Communications on Applied Nonlinear Analysis
ISSN: 1074-133X
Vol 32 No. ICMASD (2025)

Clinical Management of Anisometropic Amblyopia: Current Approaches and New Directions: A Mini Review of Literature

Keshav Jha[1], Aditya Goyal [1,2*]

[1] CT University, India

[2] Sankara Eye Hospital, India

Corresponding Author's email address: adityagoyal@hotmail.com

Article History:

Received: 12-12-2024

Revised: 25-01-2025

Accepted: 05-02-2025

Abstract:

Purpose: The purpose of this article is to provide an update on current management and recent research in anisometropic amblyopia treatment and management strategies.

Background: In children and young people, amblyopia is the most common cause of preventable blindness. The prevalence of amblyopia in childhood varies between 1-5%, although these values may differ and among the amblyopes, anisometropic amblyope is the most prevalent. When treated promptly, the majority of visual impairment and binocularity in anisometropic amblyopia can be reversed. Children can be treated using a variety of techniques, including as liquid crystal display spectacles, binocular therapy (direct stereo training, perceptual learning and dichoptic training), atropine penalization, patching, and refractive correction.

Methods: From 2015 to 2024, a comprehensive search of the literature was conducted in PubMed, Scopus, Embase, and the reference lists of papers that contained the term "amblyopia treatment or therapy."

Future directions: A vergence treatment is the primary amblyopia treatment which addresses binocularity issue. Currently, the Amblyopia patient starts vergence and depth perception treatment only after the visual acuity improved to satisfactory levels or comparable to the other eye, which may take longer time for the patient.

Keywords: Amblyopia, Anisometropic amblyopia, Occlusion, Atropine, Binocular therapy, Perceptual learning, dichoptic training, Stereopsis training

1. Introduction

Amblyopia is characterized by a unilateral or bilateral loss of visual acuity that persists following refractive correction or the removal of any pathological visual obstruction and for which there is typically no known organic explanation. It is a common neurodevelopmental disorder that causes physiological changes in the visual pathways (Gunton, 2013)(McConaughy and McGuirk, 2019). Amblyopia with a world-wide prevalence of 1.44% and approximately 1.1%-6.6% in India, accounts for significant ocular morbidity (Murali et al., 2021) (Boniquet et al., 2021). Early disruption of normal visual development can result in a wide range of neurological, perceptual, oculomotor, and clinical problems. Amblyopia is the most frequent cause of visual loss in

newborns and young children, aside from refractive error. Unilateral amblyopia has two main causes: (i) a difference in refractive error between the two eyes, resulting in lack of clear visual input to one eye (anisometropic amblyopia) and (ii) strabismus (misalignment of the optical axes) resulting in abnormal binocular interaction (strabismic amblyopia). The interocular difference that is considered "anisometropic" is 0.5 diopter sphere (DS) or diopter cylindrical (DC). Anisometropia of higher than 1 DS raises the likelihood of amblyopia (2–14.5 years) but does not always cause it. There doesn't seem to be a significant distinction between anisometropia and amblyopia (Murray and Codina, 2019).

By interfering with the emmetropization process and causing a distinct abnormality that produces cortical abnormalities in visual function, which adversely affect the emmetropization process, anisometropia results in a persistent uniocular blur that leads to amblyopia (Koo et al., 2017). **Neurophysiology** indicates dysfunction in both primary visual area (V1) & secondary visual area(V2). The most profound and consistent changes are in striate cortex pathway & extra striate cortex pathway (which process motion information) (Gopal et al., 2019).

Amblyopia impacts not only monocular vision, such as visual acuity, vernier acuity, contrast sensitivity, spatial distortion, and special interactions but also binocular functions, including binocular combination, interocular interaction and stereopsis. It also affects visuo-motor problems like initiation and execution of eye movements, reaching & grasping hand movement. They will also have problem with visual attention, processing & visuo-cognitive search like localization, visual search & scanning (Webber, 2018).

Role of binocularity in Anisometropic Amblyopia

In anisometropic amblyopia, binocularity plays a crucial role as abnormal binocular interactions, particularly central suppression of the weaker eye, are considered a key factor in the development and persistence of the condition, meaning the brain actively suppresses the blurry input from the amblyopic eye when both eyes are open, hindering visual acuity improvement in that eye; therefore, addressing binocular function is vital in treating anisometropic amblyopia. High spatial frequency deficits and contrast imbalances exacerbate suppression, leading to reduced stereopsis and abnormal binocular interactions. While some amblyopes retain gross stereopsis, fine stereopsis and binocular summation are often deficient (Rajavi et al., 2016) (Murray and Codina 2019). Stereopsis appears to offer a distinct sense of depth in the world, as demonstrated by the typical observer's experience when watching 3D displays or movies and by the notable shifts in depth perception described by those who have recovered from stereopsis. However, the brain uses a variety of clues to deduce 3D spatial relationships in visual scenes, and stereopsis is just one of them. Amblyopes with impaired stereopsis exhibit deficiencies in visually guided hand movements that are comparable to those in normally sighted participants who have one eye obscured. These deficiencies are believed to be caused by defective stereopsis rather than decreased visual acuity, unstable fixation, or impaired vergence control (Levi et al., 2015).

Role of Neuroplasticity in Anisometropic Amblyopia

Neuroplasticity is the ability of neural networks in the brain to change through growth and reorganization. This process can occur in response to learning new skills, experiencing

environmental changes, recovering from injuries, or adapting to sensory or cognitive deficits. Such adaptability highlights the dynamic and ever-evolving nature of the brain, even into adulthood. Traditionally, treatment focused on children, as cortical plasticity declines with age. However, recent research shows that the adult visual cortex retains some plasticity, enabling potential treatments like perceptual learning, binocular vision therapies, and non-invasive brain stimulation techniques. These approaches aim to enhance neural adaptability, improving vision and restoring binocular function in individuals with amblyopia (Sengpiel, 2014).

2. Methodology

The lack of robust evidence for the effectiveness of amblyopia treatment, the multifactorial nature of amblyopia therapy, and the challenge of treating amblyopic adolescents and adults have led to a significant increase in randomized controlled trials (RCTs) and new treatment modalities for amblyopia. This review will provide an update on current clinical management of amblyopia and discuss recent research for amblyopia treatment. Part I will review refractive correction, patching, penalization, and pharmacological treatments. Part II will focus on more recent strategies, including perceptual learning, dichoptic approaches, virtual reality, and direct stereopsis training. Studies in English language were identified using PubMed, ClinicalTrials.gov, Google Scholar, and reference lists of retrieved articles. The searches were performed from 2015 to 2024, for all papers containing amblyopia treatment or amblyopia therapy. We have included RCTs, prospective observational studies, pilot studies, review articles, and meta-analysis. There was no minimum length of follow-up required to include studies.

3. Current Clinical Approaches

3.1 Refractive Correction

Refractive correction is the primary step in managing anisometropic amblyopia. By providing the appropriate optical correction through spectacles or contact lenses, clinicians can balance the refractive error between the eyes. This correction allows the amblyopic eye to receive a clear image, facilitating improved visual development (Asper et al.,2018) (McGraw et al. 2019). The Pediatric Eye Disease Investigator Group (PEDIG) conducted a landmark study demonstrating that refractive correction alone significantly improved visual acuity in a majority of children with anisometropic amblyopia (Pediatric Eye Disease Investigator Group, 2002). This finding emphasizes the importance of early detection and intervention, as younger patients tend to respond more favourably to treatment (Jia et al., 2022). However, refractive correction is not without its challenges. Compliance with spectacle wear can be problematic, particularly in young children. Parental involvement and education are crucial in ensuring adherence to corrective lens use. Additionally, contact lenses may be a viable alternative for older children and teenagers, offering better cosmetic outcomes and reducing the aniseikonia - a difference in image size perceived by the two eyes - associated with spectacle wear (Papageorgiou et al.,2019).

3.2 Occlusion Therapy

Occlusion therapy, or patching, remains a cornerstone of amblyopia treatment. By covering the dominant eye, occlusion forces the amblyopic eye to work harder, stimulating its neural pathways

and promoting visual development. The effectiveness of this approach is highly dependent on patient adherence and the age at which treatment is initiated. Younger patients typically experience faster and more pronounced improvements (Kelly et al., 2016) (Tailor et al., 2022). Recent studies suggest that part-time occlusion, often more practical for families, can be as effective as full-time occlusion, providing a more flexible treatment option. Occlusion therapy is not without its drawbacks. Compliance can be a significant barrier, as children may resist wearing a patch due to discomfort or social stigma. Innovative solutions, such as adhesive patches with engaging designs and adjustable occlusion glasses, have been developed to improve adherence (Li et al., 2020) (Vagge and Nelson, 2017). According to PEDIG RCTs, 2h of daily patching is as effective as 6h for moderate amblyopia (VA 6/12 to 6/30) in children younger than 7 years and for severe amblyopia (VA 6/30 to 6/120), 6h of prescribed daily patching is just as effective as full-time patching. During patching hours, children are commonly advised to perform near activities or activities requiring hand-eye co-ordination, such as reading, drawing, playing with blocks, playing video games, tracing pictures or completing puzzles (Buckle et al., 2019).

2.3 Penalization

Penalization generally refers to the blurring of the non- amblyopic eye to induce the use of amblyopic eye. This method serves as a viable alternative to patching, particularly for patients who experience discomfort or social stigma from wearing a patch. It is usually done by overplus glass or by replacing the optical correction of the non-amblyopic eye with a plano lens or using 1% atropine to paralyze the ciliary muscle or using bangerter filters (Chen and Cotter, 2016). In cases of moderate anisometropic amblyopia, optical penalization seems effective as primary treatment, as maintenance treatment or as an alternative after patching failure, and can be combined with atropine penalization for better outcome. Bangerter filters are semi-opaque foils that can be attached to the glasses in order to reduce VA of the non- amblyopic eye. It is available in several graded densities that are designed to reduce VA to a range of 0.0 to 1.0 logMAR. It has been suggested that the filter selected has to induce a reduction of the VA of the non-amblyopic eye of 2 lines below the best-corrected VA of the amblyopic eye (Papageorgiou et al.,2019).

3.3 Pharmacological Interventions

Atropine penalizes the good eye, thereby promoting visual development in the amblyopic eye. This method is particularly useful in patients who resist patching. Atropine is as effective as occlusion therapy with the added benefit of improved compliance. potential side effects, such as photophobia and cycloplegia must be carefully monitored. Current research is exploring the efficacy of other pharmacological agents, including levodopa and citicoline, which may enhance neural plasticity and improve visual outcomes in amblyopic patients. The clinical use of these agents is limited due to the potential long term side effects of a drug with psychoactive and extrapyramidal effects in the immature nervous system (Papageorgiou et al.,2019) (Gopal et al., 2019) (Kraus and Culican, 2018).

4. New Directions in the treatment of Anisometropic Amblyope

4.1 Perceptual learning

It refers to any rather stable change in the perception of a subject as a result of the experience with one or more stimulus. The repetitive training of a visual task looks forward to develop the perceptive capacity throughout the knowledge and the control of the corporal sensations and in that way to stimulate the cortical area responsible of the trained function. It includes vernier acuity, position discrimination and contrast sensitivity which will improve the visual acuity and stereo acuity by improving the selective visual attention and visuospatial skills (Xi et al., 2015). Patients are often trained on contrast sensitivity tasks with occlusion of the non- amblyopic eye. A rotating disc on which high-contrast sine-wave gratings of six different spatial frequencies are displayed. The first grating used is the finest on which the patient can distinguish the orientation of the stripes. After some training, the grating frequencies are being increased, while the visual acuity is improved. Two different types of perceptual learning have shown to be effective in clinical research: Gabor's patches and letter optotypes by training monocularly. Gabor's patches are based on the spatial frequency and orientation of a sinusoidal gratings with a Gaussian envelope where orientation discrimination is worked. Moreover, letter optotypes are based on the fact that letter recognition is affected by crowding and interaction contours in amblyopia, thus training with letter recognition with and without crowding and orientation discrimination is carried out (Rodan et al.,2022)(Tsirlin et al., 2015).

4.2 Dichoptic Approaches

Dichoptic training originates from the idea that amblyopia is an inherently binocular disorder rooted in interocular suppression, and that an effective treatment should engage both eyes (Jin et al., 2022). In dichoptic training, participants with amblyopia are trained on tasks in which stimuli are presented dichoptically with the contrast of the image to the fellow eye attenuated in order to encourage binocular combination of the two inputs. The visual scene with reduced contrast to the better seeing eye and with normal contrast to the amblyopic eye, it will overcome interocular suppression and referred as anti-suppression therapy. With improving performance, the contrast of the visual scene shown to the better seeing eye is gradually increased until contrast is equal for both eyes (Hess and Thompson, 2015) (Liu et al., 2020) (Xiao et al., 2022) .

4.3 Virtual Reality and Video Games

Video games, movies, and other virtual content can be used to replace or blend the actual world with virtual reality technologies. These gadgets can concurrently present two eyes with separate content, which is a unique feature that could make them extremely helpful for diagnosing and treating anisometropic amblyopia. Because these devices are stereoscopic, they can easily change the images of the two eyes differ in contrast, luminance, size, position to enhance the treatment (Levi, 2023).

Video game treatments of amblyopia are targeting binocularly by improvements in display technologies like 3-D monitors (generally use anaglyphic glasses red-green or red-blue, polarized glasses, shutter glasses) and virtual reality systems that enables dichoptic presentation of separate

images to each eye by altering image contrast, brightness, clarity and spatial composition independently for the two eyes (Guo et al., 2016). Repeated exposure is achieved through presenting these image manipulations within videogames or passive media such as movies. In order to investigate their effect on amblyopia, three approaches have been developed. The first is to play a video game with the non- amblyopic eye patched, in order to improve aspects relating to crowding. The second method employs dichoptic viewing as an anti-suppression strategy, where the same background is presented to both eyes but an enriched foreground is presented to the amblyopic eye. The third strategy is to play a video game specifically designed to develop stereopsis. With many hours of exposure over periods of weeks or months, binocular treatments are hypothesised to 're-balance' the amblyopic visual system, producing improvements in visual function (Gao et al., 2021) (Kelly et al., 2016).

4.4 Direct Stereopsis training

Recent studies concludes that direct stereopsis training either in the form of global stereopsis or local stereopsis can improve the stereopsis in anisometropic amblyope. Few studies even change the patient's stereopsis from global to local. But in all the studies, their anisometropia was mild (Portella- Camino et a., 2018) (Veda Murthy et at., 2016) (Levi et al., 2015).

5. Challenges and Future directions

Despite the advancements in treatment, several challenges remain. Ensuring adherence to therapy, particularly in children, is a significant hurdle. The discomfort associated with occlusion therapy and the social stigma of wearing a patch can lead to resistance. Additionally, the variability in treatment response necessitates personalized treatment plans, taking into account factors such as the severity of amblyopia, the age of the patient, and the presence of other ocular conditions. Furthermore, the long-term sustainability of vision improvement is a concern. Studies suggest that follow-up and maintenance therapy are crucial to prevent regression of visual acuity gains. This underscores the need for ongoing research to optimize treatment protocols and identify predictors of successful outcomes.

Moreover, A vergence treatment is the primary amblyopia treatment which addresses binocularity issue. Currently, the Amblyopia patient starts vergence and depth perception treatment only after the visual acuity improved to satisfactory levels or comparable to the other eye, which may take longer time for the patient.

6. Conclusions

The clinical management of anisometropic amblyopia has evolved significantly, with a variety of effective treatment options available. While refractive correction, occlusion therapy, and pharmacological penalization remain standard practices, emerging therapies such as binocular approaches and digital platforms offer promising new directions. As our understanding of amblyopia and neuroplasticity continues to grow, these innovations hold the potential to enhance treatment efficacy and broaden the scope of recovery. Future research should focus on refining these approaches, addressing challenges in adherence, and ensuring the durability of treatment outcomes. Through continued exploration and innovation, the clinical management of

anisometropic amblyopia can be further improved, offering hope for better visual outcomes across all age groups. Innovative approaches such as VR therapy and neuroplasticity-based interventions have the potential to revolutionize amblyopia management, making treatment more engaging and effective. By embracing these advances, clinicians can offer more comprehensive care, ultimately improving the quality of life for individuals affected by anisometropic amblyopia. As research continues to unfold, the future of amblyopia treatment looks brighter, with the promise of achieving optimal visual outcomes for patients worldwide.

Acknowledgements

Finally, I wish to express my deep appreciation to my colleagues for their unwavering support and encouragement throughout this process.

References:

[1] Asper, L., Watt, K., & Khuu, S. (2018). Optical treatment of amblyopia: a systematic review and meta-analysis. *Clinical and Experimental Optometry*, *101*(4), 431-442.

[2] Boniquet-Sanchez, S., & Sabater-Cruz, N. (2021). Current management of amblyopia with new technologies for binocular treatment. *Vision*, *5*(2), 31.

[3] Buckle, M., Billington, C., Shah, P., & Ferris, J. D. (2019). Treatment outcomes for amblyopia using PEDIG amblyopia protocols: a retrospective study of 877 cases.*Journal of American Association for Pediatric Ophthalmology and Strabismus*, *23*(2), 98-e1.

[4] Chen, A. M., & Cotter, S. A. (2016). The amblyopia treatment studies: implications for clinical practice.*Advances in ophthalmology and optometry*, *1*(1), 287-305.

[5] Gao, T. Y., Black, J. M., Babu, R. J., Bobier, W. R., Chakraborty, A., Dai, S., & Thompson, B. (2021). Adherence to home-based videogame treatment for amblyopia in children and adults.*Clinical and Experimental Optometry*, *104*(7), 773-779.

[6] Gunton, K. B. (2013). Advances in amblyopia: what have we learned from PEDIG trials?. *Pediatrics*, *131*(3), 540-547.

[7] Guo, C. X., Babu, R. J., Black, J. M., Bobier, W. R., Lam, C. S., Dai, S., ... &

[8] Thompson, B. (2016). Binocular treatment of amblyopia using videogames (BRAVO): study protocol for a randomised controlled trial. *Trials*, *17*, 1-9.

[9] Gopal, S. K., Kelkar, J., Kelkar, A., & Pandit, A. (2019). Simplified updates on the pathophysiology and recent developments in the treatment of amblyopia: A review. *Indian journal of ophthalmology*, *67*(9), 1392-1399.

[10] Hess, R. F., & Thompson, B. (2015). Amblyopia and the binocular approach to its therapy. *Vision research*, *114*, 4-16.

[11] Jia, Y., Ye, Q., Zhang, S., Feng, L., Liu, J., Xu, Z., ... & Li, J. (2022). Contrast sensitivity and stereoacuity in successfully treated refractive amblyopia. *Investigative Ophthalmology & Visual Science*, *63*(1), 6-6.

[12] Jin, L., Fang, Y., & Jin, C. (2022). Binocular treatment for individual with amblyopia: A systematic review and meta-analysis. *Medicine*, *101*(27), e28975.

[13] Kelly, K. R., Jost, R. M., Dao, L., Beauchamp, C. L., Leffler, J. N., & Birch, E. E. (2016). Binocular iPad game vs patching for treatment of amblyopia in children: a randomized clinical trial. *JAMA ophthalmology*, *134*(12), 1402- 1408.

[14] Kraus, C. L., & Culican, S. M. (2018). New advances in amblyopia therapy I: binocular therapies and pharmacologic augmentation.*British Journal of Ophthalmology*, *102*(11), 1492-1496.

[15] Koo, E. B., Gilbert, A. L., & VanderVeen, D. K. (2017, January). Treatment of amblyopia and amblyopia risk factors based on current evidence. In *Seminars in Ophthalmology* (Vol. 32, No. 1, pp. 1-7). Taylor & Francis.

[16] Levi, D. M., Knill, D. C., & Bavelier, D. (2015). Stereopsis and amblyopia: A mini- review. *Vision research*, *114*, 17-30.

[17] Levi, D. M. (2023). Applications and implications for extended reality to improve binocular vision and stereopsis. *Journal of Vision*, *23*(1), 14-14.

[18] Li, Y., Sun, H., Zhu, X., Su, Y., Yu, T., Wu, X., ... & Jing, L. (2020). Efficacy of interventions for amblyopia: a systematic review and network meta- analysis. *BMC ophthalmology*, *20*, 1-9.

[19] Liu, Z., Chen, Z., Gao, L., Liu, M., Huang, Y., Feng, L., ... & Yu, M. (2020). A new dichoptic training strategy leads to better cooperation between the two eyes in amblyopia. *Frontiers in Neuroscience*, *14*, 593119.

[20] McGraw, P. V., Barrett, B. T., & Ledgeway, T. (2019). Optical treatment of strabismic amblyopia. *Ophthalmic & Physiological Optics*, *39*(5).

[21] McConaghy, J. R., & McGuirk, R. (2019). Amblyopia: detection and treatment.

[22] *American family physician*, *100*(12), 745-750.

[23] Murray, S. J., & Codina, C. J. (2019). The role of binocularity in anisometropic amblyopia.*Journal of Binocular Vision and Ocular Motility*, *69*(4), 141-152.

[24] Murali, K., Ramesh, A., Murthy, S. R., & Goyal, A. (2021). Binocular therapy as primary intervention in adults with anisometropic amblyopia.*Taiwan Journal of Ophthalmology*, *12*(3), 317-324.

[25] Papageorgiou, E., Asproudis, I., Maconachie, G., Tsironi, E. E., & Gottlob, I. (2019). The treatment of amblyopia: current practice and emerging trends. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *257*, 1061-1078.

[26] Portela-Camino, J. A., Martín-González, S., Ruiz-Alcocer, J., Illarramendi-Mendicute, I., & Garrido-Mercado, R. (2018). A random dot computer video game improves stereopsis. *Optometry and Vision Science*, *95*(6), 523-535.

[27] Rajavi, Z., Sabbaghi, H., Sharifi, E. A., Behradfar, N., & Yaseri, M. (2016). The role of interactive binocular treatment system in amblyopia therapy. *Journal of current ophthalmology*, *28*(4), 217-222.

[28] Rodán, A., Marroquín, E. C., & García, L. C. J. (2022). An updated review about perceptual learning as a treatment for amblyopia.*Journal of optometry*, *15*(1), 3-34.

[29] Tailor, V., Ludden, S., Bossi, M., Bunce, C., Greenwood, J. A., & Dahlmann- Noor, A. (2022). Binocular versus standard occlusion or blurring treatment for unilateral amblyopia in children aged three to eight years. *Cochrane Database of Systematic Reviews*, (2).

[30] Sengpiel, F. (2014). Plasticity of the visual cortex and treatment of amblyopia. *Current Biology*, *24*(18), R936-R940.

[31] Tsirlin, I., Colpa, L., Goltz, H. C., & Wong, A. M. (2015). Behavioral training as new treatment for adult amblyopia: a meta-analysis and systematic review. *Investigative ophthalmology & visual science*, *56*(6), 4061-4075.

[32] Vagge, A., & Nelson, L. B. (2017). Compliance with the prescribed occlusion treatment for amblyopia. *Current opinion in ophthalmology*, *28*(5), 454-459.

[33] Vedamurthy, I., Knill, D. C., Huang, S. J., Yung, A., Ding, J., Kwon, O. S., ... & Levi,

[34] D. M. (2016). Recovering stereo vision by squashing virtual bugs in a virtual reality environment. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *371*(1697), 20150264.

[35] Webber, A. L. (2018). The functional impact of amblyopia. *Clinical and Experimental Optometry*, *101*(4), 443-450.

[36] Xi, J., Jia, W. L., Feng, L. X., Lu, Z. L., & Huang, C. B. (2015). Perceptual learning improves stereoacuity in amblyopia. *Investigative ophthalmology & visual science*, *55*(4), 2384-2391.

[37] Xiao, S., Angjeli, E., Wu, H. C., Gaier, E. D., Gomez, S., Travers, D. A., ... & Luminopia Pivotal Trial Group. (2022). Randomized controlled trial of a dichoptic digital therapeutic for amblyopia. *Ophthalmology*, *129*(1), 77-85.