Introduction
Amblyopia literally means “dullness of vision” (Greek ambly dull, + ops, vision, sight).

It is defined as a decrease of visual acuity in one eye when caused by abnormal binocular interaction or occurring in one or both eyes as a result of pattern vision deprivation during visual immaturity, for which no cause can be detected during the physical examination of the eye(s) and which in appropriate cases is reversible by therapeutic measures.

Albrecht von Graefe is said to have defined amblyopia as the condition in which the observer sees nothing and the patient very little.

Epidemiology
Amblyopia is a growing social burden. It is difficult to measure the frequency of amblyopia in the general population. However, many regional and population specific studies have attempted to estimate the prevalence. In a metaanalysis, the global prevalence of amblyopia was estimated to be 1.44%. In another study, the prevalence was 1.1% of the school children in Southern India.

Pathophysiology
Amblyopia is one of the most common causes of vision loss in childhood. Conventionally, amblyopia has been considered as a unilateral visual diminution and hence, most definitions fail to describe the visual acuity in defining bilateral amblyopia. The mainstay of treatment consists of occluding the sound eye with patches. Choosing the appropriate duration of patching remains a source of confusion for many clinicians. There are also greatly varied opinions when it comes to deciding the upper limit of age for which patching is effective. Many clinical trials have been performed to answer these questions. This article aims to review the current literature regarding the amblyopia definition and treatment strategies to guide the clinician in diagnoses and management of amblyopia more confidently.

Abstract
Amblyopia is one of the most common causes of vision loss in childhood. Conventionally, amblyopia has been considered as a unilateral visual diminution and hence, most definitions fail to describe the visual acuity in defining bilateral amblyopia. The mainstay of treatment consists of occluding the sound eye with patches. Choosing the appropriate duration of patching remains a source of confusion for many clinicians. There are also greatly varied opinions when it comes to deciding the upper limit of age for which patching is effective. Many clinical trials have been performed to answer these questions. This article aims to review the current literature regarding the amblyopia definition and treatment strategies to guide the clinician in diagnoses and management of amblyopia more confidently.

Keywords: Amblyopia, Amblyopia Classification, Amblyopia Treatment, Patching, Perceptual Learning, Dichoptic Training.

Classification
Amblyopia can be classified based on the cause as follows:

Strabismic Amblyopia
Patients with strabismus who strongly favour one eye for fixation and who have a unilateral rather than an alternating fixation pattern are most likely to acquire strabismic amblyopia. It is more common in esotropes than in exotropes. This could be attributed to the fact that exotropia is often intermittent at its onset. Secondly, in esotropia the fovea of the deviating eye has to compete with the strong temporal hemifield (nasal retina) of the fellow eye while in exotropia the fovea competes with the weaker contralateral nasal hemifield (temporal retina).

Refractive Amblyopia
Refractive amblyopia results from consistent defocus of retinal image in one or both eyes. There are 3 types: Anisometropic, Isoametropic and Meridional.

Anisometropic Amblyopia
In anisometropic amblyopia, dissimilar refractive errors in the 2 eyes cause the image on 1 retina to be chronically defocused. This leads to active inhibition of more ametropic eye to eliminate sensory interference caused by superimposition of a focused and a defocused image originating from the fixation point (abnormal binocular interaction). Anisohyperopia > 1.5 D, Anisomyopia of > 3.0 D and, Anisoastigmatism > 2.0 D is amblyopiogenic.

Isoametropic Amblyopia
Isoametropic amblyopia (bilateral ametropic amblyopia) is a bilateral decrease in visual acuity that results from large, approximately equal, uncorrected refractive errors in the 2 eyes. The mechanism of this form of amblyopia involves the...
deleterious effect of blurred retinal images on the immature visual system. Hyperopia exceeding 4.00–5.00 D and myopia exceeding 5.00–6.00 D carry a risk of inducing isoametropic amblyopia.

**Meridional Amblyopia**

Meridional amblyopia results from uncorrected bilateral astigmatism in early childhood leading to a loss of resolving ability limited to the chronically blurred meridians. The degree of cylindrical isoametropia that produces meridional amblyopia is not known, but most ophthalmologists recommend correction when there is more than 2.00–3.00 D of cylinder.

**Visual Deprivation Amblyopia**

The least common but most severe and difficult to treat of the forms of amblyopia, visual deprivation amblyopia occurs because of an eye abnormality that obstructs the visual axis or otherwise interferes with central vision. The common causes of visual deprivation amblyopia (also known as amblyopia ex anopsia) is congenital or early-acquired cataract, blepharospasm, surgical lid closure, unilateral complete ptosis, corneal opacities, and vitreous haemorrhage. Unilateral visual deprivation amblyopia tends to be worse than amblyopia produced by bilateral deprivation of similar degree, because interocular competition adds to the direct developmental impact of severe image degradation.

**Organic Amblyopia**

The term organic amblyopia is applied to reduced visual acuity in the absence of gross, readily detectable anomalies in an eye with subtle, sub-ophthalmoscopic morphologic retinal damage. This implies that the retina is essentially normal on ophthalmoscopic evaluation but retinal or neurological damage is uncovered on further testing.

**Reverse Amblyopia**

Reverse amblyopia is a form of visual deprivation amblyopia that develops in the fellow eye as a result of patching (occlusion amblyopia) or penalization.

**Idiopathic Amblyopia**

An infrequently occurring and most intriguing form of unilateral amblyopia has been observed in the absence of the usual amblyopiogenic conditions and in apparently normal patients with a negative history for strabismus, uncorrected refractive errors, or visual deprivation. As in other forms of amblyopia, visual acuity improves after patching of the sound eye, but the amblyopia recurs when treatment is suspended. Von Noorden postulated that binocularly provoked inhibition has been conditioned during infancy by an amblyopiogenic factor, such as transient anisometropia that persists even though this original obstacle to bifoveal fusion is no longer evident (Table 1).

**Evaluation**

Amblyopia is diagnosed when a patient has a condition known to cause amblyopia and has decreased visual acuity that cannot be fully explained by physical abnormalities of the eye.

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### Table 1. Classification of Amblyopia based on aetiology.

|   |   |
|---|---|
| 1. | Strabismic amblyopia |
| 2. | Refractive amblyopia |
| | a) Anisometropic amblyopia |
| | b) Isoametropic amblyopia |
| | c) Meridional amblyopia |
| 3. | Visual deprivation amblyopia |
| 4. | Organic amblyopia |
| 5. | Reverse amblyopia |
| 6. | Idiopathic amblyopia |

### Fixation Preference

In preverbal children, with free alternation one may safely assume that amblyopia is absent. If a patient habitually prefers one eye for fixation, for instance, if a child repeatedly and strongly objects to having the fixating eye covered but does not mind if the cover is placed over the deviated eye, it is reasonable to assume that visual acuity in the deviated eye is poor.

### Visual Acuity

From a practical clinical standpoint, a difference of 2 or more lines on Snellen visual acuity chart in unilateral amblyopia and a visual acuity of 6/12 or worse in bilateral amblyopia is commonly used as a diagnostic criterion for amblyopia. However, Paliaga pointed out that any and every difference in visual acuity produced by amblyopiogenic factors should be classified as an amblyopia. Thus, in unilateral cases, a visual acuity of 6/9 to 6/12 is often considered as mild amblyopia. Though different studies use different definitions for the severity, a common description for amblyopia severity is presented (Table 2).

### Table 2: Classification of Amblyopia based on severity.

| Severity       | Visual acuity |
|----------------|---------------|
| Mild amblyopia | 6/9 to 6/12   |
| Moderate amblyopia | 6/12 to 6/24 |
| Severe amblyopia | <6/24        |

### Crowding Phenomenon

The inability to discriminate optotypes that are crowded together closely is termed as crowding phenomenon or separation difficulties. Most amblyopic eyes seem to have better single letter acuity than “Snellen” line acuity. This can be explained based on counter interaction. Crowding phenomenon is not specific to amblyopia.

### Neutral Density Filters

Neutral density filters reduce the amount of light reaching the retina. Ammann observed that neutral density filters reduce vision in eyes with central retinal lesions and glaucoma, whereas the vision of eyes with amblyopia was not reduced by such filters and was occasionally even slightly improved. This Ammann phenomenon demonstrates the relative increase in mesopic visual acuity compared to photopic conditions in eyes with strabismic amblyopia.
Near Visual Acuity
Visual acuity at near fixation has been found to be better than at distance fixation in a number of amblyopes.13,14

Fixation Pattern
Many patients with strabismic amblyopia have eccentric fixation. Such patients do not assume central fixation when the fellow eye is covered.15,16

Colour Vision
Colour sense in amblyopic eyes is often abnormal, especially when the amblyopia is severe. However, the colour vision defect resembles one detected in normal eyes when eccentric retinal areas are being tested.17,18

Contrast Sensitivity
Contrast sensitivity measured with an alternating pattern of black and white stripes (gratings) of variable width (spatial frequency) is decreased in amblyopes, especially at higher frequency.19,20,21,22,23

Treatment
Treatment of Amblyopia involves following steps:
1. Treat the cause of visual deprivation
2. Correct any significant refractive errors
3. Force the use of amblyopic eye by limiting use of the better eye

Treatment of Cause: Prompt removal of corneal and lenticular opacities is advocated to prevent visual deprivation amblyopia. Correction of significant degree of strabismus helps in achieving binocular single vision (BSV) and eliminate the cause of strabismic amblyopia.

Refractive Correction: Guidelines based on the results of Amblyopia Treatment Studies (ATS) conducted by Paediatric Eye Disease Investigator Group (PEDIG):

Full correction of astigmatism, myopia and anisometropia to provide equally clear retinal images.24 Hyperopia is either fully corrected (e.g., in cases of esotropia) or under corrected (e.g., in cases without esotropia) by no more than +1.5 D spherical equivalent (SE) with any reduction in plus sphere reduced symmetrically in the two eyes.

Two ATS studies in 3 to <7 years children have shown that refractive correction alone can lead to mean amblyopic eye visual acuity (VA) improvement by approximately 3 lines and resolution of amblyopia (equal visual acuity in both eyes or amblyopic eye visual acuity within 1 line of sound eye visual acuity) occurred in 25-33% of cases.25,26

Another study in 3 to <10 years old children concluded the mean improvement in binocular VA of approximately 4 lines.27

A follow-up interval of 6 to 8 weeks, until improvement in the amblyopic eye visual acuity plateaus, is a practical schedule for monitoring children for an optical treatment effect.

Limiting the Use of Better Eye: When patients do not respond to refractive correction alone, or VA ceases to improve, the amblyopic eye can be forced to fixate by limiting the use of better eye in following ways:
1. Occlusion therapy (patching)
2. Pharmacological penalisation
3. Bangerter filters

Patching: Occlusion of the sound eye with adhesive patches, or spectacle mounted occluders to obligate the use of amblyopic eye.

Duration
How long to patch? 2 hours of daily patching is as effective as 6 hours of daily patching for moderate amblyopia (VA of 6/12 to 6/24 or 20/40 to 20/80).28 6 hours of daily patching is as effective as full-time daily patching in severe amblyopia (VA of 6/30 to 3/60 or 20/100 to 20/400).29

In case of residual amblyopia after 12 weeks of 2 hours patching, increasing the duration to 6 hours led to further improvement in 40% of children.30

Patching Age Group:
Till what age patching is effective? 76-93% children responded to in the age group 3 to <7 years in different amblyopia types with different patching schedule. [28,29] 53% children responded to patching in age group 7 to 12 years.31

25% children responded overall to patching in age group 13 to 17 years. In the same group, response was seen in 47% among patients not previously treated.

Pharmacological Penalisation: Pharmacological penalisation is carried out by instilling a long-acting topical cycloplegic agent, atropine sulphate (1%), into the sound eye of a child with amblyopia.

Conclusions from various studies:
In moderate amblyopia, pharmacological penalisation with daily administration of 1 drop of 1% atropine in the sound eye showed similar improvement to 6 hours of daily patching in children 3 to <7 years old.32

VA improvement was slower with atropine penalisation compared to patching, but the magnitude of VA improvement at 6 months was similar.

A slightly higher degree of acceptability was reported with atropine treatment compared to patching. Less frequent administration of 1% atropine drops (weekly once) led to essentially identical improvement in VA (2.3 lines).33
In case of severe amblyopia of 20/125 to 20/400, weekend atropine administration led an average VA improvement of 4.5 to 5.1 lines in the age group 3 to <7 years, and 1.5 lines in the age group 7 to 12 years.34

Systemic side effects of Atropine: Dryness, flushing of skin, fever, confusion, unusual behaviour, and irritability rarely occurred during ATS. When such side effects occur, daily instillation of 5% homatropine eye drops can be substituted for atropine.

**Bangerter Filter Treatment:** A Bangerter filter is a translucent filter that is applied to the sound eye’s spectacle lens for full time wear for amblyopia treatment. Different densities of filters produce different degrees of defocus.

Full-time wear of Bangerter filter provided VA improvement (1.8 lines) similar to 2 hours of daily patching (2.3 lines).35 Parents reported fewer adverse effects and better compliance with the Bangerter filters than with patching.

**Clinical Relevance**

From the preceding discussion, following points can be concluded for clinical practice:

A trial of patching should be provided to all children, irrespective of the age group.

A 2-hour patching schedule is recommended for initial therapy, increasing to 6 hours in case of inadequate response. Alternatively, weekly once atropine penalisation can be substituted for inadequate response or as initial therapy in children with poor compliance to patching.

This has been summarised in an algorithmic flow chart for clinical use (Figure 1).

**Recent Advances In Amblyopia Management**

The recent advances in amblyopia therapy can be divided into binocular therapies and pharmacological therapies.

**Binocular Therapies**

In amblyopia the stereo equity is reduced and there is abnormal binocular summation.36 But some amount of binocular cortical communication still persist in amblyopia.37 The hypothesis for binocular therapies is to stimulate these persistent binocular neural circuits and thereby “awaken” the amblyopic eye.38,39 The two types of binocular therapies are:-

1. Perceptual learning
2. Dichoptic training.

**Perceptual Learning**

In 1963, Eleanor Gibson introduced the term perceptual learning which refers to long-lasting changes in perception that results from practice or experience.40 In simple words, perceptual learning works on the principle that practice makes perfect. A number of visual tasks have been developed as a means to apply perceptual learning. Repeated practice of these visual tasks improves visual performance. These include the following :-

- **Vernier Acuity Tasks**: these measures the ability to find a misalignment among 2 line segments or gratings. It can be tested unilocular or binocularly.

- **Gabor Patch Detection**: A gabor's patch consist of a sine wave grating seen through a gaussian window. The gaussian window eliminates the “sharp edges”, so the change at the edges of the grating is not as abrupt so that the waves are detected instead of the sharp edges. These gabor patches are known to match the receptive field properties of the primary visual cortex.

- **Contrast Detection Or Discrimination**: In this visual task, the observers report which of the two stimuli appears to have a higher contrast.

- **Letter Identification In Noise**: In this does the patient is asked to find a target letter or an object which is hidden among the various distractors or in noise.

Perceptual Learning Helps in improvement of the specific visual function which is required in the respective task and also the improvement in the snellen's visual acuity.
also shown reduction in the crowding phenomena due to reduction in lateral inhibition within the brain.

The drawback of perceptual learning is that most of the studies which favoured perceptual learning work done in a very small sample and long-term follow-up for the efficacy of the therapy is lacking. Moreover, the efficacy of this therapy was established in laboratory settings only and not in real life situations (Figure 2, 3, and 4). According to Figure 2:

**Figure 2:** Vernier Acuitit Testing.

**Figure 3:** GABORS PATCH which is seen through a gaussian window showing nonsharp margins.

**Figure 4:** Gabor patches.

**Dichoptic Training**

Unlike in perceptual learning where a single visual stimulus is administered to both eyes simultaneously; in dichoptic training, independent and visually different stimulus is presented to each eye. Therefore, for the completion of dichoptic training; integration of these unioocular stimuls under binocular viewing system is important. As the patient utilizes his binocular apparatus; dichoptic training helps the patient to overcome the suppression of amblyopic eye. The stimulus which is shown to amblyopic eye usually has a higher contrast than shown to the non amblyopic fellow eye. As the binocular function improves, the contrast is gradually reduced still no difference exist between the two eyes. Early studies of dichoptic training showed promising results in adult amblyopes and therefore give a potential for improvement of amblyopia outside the critical period. Recently, the dichoptic training has shifted from being clinically based to home-based training. Binocular iPad therapy involves using iPad display with lenticular overlay for the purpose of dichoptic training. It consists of a textured screen overlay of two slightly dissimilar images which when fused gives a perception of depth (example: holograms). The only difficulty with the lenticular design is that it needs stable head positioning and therefore it is difficult to use in young children and unsupervised patients. This has resulted in a recent shift from the lenticular design to the anaglyphic designs. It utilizes anaglyphic images i.e red green dichoptic images with accompanying red green glasses in the form of various iPad games. The falling block game was developed using the same principle however there was poor compliance associated as the game was not stimulating enough to allow the effective playing time. There is a need for more engaging games with reward reinforcement in order to develop interest and increase the playing time.

Interactive binocular treatment system (I-BiT) is used for treatment of amblyopia via virtual reality games and movie watching. This special software selectively stimulates the amblyopic eye without compromising the fellow eye visual acuity. Pharmacological Therapy

The pharmacological therapy /drug therapy was developed to treat amblyopia in children for whom the conventional treatment has failed and for those outside the critical period of amblyopia. The two major drugs which have been investigated for pharmacological therapy of amblyopia are levodopa-carbidopa and citicholine.

**Levodopa-Carbidopa**

It is hypothesized that the retinal levels of dopamine are decreased in amblyopia. Therefore increasing the level of dopamine can improve vision in the context of amblyopia. Levodopa is an immediate precursor of Dopamine and is FDA approved for use in neurology as a neuroprotective agent. Carbidopa is a peripheral decarboxylase inhibitor which prevents conversion of levodopa to dopamine, thereby increasing the availability of levodopa in the central nervous system.

PEDIG investigators conducted a randomised controlled trial of levodopa in treatment of residual amblyopia after patching in children of age group 7 to 12 years. They found daily administration of oral levodopa (0.76 mg/kg) with carbidopa(0.17 mg/kg) three times/ day for 16 weeks in addition to continued two hours of patching produced no clinically or statistically significant improvement in visual acuity compared with placebo and patching. Another prospective study was conducted on 19 patients in the age group 7 to 30 years, who were subject to treatment with Levodopa and Carbidopa on doses of 0.7mg/kg/day, a ratio of 4:1 divided into three daily doses for 5 weeks, combined
with full occlusion (24 hours/day) of the dominant eye. The study reported a significant improvement on the visual acuity of the amblyopic eye, which persisted up to 1 year after the treatment. Levodopa was also found to be effective in treatment of amblyopia in adults in a dose of 2 mg/kg/dose for 6 weeks.

Levodopa is usually given along with carbidopa in a 4:1 dose ratio either as oral tablet or oral suspension. 0.5 - 2 mg/kg/dose thrice a day is considered a safe and effective dose.[51]

Levodopa is available as liquid suspension but has an unpleasant taste. Its side effects include mild nausea, vomiting and headache. The gastrointestinal side effects can be reduced by adding carbidopa to levodopa. As carbidopa cannot cross the blood brain barrier, it inhibits the peripheral conversion of levodopa to Dopamine, thereby preventing its side effects.

Citicoline

Citicoline (Cytidine-5-diphosphocholine) or CDP-choline is a complex bimolecule involved in cellular metabolism. Citicoline activates the biosynthesis of structural phospholipids in the neuronal membranes, increases brain metabolism, and influences the levels of different neurotransmitters. It has been shown to increase acetylcholine, norepinephrine, and dopamine levels in the central nervous system. It is usually used to prevent nerve damage and allowed recovery from traumatic, ischemic and degenerative insults.[52] Intramuscular CDP-choline (1 g/day) for 15 days has been shown to improve visual acuity, contrast sensitivity and VEP amplitudes in both normal and Amblyopic eyes. Campos et al. reported a statistically significant improvement in VA following treatment with citicoline (1000 mg intramuscular administration, daily for 15 days) in older children, and found that significant visual improvement occurred in both amblyopic and sound eye, which remained stable for at least 4 months after stopping the treatment. Pawar et al. used oral citicoline in the dose of 250 mg OD (age <5 years) and 500 mg OD (age ≥5 years) for 6 months. After this period, citicoline was gradually tapered by giving half the dose daily for 2 months, half the dose on alternate days for another 2 months and then discontinued. The study concluded that improvement in visual acuity with citicoline plus patching was significantly more than that with patching alone, in one year of treatment.

The research work in citicoline, however, lacks behind that of levodopa. More long-term follow-up is necessary to establish long term efficacy in citicoline.

Conclusion

Amblyopia is a significant cause of diminished vision in children. Early diagnosis and treatment are the mainstay of management. Previous experience based empirical practice of full-time patching has given way to new evidence-based part-time patching practices. Pharmacological penalisation and Bangerter filters provide important alternatives to patching. Medical management of amblyopia is yet to yield convincing results but the future prospect is exciting.

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