Methods to treat amblyopia date as far back as around 900AD. The condition remains the most common cause of binocular vision loss in children, with a prevalence reported as one to five per cent in childhood.

With drives towards improved education regarding the importance of childhood vision assessments as a standard for all, our input into this condition will only continue to increase.

Because amblyopia is a neural disorder that results from abnormal stimulation of the brain during the critical periods of visual development, it is essential to understand the neural mechanisms of amblyopia in order to devise better treatment strategies. This is the focus of the following overview.

MECHANISMS

The term amblyopia is defined as defective visual acuity (VA) in one or both eyes, which persists after correction of the refractive error and removal of any pathological obstacle to vision. It is caused by inadequate stimulation of the visual system during the critical period of vision development in early childhood (<eight years). This is most marked under the age of two years. Initial severity of the amblyopia and the age of the patient at the start of treatment, the dosage of treatment has been shown to influence the visual outcome of the patient.

Amblyopia may be unilateral or bilateral and the cause may be any combination of the following three factors.

- **Light deprivation.** There is no stimulus to the retina. This is uncommon as it is likely that some light enters the eye even in dense cataract (white noise);
- **Form deprivation.** The retina receives a defocused image as with refractive errors; and
- **Abnormal binocular interaction.** This is involved in all types of unilateral amblyopia. It occurs when incompatible images are formed on the fovea.

The prognosis for achieving good VA decreases when more than one of these factors are present together in one case.

Amblyopia can be classified into the following five types.

- **Stimulus deprivation.** This is as a result of lack of adequate visual stimulus in early life. This can affect one or both eyes, can be complete, ie. little or no light enters the eye and no image is formed, or it can be partial, ie. allowing some passage of light and the formation of a poor-quality image. It is caused by conditions such as ptosis, congenital cataract, or other opacities such as vitreous or corneal and also nystagmus.
- **Ametropic.** This is bilateral amblyopia as a result of high degree of uncorrected bilateral refractive error; both spherical and cylindrical errors can cause this type.
- **Strabismic.** This is the consequence of constant, or near constant, unilateral strabismus with onset in childhood. Although far more common in patients with manifest strabismus, those with intermittent/decompensating strabismus do require monitoring.
- **Meridional.** This is the result of uncorrected astigmatism, where one or both eyes are predominantly astigmatic. The mechanism for this is that a relatively clear image is formed along the more emmetropic axis, but a blurred image is formed along the more ametropic axis, giving rise to meridional amblyopia in the more ametropic direction.
- **Anisometropic.** This is as a result of a significant difference in the...
refractive error between either eye, where one eye has the visual advantage at all distances. This usually occurs when the difference is more than one dioptre.

The refractive error (measured in dioptre) that is thought to be capable of inducing amblyopia is shown in Table 1.

Wiesel and Hubel7,8 and a large body of subsequent work20-23 have demonstrated that abnormal visual experience results in alterations in functional properties and anatomic architecture in the primary visual cortex (V1) (see Box 1); and that more profound changes are seen in animals with early visual deprivation than in those with anisometropic or strabismic amblyopia.

It has been shown that amblyopia leads to a neuronal acuity (spatial resolution) deficit for mid- to high-stimulus spatial frequencies in V124. In addition, amblyopia is associated with a reduction in binocularity driven neurons in V1, a reduction of V1 neurons driven by the amblyopic eye, and increased binocular suppression7,8,17,24-27. Furthermore, recent work using dichoptic (simultaneous binocular stimulation) visual evoked potential (VEP) has shown that suppression likely originates from V128.

Recently, it has been shown that the monocular vision in adults with amblyopia can be improved after a 10-minute application of repetitive transcranial magnetic stimulation (rTMS) to the visual cortex, suggesting that a significant part of the monocular vision loss might be suppressive in nature31. The effects of repeated applications of rTMS are currently being investigated, and it is also possible that rTMS may enhance the effects of current treatments32.

These findings are consistent with the notion that the connections from the amblyopic eye may be suppressed during their lifetime rather than being destroyed. The predominant theory suggests that amblyopia results from a mismatch between the images of two eyes; one eye is favoured and the other eye is suppressed33. Animal studies34 and clinical evidence35 have also indicated that suppression is a key mechanism that causes amblyopia.

Table 1: Refractive error (measured in dioptres) thought to be capable of inducing amblyopia6

<table>
<thead>
<tr>
<th>TYPE OF ERROR</th>
<th>SUBTYPE</th>
<th>ERROR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anisometropia (asymmetric)</td>
<td>Hypermetropia</td>
<td>1.50</td>
</tr>
<tr>
<td></td>
<td>Astigmatism</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td>Myopia</td>
<td>2.00</td>
</tr>
<tr>
<td>Symmetrical</td>
<td>Hypermetropia</td>
<td>4.50</td>
</tr>
<tr>
<td></td>
<td>Myopia</td>
<td>3.00</td>
</tr>
</tbody>
</table>

**Box 1: What is the V1?**

The primary visual area (V1) of the cerebral cortex is the first stage of cortical processing of visual information. Area V1 contains a complete map of the visual field covered by the eyes. It receives its main visual input from the lateral geniculate nucleus of the thalamus (LGN), and sends its main output to subsequent cortical visual areas29.

**WHAT IS A VEP?**

A visual evoked potential is an evoked potential caused by a visual stimulus, such as an alternating checkerboard pattern on a computer screen. Responses are recorded from electrodes that are placed on the back of the head and are observed as a reading on an electroencephalogram (EEG). These responses usually originate from the occipital cortex, the area of the brain involved in receiving and interpreting visual signals30.

**Figure 1:** Patching remains a common treatment method for amblyopia

**MANAGEMENT**

Amblyopia is mainly treated using occlusion of the non-amblyopic eye (Figure 1), which has continued largely unchanged since it was first described in the literature in 836AD by an Islamic physician36,37. However, the treatment choice does vary slightly depending on the type of amblyopia present. Standard treatment practices for amblyopia include spectacle correction, occlusion therapy and atropine penalisation. In the past, patients were typically treated with occlusion therapy, and this largely remains the treatment of choice amongst most eyecare professionals.

However, the same common problems remain: lack of compliance and regression following discontinuation of treatment. It has been shown in several recent pieces of research that lack of compliance can act as a barrier to sufficient increases in VA of the amblyopic eye38,39. Compliance has shown to be affected by the following: a lack of understanding by the patient/parent; the age of the patient; attendance of follow-up appointments; and allergy to the patch.

Improvement of written information provided, positive reinforcement, discussions with GP and children services when appropriate, along with provision of alternative forms of treatment such as fabric patches, cycloplegic drugs40 and optical penalisation41,42, pose as viable and equally effective options in the constant battle we face against patient compliance.

PEDIG – the Paediatric Eye Disease Investigator Group – was formed in 1997 and has created several studies in the pursuit of determining other viable treatment options and their effectiveness. One of the major focuses has been the evaluation of different treatment modalities for amblyopia. The results of PEDIG’s
Box 2: Notable research on amblyopia

The most notable research literature to date, which is used as the basis for evidence-based practice within the acute Hospital Eye Service today.

PEDIG 2002
Improvement was initially faster with patching, but atropine was better tolerated. Mean improvement of 3.16 lines with patching and 2.84 with atropine44.

PEDIG 2003
There was no significant difference in the improvement of VA when patched for two hours vs. six hours in patients with moderate amblyopia45.

PEDIG 2003
There was no significant difference in the improvement of VA when patched for six hours vs. full-time occlusion for patients with severe amblyopia46.

PEDIG 2003
A beneficial effect of atropine is present throughout the age range of three years old to younger than seven years old, and with an acuity range of 20/40 to 20/100. A shift in near fixation to the amblyopic eye is not essential for atropine to be effective in all cases47.

PEDIG 2004
Recurrence occurred in 21 per cent of patients, 40 per cent detected within the first five weeks48.

PEDIG 2004
Weekend atropine is as effective as daily atropine for children with moderate amblyopia49.

PEDIG 2005
Treatment in older age groups (age seven to 18 years) with patching and atropine superior to optical correction alone50.

PEDIG 2006
A large percentage (77 per cent) of children with anisometropic amblyopia improve two or more lines of vision within 15 weeks of wearing glasses. Children with less anisometropia and better baseline VA tend to show the most improvement with spectacles alone51.

PEDIG 2007
Visual acuity improvement occurring during amblyopia treatment is sustained in most seven to 12-year-olds for at least one year after discontinuing treatment other than spectacles52.

PEDIG 2008
Performing common near activities does not improve VA outcome when treating anisometropic, strabismic or combined amblyopia with two hours of daily patching. Children with severe amblyopia may respond to two hours of daily patching53.

PEDIG 2008
Treatment with atropine or patching led to similar degrees of improvement among seven to 12-year-olds with moderate amblyopia. About one in five achieved visual acuity of 20/25 or better in the amblyopic eye54.

PEDIG 2009
Weekend atropine can improve visual acuity in children three to 12 years of age with severe amblyopia. Improvement may be greater in younger children55.

PEDIG 2008 & 2011
Initiating treatment before the patient is five years old will yield greater improvement and stability of VA compared with treatment initiated in children seven to 17 years old56,57.

PEDIG 2012
Optical treatment alone of strabismic and combined-mechanism amblyopia results in clinically meaningful improvement in amblyopic eye visual acuity for most three to <seven-year-old children, resolving in at least one quarter without the need for additional treatment58.

PEDIG 2013
When amblyopic eye VA stops improving with two hours of daily patching, increasing the daily patching dosage to six hours results in more improvement in VA after 10 weeks compared with continuing two hours daily59.

PEDIG 2015
Data showed that two hours of daily patching often leads to robust VA improvement, and younger children tend to improve more with patching. Children with worse VA when starting patching tend to improve more, but those with better baseline VA are more likely to achieve amblyopia resolution60.

ROTAS COOPERATIVE 2007
No significant difference in the VA outcome when comparing six hours of occlusion to 12 hours61.

ROTAS COOPERATIVE 2005
To achieve a dose rate of four hours of actual wear, a prescribed dose of six hours is actually required62.

MOTAS 2004
Stewart et al reported a similar finding that 82 per cent of improvement occurred in the first six weeks of treatment and that almost all improvement had occurred after 12 weeks. They also found that a dose above two hours did not affect the final visual outcome63.

CLEARY 2000
Maximum improvement occurs in the first 400 hours of occlusion, within the first three to six months of treatment64.

SACHDEVA ET AL 2013
Sachdeva compared the efficacy of ‘split hours part-time patching’ and ‘continuous hours part-time patching’ for the treatment of anisometropic amblyopia. Both patching regimens lead to significant and comparable improvement in BCVA in anisometropic amblyopia up to six months of follow-up65.
### Negative Consequences of Treatment

| Amblyopia Treatment Studies have revolutionised the treatment of amblyopia and form the evidence base for many professionals’ treatment choices. The most notable literature used as the basis for evidence-based practice within the acute hospital eye service today are outlined in Box 2.

- **Children wearing glasses or occlusion were 35-37 per cent more likely to be victims of physical or verbal bullying.**
- **Children felt stigmatised (sense of shame, embarrassment, etc) in relation to their amblyopia but only when treatment had begun.**
- **Holmes et al (2003) reported little impact of the treatment on the child or the family. Hrisos (2004): treatment had no impact on child’s global well-being or behaviour.**
- **Restrictions to choice of career – mostly those involving driving or flying.**
- **Side effects of the treatment particularly atropine.**
- **Impaired motor tasks – binocularity important for catching and prediction motion tasks.**
- **People with amblyopia (including those treated successfully and those whose treatment has failed) often have restricted career options and reduced quality of life.**

### Negative Consequences of Amblyopia

<table>
<thead>
<tr>
<th>Children wearing glasses or occlusion were 35-37 per cent more likely to be victims of physical or verbal bullying.</th>
<th>Risk of permanent visual loss in better eye for amblyopes: 32.9 per 100,000 population.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children felt stigmatised (sense of shame, embarrassment, etc) in relation to their amblyopia but only when treatment had begun.</td>
<td>Anxiety about losing vision in the fellow eye.</td>
</tr>
<tr>
<td>Holmes et al (2003) reported little impact of the treatment on the child or the family. Hrisos (2004): treatment had no impact on child’s global well-being or behaviour.</td>
<td>Adults with history of amblyopia: 52 per cent interfered with school, 48 per cent with work, 50 per cent lifestyle, 40 per cent sports, 36 per cent career choice.</td>
</tr>
<tr>
<td>Side effects of the treatment particularly atropine.</td>
<td>Restrictions to choice of career – mostly those involving driving or flying.</td>
</tr>
<tr>
<td>People with amblyopia (including those treated successfully and those whose treatment has failed) often have restricted career options and reduced quality of life.</td>
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with an emphasis on the use of binocular vision stimulation as a means of improving visual acuity, but also binocular functions. The use of visual stimulation and games as a platform for amblyopia treatment is a particularly exciting area, as it overcomes many of the shortcomings of patching therapy, such as lack of motivation due to stigma, and with few recognised side effects.

The first version of this treatment was based on the dichoptic global motion task (Figure 3) modified for the measurement of suppression was converted to one that was better aimed at holding the attention of a child over a longer period with, namely, a version of the popular video game Tetris (Figure 4). The game was viewed dichoptically, in which the amblyopic eye sees only falling blocks that are of high, fixed contrast, while the fellow fixing eye sees only the more superficial ground plane blocks into which the falling blocks have to be keyed. These ground plane blocks are of low but variable contrast. The less relevant, deeper ground plane blocks are seen by both eyes to aid fusion.

With an anaglyph version of the treatment now devised that will work on a range of handheld platforms, and allows for games other than Tetris to be played, dichoptic perceptual learning designed to strengthen binocular combination by reducing suppression, has been seen to improve both stereopsis and acuity in adults and children with amblyopia.

With further advancements in technology come adaptations continuing to be developed and researched, such as the I-BiT (Interactive Binocular Treatment) device, which works by providing different information to each eye. The I-BiT allows the patient to play a computer game or watch a DVD, which is displayed via virtual reality technology in such a way as to provide a treatment for amblyopia.

The basic principle is that the amblyopic or ‘lazy’ eye is shown the more interesting part of the game or DVD, such as stars to collect or obstacles to avoid, whilst the non-amblyopic or ‘good’ eye is shown the less interesting part, such as the background. This means both eyes receive an image simultaneously but the brain has to use the lazy eye in order to watch the DVD properly or play the game.

The novelty of the I-BiT Plus system (Figure 5) is that the treatment does not require the non-amblyopic eye to be patched. The I-BiT Plus system is synchronised with the shutter glasses so that each eye only sees the image intended for that eye. Shutter glasses work by alternately shutting off the left and right eyes so that only one eye can see the screen at any time. This happens so quickly that the brain does not realise that each eye is being stimulated separately and the viewer does not experience any flickering. The patient wears the shutter glasses and the I-BiT Plus software will provide more information to the lazy eye when watching a DVD or playing a computer game.

In an early, uncontrolled pilot study of 10 patients who received three hours of I-BiT treatment per week, there was a “clinically significant improvement of 0.125LogMAR units or more” in six of the nine patients who finished the pilot study. In a more recent randomised controlled trial, 75 patients, aged from four to eight years, with dichoptic stimulation in all three arms, found modest vision improvement in all three arms; treatment pas well tolerated and safe.
Several more pilot studies have reported results of a binocular treatment for amblyopia using reduced fellow eye contrast to allow the amblyopic individuals to experience binocular vision. Under investigator supervision, a total of 37 adults and 14 school age amblyopic participants in six studies practised binocular tasks for one to four weeks using a haploscope, video goggles, or an iPad with a lenticular overlay to separate the monocular images\textsuperscript{89-97}. Early results in uncontrolled trials performed in children and adults have shown improvements in visual acuity and stereocuity\textsuperscript{4.}. However, initial studies by PEDIG in 2016 suggested that VA improvement with this particular binocular iPad treatment was not as good as with two hours of prescribed daily patching\textsuperscript{89}.

**SUMMARY**

Repeated binocular iPad gameplay as well as passive dichoptic viewing, with the use of anaglyph or shutter glasses, have been shown to significantly improve visual acuity in amblyopic children and both look set to be promising new treatments for childhood amblyopia – and possibly further into adulthood.

The maximum improvement that may be achieved is yet to be determined\textsuperscript{97}, with most studies still in their early phases. With small patient cohorts, the extent at which these devices can be utilised in the treatment of amblyopia is yet to be seen fully. As an orthoptist, I’m keenly awaiting the research that involves those patients with strabismic amblyopia, also encompassing the older age-groups, and the prevalence of any associated risks such as intractable diplopia.

The current method of treatment, through monocular occlusion, does not allow for or promote binocular cooperation, the absence of which may underlie residual and recurrent amblyopia. With evermore studies looking into the efficacy of such treatments as presented above, in comparison to the standard practises currently in place, exciting times lie ahead for us all.

Thanks to our improved understanding of the mechanisms of amblyopia, we are now able to look to extending our treatment modalities through the use of innovation and technology. These binocular games that aim to rebalance contrast to overcome suppression are a promising step in the right direction for the future management of amblyopia. In addition to their efficacy and durability, they are fun, engaging and result in better compliance than patching, whilst imposing little risk for adverse psychosocial effects\textsuperscript{45}.

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RESOURCES

- http://www.tetris.com
- www.amblyz.com
- www.amblyopiagames.com
- http://eyetronix.com/
- http://eyecclean.com/eyeslearn/
- http://www.lazy-i-bit.co.uk/publications.html
- http://www.amblyotech.com/
- http://dpatch.ca/
- http://duovision.com/the-lazy-eye-tetris/
- https://www.brighteyestampa.com/2015/02/20/amblyopia-research/

NEW GAME APPS

- Honey Rush Lazy Eye App
- Lazy Eye Breaker App
- Amblyo Match Lazy Eye App

(The above apps should be used with Anaglyph 3D glasses.)

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