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INTEGRATED STUDY MASTER'S THESIS

New Modalities for the Treatment of Amblyopia

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Summary

Amblyopia is a neurodevelopmental disorder currently described as the leading contributor to decreased vision amidst children. This literature review investigates further into a modern approach to treat amblyopia. While classical treatments such as patching, atropine drops and optical correction exist, they are limited to a younger population, specifically under the age of 7 as the efficacy of treatment is higher and has prolonged effects. This is due to the sensitive period of development. Newer treatment methods, namely perceptual learning, dichoptic training, and liquid crystal glasses have opened new doors and have started to create an alternative route into treating not only younger children but also older children and even adults. As a result of this emerging treatment, this literature review investigates a small portion from the vast studies that have been published to find a conclusion whether new treatment modalities are more successful than the classical treatments. Particularly, perceptual learning and dichoptic training have had promising results and the success rates have been as favourable as patching.

Key words and abbreviations:

Amblyopia
Binocular treatment
Refractive error - Anisometropia
Strabismus
BCVA- Best corrected visual acuity (1)
VA – Visual acuity (2)
BSV – Binocular single vision
PEDIG: Paediatric Eye diseases investigator group
LogMAR: Logarithm of the Minimum Angle of Resolution

Introduction

Background

Amblyopia, or otherwise known as 'lazy eye' is a visual developmental disorder characterized more commonly as a "unilateral reduction of best-corrected visual acuity (BCVA)" (1,2). Although less common, the likelihood for bilateral amblyopia also exists (1,3–5). Recent findings have changed the definition and aetiology of the disease leading amblyopia to be regarded as a binocular disorder with developmental deficits in the cerebral cortex (6). This condition develops during the "sensitive period of visual development" typically between birth and 7 to 8 years of age (7,8). Immediate detection and treatment of Amblyopia is critical for the best prognosis (3). The prevalence of this disease is between 1-5% of the world's population (9) and it is the second most frequent cause of vision loss in infants and children (2). According to The National Academies of Science, Engineering and Medicine (NASEM), amblyopia is identified as one of the 'avoidable visual impairments' and many individuals in society are unaware of the presence of this disease (4,10). The NASEM places a high emphasis on the importance of screening methods (4,10). If children are left untreated, the amblyopic eye will always have a limited visual potential in comparison to the normal eye (11). Children who have amblyopia have a decreased quality of life compared to a normal child (8). It has also been proven that the academic performance of kids with amblyopia are substandard (8).

Aetiology/ Risk Factors:

Several different factors can lead to the development of amblyopia. These can be categorized as refractive, strabismus, mixed and stimulus deprivation. (7) External factors and less common features are also mentioned.

Classifications:

Refraction:

Refractive error is also amongst one of the primary causes of vision loss (12,13). Refractive error can be further classified as myopia (short-sightedness), hyperopia (far-sightedness) and astigmatism (non-spherical error). (14)

Isoametropic:

Isoametropic amblyopia is a type of refractive error where the visual acuity is attenuated bilaterally. It is the outcome of a substantially uncorrected refractive error but roughly equal changes in both eyes. (15)

Anisometropic:

Anisometropia is a condition where an individual is affected by a difference of refractive error ≥ 1.0 D between both eyes (16). The pair of eyes are unequally focused leading to a vision impairment in one eye.

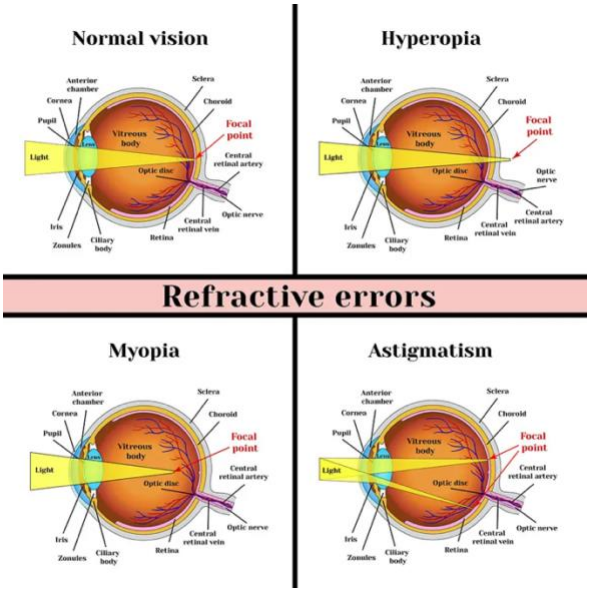

Image 1 (17)

Strabismus:

Strabismus in simple terms is the positional misalignment of the eyes (18). In other words, one eye has a normal output and the affected eye is aligned inwards, upwards or outwards, generally towards another direction when eyes are fixed straight ahead (18,19). Strabismus can lead to amblyopia as a result of deviation of the eye. Since visual output is diminished in the affected eye, the brain ignores signals and therefore focuses from the 'normal' or more dominant eye. Hence the classification, strabismic amblyopia. (1)

Stimulus Deprivation:

Stimulus deprivation amblyopia results as a secondary disease and it occurs due to the occlusion of the 'passage of light' (20). The blockage leads to the production of an indistinct visual image on the retina and result from diseases such as cataracts, ptosis, corneal opacity and or high uncorrected astigmatism (21,22).

Mixed:

Mixed is a type of amblyopia that has developed as a consequence of two amblyogenic factors (23). For instance, a common mixed amblyopic diagnosis would be when a patient has both anisometropic refractive error in combination with Strabismus and therefore leading to amblyopia (23).

Occlusion/ Reverse amblyopia

Occlusion amblyopia or reverse amblyopia is not particularly a common phenomenon and is seldom. Nevertheless, this type of amblyopia exists and primarily affects the healthy eye due to prolonged hindrance of the vision. It is most often when the ciliary muscle is paralysed due to pharmaceutical means or even patching of the eye. The VA returns to ordinary state when the treatment is concluded. (1,24)

Environmental risk factors from smoking:

A few articles have mentioned research in the effects of non-biological factors as a cause for amblyopia. Although limited in conclusive results and ergo subject to change in the future, these analyses concluded that maternal smoking is indeed a risk factor for amblyopia, in general, eye diseases. (12,25)

Epidemiology/ Prevalence:

Multiple studies have reported that approximately 1-5% of the world's population are affected by amblyopia (9). These results can vary depending on the continent and group of people studied (26). In terms of strabismic amblyopia, an article review published by the Cochrane Database of Systematic Reviews (19), state that if either one of a child's parent are diagnosed with strabismus, then this child has 4 times the risk of development of strabismus in comparison to parents with no strabismus. The authors continue on to quote that *"65% of affected children have a close relative with strabismus"* (19). Most of the cases of amblyopia go unnoticed until the admission into school and so, diagnosis can be made from birth till the ages of 7 or 8 (8). This visual impairment however can affect all age groups ranging from children, adolescents and the elderly especially if individuals were left untreated (8). If the children are smaller than normal during the gestational period, have a premature birth, delayed development, the risk for amblyopia is higher (24).

Pathophysiology

Primarily, amblyopia was thought to be a monocular disease and with several new theories to contradict this belief, it is now recognized as a binocular disorder (6,27,28). It is important to understand the meaning of binocular vision and to answer the question – 'what is it?' before delving into the pathology.

In 'Pickwell's Binocular Vision Anomalies" by Bruce J. W. Evans, the author describes binocular vision as the harmonization of an individual's visual percept from both eyes into one singular

binocular output. In order for a person to have normal binocular vision, it is important that the anatomical, motor and sensory systems of the optics are functioning correctly and without disturbances. (29)

In chapter 2 of the "Handbook of Clinical Neurology" written by Dennis M Levi (22), the author goes on to explain the several phenomenon of various scientists and researchers and what results they have surmised. A comprehensive understanding can be made that amblyopia is seldom to occur after the ages of 6-8. Thus, leading us to hypothetically conclude that amblyopia does in fact have a sensitive period for development. D.M. Levi further explains the "Detroit Model" introduced by himself and A. Carkeet, which explores the idea that the visual functions that developed the earliest are less prone to be affected by the abnormal visual input. Whereas visual functions that that developed the latest have the opposite effect, meaning that they have increased vulnerability to pattern deprivation. He briefly mentions the studies that the researchers conducted which prove the theory that the disease is a result of early deprivation. (22)

The crucial phase for the development of amblyopia as mentioned before is from birth to 7 or 8 years of age. In this period, most diseases that are diagnosed in children such as strabismus, refractive error, cataract and ptosis are considered eminently amblyogenic. Abnormal visual outputs can severely damage the cortical development till the age of 7 or 8 as cortical plasticity is the highest during this period. The plasticity after this age decreases and completely disappears around the age of 50. (7)

The reduction of best correct visual acuity (BCVA) due to amblyopia is not directly caused by a structural abnormality in the eye or brain (5). As mentioned before, abnormal visual stimulation during the early stages of life impairs the brain's ability to understand how to process visual information. In the *"Handbook of Paediatric Strabismus and Amblyopia"* by Kenneth W. Wright et al., the authors mention the pathophysiology of the disease (30). There are two specific types of abnormal visual stimulation, and these are pattern distortion and cortical suppression (30). Pattern distortion is when the output of the retinal image is blurred. In contrast, cortical suppression is the continuous restraint of one eye (30). Both abnormal visual stimulation types can arise alone or at the same time to develop amblyopia during the sensitive period. To explore the pathophysiology deeper, an experiment was undertaken on animals to see the underlying cause of the disease. Amblyopia was induced in animals with incomplete visual development by monocularly or binocularly obscuring the retinal image and or provoking strabismus. It was observed that pathological indifferences were found in the Lateral Geniculate Nucleus (LGN) and striate cortex in

monkeys with amblyopia triggered by visual suppression. Out of the 6 layers of the LGN, only 3 layers that respectively correlate to the eye with normal vision developed. Regarding the striate cortex, the ocular dominance columns were compromised due to the blurred vision on one of the eyes. The book includes images of the specimen samples of normal vision with dominate dark columns and the specimen of restricted vision with incomplete columns of the striate cortex. Consequently, it was summarised by K.W.Wright that abnormal vision resulted by amblyopia is a result of brain damage. (30)

History:

A thorough section from the book of "Strabismus", called "The history of the treatment of Amblyopia" written by S.E. Loudon and H.J. Simonz investigates the development of the disease and how it has come about. Dating back to the 480 BC time period, Hippocrates, the Greek physician and philosopher termed decreased visual acuity in humans as what we know today as – 'Amblyopia'. Amblyopia is a Greek term which translates verbatim to *"Dimness/dullness of vision"* of which '*Ambly-'* means dull and *'Ops'* means vision. At the time of 480 BC, amblyopia was not thought of as a disease but more so a consequence of another pathological problem of the body. Treatment of choice for Amblyopia were several different nutritional foods. Leading into the Byzantine empire, Thabit ibn Qurrah ibn Marwan al-Harrani, a scholar in mathematics, medicine, astronomy, and translation is responsible for the introduction to occlusion therapy. He wrote the book "Vision and perception" where he unfolds his new method of patching the normal eye in order to treat strabismus. Over hundreds of years, new invasive and non-invasive treatment methods were continuously pursued and experimented to treat the misalignment of eyes. Patching till to this day has been considered as one of the most effective and inexpensive treatment methods. (31)

Purpose

The purpose of this paper is to conduct a literature review using published articles to assess the success of new modalities of amblyopia treatment. Furthermore, producing a thorough, comparative analysis between previous, current, and new treatments.

Methods

This systematic literature review encompasses a range of articles taken from reliable scholar platforms such as PubMed, NCBI, Google Scholar, MDPI, American Academy of Ophthalmology (AAO), British Medical Journal (BMJ) and Science Direct to yield an extensive review on 'New modalities for the treatment of Amblyopia'. Literature research began in October 2024 and lasted

till April 2025. Specific inclusion and exclusion criteria have been applied to meet the eligibility standards.

Inclusion Criteria:

- Predominantly articles in English but any language is acceptable
- Articles relevant to the topic
- Studies and results on humans and animals
- Research articles with participants of all ages
- Free full texts accessed via the university data base

Exclusion Criteria:

- Studies published before 2014
- Paid articles
- Treatment of other eye diseases

This analysis is restricted to articles published within the last 10 years. Key terms such as "Amblyopia treatment", "Binocular vision therapy", "Refractive error treatment", "New amblyopia treatment" and "Strabismic amblyopia" were used to narrow and specify the research. The exact term "New amblyopia treatment", further filtered to the publication date as "2015 to present" and "Free full text", yielded 277 results on PubMed. There was a higher yield for amblyopic treatment of children in comparison to adults. However, patient age in terms of research were not restricted in this literature review. This review analyses articles under the sub section of "clinical trials/study" and "randomized clinical trials". After applying these filters, it reduced the article availability to 15. Only 11 articles out of the 15 were relevant to this topic as the other literature mostly covered updated research of classical treatments of amblyopia. Most of the literature covered the basis of therapy through video games and there were insufficient literature or lack thereof for other newer treatment modalities using these key terms. Furthermore, each new modality was searched separately using the variety of scholar engines and the best fitted articles from the search result were evaluated. Whereas, using different key terms such as "Binocular treatment amblyopia" yielded 35 studies, of which a few publications overlapped with the previous search. Some experimental studies were not shown in these filtered results and were also specifically sought out on the scholar platforms. Several published articles were study protocols for randomised control trials and results were yet to be published. Therefore, study protocols were disregarded unless a follow-up publication had been made with updated results or were relevant to other findings. Meta-analyses were later included as a comparative measure, particularly to assess similarities and correlations between this literature review and other studies. Not many meta-analyses could be included as they were irrelevant to this literature review and or access was restricted.

Screening

Amblyopia screening is widely implemented in schools, healthcare communities and communities as a preventative measure. In children, between the ages of 3 and 5, screening is highly encouraged as the benefit of an early diagnosis can lead to a better prognosis over time. A review by Birch et al. (2021) wrote an article on the advances of screening and treatment of amblyopia and its importance (28). It was mentioned that repeated early screening lowered the prevalence of amblyopia and enhanced the visual acuity (VA). The screening methods that are the most often used is VA testing with visual acuity charts such as the Snellen and logMAR chart. There are screening methods that are automated, and they are straight forward to use but often result in a false positive outcome. The article further explores newer methods of screening that are seen as more reliable. Reliable screening tests are a necessity as higher health care costs, increased anxiety in families and the population have resulted due to false positive results. Therefore, leading to decreased confidence in these screening methods. A few alternatives that have been developed are the "retinal birefringence screening, optokinetic nystagmus VA screening and AI (artificial intelligence)". (28)

Another article focusing on detection and treatment of amblyopia written by McConaghy et al. (2019) explains screening of amblyopia more thoroughly (32). As mentioned previously, the clinical recommendation for visions screening for amblyopia is between 3 and 5. The U.S. Preventive Services Task Force (USPSTF)(32) have found insufficient findings that screening children under 3 years of age is in fact beneficial. If they present with a VA of 20/40 or less and or 20/32 or less in children >5 years, further examination is required. Meanwhile, when conducting a physical examination, all possible ocular diseases and deformities should be assessed, and vision screening guidelines should be used. 'Photoscreening' is an alternative method which uses flash photography to assess the likelihood amblyopia in young children who have poor compliance to vision charts. Overall, screening plays an important role in preventing undiagnosed amblyopia and therefore provides a chance to commence treatment in the sensitive period of development. (32)

Treatment

The approach to treatment of amblyopia depends on the aetiology of the disease. Historically speaking, as mentioned before, patching has shown to be one of the most effective and oldest treatment methods for individuals with amblyopia (33). Other treatments that have been used for decades are optical correction and pharmacological treatments - specifically the use of topical atropine or oral levodopa-carbidopa (34). Patching, optical correction and pharmacological treatment would be grouped into the classical treatments of amblyopia or as the mainstay gold

standard techniques (34). Funded by the National Eye Institute (NEI), The PEDIG (Paediatric Eye Diseases Investigator Group) are responsible for the accumulation of clinical research towards strabismus, amblyopia, and other eye diseases that children are affected from (35). The PEDIG have proved the success rates of these classical treatments, have pursued further research in newer treatment options and advised against unsuccessful modalities (35). Binocular amblyopic treatment has increasingly shown to be a viable option for the future which will be mentioned later in this literature review. (36)

Classical Treatment:

In a general point of view, the classical treatments have shown to be endured well by patients (9). Not only are these treatments non-invasive, but they are also quite inexpensive (9). Optical correction, patching, and pharmacological treatment have shown positive changes in the BCVA (9). As a general introduction to each treatment method, the article *"Amblyopia Preferred Practice Pattern"* from the American Academy of Ophthalmology, written by Michael.X.Repka et al., has been mentioned throughout (24).

Optical correction

As mentioned by the PEDIG and a plethora of articles, optical correction, standalone is the first-line treatment for strabismic and anisometropic-refractive error amblyopia (7,24,34). Refractive error being the most prominent vision problem world-wide, optical correction alone would treat the core of the disease and ultimately improving the odds for amblyopia (24,37). Concurrently, children till the age of 17 with refractive error amblyopia are given refractive error treatment before any other options (7). So to say, if visual acuity shows immediate improvement with eye glasses, the underlying disease may not be considered as amblyopia but solely refractive error disease (24). However, a study shows that wearing eyeglasses for at least 18 weeks has the potential to improve the VA in children of ages 3-7 with untreated anisometropic amblyopia eye by 2 or more lines (24). A study done by the PEDIG, where participants with orthotropic anisometropic amblyopia were treated with optimal optical correction also concluded that vision was improved by 2 or more lines and even resolved in 27% of the participants (29).

Patching

In circumstances where glasses do not improve amblyopia, either in combination with optical correction or other treatments, patching is the second-line treatment (7,24). Depending on the age of the child and disease severity, the treatment is moderated. The American Academy of

Ophthalmology refer to a randomized clinical trial that concluded an approximate treatment regime (24). The research determined that patching at a 6-hour frequency per day for high-grade amblyopia and 2-hour frequencies for less serious cases for a few months to several years have shown to improve the BCVA (24). Severe amblyopia would be considered as 20/100 to 20/400 (0.70 to 1.30 logMAR) whereas moderate amblyopia would be 20/40 to 20/80 (0.30 to 0.60 logMAR) vision (24). Retrospectively, patching longer than necessary has shown to lead to weakness and develop new deficits of the normal eye (38).

Pharmacological treatment

Pharmacological treatment is introduced when both optical correction and patching do not effectively help the child (39). Variables such as low tolerance to both treatments can be the contributor (39). Pharmacological means that are designed to generate cycloplegia of the sound eye is generally acceptable for children who have not improved their VA with other lines of treatment (24). An effective method that has been widely used is the Atropine 1% solution – the solution is given to children with mild to moderate amblyopia who are between the ages of 3 and 15 and it is administered in the non-amblyopic eye (24). The AAO further elaborate that atropine solution is the most effective if the sound eye is hyperopic and the purpose of the solution is to paralyze the ciliary muscle causing the vision to lose focus (24).

A randomized clinical trial was conducted by the PEDIG to compare atropine solution as a first line treatment versus patching (40). The experiment included 419 participants under the age of 7 with moderate amblyopia either receiving patching or atropine solution as the primary treatment (40). The discovered findings were that a drop of 1% atropine solution had the same effect as those who had 6 or more hours of patching daily for 6 months (40). In essence, the PEDIG concluded that both atropine solution and patching have similar outcomes (40). Even though patching may have proven to show faster results overall, atropine solution was considered as cost effective, socially compliable and it is easier to apply (41).

Atropine solution has been positively commended by some articles. On the contrary, some research claim that this method of pharmacological treatment combined with optical deprivation has led to treatment induced amblyopia in the normal eye (24,41). Temporary decline of the VA from the atropine solution is seen in the sound eye and documented more often than patching (24). The pharmacological treatment is also reported to have induced photosensitivity and conjunctival irritation in children (24). Adverse symptoms were also mentioned such as xerostomia, xeroderma, fever, delirium, tachycardia and possible toxic side effects to children under 3 years of age as a result of insufficient research (24).

Bangerter Filters:

The Bangerter filter is a translucent filter, and it is a type of treatment that is considered as a partial occlusion technique similar to patching. The main purpose of these filters are to simply adhere to spectacles on the lens of the normal eye. (24)

A research article written by Chen et al. (2015) assessed whether partial occlusion using Bangerter filters can reduce suppression of the amblyopic eye as well as if it could lead to improved binocular summation. They reviewed another randomised trial where partial occlusion using filters were compared to full occlusion using the patching technique. The result concluded that partial occlusion had a worsened effect than expected and did not lead to better results. In their own research, 2 experiments took place. The purpose of the first experiment was to evaluate the outcome of Bangerter filters on interocular suppression of patients with amblyopia vs normal individuals as a control subject. Ultimately, it led to the conclusion that the filters have a chance of improving binocular vision as it helped decrease the suppression of the amblyopic eye. Taking experiment 1 into consideration, experiment 2's aim was to try to assess the likelihood of binocular contrast summation in observers with amblyopia in specific monocular and binocular visual settings. The research article concluded with their hypothesis being successful – amblyopic observers have the ability to have binocular vision, but it was limited to the specific environment and not in normal conditions. A difference was noted between the participants with amblyopia and the control subjects. The control subjects showed limited binocular summation in comparison to the experiment subjects. On the contrary to their hypothesis being supported, the authors explained that the bangerter filters impair Randot's stereopsis and that this form of treatment is better for short-term treatment than long-term. (36)

Ineffective/ Less common treatment methods:

Use of Levodopa-Carbidopa:

Similar to atropine solution, levodopa-carbidopa is a pharmacological based treatment for amblyopia. The mainstay of this treatment was to use it as adjuvant therapy to patching (39). The route of administration is oral. Levodopa increases the levels of dopamine in the body and likewise it was believed to be able to improve the VA (33). The use of levodopa-carbidopa as a treatment method has uncertain conclusions (30). A randomised placebo controlled clinical study carried out by Sofi et al., assessed the efficacy of levodopa-carbidopa as management for the treatment of amblyopia (42). Participants were split into two groups and were either prescribed with levodopa-carbidopa or null with full time occlusion of the normal eye for 3 months (42). The study finalized

that both the control and experimental group had remarkable improvement (42). However, the group treated with additional levodopa-carbidopa showed to have even more substantial results in comparison (42). Conversely, after numerous other research lasting several years, particularly by the PEDIG, many articles have attested that the use of levodopa has shown no benefit towards the improvement of VA (7,33,43).

Surgical Treatment:

Surgical treatment is not a primary treatment choice for amblyopia as its normally indicated for deprivation amblyopia, a secondary cause of the disease. Moreover, surgical techniques are still in development; most clinical trials have not yet published results or few surgical methods are considered controversial (3,7,24,44). Deprivation amblyopia include ptosis, cataract, severe strabismus, corneal opacities and or vitreous haemorrhage (24). In these cases, treating the underlying cause will slowly improve the susceptibility of amblyopia. Another often talked about surgical methods is refractive surgery to treat anisometropic amblyopia (3,24). An article published by the Indian Journal of Ophthalmology written by S. Gopal et al briefly mention the success rates of refractive surgery (7). The article notes that refractive surgery has shown to have benefits in the children population who have had poor adherence to classical treatments or prescriptive glasses (7). Surgical methods such as Clear Lens Extraction (CLE), Photorefractive keratectomy (PRK) and phakic Intraocular Lens (pIOL) were discussed (7). However, at the same time, there is not enough results to prove the theory that these surgical techniques are effective (7).

Literature Review and Data analysis

This literature review entirely focuses on the new treatment modalities of amblyopia. The efficacy of the new treatment modalities will be analysed in comparison to the old treatment methods.

New Mechanisms

Binocular Treatment:

Classical treatment methods have shown visual improvement in amblyopic patients, however many individuals do not attain a normal VA or some patients tend to enter the reverse effect where the vision worsens (28). The aetiology of the amblyopia has since then evolved and researchers have a newer outlook that amblyopia should be sought out as a binocular disease rather than a monocular disorder (6,27,28). Due to this updated standpoint, the treatment methods have likewise developed. Some of the binocular treatment methods that will be mentioned in this literature review are Liquid

Crystal Glasses (LCG), Perceptual Learning (PL), video games or virtual-based tasks and dichoptic treatment. These treatment modalities can also be termed as behavioural training as they refer to vision-based exercises (45). Methods mentioned out of the binocular range are Transcranial Magnetic Stimulation (TMS) and acupuncture. All research articles were approved by their respective ethics committee in order to conduct their experiments. FDA approved treatments mentioned in this literature review include Luminopia (Dichoptic training) and RevitalVision (Perceptual learning) (46,47). CureSight which is also a dichoptic training method is FDA-cleared (46).

1. *Liquid Crystal Glasses:*

Liquid crystal glasses (LCG) are a newer alternative to patching (28). The mechanism behind the LCG are that the lens of the non-amblyopic eye have a crystal opacity filter that is regulated and controlled by an electronic on and off transmission (28,48). The frequency of the flickering between the clear and opaque lens is modified according to the grade of amblyopia whilst considering the age of the individual and length of treatment required (48). LCG's in general are approved by the FDA (49).

A randomized pilot study carried out by Yuan et al., published in 2021 used Alternative Flicker Glass (AFG), a type of LCG to investigate the efficacy of an alternative occlusion method in Shanghai, China (50). 40 children with anisometropic amblyopia, aged 7 to 13, who met the eligibility criteria participated in this study, and the treatment was measured against traditional patching. By using AFG, a treatment method designed to target binocular exchange in vision, it was assumed that it would minimize the suppression of the weaker eye. The AFG consists of an electronic LCD display where images are presented to both the normal and amblyopic eye in a programmed setting. The AFG has the ability to display the images in an alternating manner between both eyes. The BCVA, contrast sensitivity function (CSF) and stereoacuity were evaluated prior to and post treatment. AFG participants were prescribed to wear the frames for one hour per day, 7 days a week and children with patches had to wear it two hours per day, 7 days a week. Progress checks were made at 3 weeks and 12 weeks post-treatment. The baseline for the BCVA measured through logMAR in the AFG group was 0.45 ± 0.20 and 0.53 ± 0.20 in the patching group. The results in the visual acuity at 12 weeks were 0.28 ± 0.19 in the AFG group and 0.35 ± 0.18 for children treated with patches, all results were with 95% confidence interval (CI). Thus, representing remarkable improvement in the BCVA for both groups. Regardless of the significant improvement, the authors concluded that there were no considerable differences between the AFG and patching in terms of the BCVA. The CSF was measured at 3, 6, 12 and 18 cycles per degree of spatial

frequencies at the preliminary point and re-evaluation days. There was quite a significant difference between the new treatment vs the classical treatment. At the 3-week mark, all cycles excluding 18 cycles per degree spatial frequency already presented with enhanced results for the AFG group. 18 cycles per degree spatial frequency only showed substantial improvement at the 12-week mark. As opposed to the patching group, a notable difference was found merely with the 3 cycles per degree spatial frequency both at 3 and 12 weeks of the follow up visits. Hence, the spatial frequency of 6, 12 and 18 cycles per degree was evidently noted in the AFG participants in comparison to the patching. Stereoacuity attained similar results concluding that the AFG individuals had substantial results whereas the patchers only had slight improvements. The authors stated that this study had a handful of limitations, especially with most of the participants still having visual deficits during the final evaluation check. In addition, there are still some uncertainties of whether there might be a relapse in the VA after treatment cessation. It should also be taken into consideration that this was a pilot study with a small number of participants and not all forms of amblyopia were tested. The article highlighted that more research is required but these results have produced a promising future in the use of AFG. (50)

2. *Perceptual Learning:*

Perceptual learning has proven that visual performance has increased by provoking visual plasticity when treated with patient-specific, repetitive computerized tasks (48). In PL treatment, the individual completes tasks on a screen with the best corrected visual acuity (BCVA) while the normal eye is occluded (51). To state otherwise, patients practice recognizing patterns of repeated visual stimuli (2). Research regarding perceptual learning as a treatment has overwhelmingly exceeded since the 1960's, especially with the contribution from Eleanor Gibson (2,38). The types of perceptual learning techniques that have been used are Vernier acuity, Gabor detection, letter identification in noise, positional discrimination with or without noise and contrast detection (2,38). The purpose of this treatment method is the idea that practicing these tasks regularly produces drastic and prolonged improvement in the VA and neural processing (38,52). Furthermore, most of the classical treatment has little to no impact on older children and adults whereas a considerable amount of research has proved that perceptual learning is in fact beneficial in these age groups (7,38,39,51). Particularly, differences have been seen in the VA, contrast sensitivity and improvement in the letter recognition tasks (2). Countless articles were mentioned in a mini review by D.M. Levi and R.W. Li (38). The basis of this review finalized the following – the findings from different researchers were that even after approximately 3 – 18 months of regular VA testing, the improvements in the acuity have reported to be long lasting (38). Before the introduction of these

current PL treatments, the Cambridge Stimulator (CAM) has been acknowledged as one of the first breakthroughs for perceptual learning mechanisms (2,51). The CAM mechanism encompasses high contrast slow moving rotating stripes of which the patient views passively (51). Nonetheless, this form of treatment is controversial as some studies have presented with differing results and it is not so commonly used nowadays (51,53). Although the introduction to perceptual learning (PL) dates back to the 20th century, interactive software tools have significantly improved and has shown to increase treatment compliance in patients (48). Therefore, PL has risen as a new and updated treatment method for amblyopia.

The Indian Journal of ophthalmology published a prospective cohort study by Shah et al. (2022) on the basis of perceptual learning as a treatment procedure for amblyopia (54). 47 participants who were of a mixed age population (mean: 14.11 $\pm$ 7.13 years) with 23 females and 24 males were a part of this cohort study. The mixed age group holds significance as it would allow for a correlation to be made of whether this treatment would still be beneficial in older children who are physiologically past the critical period of visual development. The main objective of this cohort was to evaluate how PL improves vision of amblyopes, of which, hand-eye coordination was measured alongside. All types of amblyopia were included in the study and no restrictions were placed here. The visual aspects that were examined were distance, stereopsis, contrast sensitivity and handwriting. Each child underwent 20 sessions lasting 30 minutes per session and had a follow up after one month. Before the commencing of the study, 28 children had normal alignment of the eyes (orthophoria) and after the treatment, 30 children attained orthophoria. Strabismic and refractive error amblyopia were the most prominent types that the individuals had. Between these two groups, the visual outcome had shown no notable changes. On the contrary, other aspects such as the VA, stereopsis and contrast sensitivity had shown remarkable differences between the groups before and after the therapy. The varying demographic did not pose any considerable variations either. The authors summarized that this learning method has potential, but their study had a relatively small sample size and follow-up time to assess the aftereffects of this treatment were not long enough. Their suggestion was to continue this cohort study but in combination of other classical treatments of amblyopia. The silver lining of this study however was that it solidified the fact that treatment should not be limited to younger children. It opens opportunities for patients who have been diagnosed with amblyopia later than the sensitive period of visual development, they still have a chance to undergo treatment and expect potential changes. (54)

2.1 RevitalVision

A research article has been published in the Journal of The College of Optometrists in Vision Development, Volume 8, Issue 4 – *"Vision Development and Rehabilitation"*, written by Magdalene et al. (2022) on the principle of neural vision PL as a treatment for unilateral and bilateral amblyopia (55). The objective of the prospective observational study was to investigate the performance and success of RevitalVision which is an individualized, non-invasive PL software programme that is designed to improve the BCVA of adult amblyopes who are resistant to occlusion therapy. Hence, participants who were eligible for this study previously should have had a minimum of 6 months of unsuccessful part-time or alternate occlusion methods to treat their amblyopia but resulted with no visual improvement. The research was conducted in India and 45 individuals were evaluated with an age range of 8-48 years of age. The primary outcome that was analysed was the BCVA. Subjects with refractive, deprivation, combined and strabismic amblyopia took part in this research. A baseline examination was performed which included subjective and objective values of refractions, cycloplegic refractions and the distance BCVA. The software of RevitalVision analyses each user's weakness depending on how they answer to the training sessions and the algorithm modifies itself to become patient specific. The programme consists of repetitive interactive visual performance tasks (VPT) which have shown to trigger an increase in neural responses leading to a greater activation in the visual cortex and therefore improving the visual function. During the therapy, individuals wore Gabor patches for lateral masking and had headphones to listen to the responses of the programme as well as to decrease surrounding noises. The patients were required to finish 40 training tasks over a 3-month period. Due to the varied age range, the subjects were separated into specific age groups such as children (8-12), teens (13-18), young adults (19-29) and older adults (30-60). The mean VA before the training was 0.55 ± 0.24 logMAR. After the training, the results were statistically significant and had improved to which led to a mean difference of 0.20 ± 0.17 logMAR. Individuals with unilateral amblyopia, on average showed one line improvement and 5 individuals did not respond to the treatment. With the bilateral amblyopes, there were 4 subjects who showed one to two lines of improvement and one did not show any. The best improvement was seen in refractive and or combined mechanism amblyopia. No line improvement was seen in deprivation amblyopia. The average visual acuity change was 2.2 lines among all participants. As BCVA had shown significant changes, the use of RevitalVision has resulted in positive remarks and therefore deemed as a potentially beneficial treatment method, especially for individuals that react poorly to occlusion methods. Some of the limitations to keep in mind are the imbalanced number of participants between unilateral and bilateral amblyopes. Not only, the examiner was unmasked and therefore it could have led to biased results. (55)

3. Dichoptic Treatment/ Binocular digital therapy:

In dichoptic training, each eye receives a separate stimulus whilst the dominant eye is presented with a lower contrast stimulus to the balance out the suppression (48). When creating this varied contrast and stimulus in vision, it allows the amblyopic eye to train without being overpowered by the sound eye (48). If the individuals show improvement in vision, then the severity of the contrast is progressively increased until both eyes are equal (48). Synonymously, the main method of dichoptic treatment uses digital therapy settings such as movies, video games and digital tasks. Video games have spiked as an interactive, binocular treatment where it has proven to enhance visual functions of adult and child amblyopes (45,48,51). It has been suggested that playing video games have the potential to augment different visual processes such as light or contrast sensitivity, visual crowding and visual attention (48). Each visual process is targeted using a different manner of therapy (48). Due to the synchronization of video game play, digital mode therapy and dichoptic treatment, all of the studies in correlation will be mentioned in this section.

3.1 Luminopia One

A phase 3 randomized control trial written by Xiao et al. researched the use of digital therapeutics in the form of dichoptic training to treat several conditions (2022) (56). This article was solely focused on treating amblyopia through the dichoptic therapy called Luminopia One. The study took place between 2019 and 2020 and 105 children, aged 4 to 7, took part in this experiment in the United States. The randomization of the participants was 1:1 where 51 children were in the treatment group and 54 were a part of the control. Types of amblyopia taken for this study were treated or untreated mild strabismus, anisometropic or mixed amblyopia. Participants were required to have refractive error correction and should be wearing the corrective glasses during the experiment. Specific dioptres, VA of 20/40 to 20/200 (0.30 to 1.0 logMAR) of the amblyopic eye and at least a difference of 3 or more lines between both eyes were a part of the eligibility criteria. Children in the experimental group were advised therapy for 12 weeks where they were treated for 1 hour daily, 6 days per week whilst having refractive correction 24/7. The participants had access to a cloud-library where they were permitted to select between 546 hours of television shows and movies. A software was implemented where the video content is manipulated and streamed in a dichoptic manner using a head-mounted display which produced a therapeutic visual input. The ‘therapeutic visual stimuli comprised of 2 specific factors; the normal eye had a reduced total contrast of 15% in comparison to the amblyopic eye and secondly, additional dichoptic visual elements or namely ‘dichoptic masks’ were layered over the video images to encourage the eyes to function binocularly. The control group were required continued full-time refractive error

correction for 12 weeks. They were not allowed to undergo other amblyopia treatment options and in case the children were having treatment, they would have to stop at the time of admission. After 12 weeks of assessment, the final results were that the VA of the treatment group had significantly shown a positive change by 1.8 lines whereas the control group was only by 0.8 lines. the overall improvement was positive, and no adverse effects were noted. The authors however mentioned that they did not observe improved stereoacuity and extended research would be required to understand it. Although limitations did exist in this RCT, as the dichoptic training method was not compared to classical treatments such as patching or pharmacological treatment. Thus, conclusion of whether the newer treatment is better than the classical treatment can be debatable due to lack of information in this specific article. However, the authors have acknowledged that it was one of the first RCTs for dichoptic treatment of amblyopia which was successful. (56)

3.2 Video Games

Similarly, another RCT on contrast-rebalanced binocular treatment was performed in the United States and this article was published by Jost et al. (2020) (57) . This prospective study includes 63 children between the ages of 4 and 10 with either strabismic, anisometropic or mixed amblyopia. The participants were temporarily given android tablets with a pre-set action based dichoptic video game called 'Dig Rush' and "Monster burner" that had a contrast-rebalancing technique. The principle of suppressing the sound eye in order to relieve suppression of the amblyopic eye was applied through this contrast mechanism. Anaglyphic glasses were used by the children while playing games to allow both eyes to view what the other eye sees. The amblyopic eye would be able to see the low contrast images perceived by the normal eye and likewise the normal eye could see the high-contrast images seen by the amblyopic eye. The advised treatment duration was 1 hour per day, 5 days a week for 8 weeks, totalling to 40 hours of game play. The contrast for the amblyopic eye was always set to 100% while the normal eye was initially set to 20% contrast for all groups. 4 different protocols were assessed for this study – 0%, 5% or 10 % daily increments over an 8-week period. Only one of the protocol groups has a reset to the initial contrast at the 4-week mark and again increased by 10% daily for the remaining 4 weeks. The vision assessments were made at day point, 2, 4, 6 and 8 weeks and tested the monocular BCVA, stereoacuity; degree of size, severity and depth of suppression using the dichoptic eye chart. A majority of the children, approximately 85% of the first and fourth group with 10% contrast increments reached full 100% contrast in the non-amblyopic by 4 weeks. By comparison, only 30% of the groups with 5% and 0% contrast protocols reached 100%. Overall, the VA of the amblyopic eye of all groups had similar results. Baseline BCVA was 0.47 ± 0.14 logMAR and resulted in an average improvement of 0.14 ± 0.08 logMAR at 8 weeks. The BCVA had remarkably improved in all 4 groups after 8 weeks. Only 5

children reacted poorly to the dichoptic therapy, one of the children got worse by 1 line and four children did not show any improvement. On average, the changes in VA whether an improvement or regression, the logMAR ranged between -0.1 to 0.3 or respectively -1 to 3 lines. Another observation that was noticed is younger children seemed to have responded better to the treatment and had a greater VA difference than older children. In addition, 6 children who were nil to prior amblyopic treatment had significantly progressed further than the other children, respectively with a difference of 0.8 lines. Likewise, the other factors such as random dot stereoacuity, extent and depth of suppression had also improved. Jost et al. quoted that the significant difference they saw in younger children proved the fact further that binocular treatment is more efficient for younger children than the older. This research had 2 limitations. One being that this study lacked a follow-up evaluation on the long-term basis. They had stated that the results did produce a positive outcome of 92% improving their VA at 8 weeks, however 60% of the participants were still amblyopic and had restarted patching for their treatment. The second limitation in this study was failing to keep anonymity of each protocol group which could have caused biased results. To conclude the study, the treatment method was effective and profitable. Not only was there a mean of 1.4-line difference in visual acuity, 40% of the participants achieved at least a minimum of 20/32 (Snellen chart) (0.20 logMAR) at the 8-week mark. (57)

Instead of exclusively researching videogame based binocular treatment with younger children, a double-blind placebo controlled RCT by Guo et al., (2016) was conducted with older children and adult amblyopes (58). This study was titled “Binocular treatment of amblyopia using video games (BRAVO)…”. 108 participants aged 7 years or older, with unilateral anisometropic, strabismic or mixed amblyopia from 5 research sites over New Zealand, Canada, Hong Kong and Australia were involved. Participants should have met the PEDIG criteria using the cycloplegic refraction method for assessing optical correction within the first 6 months of the study entry. The children and adults were required to have worn their optical correction prior to commencing of the study for at least 16 weeks or more. The study is exclusive to those with a BCVA of 0.30 – 1.00 logMAR in the amblyopic aye and $\leq$ 0.10 logMAR in the sound eye. The Early Treatment for Diabetic Retinopathy Study (E-ETDRS) was used as the measuring tool for the VA. Any other ocular diseases or pathology were excluded. During the treatment study, participants were required to continue wearing their optical correction continuously until the last follow-up visit. This was to eliminate the possibility of optical correction as the influencing factor. The individuals were split into 3 different age groups, pre-teens, 13-17 and 18 years and above and randomly allocated on a 1:1 basis to the treatment (active) or placebo group. The treatment period lasted 6 weeks and each person was assigned to play an interactive falling-block game using an iPod touch for 1-2 hours

every day with a maximum of 3 spaced out session per day while wearing red-green anaglyphic glasses for 6 weeks. The active treatment group involved a particular number of high contrast blocks presented to the weaker eye and the remaining blocks to be a lower contrast for the normal eye. Each difference in contrast was adapted to the individual's needs. The anaglyphic glasses help separate the images viewed by each eye. Furthermore, if the participants have effectively played the game, the contrast of the normal eye will be increased accordingly. Not only, the game had several technical aspects that modified the game settings depending on the success of gameplay. Factors such as length of one game session, quality of play and scoring were monitored and thus influenced decreasing or increasing the contrast of the normal eye. Control group have the same treatment protocol with the use of anaglyphic glasses and optical correction, except both eyes see the exact images with no contrast difference involved. Follow-ups were measured at 3, 6, 12 and 24 weeks after randomisation. The main assessment factor was the distance BCVA of the amblyopic eye, this and other factors such as stereopsis, angle of strabismus and interocular suppression were measured throughout the 24 weeks. During 2016, the results were still in progress. (58)

In 2018, the results of the BRAVO study were published by Gao et al. in a new publication (59). The sample size had decreased and increased, and the final size was 115 with predominantly male participants. The initial hypothesis of the researchers was that the active treatment group would perform better in terms of the VA of the amblyopic eye. The mean improvement of the amblyopic eye distance VA from the primary visit was 0.06 (SD: 0.12) logMAR and 0.07 (SD: 0.10) logMAR of the placebo group at the 6 weeks mark. The statistical difference is therefore clinically insignificant between the placebo and treatment group and has therefore failed to prove hypothesis. The measurements between the age groups, amblyopia type or stereopsis also presented with no mentionable differences. The stereoacuity, interocular suppression, angle of strabismus and other factors, which were termed as the secondary outcomes additionally presented with no considerable changes. These results contradict the other studies who have conducted dichoptic based amblyopia treatment as they have proven successful. Limitations that existed in this publication were regarding the monitoring of participants' attention during video game play. They believe that it may have decreased or affected the results in the active treatment group. (59)

A randomized, two-parallel control trial by Razavi et al. (2021) (60), analogous to previous research articles, published a study protocol comparing a binocular game to patching in the treatment of mild to moderate amblyopia. 44 patients of ages 4 to 12 with untreated anisometropic amblyopia (inclusion criteria: BCVA $\geq$ 0.2; spherical equivalence difference $\geq$ 0.50 dioptre between 2 eyes; difference in astigmatism $\geq$ 1.50 dioptre; interocular difference of minimum 2

lines) took part in Iran. The main purpose of this trial was to investigate the success of the binocular game in comparison to patching when advised for 3 months of play. A specific app was designed for the purpose of this study called Pivot which consisted of 30 core levels and 200 levels overall. Each level is only locked after successful play starting from the first level. The game can be moderated to every individual's needs such as speed, focus, duration of play and participation in the gaming community. Similar to previous studies using video games as a treatment method, the experimental group received red-green anaglyphic glasses. Game play was advised 30 minutes per session, twice a day, 5 days per week for 4 weeks. After the first month, game play is reduced to 2 days a week for 8 weeks. As the children progress in levels, an automatic increase in speed is applied to progressively trigger the amblyopic eye. The application had an automatic statistical analysis which the researchers had access to and provided the necessary data of the player's activity. The control group were required to patch the normal eye for approximately 2 to 4 hours per day for 3 months. The outcomes were measured at 2 weeks, 1, 2 and 3 months after initial randomization. The main result that was tested for was the VA at the starting point and then at the 3 months mark. The secondary result was the VA measured at each check point mentioned before. The authors are yet to post the results of the study; however, they have confirmed success in the pilot study and from the approval committee that this game has a huge potential to benefit kids with anisometropic amblyopia. Researchers are constantly trying to improve amblyopic treatment, especially with the use of video games to destigmatize amblyopic therapy. The main goal is to offer an alternative to patching as it may come with psychological or social stress. (60)

3.3 CureSight

Wygnanski-Jaffe et al. (2022), have published a multicentre RCT on an "eye-tracking-based dichoptic treatment" (CureSight), that is completed at home (61). 103 participants, aged 4 to 9, with anisometropic, small-angle strabismic or mixed amblyopia were randomized into the CureSight treatment group or into the control – the patching group. CureSight is specifically developed to treat amblyopia using dichoptic means. While the eye movements are tracked, the visual stimuli are separated into two different monitors which involve tracking and separating the data of each eye. CureSight involves the passive watching of video content tailored to each individual's preference (with parents' approval). The programme's software displayed to the normal eye blurs the central vision of the presented visual stimuli to enhance the use of the amblyopic eye. The higher the degree of VA difference between the eyes, the stronger the scale of blurring. The researchers' main hypothesis was to prove that binocular amblyopic treatment is not worse than patching in terms of visual acuity improvement. To prove this theory, patients were allocated with 90 minutes of

viewing per day, 5 days a week for approximately 4 months (total – 120 hours). All participants of the treatment group used anaglyphic glasses to separate the viewing channels between the sound and weak eye. The patching group were prescribed to occlude the normal eye for 2 hours per day, 7 days a week for 4 months. Inclusion and exclusion criteria for eligible participants are vast and can be found in the study itself. A few of the criteria mentioned are that the children must have had no prior amblyopia treatment, or discontinued treatment for a minimum of 8 weeks prior to screening. The VA must be 20/40 (0.30 logMAR) or better for 4-year-old children. The VA must be 20/32 (0.20 logMAR) or better for children 5 years or older. Specific measurements for astigmatism, myopia, anisometropia, hypermetropia etc. were mentioned. Follow-up evaluations were made around every 4 weeks. The primary outcome was the measurement of the VA from the baseline versus the end point result in both groups. On the primary visit, the mean VA for the CureSight group was 0.37 ± 0.15 and 0.37 ± 0.14 logMAR in the patching group. The mean SD improvement at the 16-weeks mark was 0.28 ± 0.13 and 0.23 ± 0.14 logMAR respectively. LogMAR results translate to a progress of 2.8 lines in the VA of the amblyopic eye over 16 weeks. 79% of the patients in the binocular treatment group had shown 2-lines or more improvement whereas patching resulted 61% improvement. The authors mentioned that within the varied age group of children, they were further sub-grouped into younger children from 4 to 7 and older children from 7 to 9. The results proved that even with a differing age group, no prominent changes due to age difference affected the VA improvement. It was further explained that patching and CureSight had similar results till the 12-week mark, after that, the patching group had plateaued and CureSight continued to improve even after 16-weeks. In summary, this novel treatment approach had proven to be as beneficial as patching. The advantageous point of CureSight in comparison to other videogame based dichoptic therapy is that the participants do not require video game skills and could simply watch the preferred video content. (61)

Wygnanski et al. released an updated version of the study which reported the long-term results of the RCT using the CureSight programme (2024) (62). In this follow-up study, 43 out of the 103 patients from the initial study, who had successfully completed the 16 weeks treatment were planned to be evaluated. 38 patients had a follow-up at 12 weeks post treatment and of these, 27 were evaluated 1 year (52 weeks) after the treatment and were eligible for this update study. 5 patients out of the planned follow-up group had to be excluded due to various reasons. Of which, 11 more patients were excluded after the 12-week post-treatment follow up either due to unattendance or having had additional amblyopic treatment. The mean difference of the evaluated sub-group after 16 weeks of treatment resulted with the amblyopic VA improvement by 0.3 ± 0.12; stereoacuity mean improvement of 0.52 log arcseconds and the binocular visual acuity also had a positive result

of 0.13±0.11 logMAR. No significant differences were found in the mean VA of the amblyopic eye 12 weeks post treatment, results were stable. At the 52-weeks mark after treatment, there was a slight regression in the amblyopic eye VA, the logMAR worsened by 0.06±0.11. Even though, the logMar showed a partial decline, the overall residual gain (0.2±0.14 logMAR) compared to the baseline still maintained substantial. Stereoacuity remained the same at both 12 weeks and 52 weeks post-treatment. Likewise, binocular VA resulted in no notable changes at the 12-week mark. However, after a year, the mean binocular VA declined by approximately 2 chart letters 0.038±0.02 logMAR. Similar to the amblyopic VA, residual gain (0.09±0.09 logMAR) was nevertheless prominent in comparison to the baseline. Amblyopia relapse occurred in 2 individuals at 12-weeks post treatment. No other recurrences were reported by the study. CureSight can therefore be concluded as a very successful treatment option for amblyopic children. The main benefit of this programme is the short treatment time resulting in prolonged benefits, at least for a minimum of one year post-treatment. (62)

3.4 BALANCE

Dahlmann-Noor et al. (2024) have written an article on a phase 2a RCT on balanced binocular viewing as a treatment method for unilateral amblyopia in children (63). This treatment method was called BALANCE and their purpose was to evaluate the effects of dichoptic balanced binocular viewing (BBV), specifically its safety. 32 children between the ages of 3 to 8 in the United Kingdom took part in the study for 16 weeks of treatment. 20 children attended the 16 weeks post-treatment follow-up. The VacMan suppression test was used to accurately measure changes in the amblyopic eye, and it asks the subjects to detect the elements which vary in contrast (which are presented differently to the amblyopic and normal eye). Corrective glasses were worn throughout the study if required. To briefly explain the procedure, several interviews were conducted with the family to create an appropriate treatment plan for their children. The BBV therapy was given through a gaming console called the Nintendo 3DS which had the ability to display varied movie images to each eye without the need for specific glasses (a parallax barrier was used). Age-appropriate movies were given to the children to watch. The finalized plan was 2x30min sessions with a follow up at every 8 weeks. Based on the difference in interocular VA, the movies would be shown at a high medium or low contrast level (blur) to the amblyopic eye. The randomization was 1:1 and those not in the treatment group were assigned to 2 or 6 hours of occlusion (depending on severity) or one drop of 1% atropine twice a week as a means of a control group. The primary outcome measured in this study are the changes in the suppression or interocular balance. The interocular balance had greater suppression in the control group than the treatment group at

baseline. Towards 8 weeks and 16 weeks, the values of the control group had significantly decreased. Whereas the treatment group decreased slightly at the 8-week mark and the results plateaued till the 16-week mark. There were no statistical differences observed in the interocular balance/suppression between the two groups. BCVA had visible improvement in both groups from baseline till the endpoint. Similar to the interocular balance, no drastic differences were seen between the BBV and occlusion group in the BCVA. Although, both groups showed an approximate improvement of 2 lines on the logMAR chart. The study phased challenges such as treatment adherence (56% – 59%) and enrolment difficulties (due to COVID-19 lockdowns). Increased reduction of participants occurred due to a myriad of reasons and or were ineligible to take part. Overall, the BBV did not reduce suppression on a significant level, nevertheless, the improvement in VA was observed. (63,64)

3.5 Bynocs/ AmblyGo

Bynocs is a computer program that is termed as a 'brain-training' treatment method for amblyopia. The company has proven its high efficacy and has also shown to improve vision in children and adults. The program is called AmblyGo and the software has a variety of computer games which is tailored to each individual. In addition to the game play, users must also wear red-green anaglyphic glasses. The treatment consists of 30 minutes per game play divided into 30 sessions. Similar to other dichoptic treatment, contrast differentiation is used in AmblyGo to challenge the weaker eye and to reduce suppression. In the Bynocs website, the results were provided by Dr Cummings on the amblyopic patients whom he treated with this program. 45 patients between 13 and 65 years of age took part. It was concluded that this form of dichoptic therapy has proven to be greatly effective. Quite a few articles have been published using Bynocs as a treatment method, however not all articles have been mentioned due to lack of accessibility. (65)

An article written by Piñero et al. researched the visual performance of children using the Bynocs program in Spain (2023) (66). A quasi-experiment was conducted where 23 children with anisometropic amblyopia, aged 5 to 15, took part. Any ongoing treatment that participant underwent was discontinued for the purpose of this study. As recommended by the company itself, 30 minutes per session for a total of 30 sessions (15h) was assigned to the individuals for 6 weeks. Follow-ups were made at baseline, 2, 4 and 6 weeks. VA values were 0.28 ± 0.24 logMAR at the baseline visit and at the 6-week mark it was 0.13 ± 0.20 logMAR. VA presented with a significant difference not only in the amblyopic eye but also in the dominant eye. The binocular function was assessed in addition to the VA which also showed notable improvement and therefore bettering the stereopsis. Some factors to consider in this study are that the severity of amblyopia was not limited

and the individuals that took part did in fact have low to mild amblyopia. Other limitations were also present in this study, but in the general aspect, this study concluded that Bynocs is an efficient treatment method for amblyopes. (66)

4. NEIVATECH

A single-arm prospective pilot study using a new amblyopic treatment method called NEIVATECH was conducted in Spain by Leal-Vega et al. (2024) (67). The NEIVATECH system is novel treatment described as a 'serious game' which offers binocular vision training to amblyopes through an engaging and captivating virtual reality platform. The system provides several games presented via a combination of two binocular treatment methods – perceptual learning and dichoptic training. A head mounted display (HMD) was used to present the subject with several mini tasks or games. Prospects were given 9 hours of therapy which was advised to be completed over 18 sessions of 30-minute cycles distributed over one month. This design was specifically used to treat older children who have non-adherence to patching. A minimum of 3 attendance per week was required by the participants. 12 participants previously treated for amblyopia (non-compliant to patching), with an age range older than 7 years old with amblyopia. Patients with other ocular diseases, pathologies, neurodevelopmental disorders, persistent strabismus (or angle of deviation greater than 10 prism dioptres) and previous amblyopia treatment at least 2 months before start of the NEIVATECH were excluded. Gabor patches were embedded in the system which were presented binocularly but seen only by the weaker eye. The technology uses the Best PEST system (Parameter Estimation by Sequential Testing) which modifies the difficulty of each game depending on the performance of the participants. The primary outcomes measured in this study were the monocular BCVA, monocular contrast sensitivity, binocular fusion sensitivity (BFS) stereopsis, and several other parameters. Statistically significant improvements were seen in the near BCVA, BFS and distance negative fusional vergence (NFV). All significant results were marked with an asterisk provided in the results table of the study. Near BCVA improved from 0.46 ± 0.37 to 0.34 ± 0.26 logMAR of the amblyopic eye and 0.06 ± 0.06 to -0.03 ± -0.04 logMAR in the strong eye. Both had a p value of 0.022. The BFS represents how efficiently the two separate images of the weaker and stronger eye are fused into one single output. BFS improved from 2.81 ± 2.38 to 2.41 ± 2.23 log arcsec (p value = 0.045). The NFV is also a factor that correlates with binocular alignment, the distance NFV break point initially had 12.67 ± 8.00 and dropped down to 6.40 ± 6.00 PD and recovery point changed from 5.00 ± 4.00 to 3.60 ± 4.00 PD. All other factors were insignificant and had a p value greater than 0.05. The sample size is particularly small but results were compelling, similar to other pilot studies and has also been described to have a future in amblyopic treatment. (67)

5. *Donepezil*

Recently, there has been question whether Donepezil, an acetylcholinesterase inhibitor (AChEI) would enhance perceptual learning to aid as an amblyopia treatment. It has been suggested that Donepezil increases synaptic levels and therefore induce changes in the neural plasticity of adult amblyopes. A pilot study (2017) carried out by Chung et al. published a pilot study in the United States to evaluate the efficacy of Donepezil while individuals trained simultaneously with PL (Tasks included letter identification) (68). The first phase included amblyopes training without Donepezil which had produced positive changes in a previous study, specifically in the contrast sensitivity. In the second phase, individuals were administered 5mg oral donepezil and completed PL training. The study is marginally small as only 11 adults with strabismic, anisometropic, mixed or congenital cataract + strabismic amblyopia, aged 18 to 65, took part. For means of control, 1 out of the eleven observers participated in PL therapy without ingesting Donepezil. The therapy was entirely focused unilaterally, the sound eye was patched, and individuals wore their best corrective glasses. As the half-life of donepezil is 80 hours, the researchers stated that each of the individuals had started to take oral donepezil 3 days before commencing treatment. The first phase (single-letter identification task without donepezil ingestion) had a total of 10 sessions lasting 10 days which had 100 blocks of training. Total number of participants reduced to 9 + 1 control participant due to unmentioned reasons. 6 out of the 9 individuals were available for the second phase, the remaining 3 did not return. The assessment to phase 1 occurred 4 days after and phase 2 (Flanked letter training task) began 2 to 6 weeks later. The summary of the results was that donepezil had absolutely no impact on the efficiency of perceptual learning. The values before and after using the AChEI did not show to be better and in fact the authors had observed that it had slowed down the progress of completing the PL tasks. Factors that should be taken into consideration was that this trial was only a pilot study and the group of participants were small. Additionally, it was not a randomized control study and participants knew they were taking medication which could have created a placebo effect. Furthermore, the number of participants also decreased after phase 1. The calculations however were sufficient to make an overall conclusion that donepezil had no statistically significant improvements. (68)

Another open label pilot study on the use of donepezil and amblyopia recovery was carried out by Wu et al. (2023) (69). 16 participants aged 9 to 37 years, with residual anisometropic, strabismic or mixed amblyopia were prescribed oral donepezil for 12 weeks continuously. Participants less than 18 years of age had to patch their stronger eye for a minimum of 2 hours daily for 4 weeks before the start of the process. During the process, all individuals wore their best optical corrective glasses. The donepezil dosage range started off between 2.5 to 5.0mg depending on the

age. 2.5mg were given to subjects under 18 and 5.0mg for 18 years or older at the start. If the VA of the amblyopic eye did not improve by one line, 4 weeks after the previous visit, the dosage was increased by 2.5mg till a maximum dose of 7.5 to 10.0mg. subjects under 18 also continued patching for 2 hours every day. Follow-up visits were done at 4, 8, 12, and 22 weeks. The 22-week mark was a follow up to assess post-treatment effects (10 weeks after treatment cessation). The mean BCVA of the amblyopic eye was 20/140 (0.85 logMAR) amongst all age groups, 20/125 (0.80 logMAR) in subjects under 18 years of age and a range of 20/63 to 20/250 (0.50 to 1.10 logMAR) in subjects 18 or older. At 12 weeks of treatment, the BCVA had similar improvements amid all the age groups. <18 and ≥18 showed a median improvement of 0.8 lines and 1.2 lines respectively. 25% of the participants had improved by ≥ 2 lines. The mean stereoacuity was 3.5 log arcsec and was observed to be approximately in the same range between the age groups. After 12 weeks of treatment, results did not change since the baseline measurement. Mild adverse effects were present but were self-limiting. Individuals had most often complained of GI problems, headaches, feeling faint or fatigue as their symptoms. Contradicting the previous study on donepezil, conducted in 2017, the results of this study lead to a conclusion that the VA of the amblyopic eye has the possibility to improve with donepezil with time. It was mentioned that the gains in VA remained 10 weeks after the treatment had been stopped. The limitation of this study would be the small number of participants and the study lacked a control group. There were no conclusive measurements regarding stereoacuity, but it can be overlooked as BCVA was the primary outcome. Donepezil as a treatment method still requires more research. (69)

6. *Transcranial Magnetic Stimulation:*

A non-invasive brain stimulation technique known as Transcranial magnetic stimulation (TMS) has increased in recognition as an approach to amblyopic treatment (48). With TMS, the cortical excitability of the visual cortex can be influenced and therefore induce changes in the binocularity of vision (70). This neurostimulation/ neuromodulation technique was established by Anthony Barker in 1985 (70). Electrical currents are stimulated in the cortex via the coils that are positioned next to the scalp thereby forming a magnetic field and a new electrical current is induced in the cerebral cortex (70). Numerous studies have indicated that repetitive Transcranial Magnetic Stimulation (rTMS) has the ability to provoke neuronal changes (48,70). In turn, hypothesizing that the brain still has neuronal plasticity after initial years of development to allow the eyes to regain normal vision in children and even in adults (48,70).

To understand the fundamental mechanism of rTMS and how it influences the visual cortex plasticity, a randomized control trial study by Zheng et al. (2023), was performed on adult rats in

China (71). The study used 63 Wistar rats inclusive of female and male genders and were separated into 4 groups of 2 control groups and 2 monocularly deprived groups who will receive the treatment. One of the control and treatment groups were assigned to the sham stimulation and the other control and treatment groups were assigned rTMS. The rats were monocularly deprived to induce amblyopia using pharmacological means. rTMS was delivered to alert test animals through a coil whilst the body was wrapped in a towel with a fixed head. As a summary of the experiment method, each group of rats received flash visual evoked potentials (VEPs) before and after treatment; a visual cliff test was performed to assess depth perception also before and after treatment, one group of 16 rats were euthanized post treatment to measure the synaptic plasticity; western blot, immunofluorescence and Golgi staining were used to observe the structures of the brain specimens at microscopic level. To summarize the article, it has been concluded that low frequency rTMS has in fact enhanced the visual function in adult rats with amblyopia. In contrast to Sham stimulation, the rTMS has increased the renewal of the contralateral and ipsilateral balance of the eyes which was caused by the monocular deprivation (MD). No difference was found in depth perception; the MD group treated with rTMS had an increment of the specific synaptic plasticity genes in the visual cortex and lower GABA levels compared to the sham group. Likewise, the article also stated that the rTMS facilitated a visual cortex of an early-stage appearance. Hence, solidifying further that transcranial magnetic stimulation has a positive effect in the visual cortex' plasticity of amblyopic rats. Different frequencies are also inducing an effect on the brain. It has been mentioned that a higher frequency of rTMS promotes brain activation and a lower frequency has shown to reduce the excitation of the brain. In order to influence the excitation ratio of inhibition in amblyopic rats, a lower frequency was used because it suppresses the visual cortex of the amblyopic eye. The lower frequency allows space to restore the balance between inhibition and excitation of the amblyopic and normal eye. According to the authors, several limitations were present in this RCT. A coil that produced a larger stimulation than required was used and predicted to have affected multiple areas. It could not be narrowed to one particular region and therefore it was insufficient to compare to the stimulatory area of the human cortex. Secondly, the duration of observation of this RCT were moderately brief. Furthermore, the long-term effects of rTMS are rather unknown. Additionally, the amblyopia was induced with monocular deprivation, thus other forms of amblyopia have not yet been explored. Further research in this therapy method is required for conclusive or improved results. (71)

7. *Acupuncture:*

Acupuncture as a treatment method has been minimally mentioned and only a few articles and randomized clinical trials can be found to support this approach. Nevertheless, the outcome for this technique has produced positive results and it is becoming more acquainted even if it may be regarded as an unconventional technique (48).

Kim et al. released an article in 2020 titled "Acupuncture for Paediatric Bilateral Amblyopia" (72). A retrospective review was conducted in Korea using medical records of children with bilateral refractive amblyopia. Patients of 5 to 13 years of age and those who have been wearing optical glasses for more than a year at the first visit were included. The binocular VA should be below 20/30 (0.18 logMAR) and the spherical equivalent criteria was limited to either lower than -6.0 D or higher than 4.0 D. If the inclusion criteria fit, all children were eligible for 6 months of continuous acupuncture treatment in addition of consent given. Children with strabismus, other neuro-ophthalmologic disorders, defects in the retina or ocular media were excluded. 15 acupuncture points were applied to patients bilaterally and unilaterally using stainless steel, 30mm long and 0.25mm width needles. The therapy was 15 minutes long and an infrared heat lamp was used in the process to maintain the eye's warmth. The BCVA was measured using the Han's visual chart at the initial starting day and once again after 6 months as well as the spherical equivalent, astigmatism, and number of acupuncture sessions. The study was particularly small and niche as the final number of patients selected for this treatment method were 7, of which were 4 males and 3 females. Final number of sessions of acupuncture for the patients were an approximate of 45. There was no correlation of positive results between male and female. However, the study concluded that overall, the BCVA increased greater than 20/30 after the acupuncture therapy in 4 patients out of the 7. All of the patients that showed improvement were above the age of the sensitive period of development which was stated as 7 in this article. No participant had complained of any side effects. The purpose of this study was based off proven research that acupuncture enhances brain-derived-neurotrophic factor (BDNF) in the cells of the retina and thus enhancing the visual function through regulation of dopamine production. The study mentions that dopamine has shown to help recovery from amblyopia. Not only, peripheral acupuncture is meant to increase circulation of retinal blood flow and therefore bettering the VA. The article however presented with particular limitations. The authors mentioned that it would have been difficult to conduct the study if they had excluded participants who have had optical correction as an amblyopic treatment. Hence why the participants that were chosen were limited to those who had shown no improvement with optical correction for 1 year to eliminate bias. It was also mentioned that evaluation of the effects of

treatment had a few difficulties due to the continuous acupuncture sessions. Moreover, acupuncture as a treatment method for amblyopia should be further studied. (72)

Meta-analysis Review

A meta-analysis using literatures on binocular treatment, particularly dichoptic training, was conducted by Roda et al. in 2021 (73). 5 publications which were randomised control trials were analysed. The population group were all children with either anisometropic, strabismic or combined amblyopia. None of the studies mentioned in this publication were used in this literature review but the games or programmes used are similar. The dichoptic games were measured against patching as a control group. The training games included by each article were action/adventure, falling blocks, I-BiT, binocular and on the iPad. All the studies concluded in a p-value of 0.464 meaning non-significant results were found. Hence, there was no substantial improvement or difference in the vision between binocular treatment methods and patching. There was quite a high variation in the results between each of the publications. Only 1 out of the 5 studies was an outlier and if this study was not included, patching had a better outcome than binocular treatment. Roda et al., summarised that though no difference was found to prove whether binocular treatment is better than patching, it can still be considered as an alternative treatment method for children with amblyopia. (73)

Alternatively, a meta-analysis on VR (dichoptic training) as a treatment method for amblyopic children had differing results. This publication was written by Shao et al. and took place in 2023 (74). 10 studies with a total of 459 participants were analysed. Inclusion criteria entailed of RCTs, children with amblyopia and those specifically treated with VR mechanisms. Two articles in this literature review overlapped with the publication by Shao et al., these included the I-BiT programme from Herbison et al. and LuminopiaOne by Xiao et al. The visual acuity had improved by 0.07 logMAR throughout the 10 studies. In terms of heterogeneity, great variability was established. This is due to sample size, severity of amblyopia and the final findings of the studies. Another observation that was noted is that children under 7 years of age had better results than the older age group. It was also found that shorter treatment sessions had greater compliance and results. While lengthier sessions did not produce statistically significant changes. This meta-analysis supports the statement that the maximum efficacy rate of amblyopia treatment is in younger children, where neuroplasticity is still malleable. In addition, VR therapy is highly supported as a potential amblyopia treatment modality and has observed to have promising results. (74)

Summary of Results

Literature Review Summary											
Authors	**Year**	**No. of Parcticipants**	**Age Range (Years)**	**Amblyopia Type**	**Treatment**	**Control**	**Length of Treatment**	**Results - BCVA (LogMAR) - Amblyopic Eye**	**Follow-Up**	**Country**	**Comments**
Yuan et al. (50)	2021	40	7 to 13	Anisometropic	Liquid Crystal Glasses - Alternative Flicker Glass	Patching	1 hour/day/7 days a week for 12 weeks	**Improvement:** AFG: 0.45±0.20 → 0.28±0.19 Patching: 0.53±0.20 → 0.35±0.18	3-weeks and 12-weeks	China	Remarkable improvements in both groups were found for BCVA. Overall, CSF had a better improvement in AFG than the patching group.
Shah et al. (54)	2022	47	**Mixed age group** - Mean: 14.11 ± 7.13 years	All types	PL with Hand-Eye coordination	N/A	30 mins per session (Total - 20 sessions) for 1 month	BCVA results **not provided** but mentioned that remarkable differences have been observed before vs. after treatment	After 1-month	India	Strabismic and refractive amblyopes were the predominant subtype. Distance, stereopsis, CS and handwriting were also assessed which also showed positive changes.
Magdalene et al. (55)	2022	45	8 to 48	Refractive, strabismic, combined or deprivation	PL: RevitalVision	N/A	40 training tasks over a 3-month period	**Improvement:** 0.55±0.24 → 0.34±0.23	After the 3 month period	India	One to two lines of improvement were seen in the VA chart and successful compliance was noted with this treatment.
Xiao et al. (56)	2022	105	4 to 7	Mild strabismus, anisometropia or mixed	DT: Luminopia One	Refractive error correction	1 hour/day/6 days a week for 12 weeks	**Improvement:** Treatment: 1.8 lines Control: 0.8 lines	After 12 weeks	United States	Refractive error correction was worn throughout the treatment and full-time in the control group.
Jost et al. (57)	2020	63	4 to 10	Strabismic, anisometropic or mixed	DT: Video games - Monster Burner/ Dig Rush	Placebo treatment (0% contrast)	1 hour/ 5 days a week for 8 weeks - 40 hours of total game play	**Improvement:** 0.47±0.14 → 0.14±0.08 LogMAR	Baseline, 2, 4, 6, 8 weeks	United States	Anaglyphic glasses were used with the treatment. Different contrast protocols were assigned and stereoacuity, severity and depth of suppression were also assesed and showed improvement. 5 children responded poorly but other participants had a postitive outcome.
Guo et al. (58) & Gao et al. (59)	2016-2018	115	Older children and adults: >7 years old	Unilateral anisometropic, strabismic or mixed	DT - Video games: iPod touch (falling blocks)	Placebo video game - no contrast difference between eyes	1-2 hours, 3 spaced out sessions/day for 6 weeks	Mean difference from baseline: Treatment: 0.06 LogMAR Placebo: 0.07 LogMAR **No statistical differences found**	3, 6, 12, and 24 weeks	New Zealand, Canada, Hong Kong, Australia	The falling blocks game were played while wearing anaglyphic glasses, both eyes were presented with different contrast images.
Razavi et al. (60)	2021	44	4 to 12	Anisometropic	DT - Video game (app): Pivot	Patching	30 minute sessions, twice a day/ 5 days a week for 16 weeks	Final results are yet to be published, but authors **confirmed success of treatment**	2 weeks, 1, 2 and 3 months	Iran	Purpose of this study was to offer an alternative to patching and therefore reduce psychological or social pressures.

Table 1 – (PL = Perceptual Learning; DT = Dichoptic Training; CS/CSF= Contrast Sensitivity Function)

Table 2

Literature Review Summary - Table 2											
Authors	**Year**	**No. of Parcticipants**	**Age Range (Years)**	**Amblyopia Type**	**Treatment**	**Control**	**Length of Treatment**	**Results - BCVA (LogMAR) - Amblyopic Eye**	**Follow-Up**	**Country**	**Comments**
Wygnanski-Jaffe et al. (61)	2022	103	4 to 9	Anisometropic, small-angle strabismic or mixed	DT: CureSight	Patching	90 minutes/ day/ 5 days a week for 4 months (Total: 120 hours)	CureSight: 0.37±0.15 → 0.28±0.13 Patching: 0.37±0.14 → 0.23±0.14 (2.8 lines **improvement** in the amblyopic eye)	Every 4 weeks	Israel, United States	Promising results were observed as the VA improved regardless of the age difference. Patching and CureSight had similar improvements but this treatment method can be regarded as beneficial.
Wygnanski-Jaffe et al. (61)	2024	27	4 to 9	Anisometropic, small-angle strabismic or mixed	DT: CureSight	Patching	90 minutes/ day/ 5 days a week for 4 months (Total: 120 hours)	CureSight baseline: 0.37±0.15 LogMAR regression by 0.06±0.11 Overall residual gain remained: 0.2±0.14 LogMAR = **POSITIVE outcome**	12 weeks, 52 weeks post treatment	Israel, United States	Publication continued based on long-term results, 52 weeks post treatment. Which showed there was only a slight regression but the general improvement of the VA of the amblyopic eye still remained.
Dahlmann-Noor et al. (63)	2024	32	3 to 8	Unilateral anisometropic, strabismic or mixed	DT: BALANCE (Nintendo 3DS) - BBV	Occlusion/ atropine drops	2 x 30 minutes sessions/ day for 16 weeks	**No drastic differences** were seen but there was an approximate improvement of 2 lines in both control and treatment groups	8-week and 16-week mark + 16 weeks post treatment	United Kingdom	Corrective glasses were worn throughout treatment. Balanced binocular viewing did not reduce suppression. **Improvement was still observed in the VA.** 20 children attended the post-treatment follow-up.
Piñero et al. (66)	2024	23	5 to 15	Anisometropic	DT: Bynocs/AmblyGo	N/A	30 mins per session x 30 sessions for 6 weeks (Total: 15h)	Baseline: 0.28±0.24 logMAR 6 weeks: 0.13±0.20 logMAR	Baseline, 2, 4 and 6 weeks	Spain	Significant differences in the visual acuity were noted in both the amblyopic and dominant eye. Stereopsis also showed improvement.
Leal-Vega et al. (67)	2023	12	Older Children: 7 to 15	Not mentioned	PL + DT: NEIVATECH	N/A	18 sessions of 30-min cycles over 1-month (Total: 9 hours)	**Near BCVA:** 0.46±0.37 → 0.34±0.26	Baseline and 1-month	Spain	Subjects with non-adherance to patching were selected. BFS, distance NFV break point and recovery point also improved. Other factors were insignificant.
Chung et al. (68)	2017	9 + 1 control	18-65	Strabismic, anisometropic, mixed, strabismic + congenital cataract	Donepezil + PL + Patching	1 control participant	2 phases- 10 sessions over 10 days with 100 blocks of training per phase	**No statistically significant** improvements were found	4 days after phase 1. Phase 2: 1 week, end of treatment	United States	Participants dropped from 11 to 9 and only 6 out of the 9 returned for phase 2. Phase 2 commenced 2-6 weeks after phase 1.
Wu et al. (69)	2023	16	9 to 37	Residual anisometropic, strabismic or mixed	Donepezil	N/A	12 weeks of 2.5 to 5.0mg oral donepezil till a max of 10.0mg	Average improvement: 1.2 lines **Median improvement at 12 wks:** <18 yrs: 0.8 lines ≥18 yrs: 1.2 lines	4, 8 ,12, 22 weeks (10 weeks post-treatment)	United States	Individuals wore the best corrected optical glasses during the treatment. Those younger than 18 wore patches as well. Improvement was observed regardless of age. Gains in VA remained stable even after 10 weeks of treatment cessation.
Zheng et al. (71)	2023	63 (Rats)	N/A	Monocularly deprived	rTMS	Control groups without amblyopia - Sham vs. rTMS	N/A	Results based on visual cortex plasticity: Visual function observed to be enhanced and produce a **positive effect**	N/A	China	This article is an animal study and results will be analyzed differently to other articles mentioned in this review. No difference was found in depth perception. rTMS increased specific synaptic plasticity genes in the visual cortex.
Kim et al. (72)	2020	7	5 to 13	Bilateral refractive	Acupuncture	N/A	6 months - approximately 45 sessions, 15 mins per session	**BCVA increased** in 4 out 7 patients	Baseline and 6 months	Korea	The study was very small and requires more research.

Discussion

This literature review intended to explore new treatment possibilities for amblyopia and its efficacy rate. Moreso, a comparative analysis was conducted to assess whether classical treatments remain to be the gold standard or if newer treatment modalities have a chance to overtake current regimens. A mixed set of results were found depending on the type of treatment. Scholar engines have resulted in an abundance of articles. However, the focus was primarily on randomised control trials or clinical studies. RCT's, or clinical studies provided deeper insights to the new studies such as direct results, advantages, and or limitations. Hence, research on newer treatment modalities could be thoroughly analysed and a general consensus could be made by using clinical studies. Meta-analyses were also later mentioned to find parallels or differences between the studies. Due to selection of articles being limited to the last 10 years, many publications had to be disregarded. Not only, some were irrelevant or repetitive in terms of the treatment type and therefore not selected. One example that could be mentioned is dichoptic training, where most of the video game therapy belonged to this treatment category. Several video game therapies either used anaglyphic glasses, contrast rebalancing techniques and required participants to play games on tablets/VR. Only a few of these articles were mentioned in this literature review to reduce repetition. One common factor that was always assessed among the binocular treatments was the best corrected visual acuity. Other factors such as stereopsis, stereoacuity, contrast sensitivity, BSV were measured but not in all the studies. For that reason, to have a common ground, BCVA was the main comparative factor in this review.

The LCG treatment is similar to patching, an occlusive way to treat amblyopia using technology. In the study by Yuan et al., the AFG occlusion method had a better outcome than their control group which used patching. However, the post-treatment BCVA resembled one another. The sample size in this study was small but larger than other trials mentioned in this review.

Perceptual learning and dichoptic training were the most researched and published out of the new modalities. Additionally, they had the most promising results out of all the other methods mentioned. Both studies from Shah et al. and Magdalene et al. conducted in India, presented with successful improvement in VA for perceptual learning techniques. Sample sizes were almost the same and the age group tested included younger and older individuals. These results are significant as classical treatments are targeted more towards children under 7. Perceptual learning on the other hand, has provided results to confirm that people, even after the sensitive period of development, can in fact induce change. Therefore, a new treatment pathway has opened for those who have had failed or no treatment against amblyopia earlier in their life. Literatures that researched dichoptic training had varied age groups. A correlation that could be found is that the BCVA had improved

approximately 1 to 3 lines in individuals throughout all the studies in this treatment group. One failed study was conducted by Guo et al. on dichoptic training through an iPod touch. Researchers could not find a difference in results between the control and treatment group. Treatment conditions were very similar to the study conducted by Jost et al. (Monster burner/ Dig rush), but participants had a longer treatment period and had shown improvements. The study by Guo et al. (Falling blocks – iPod touch) was the only one with the shortest duration of treatment compared to the others with a total of 6 weeks. Even though it was not mentioned, there is a possibility that this factor could've hindered the results. Four publications on the topic of dichoptic training completed research using patching or other occlusive means as a control group. One worth mentioning is CureSight by Wygnanski-Jaffe et al. Participants had similar improvements to the patching group, except follow-ups were conducted at 52 weeks post-treatment and results were noteworthy. Regression of BCVA occurred slightly but the general values of the VA remained even after one year which is extremely significant and promising.

Donepezil is a novel therapy that was also included in this review. Two articles were analysed, and both contradicted each other. One article by Chung et al. assessed whether donepezil (in combination with PL and patching) had any treatment effects for amblyopia. The sample size was extremely small, age group was between children and older adults and no statistical differences were found. On the contrary, Wu et al. also released a study on the use of donepezil which resulted in positive results. The number of subjects were slightly greater, consisted of mixed age groups, treatment length was longer, but individuals who required patching and or best corrected optical glasses, were provided. It could be questioned whether the length of treatment or the use of an additional treatment modality could have influenced the results. On the other hand, the study by Chung et al. also used classical treatment in combination with donepezil and had resulted with no desired effects.

The rTMS treatment study by Zheng et al., did not measure BCVA due to the nature of circumstances (an animal study was conducted). However, after extensive research post-mortem of the rats, the plasticity of the visual cortex was profound and visual functions showed improvements. This treatment approach could be implemented on humans with further research and would have the potential to be an alternative method of therapy.

Similar to the rTMS, a less commonly researched mechanism and unconventional approach to amblyopia treatment is acupuncture. One study by Kim et al. did research the effects of this non-binocular approach to assess efficacy. Unexpectedly, even with an extremely small sample size, 4 out of the 7 participants had improved their BCVA without any other amblyopia treatment. This is more than a 50% success rate and this form of treatment should be further evaluated.

One correlation between almost all the studies is that BCVA had resulted in positive changes. One of the recurrent limitations in these studies were that the study size was small and therefore authors encouraged or suggested to conduct a large-scale study to truly evaluate the efficacy of these new treatments. The design of each research was variable. A number of studies were pilot, and some did not establish a good regime for follow-up visits. This poses a risk for invariability and limited confidence in the published results. To get an adept understanding of new amblyopic treatment modalities, more research articles should be extensively reviewed and analysed.

Conclusion

To this day, patching has been the number one, safe and well-known approach to treating amblyopia. There are new treatment methods that aim to fight against the psychological and social challenges that individuals may face while being patched. Though, this may not be the only reason that newer approaches have been researched. With continuous development in technology, amblyopes are beginning to have more options when choosing their treatment. This literature review has come to an overall finding that new modalities such as LCG, perceptual learning, dichoptic training and even rTMS, acupuncture and donepezil have improved or have the potential to improve the VA and binocular summation of individuals with amblyopia without having to go through classical treatments. For those non-compliant to patching, perceptual learning and or dichoptic training has proven to be the best alternative therapy. Perceptual learning particularly, has shown to also improve amblyopia in older populations. Nevertheless, larger scale studies or more research should be conducted to obtain results with higher certainties.

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