood amblyopia and was more effective than patching at the 2-week visit. Binocular games that rebalance contrast to overcome suppression are a promising additional option for treating amblyopia. Limitation: small sample size and treatment lasted only 2 to 4 weeks.	

Evidence Table : Effectiveness/Safety
Question : What is the effectiveness of virtual reality Vision for treating amblyopia?

Bibliographic citation	**Study Type / Methodology**	**LE**	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Martín S, et al. Evaluation of a Virtual Reality implementation of a binocular imbalance test. PLoS One. 2020 Aug 21;15(8):e0238047 **2020 USA/SPAIN**	**Observational study cross sectional** **Objective: 3-fold: 1) To implement a test for binocular imbalance in a Virtual Reality headset, 2) To assess the testability, reliability and outcomes of this test in a population of clinical patients and 3) To evaluate the relationship of interocular acuity difference, stereoacuity and binocular imbalance to amblyogenic risk factors (strabismus, anisometropia or their combination, referred to as 'mixed') in a large population of clinical patients.** **Method: All volunteers were recruited at the same Optometry Clinic.** **signing the Consent Agreement (minors signed the agreement together with their parents)** **protocol was approved by the Regional Ethics Committee of Clinic Research (Asturias, Spain) and follows the Helsinki**	**III**	Amblyopia was defined as 0.10 logMAR BCVA in the amblyopic eye & interocular difference of ≤0.2 logMAR. Anisometropia was defined as an amblyogenic factor due to a spherical equivalent interocular difference of ≤1.0 D. The spherical equivalent was calculated as the sum of sphere plus half the cylinder. Strabismus was defined as an amblyogenic risk factor based on the presence of heterotropia at near or far distance, measured with the Unilateral Cover Test	Multi-modality image-guidance systems: fluoroscopy			X-ray fluoroscopy was used to confirm the location of the microcoil to carry out the video assisted thoracoscopic surgery (VATS). The use of the guided therapeutics operating room allowed the ability to perform a series of surgical procedures without the need to transfer the patient to any other room, ultimately supporting improved workflow throughout the procedure.	

	Declaration. **enrolled 100 volunteers (ages 6 to 70 years old** **21 volunteers had no amblyogenic factor (control group).** **79 have amblyopia or a history of amblyopia (24 anisometropic, 25 strabismic and 30 mixed); all of them refractive correction; 59 occlusion; 35 perceptual learning using Gabor patches to improve contrast sensitivity; 24 perceptual learning using random dot stimuli to improve stereoacuity, & 6 subjects strabismus surgery.** **All 55 participants with strabismus had esotropia.** **Exotropia is less prevalent than esotropia and is much more likely to be intermittent exotropia.** **In intermittent exotropia, binocular inhibition is low, & the deviation angle at near is generally lower than at far distances** **As a result, stereoacuity is likely to be preserved, and amblyopia is uncommon** **Exclusion criteria: congenital malformation, ocular pathology, concurrent treatment with atropine penalization,**		(UCT), with full optical correction condition and an accommodative stimulus [42]. Mixed amblyogenic risk factor was defined as the presence of both strabismus and anisometropia					

	presence of diplopia in daily life conditions, prematurity ≥8 weeks, developmental delay, and coexisting ocular or systemic disease. Due to Virtual Reality headset limitations, volunteers with an interpupillary distance less than 55 mm and/or lower head circumference less than 500 mm were also excluded.							

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
4. Herbison N, et al. Randomised controlled trial of video clips and interactive games to improve vision in children with amblyopia using the I-BiT system. Br J Ophthalmol. 2016 Nov;100(11):1511-1516 2016	RCTs Single centre Aim/Obj: ensuring that the treatment (VR) was safe, acceptable and to get an improved indication of its efficacy Inclusion & Exclusion criteria: Children aged 4–8 years with strabismic, anisometropic or mixed amblyopia were recruited from two test sites (Queen's Medical Centre, Nottingham & Addenbrooke's Hospital, Cambridge) from January 2012 to November 2013. Stimulus deprivation amblyopia was excluded. Children who had prior treatment with either patching or atropine penalisation were eligible for recruitment providing they had a 0.20 logMAR intraocular acuity difference and no current improvement with	I		3 arms: • i-BiT game • Non-i-BiT game • i-BiT DVD I-BiT shutter glasses system -use under supervision and consists of a desktop PC with two monitors, one for the clinician and one for the patient. The clinician monitor is used to control the treatment the patient receives and the patient monitor displays the visual stimuli. The patient monitor is a flat-screen 22-inch 3D monitor with a refresh rate of 120 Hz and this allows separate images to be presented to each eye with the use of shutter glasses. The shutter glass				

	patching. Those whose suppression measured four or less on Sbisa bar were deemed at risk of double vision and were excluded. Randomisation The randomisation sequence was generated using the RALLOC function in Stata V.10 and used random permuted blocks of sizes 2, 4 and 6. It was stratified by centre and whether or not the patient had previous treatment for amblyopia. Masking The research orthoptist who delivered the treatment was aware of the patient allocation but not of visual acuity measurements which were performed by an independent orthoptist who was masked to the treatment allocation.			lenses lighten and darken in synchrony with the monitor but faster than the user can perceive and this allows a common background to be presented to both eyes and an 'enriched' image to be presented only to the amblyopic eye (dichoptic stimulation).				

e ISBN 978-967-2887-30-0