Childhood amblyopia: A systematic review of recent management options

Saif H. Alrasheed[1,2], **Sulaiman Aldakhil**[1]

Access this article online

Quick Response Code:

Website: www.saudijophthalmol.org

DOI: 10.4103/sjopt.sjopt_212_23

Abstract:

This study reviews the current information on treatment of childhood amblyopia, with the goal of improving visual functions. The authors searched various online databases including PubMed, Web of Science, ProQuest, Scopus, Google Scholar, Ebsco, and Medline. The articles, published between 2002 and 2023, included in this study were used to assess the different modalities for the management of different types of childhood amblyopia.The final systematic review included 41 studies from different countries, covering 4060 children with a mean age 6.8 ± 124 years. The findings showed that childhood amblyopia commonly treated through a systemic approach, i.e., starting with treatment of refractive errors with given optical adaptation time, followed by visually stimulating amblyopic eye by covering the dominant eye with patching, Atropine or Bangerter filters. Refractive adaptation period of 18–22 weeks has proven to show a significant improvement in visual acuity. It has been confirmed that 2 h patching is effective for the first time treated amblyopes, and if there is no improvement, increase the period to 6 h daily. Novel methods that improve binocular function such as dichoptic, perceptual training, video gaming, and drugs that facilitate visual neuroplasticity, are useful in the treatment of amblyopia that is not responsive to conventional therapy. The study concludes that significant evidence show that childhood amblyopia is treated through a systemic approach. Starting from correcting refractive errors with a period of optical adaptation, followed by patching therapy and atropine penalization. New methods that improve the binocular functions and medications that facilitate visual neuroplasticity have found to be useful in the treatment of amblyopia that is not responsive to conventional treatment.

Keywords:

Atropine penalization, childhood amblyopia, dichoptic training, patching, refractive adaptation

Introduction

Amblyopia, sometimes known as "lazy eye," is a disorder defined by a loss in vision in one or both eyes caused by abnormal interaction between the two eyes during a critical stage of neuronal development in the visual cortex.[1,2] The majority of visual development occurs within the first 3 years of life, with the first decade of life regarded to be the important or sensitive time for human visual development.[3] Disorders that affect the normal visual development during the sensitive period, due to anisometropia, strabismus, refractive error, and/or lack of transparency of the ocular media, either unilaterally or bilaterally, may result in permanent visual impairment (VI); thus, it is critical to identify and treat such disruptions rapidly.[3,4] According to the World Health Organization, VI is a major public health concern in many countries, and among children, amblyopia is the second leading cause of VI, with a global prevalence ranging from 1.5% to 4%.[2,5-7]

Amblyopia occurs due to abnormal visual processing throughout the early stages of life; at birth, the visual acuity (VA) is poor due to the visual system's underdevelopment. To promote optimal visual development, it is necessary to provide suitable visual stimulation, such as clear retinal images, equal clarity of images in both eyes, and proper alignment of the eyes.[8,9] As the neurodevelopment of visual centers begins to get stimulated by clear retinal images, the VA improves quickly during the 1st few months of life.[8-10] The authors[8,9] reported that extent of

[1]Department of Optometry, College of Applied Medical Sciences, Qassim University, Qassim, Saudi Arabia, [2]Department of Binocular Vision, Faculty of Optometry and Visual Sciences, Al-Neelain University, Khartoum, Sudan

Address for correspondence:
Dr. Saif H. Alrasheed, Department of Optometry, College of Applied Medical Sciences, Qassim University, Qassim, Saudi Arabia.
E-mail: s.rasheed@qu.edu.sa

Submitted: 22-Aug-2023
Revised: 29-Oct-2023
Accepted: 22-Nov-2023
Published: 06-Jan-2024

How to cite this article: Alrasheed SH, Aldakhil S. Childhood amblyopia: A systematic review of recent management options. Saudi J Ophthalmol 2024;38:201-13.

the critical period for visual development usually starts from birth to 3 years of age. The process of visual development continues until the age of 7–8 years, which is a sensitive period. However, as childhood progresses, the neural plasticity for visual development gradually decreases.[11]

There are geographic differences in the treatment of childhood amblyopia, but the most effective management options are refractive correction, patching, and penalization with atropine drops or Bangerter filters, particularly when started at young age. These traditional approaches are considered the backbone of treatment. Recently, novel strategies for treating childhood amblyopia that involve computerized visual training with varied stimuli have been developed and used.[12] While optical correction may not immediately restore normal vision in amblyopia, it has been established that prolonged use of optical correction result in vision improvement in individuals with high ametropia associated with bilateral amblyopia.[13,14] Prior to 2002, the primary initial therapy for unilateral amblyopia, according to Asper *et al*.,[14] was to occlude the healthy eye. Both Moseley *et al*.[15] and Wallace *et al*.[16] offered evidence that correcting refractive errors can lead to significant vision improvement in the amblyopic eye over time, regardless of whether the amblyopia was caused by anisometropia, strabismus, or a combination of both. Studies[14,17] have shown that the duration of VA improvement can last from 4 to 6 months. Therefore, it is now widely recognized that the period of wearing spectacles known as "optical treatment" or "refractive adaptation" is essential in the initial stages of childhood amblyopia treatment.[14] Many studies have advocated incorporating an optical treatment phase lasting 4–18 weeks.[18,19]

Birch[20] reported that the binocular method for treating amblyopia aims to eliminate residual amblyopia while also improving the poor binocular vision functions and fine motor skills associated with childhood amblyopia. The Pediatric Eye Disease Investigator Group (PEDIG) is a group of pediatric ophthalmologists funded by the National Eye Institute of the United States to conduct clinical investigations on pediatric eye disorders. They conducted numerous research to evaluate the efficacy of treating amblyopia using optical correction, patching, atropine penalization, and other ways of treatment, and they discovered a significant difference in visual improvement depending on the type and severity of amblyopia and the management modalities used.[8] Therefore, the current study was conducted to review up-to-date information on the treatment options of childhood amblyopia using different management modalities.

Methods

Search plan and selection criteria

The study was performed in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, 2020.[21] The authors searched various online databases including PubMed, Web of Science, ProQuest, Scopus, Google Scholar, Ebsco, and Medline. They searched for studies published between 2002 and 2023. The evaluation of the quality of each study included in this review was conducted using the assessment tool developed by Downs and Black.[22] Furthermore, each of the chosen articles was reviewed and given a score based on a 10-item scale, as illustrated in Table 1. The articles included in this systematic review were conducted to evaluate various treatment strategies for various forms of childhood amblyopia. The search keywords were (optical correction OR refractive correction) OR (patching OR occlusion OR Bangerter filters) OR (atropine drops OR atropine penalization) (vision therapy OR binocular therapy OR video game play OR Dichoptic display therapy) OR (pharmacologic therapy OR drugs therapy) or (surgical treatment) and childhood amblyopia (anisometropic amblyopia OR refractive amblyopia OR ametropic amblyopia OR strabismic amblyopia). This review was limited to peer-reviewed articles published in English language journals. Only studies conducted on treatment amblyopia for children using different management options for several types of amblyopia were considered for inclusion. Articles were excluded if they were not done on children and did not evaluate amblyopia treatment. Furthermore, this review excluded meeting abstracts, editorial discussions, conference papers, and studies that lacked fundamental data collection as shown in Figure 1.

Data extraction

The authors evaluated the title and abstract of all articles and extracted essential data such as the first author's name, year of publication, the country where the study was conducted, characteristics of the subjects (age, sample size), types of amblyopia, and treatment. These details are presented in Tables 1 and 2.

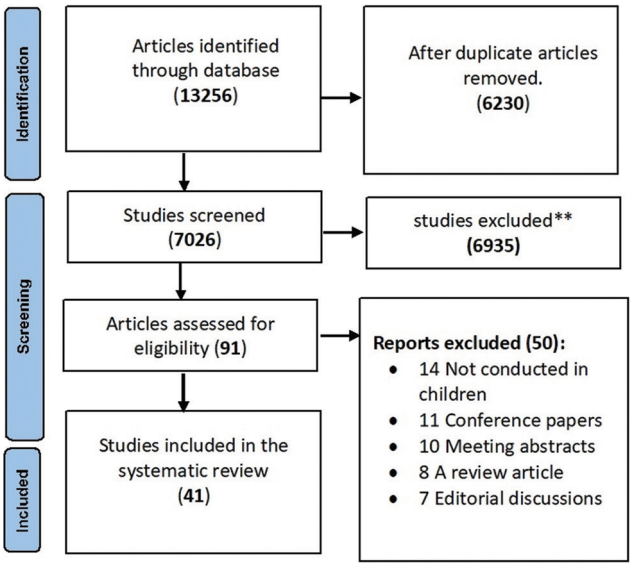

Figure 1: Documentation of articles used in the present systematic review

Table 1: Characteristics of studies assessed childhood amblyopia management

First author and year of study	Country	Age group (years)	Age, mean±SD	Sample size	Quality assessment score
Kadhum *et al*., 2023[23]	Netherlands	4–12	5.8±0.8	96	10
Liu *et al*., 2021[24]	China	6–16.5	10.9±2.8	27	10
Knox *et al*., 2012[25]	United Kingdom	5–4	8.5±2.6	14	9
Kelly *et al*., 2018[26]	USA	4–10	7.0±1.8	41	10
Roy *et al*., 2023[27]	India	5–15	-	55	9
Dadeya *et al*., 2009[28]	-	3–12	-	30	8
Cotter *et al*., 2006[29]	Multicenter	3–7	5.2±0.9	84	10
Cotter *et al*., 2012[30]	Multicenter	3–7	-	146	9
Chen *et al*., 2007[31]	Taiwan	3–7	5.3±0.8	60	10
Wallace *et al*., 2007[32]	Multicenter	3–11	5.1±1.3	113	10
Repka *et al*., 2003[33]	Multicenter	<7	5.1±1.1	189	10
Holmes *et al*., 2003[34]	Multicenter	<7	-	175	10
Stewart *et al*., 2007[35]	United Kingdom	4–6	5.6±1.5	97	9
Alotaibi *et al*., 2012[36]	Saudi Arabia	–	-	130	8
Pediatric Eye Disease Investigator Group, 2002[37]	Multicenter	<7	5.3±1.1	419	10
Repka *et al*., 2005[38]	Multicenter	<7	5.3±1.1	419	10
Repka *et al*., 2004[39]	Multicenter	<7	-	186	10
Repka *et al*., 2009[40]	Multicenter	3–12	4.4	100	10
Laria *et al*., 2011[41]	Spain	3–11	6.13±1.82	62	10
Agervi *et al*., 2009[42]	Sweden	-	4.4	80	9
Rutstein *et al*., 2010[43]	Multicenter	3–10	6.3±1.62	186	10
Yang *et al*., 2003[44]	China	-	-	5	8
Repka *et al*., 2010[45]	USA	8–17	11±2	33	10
Repka *et al*., 2015[46]	USA	7–12	-	139	10
Polat *et al*., 2009[47]	Israel	7–8	7.3	5	9
Bossi *et al*., 2017[48]	United Kingdom	3–11	6.6±2.9	24	10
Guo *et al*., 2016[49]	Multicenter	>7	-	108	10
Li *et al*., 2014[50]	USA	4–12	-	50	10
Birch *et al*., 2015[51]	USA	3–7	-	50	10
Holmes *et al*., 2016[52]	Multicenter	5–12	8.5±1.9	385	10
Kelly *et al*., 2016[53]	USA	4.6–9.5	6.7±1.4	28	10
Huang *et al*., 2008[54]	Taiwan	3–7	4.91	105	10
Abu-Ain and Watts, 2023[55]	United Kingdom	2–7	-	12	9
Morya *et al*., 2023[56]	India	-	14.16±3.49	23	10
Wu *et al*., 2023[57]	USA	8–17	-	16	10
Hsieh *et al*., 2022[58]	China	7–10	7.78±0.88	36	10
Li *et al*., 2023[59]	United Kingdom	-	-	8	9
Dadeya and Dangda, 2016[60]	India	4–7	6.03±1.14	40	10
Al Ammari and Al Shamlan, 2019[61]	Saudi Arabia	-	7.04±2.63	51	9
Jafari *et al*., 2014[62]	Iran	4–6	-	40	8
Scheiman *et al*., 2008[63]	Multicenter	7–12	-	193	10
All			6.80±1.24	4060	

SD: Standard deviation, PEDIG: Pediatric eye disease investigator group

Results

Characteristics of the included studies

A total of 13,256 articles were identified by the authors as illustrated in Figure 1. We reviewed a total of 6457 articles after removing those with duplicate titles. Upon reading the abstracts of the 7026 articles, we excluded 6935 articles which are not meet the inclusion criteria. Subsequently, we further excluded 50 articles after reading their full texts as the essential information is missing. The final systematic review included 41 quality-assessed articles from different countries as shown in Tables 1and 2. The studies included in our systematic review spanned from 2002 to 2023 and involved a total sample size of 4060 children, with a mean age of 6.80 ± 1.24 years.

Discussion

Refractive correction

Previous studies[23,29-32,61] [Table 2] showed that correcting any refractive error by prescribing a full cycloplegic correction, for children aged 3–7 years, with a duration of wearing spectacles correction 2–3 months is the initial step in the treatment of childhood amblyopia, regardless of whether the amblyopia is caused by anisometropia, strabismus, or a combination of both. The prescription of the optimal refractive correction results in

Table 2: Summary of childhood amblyopia treatment modalities

First author and year of study	Types of amblyopia	Baseline VA in amblyopic eye	Treatment and duration	Treatment outcome and conclusion
Kadhum *et al*., 2023[23]	Different amblyopia	0.2 logMAR	Dichoptic versus occlusion, for 24 weeks	Dichoptic therapy with action-video games 15 times more effective than with patching
Liu *et al*., 2021[24]	Different amblyopia	0.28 logMAR	Dichoptic training, for 24 weeks	Dichoptic exercise had significant improvement in VA, in mild amblyopia, and restore, the stereoacuity
Knox *et al*., 2012[25]	Different amblyopia	0.51±0.27 logMAR	Dichoptic training, for week	Improvement the VA in amblyopic eye to 0.42±0.28 logMAR, with improved in stereo-function
Kelly *et al*., 2018[26]	Different amblyopia	0.3–0.8 logMAR	Binocular treatment, for 2 weeks	VA and stereoacuity, improved in amblyopic eye after undergoing binocular treatment
Roy *et al*., 2023[27]	Anisometropic amblyopia	0.74±0.19 logMAR	Dichoptic video game versus 6 h occlusion, for 3 months	Dichoptic therapy yielded superior outcomes in enhancing contrast sensitivity and near stereoacuity
Dadeya *et al*., 2009[28]	Strabismic amblyopia	-	Levodopa/carbidopa, for 3 months	Administration of levodopa/carbidopa lead to improve in VA, particularly under 8 years of age
Cotter *et al*., 2006[29]	Anisometropic amblyopia	20/40–20/250	Optical treatment, 3 months	Correcting RE result in an improvement in VA in at least one-third of children their aged 3–7 years with anisometropic amblyopia
Cotter *et al*., 2012[30]	Strabismic and combined strabismic-anisometropic	-	Optical treatment, for 3 months	Children aged 3–7 years with strabismic and combined-mechanism amblyopia, RE correction alone can result in significant improvement in VA, with at least one-quarter of cases
Chen *et al*., 2007[31]	Anisometropic amblyopia	0.2 logMAR	Optical treatment, for 3 months	With optical treatment alone, children with untreated anisometropic amblyopia achieved approximately four-line improvement in VA and resolved in half
Wallace *et al*., 2007[32]	Bilateral refractive amblyopia	0.50 logMAR	Optical treatment, for 1 year	Treatment of bilateral refractive amblyopia with optical correction improves binocular VA, with most patients achieving a VA of 20/25 or higher
Repka *et al*., 2003[33]	Strabismic and anisometropic	20/40–20/80	2 h versus 6 h patching, for 4 months	2 h of daily patching produce improvement in VA similar to 6 h of patching
Holmes *et al*., 2003[34]	Different amblyopia	20/100–20/400	Full-time patching versus 6 h, for 4 months	6 h of everyday patching yields an improvement in VA similar to improvement by full-time occlusion in the treatment of severe amblyopia from 3 to 7 years of age
Stewart *et al*., 2007[35]	Strabismic and anisometropic	-	6 h patching versus 12 h	6 h of daily patching and 12 h of patching had similar VA outcome
Alotaibi *et al*., 2012[36]	Strabismic and anisometropic	-	Part-time patching with or without near activities, for 12 weeks	Performing near task through occlusion therapy improves the VA more than occlusion alone
Pediatric Eye Disease Investigator Group, 2002[37]	Strabismic and anisometropic	20/40–20/100	6 h patching versus atropine, after 4 months	6 h of daily patching and atropine produce similar VA improvement in the amblyopic eye for children aged 3–7 years
Repka *et al*., 2005[38]	Strabismic and anisometropic	20/40–20/100	6 h patching versus atropine, for 2 years	Atropine or occlusion for 2 years produced similar improvement in VA for moderate amblyopia in children aged 3–7 years
Repka *et al*., 2004[39]	Strabismic and anisometropic	20/40–20/80	Daily versus weekend atropine, for 4 months	Improvement in VA provided by weekend atropine for moderate amblyopia in children aged 3–7 years is comparable to daily atropine treatment
Repka *et al*., 2009[40]	Strabismic and anisometropic	20/125–20/400	Weekend atropine, for 18 weeks	Weekend atropine leads to an improvement in VA in children with severe amblyopia. Younger children have a greater improvement in VA compared to older ones
Laria *et al*., 2011[41]	Anisometropic amblyopia	0.1 logMAR	Bangerter filters, for 12 months	Bangerter filters can be an effective treatment for mild to moderate anisometropic amblyopia
Agervi *et al*., 2009[42]	Anisometropic amblyopia	0.4 logMAR	Optical correction with Bangerter, for 12 months	In anisometropic amblyopia, a faster improvement in VA by using Bangerter filters compared to optical correction alone
Rutstein *et al*., 2010[43]	Strabismus and anisometropia	20/40–20/80	Bangerter filters versus patching, for 24 weeks	Patching is slightly better in improving VA than Bangerter filters
Yang *et al*., 2003[44]	Different amblyopia	-	Levodopa/carbidopa, for 7 weeks	Levodopa influences amblyopia at the visual cortical level
Repka *et al*., 2010[45]	Strabismic and anisometropic	20/50–20/400	Levodopa combined with patching, for 9 weeks	Use of levodopa as a treatment for residual amblyopia was well-tolerated and can potentially improve VA

Contd...

Table 2: Contd...

First author and year of study	Types of amblyopia	Baseline VA in amblyopic eye	Treatment and duration	Treatment outcome and conclusion
Repka *et al*., 2015[46]	Strabismic and anisometropic	20/50–20/400	Levodopa, for 16 weeks	Administration of oral levodopa in conjunction with 2 h patching did not result in a significant improvement in VA
Polat *et al*., 2009[47]	Strabismus and anisometropia	6/12–6/30	Perceptual learning, for 20 weeks	Perceptual learning technique can effectively treat amblyopia in children, even in cases where conventional treatment such as patching has been unsuccessful
Bossi *et al*., 2017[48]	Strabismic and anisometropic	0.2 logMAR	Binocular treatment, for 24 weeks	A home-based binocular therapy for amblyopia, which includes remote monitoring, can lead to significant and quick improvements in visual function
Guo *et al*., 2016[49]	Anisometropic and strabismic	0.2 logMAR	Binocular treatment, for 24 weeks	Binocular treatment led to significant improvement in VA
Li *et al*., 2014[50]	Anisometropic and strabismic	0.47±0.03 logMAR	Binocular iPad treatment, for 4 weeks	Treatment involving binocular iPad led to a quick improvement in VA, and the improvement was maintained for a minimum of 3 months after the treatment was stopped
Birch *et al*., 2015[51]	Anisometropic and strabismic	0.43±0.03 logMAR	Binocular iPad treatment, for 4 weeks	Repeated exposure to binocular stimulation through dichoptic iPad game play was found to be a more effective treatment compared to sham iPad game play
Holmes *et al*., 2016[52]	Different amblyopia	20/40–20/200	Binocular iPad game versus patching, for 16 weeks	VA improved 1.05 lines in the binocular group and 1.35 lines in the patching group
Kelly *et al*. 2016[53]	Strabismus and anisometropia	0.48±0.14 logMAR	Binocular iPad versus patching, for 2 weeks	Binocular iPad game more effective than patching and binocular games help to overcome suppression
Huang *et al*., 2008[54]	Refractive	0.42±0.08	CAM vision stimulator, for 3 months	CAM treatment result in significant improvement in VA
Abu-Ain and Watts, 2023[55]	Different amblyopia	0.6–1.9 logMAR	Occlusive contact lenses, for 6 months	Occlusive contact lenses are a useful assistant in the treatment of amblyopia that not responsive to conventional therapy
Morya *et al*., 2023[56]	Refractive	1.39±0.25 logMAR	Posterior chamber phakic IOL	Posterior chamber phakic IOL is an effective alternative treatment of amblyopia in patients who do not comply with optical correction or refractive surgery
Wu *et al*., 2023[57]	Different amblyopia	20/125	Donepezil, for 12 weeks	Residual amblyopia improves in children treated with donepezil
Hsieh *et al*., 2022[58]	Refractive amblyopia	0.39±0.24	Binocular vision therapy, for 9 months	Vision therapy combined with conventional treatment (optical correction and part-time patching) is more effective than conventional treatment alone
Li *et al*., 2023[59]	Different amblyopia	20/32–20/200	3D video games, for 8 weeks	3D video games have significant improvement on VA and stereoacuity
Dadeya and Dangda, 2016[60]		0.84±0.19	Television video games, for 12 weeks	Occlusion therapy with video games may be considered beneficial for the visual development of children with amblyopia
Al Ammari and Al Shamlan, 2019[61]	Anisometropia	0.94±0.47	Optical correction versus patching, for 16 months	Improvement in VA with both optical correction and patching is higher in patients with hyperopic in contrast with myopic or mixed anisometropia
Jafari *et al*., 2014[62]	Anisometropia	0.40±0.08 logMAR	CAM vision stimulator	The addition of CAM visual stimulation to conventional occlusion is likely to enhance VA and stereopsis
Scheiman *et al*., 2008[63]	Strabismic anisometropic	20/40–20/100	2 h patching versus weekend atropine, for 17 weeks	Weekend atropine and 2 h of patching demonstrated comparable levels of improvement in VA

IOL: Intraocular, 3D: Three-dimensional, CAM: Cambridge visual stimulator, LogMAR: Logarithm of the minimum angle of resolution, RE: Refractive error, PEDIG: Pediatric eye disease investigator group, VA: Visual acuity

a clear and focused image on the fovea, leading to a significant improvement in VA. The most of considerable improvement in visual functions is observed during the few weeks of wearing refractive correction.[64] The American Academy of Ophthalmology published the Preferred Practice Pattern guidelines in 2018, which offer a set of recommendations for determining the need for refractive correction in children.[16] Many studies[14,18,19,50,51] demonstrated that the initial line of treatment for childhood amblyopia is called "optical treatment" or "refractive adaptation," and this phase lasts from 18 to 22 weeks, with steady improvement in VA. Previous systematic review and meta-analysis[14] provided convincing evidence of the efficacy of refractive adaptation in the treatment of childhood amblyopia. The study concluded that the optical treatment, whether for refractive, strabismic, or combined mechanism amblyopia, can result in significant improvement in VA in children aged 3–7 years old and as well as older children. In many cases, this treatment method can even lead to the resolution of childhood amblyopia.

Cotter *et al*.[29] recommended that the refractive correction of amblyopia should be the first line of treatment in children with

uncorrected refractive error. It has been also reported that in children with anisometropic amblyopia, correcting refractive errors lead to an improvement in VA for at least one-third of children between the ages of 3 and 7 years old. Another study conducted by Cotter *et al*.[30] to assess the effect of refractive correction in children their aged 3-7 years old with combined strabismic–anisometropic amblyopia after 18 weeks of using the correction. The findings showed that refractive correction alone can result in significant improvement in VA; this enhancement is clinically noteworthy and observed in most cases, with at least one-quarter of cases resolving without the need for further treatment. Cotter *et al*.[30] recommended that the period to attain the maximum result of refractive adaptation is 18–22 weeks for the children aged 3–7 years and older. This study[30] also shown that there was heterogeneity in terms of gaining improvements in amblyopic eye VA, with around 50% of the children achieving their greatest acuity within 9 weeks, 90% within 18 weeks, and all within 45 weeks. In addition, Chen *et al*.[31] reported that after 2 months of wearing correction, children 3–7 years old with untreated anisometropic amblyopia improved by around four lines with optical treatment alone. Furthermore, Wallace *et al*.[32] conducted a study to evaluate the effectiveness of optical correction on treatment of bilateral refractive amblyopia. They observed that treating bilateral refractive amblyopia in children aged 3–11 years, with optical correction with the majority of patients reaching a VA of 20/25 or greater after 1 year of treatment. Stewart *et al*.[18] found that treating newly diagnosed amblyopic children (mean age 5.1 ± 1.4 years) with refractive error correction alone for 18 weeks resulted in considerable improvement in VA. In addition, the refractive correction during childhood has the potential to alter the degree of strabismus angle in cases of accommodative esotropia, decrease the angle of deviation in partially accommodative esotropia, or correct the deviation in fully accommodative esotropia.[65,66] As mentioned above, there is important evidence in the previous studies that correcting childhood refractive errors, with optical interventions with duration of 2–3 months leads to a significant improvement in VA.

Patching/occlusion

The practice of patching the healthy eye was standard treatment for unilateral amblyopia since 1743, has been known as a suitable option for treating children with anisometropia who fail to achieve complete improvement in VA with optical correction.[1,67] When the VA in the amblyopic eye does not show any further improvement despite using optical correction, and remains a difference of 0.20 logMAR or greater between two eyes, occlusion therapy is recommended.[68,69] On the other hand, there is still a variable difference in the time of patching schedules used in different countries.[69] The PEDIG initiated randomized controlled trials (RCTs) in 1998 to assess various patching procedures for different levels of amblyopia, for a period of 4 months. According to their findings, 2 h of daily patching is as effective as 6 h in children under the age of 7 years with moderate amblyopia (VA from 6/12 to 6/30). In contrast, for children of the same age with severe amblyopia (VA from 6/30 to 6/120), 6 h of daily patching is as effective as full-time patching.[33,34]

Earlier studies[33-38] [Table 2] conducted on various forms of amblyopia in children with the mean age of 6.80 ± 1.24 years after refractive adaptation or optical correction for 3 months or more. They showed a significant improvement in VA after patching for a period of 3 months to 2 years. Stewart *et al*.[35] conducted a study to assess the effect of 6 h of patching compared to 12 h in children (mean age 5.6 ± 1.5 years) with strabismic and anisometropic amblyopia. They found that 6 h of daily patching and 12 h of patching result in a similar VA improvement. In addition, Alotaibi *et al*.[36] showed that performing near activities such as reading or playing video game through patching therapy improves the VA more than patching alone. Pediatric Eye Disease Investigator Group[37] performed a study to assess 6 h of patching VS atropine penalization in children with strabismic and anisometropic amblyopia. The findings showed that 6 h of daily patching and atropine produce similar improvement in VA for children aged 3 to7 years old. In addition to that, Repka *et al*.[38] reported that atropine or patching for 2 years produced similar improvement in VA for moderate amblyopia in children aged 3–7 years. Previous studies[20,70,71] showed that patching for 2 or 6 h can improve VA in children with anisometropic amblyopia, but some of children remain have difficulties in binocular vision fusion. Even if the VA deficit in children with anisometropic amblyopia is resolved through occlusion, they may still have poor stereoacuity compared to their normal peers. This could be due to either the monocular viewing conditions during the patching period or the unilateral amblyopia itself, which can affect the binocular vision function.

Atropine penalization

Atropine penalization has become a widely recognized and accepted method for treating childhood amblyopia and it is commonly used as a substitute for occlusion therapy. Atropine eye drops 1% is commonly used to help children who struggle with adhering to occlusion therapy or to ensure treatment progress. It induces optical defocus in the healthy eye by paralyzing the ciliary muscle result in decreasing in VA. Atropine penalization has a cycloplegic effect, similar to occlusion therapy, which forces the amblyopic eye to be used, especially for near activities. The most effective use of atropine penalization occurs when the nonamblyopic eye has hyperopia.[39] Previous studies conducted by the Pediatric Eye Disease Investigator Group[37,38] reported that 6 h of daily patching and atropine penalization for a period of 2 years produce similar VA improvement in the amblyopic eye for children aged 3–7 years.

A study led by Repka *et al*.[39] compared daily atropine with weekend atropine in children with combined strabismic-anisometropic amblyopia over a 4-month period. They found that the improvement in VA provided by weekend atropine for moderate amblyopia in children aged 3–7 years is

comparable to daily atropine treatment. Furthermore, a study by Repka *et al*.[40] found that weekend atropine treatment for 18 weeks improves VA in children aged 3–12 with severe amblyopia. With this treatment strategy, younger children may experience a greater improvement in VA compared to older ones. In addition, a study by Scheiman *et al*.[63] compared the effectiveness of 2 h of patching versus weekend atropine treatment for children (ages 7–12) with anisometropic and/or strabismic amblyopia over 17 weeks. Their findings demonstrated that both atropine and patching improved VA in children with moderate amblyopia, with approximately one in every five children achieving VA of 20/25 or better in the amblyopic eye. Earlier, it was supposed that fixation switch to the amblyopic eye was needed for atropine therapy to be effective; therefore, atropine was considered unsuitable for severe amblyopia. However, the PEDIG studies have provided evidence to challenge this belief by demonstrating that a fixation shift is not a prerequisite for improvement of VA in childhood amblyopia with atropine treatment.[72] Felius *et al*.[73] reported that atropine penalization having comparable results to patching, it is still considered a secondary choice in treatment of childhood amblyopia. The rationale behind this decision is unclear, given that atropine has several advantages, such as better tolerability, improved cosmetic acceptability, enforced compliance upon instillation, and reduced emotional stress for both the child and their family. In fact, atropine penalization considered a secondary option may have several systemic side effects including dry mouth, increased heart rate, confusion, sensitivity to light, eye pain, and headaches. It has been observed that temporary vision decrease in the nonamblyopic eye is more common with atropine treatment compared to patching. Therefore, Pediatric Eye Disease Investigator Group[37] recommended that it is crucial to carefully monitor vision when undergoing atropine penalization for the children with amblyopia.

Bangerter filters treatment

Bangerter filters have been used in the western countries 60 years as a supplementary treatment for childhood amblyopia. They are commonly used after patching therapy and help transition patients from occlusion therapy. The filters are positioned at the back of the spectacle lens for the healthy eye, and they are intended to be worn constantly. These filters are available in a variety of densities, which are intended to decrease the VA to a level between 6/6 and 6/60. Commonly, a filter is chosen that decreases VA in the healthy eye to a level lower than the VA of the amblyopic eye. Experts recommend using a Bangerter foil bar to determine the appropriate filter density. The density of the filter should increase gradually until the patient's VA declines, helping to select the right density. It is recommended to choose a filter that reduces the VA of the nonamblyopic eye by two lines below the best-corrected VA of the amblyopic eye.[74] However, there are some concerns associated with used of Bangerter filters in the treatment of childhood amblyopia. First, the level of visual degradation caused by the filters may not always match the predicted levels. Second, the filters may fade over time with use. Finally, the reduction in VA caused by the filters may not remain stable over time.[75] Furthermore, the use of a high-density filter (with a density of 0.1) to reduce VA to 6/60 might have resulted in children overlooking or ignore the spectacles and the Bangerter filter. According to a report by Rutstein *et al*.,[43] both children and their parents show a preference for Bangerter filters as a treatment option over patching. This indicates that Bangerter filters may be good option for longer durations therapy compared to patching.

Laria *et al*.[41] conducted a study to assess the effect of Bangerter filters therapy after optical adaptation in children aged 3–11 years with anisometropic amblyopia for 1 year period. They reported that Bangerter filters can be an effective treatment for mild to moderate anisometropic amblyopia. Agervi *et al*.[42] found that children with anisometropic amblyopia, with an average age of 4.4 years, exhibited faster VA improvement when employing Bangerter filters compared to utilizing solely optical correction. This improvement was observed over a period of 1 year. Alternatively, Rutstein *et al*.[43] conducted a 6-month study to compare the efficacy of Bangerter filters over patching for children aged 3–10 years with strabismic and anisometropic amblyopia. They found that patching improves VA slightly more than Bangerter filters. Bangerter filters, on the other hand, are a suitable option to consider for the initial treatment of moderate amblyopia.

Active vision therapy for childhood amblyopia

Active vision therapy, including binocular therapy, dichoptic therapy, perceptual learning, anaglyph glasses, and specific video games effectively improve VA and binocular functions in children with anisometropic and strabismic amblyopia.[75-79] A recent systematic review was conducted to assess the effectiveness of active vision therapy on treatment of childhood amblyopia. The study showed that active vision therapy is a good option for the treatment of anisometropic amblyopia. The review highlighted that the currently available scientific evidence from reviewed studies is not sufficient. The study recommended it is better to conduct more randomized clinical trials to confirm the obtained results and enhance vision therapy techniques. This will lead to a better understanding of the specific neural mechanisms involved.[80]

Binocular therapy

According to Birch,[20] the existing treatments for childhood amblyopia have been successful in improving VA. However, a considerable number of children with amblyopia still face ongoing challenges with binocular functions and fine motor skills. These difficulties put them at risk for recurrent amblyopia in the future. Birch[20] reported about childhood amblyopia evaluation using electrophysiological, risk factor analysis, imaging, and binocular skill assessment. Birch[20] suggested a novel binocular approach for treating childhood amblyopia to achieve two objectives: first, to eliminate residual and recurrent amblyopia, and second, to enhance the poor ocular motor function and fine binocular skills that are commonly associated with amblyopia.

Kelly *et al*.[26] conducted a study to assess the effectiveness of binocular games as a treatment for childhood amblyopia in children aged 4–10 years. The researchers found that VA and stereoacuity significantly improves in children with amblyopia after undergoing a 2-week period of binocular treatment. In addition, a study conducted by Guo *et al*.[49] demonstrated that the use of binocular treatment resulted in a significant improvement in VA in children between the ages of 7 and 17 who were diagnosed with anisometropic and strabismic amblyopia. This improvement was observed over a period of 24 weeks. In a study conducted by Li *et al*.,[50] it was found that a treatment utilizing binocular iPad usage for a duration of 4 weeks in children aged 4–12 years with anisometropic and strabismic amblyopia result in rapid improvement of VA. Furthermore, the observed enhancement in VA persisted for at least 3 months following the treatment. In addition, Birch *et al*.[51] found that in children aged 3–7 years with anisometropic and strabismic amblyopia, repeated exposure to binocular stimulation through dichoptic iPad game play, over a period of 4 weeks was found to be a more effective treatment option compared to sham iPad game play. Holmes *et al*.[52] investigated the efficacy of a binocular iPad game vs. part-time patching in children aged 5–12 years with a trial lasted 16 weeks, and the results showed that the VA of the amblyopic eye improved by 1.05 lines in the binocular group and 1.35 lines in the patching group on average. In addition, a study by Kelly *et al*.[53] found that children between the ages of 5 and 10 with anisometropic and strabismic amblyopia can be successfully treated with a binocular iPad game, over a period of 2 weeks. This game was found to be more effective than patching alone, and it also helped overcome suppression. In a recent study by Hsieh *et al*.[58] revealed that in children aged 5–10 years with refractive amblyopia, vision therapy for period of 9 months combined with conventional treatment (optical correction and part-time patching) is more effective than conventional treatment of amblyopia. The authors[59,60] studied the impact of TV and three-dimensional video games on the treatment of amblyopia in children aged 4–10 years over 8 weeks. The findings indicated a significant improvement in VA and stereoacuity.

Dichoptic training

Dichoptic training uses separate stimuli for each eye, with the fixing eye exposed to lower-contrast stimuli. This method aims to prevent suppression and promotes binocular single vision.[81] Thus, dichoptic therapy actively promotes binocular fusion by presenting a stronger stimulus to the amblyopic eye compared to the fellow eye.[20] Commonly, there are three methods used to achieve the goal of dichoptic therapy in the treatment of childhood amblyopia. The first method involves lowering the contrast of the image presented to the normal eye, known as antisuppression therapy. The second method is called the balanced binocular viewing, which blurred the image presented to the normal eye. The third method, interactive binocular treatment, can be achieved by presents various components of a visual scene to each eye; this requires the integration of information from both eyes to perceive.[82]

A recent study by Roy *et al*.[27] compared the effectiveness of dichoptic video games to 6 h patching in children aged 5–15 years with anisometropic amblyopia, over a period of 3 months. The researchers found that dichoptic therapy was more effective than patching in improving contrast sensitivity and near stereoacuity. In addition, dichoptic therapy achieved comparable results to patching in terms of improving distance and near vision. Furthermore, Kadhum *et al*. 2023[23] reported that dichoptic therapy for the children aged 4–12 years with action-video games, over a period of 24 weeks under supervision was 15 times more effective than occlusion at home. In a study conducted by Knox *et al*.,[25] dichoptic therapy was found to improve VA in the amblyopic eye (from 0.51 ± 0.27 to 0.42 ± 0.28) logMAR, for children mean age 8.5 ± 2.6 years over the course of a week. The conclusion drawn from the study was that dichoptic-based therapy not only improved monocular VA but also enhanced stereofunction. In addition, the study by Liu *et al*.[24] found that the dichoptic exercise significantly improved VA, in children aged 6–16 years over the course of a week 24 weeks with mild amblyopia, and restored stereoacuity in some cases.

Perceptual training

Perceptual training improves sensory performance through regular practice and challenging visual activities that strengthen neural pathways, resulting in long-term visual improvement.[83] Dosher and Lu[83] reported that perceptual training can be better explained as the enhancement of brain network functions that integrate various cognitive processes such as sensory processing, decision-making, attention, and reward processing this improve plasticity and system stability. Perceptual learning theory was first applied through the Cambridge Visual Stimulator (CAM) system, which involved presenting high contrast rotating gratings to the children and allowing them to view the stimuli with their amblyopic eye.[84] Despite the promising initial results of using the CAM vision stimulator, its use has declined significantly due to subsequent controlled studies[85,86] that failed to demonstrate any advantages over conventional patching in treatment of childhood amblyopia. However, the emergence of interactive software tools has sparked renewed interest in using visual stimulation for perceptual learning as a novel method for treating childhood amblyopia.

Polat *et al*.[47] conducted study to assess the efficacy of perceptual training on strabismic and anisometropic amblyopic children with mean age of 7.3 years, over a period of 20 weeks. They reported that the perceptual training can effectively treat amblyopia, even in cases where conventional treatment such as patching failed to achieve improvements in the VA. Huang *et al*.[54] showed that the use of CAM vision stimulator for children aged 3–7 years with refractive amblyopia resulted in significant improvement in VA within a period of 3 months. However, children <4 years old and those with myopia may experience less improvement in VA outcome following CAM

treatment. In addition, Jafari *et al*.[62] performed a study to assess the effect of CAM vision stimulator on children aged 4–6 years with anisometropic amblyopia. The finding showed that the addition of CAM visual stimulation to conventional occlusion therapy is likely to enhance VA and stereopsis.

Medication-based treatment for childhood amblyopia

Levodopa/carbidopa therapy

The neurotransmitter dopamine is found in the retina and cortex plays a role in visual cortical plasticity. Iuvone *et al*.[87] conducted a study on monkeys and revealed that the concentration of dopamine in the retina decreases when one eye is covered with an opaque contact lens, in comparison to the uncovered eye. In addition, the occlusion of one eye with an opaque contact lens caused a decrease in the level of tyrosine hydroxylase activity in the retina of monkeys. This enzyme is essential for the synthesis of dopamine, and a reduction in its activity would lead to a corresponding decrease in dopamine levels. The common medication for childhood amblyopia is a combination of levodopa and carbidopa. Carbidopa helps increase the amount of levodopa that reaches the brain by blocking its conversion to dopamine outside the brain, thereby reducing the required concentration. Gottlob and Stangler-Zuschrott[88] found that a single administration of levodopa result in a significant improvement in contrast sensitivity and reduction in the size of the scotoma associated with fixation point in patients with strabismic amblyopia. Moreover, Yang *et al*. showed that oral administration of levodopa/carbidopa (0.5/0.12 mg/kg) three times per day for 7 weeks in older children influences amblyopia at the visual cortical level. The authors suggested that functional magnetic resonance imaging can be a useful tool in assessing changes of visual cortical activity after the treatment.[44]

Dadeya *et al*.[28] reported that the administration of oral levodopa/carbidopa three times per day for 3 months has been shown to improve VA in children with strabismic amblyopia, particularly in children under 8 years of age. A recent study by Repka *et al*.[45] investigated the effectiveness and safety of using levodopa combined with patching in children with strabismic and anisometropic amblyopia. The study involved giving children capsules containing levodopa combined with carbidopa at a dosage of 0.17 mg/kg three times a day for a duration of 9 weeks. The results showed that the use of levodopa in treating residual amblyopia in children aged 8–17 years was well-tolerated and had the potential to improve their VA. Conversely, Repka *et al*. on their another study[46] reported that in children aged 7–12 years with residual amblyopia, the administration of oral levodopa three times a day for a duration of 16 weeks in conjunction with 2 h patching did not result in a significant improvement in VA compared to a placebo and patching treatment. Comparing the above-mentioned studies is challenging due to differences in study design, patient characteristics (age, type, and severity of childhood amblyopia), prior treatments, levodopa dosage, and duration of follow-up. In addition, many of these studies lacked double-blind, placebo-controlled designs and had small sample sizes with short follow-up periods. Recently, Razeghinejad *et al*.[89] reported that there is no agreement on the appropriate dosage and duration of levodopa therapy for childhood amblyopia, and the impact of levodopa on amblyopia is often short-term.

Donepezil therapy

Donepezil is the most prescribed medication for Alzheimer's disease. Donepezil primarily enhances cognition and function by blocking the action of the acetylcholinesterase enzyme in the brain. Donepezil, a medication commonly used to treat Alzheimer's disease, can have effects on multiple aspects of the disease's underlying mechanisms.[90] Recently, Wu *et al*.[57] reported that in adult mice, the administration of acetylcholinesterase inhibitors has been shown to facilitate visual neuroplasticity and support the process of recovering from amblyopia. Furthermore, Wu *et al*.[57] conducted study in patients with mean age 16 years with residual anisometropic and strabismic amblyopia treated with daily oral donepezil for 12 weeks. They found that older children treated with donepezil showed improvement in residual amblyopia, suggesting that pharmacological modulation of visual cortex plasticity could potentially cure amblyopia. However, the current review identified only one paper with a small number of patients using donepezil for childhood amblyopia treatment, indicating the need for further studies to establish the effectiveness of acetylcholinesterase inhibitors in treating amblyopia.

Occlusive contact lenses

Earlier studies[91,92] reported that occlusive contact lenses have been employed in the management of amblyopia with positive outcomes, as it has not only resulted in an improvement in VA but also in increased compliance with subsequent patching therapy. A recent study by Abu-Ain and Watts[55] evaluated the effectiveness and risks associated with occlusive contact lenses in treating children with several types of amblyopia, over a period of 6 months. These children had previously been unsuccessful in their conventional amblyopia treatment using occlusion and atropine penalization. They found that occlusive contact lenses are a useful assistant in the treatment of childhood amblyopia, which is not responsive to conventional therapy, the side effect profile is acceptable, but the patients require intensive checkup visits.

Surgical treatment of childhood amblyopia

Refractive surgery is a successful treatment in children with severe anisometropia and isometropia accompanied by amblyopia when glasses or contact lenses are not effective. Stahl[93] revealed that the field of refractive surgery in children has progressed slowly due to the strict guidelines and concerns regarding the potential long-term effects on the developing eye. Consequently, there are few publications available on this topic. In recent times, there has been a shift in research focus toward intraocular (IOL) procedures as an alternative to laser refractive surgery in treatment of childhood amblyopia. Researchers[94-96] propose that implanting IOL lenses is a safe approach to treat refractive amblyopia in children with

anisometropic hyperopia or myopia who do not comply with conventional treatment. Recently, Morya *et al*.[56] reported that posterior chamber phakic IOL considered to be an effective alternative treatment of amblyopia in patients who do not comply with glasses, contact lenses, or refractive surgery. Furthermore, Sun and Kraus 2023[97] reported that clear lens extraction (CLE) and refractive lens exchange (RLE) can be considered a potential option for the treatment of childhood amblyopia with high refractive errors. These procedures are particularly beneficial when traditional treatments failed to improve the vision for amblyopic children or when the child has coexisting neurodevelopmental disorders. Although studies have demonstrated encouraging outcomes in enhancing visual results among children with high refractive error, along with low complication rates. Sun and Kraus[97] recommended that additional research is required to investigate the long-term safety and effectiveness of CLE and RLE procedures.

Conclusion

Childhood amblyopia is currently treated through the multiple approaches [Figure 2]. Correcting child refractive errors with given time of optical adaptation, followed by visually stimulating the amblyopic eye while patching the dominant eye. The patching can be achieved through different methods such as occlusion, atropine penalization, and Bangerter filters. The reviewed studies showed that the period of patching depend on severity of amblyopia, whereas the part time occlusion found effective in the most types of childhood amblyopia. Several RCTs over the last two decades by PEDIG have provided well-documented evidence of the effectiveness of refractive correction and patching as a treatment for childhood amblyopia. To enhance binocular functions and adherence to treatment for the children with amblyopia, there have been a promising outcome in the binocular treatment approaches. New strategies that used dichoptic treatment, which involves simultaneous binocular visual stimulation. These methods aim to enhance VA, binocular functions, and promote stereoacuity. The reviewed studies showed that used of active vision therapy, perceptual learning such as CAM visual stimulator and the novel interactive software tools have satisfactory results in treating childhood amblyopia. Furthermore, some studies showed drugs such as Levodopa and Donepezil influences visual cortex plasticity and showed improvement in the VA in children with amblyopia. In addition, occlusive contact lenses are considered a good option in children who not compliance with conventional treatment of amblyopia. Recently, posterior chamber phakic IOL is reported to be an effective alternative method for the treatment of children with amblyopia who do not comply optical correction and refractive surgery. In addition, CLE and RLE are reported as a good option for the treatment of childhood amblyopia associated with high refractive errors.

Acknowledgment

The authors would like to thank Dr. Naveen K Challa for his help in editing the manuscript.

Financial support and sponsorship

Nil.

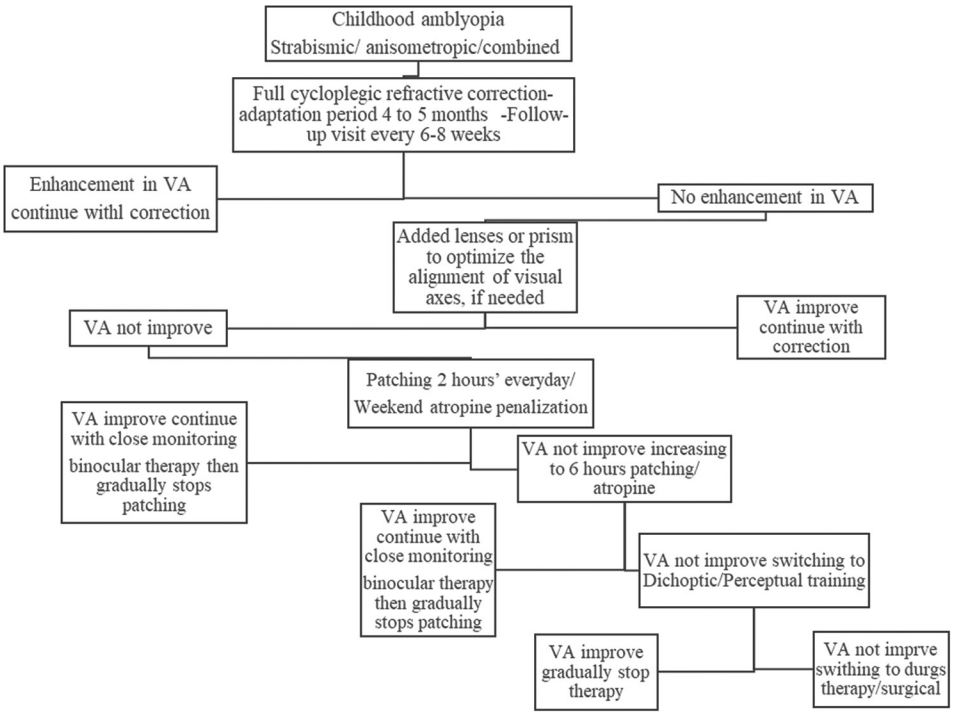

Figure 2: A systematic method for management of childhood amblyopia. VA: Visual acuity

Conflicts of interest

There are no conflicts of interest.

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