Amblyopia

Jonathan M Holmes, Michael P Clarke

Results from recent randomised clinical trials in amblyopia should change our approach to screening for and treatment of amblyopia. Based on the current evidence, if one screening session is used, screening at school entry could be the most reasonable time. Clinicians should preferably use age-appropriate LogMAR acuity tests, and treatment should only be considered for children who are clearly not in the typical range for their age. Any substantial refractive error should be corrected before further treatment is considered and the child should be followed in spectacles until no further improvement is recorded, which can take up to 6 months. Parents and carers should then be offered an informed choice between patching and atropine drops. Successful patching regimens can last as little as 1 h or 2 h a day, and successful atropine regimens as little as one drop twice a week. Intense and extended regimens might not be needed in initial therapy.

Lancet 2006; 367: 1343–51

Department of Ophthalmology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA
(Prof J M Holmes BM BCh); **and Department of Ophthalmology, University of Newcastle upon Tyne, Newcastle, UK**
(M P Clarke FRCOphth)

Correspondence to:
Prof Jonathan M Holmes
holmes.jonathan@mayo.edu

This Seminar provides an update on recent developments in amblyopia research that affects screening, diagnosis, and treatment. Only in the past 5 years have multicentre, randomised controlled trials addressed amblyopia treatment issues. These studies not only help clinicians and parents in choosing appropriate therapies, but also inform screening policy, which is of general interest. We first summarise common definitions of amblyopia, discuss the diagnosis of amblyopia, and describe recent studies of screening for amblyopia and the implications of treatment trials on screening. We then present the existing evidence on whether the disorder should be treated and summarise recent treatment studies, providing specific recommendations.

Definition of amblyopia

Amblyopia has traditionally been defined by what it is not, rather than by what it is. Definitions often include aphorisms such as a disorder "in which the patient sees nothing and the doctor sees nothing".[1] Based on animal studies[2] and functional human neuroimaging,[3] amblyopia can be defined as a disorder in which there is dysfunction of the processing of visual information. This dysfunction is usually detected and evident as reduced recognition visual acuity, although the abnormalities include many types of visual function.[4] Although clinical ocular examination is most often entirely normal in amblyopia, microscopic anatomical and structural abnormalities have been found in the retina,[5] lateral geniculate bodies,[6] and visual cortex.[7]

Amblyopia results from degradation of the retinal image during a sensitive period of visual development, which historically has been thought to be the first 7 years of life.[8] The sensitive period for development of amblyopia might not be the same as the sensitive period during which treatment is possible. The degradation of the image, and subsequent central suppression that leads to amblyopia, results from one of three causal processes (table 1).

Therefore, amblyopia never occurs in isolation. The disorder is not the cause, but the effect of another pathological process. Amblyopia can also be thought of as resulting from either disuse due to the absence of a clear image on the retina (anisometropia or deprivation), or misuse due to abnormal binocular interaction (strabismic). A widely accepted definition of amblyopia based on visual acuity is 2 or more Snellen or logMAR lines difference between eyes in best-corrected visual acuity. A one-line difference is usually a normal result, based on test-retest variability.[9]

Epidemiology of amblyopia

Amblyopia is the most common cause of monocular vision loss in children with an estimated prevalence of 1–5%, depending on population and study.[1] Because of the failure of detection or treatment, amblyopia continues to be an important cause of vision loss in adults, with an estimated prevalence of 2·9%.[10] A study by the National

	Features	Unilateral or bilateral effect
Strabismus (ocular misalignment)	Each eye does not have the same image on the fovea	Unilateral
Anisometropia (difference in refractive error)	One foveal image is more blurred than the other	Unilateral
Deprivation (including ametropia—ie, large symmetric refractive errors)*	Physical obstruction of one image (eg, cataract, ptosis, or bilateral blur from uncorrected refractive error)	Either

*Amblyopia is the residual visual deficit after the physical obstruction is removed and appropriate optical correction is provided.

Table 1: **Causes of amblyopia**

Search strategy and selection criteria

We searched MEDLINE (1966 to 2005) and the Cochrane Library (to 2005), and used the search term "amblyopia". We mainly selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Several review articles or book chapters were included because they provide comprehensive overviews that are beyond the scope of this Seminar. The reference list was subsequently modified during the peer-review process on the basis of comments from reviewers.

Eye Institute in the USA, showed amblyopia to still be the leading cause of monocular visual loss in people aged between 20 and 70 years.[11]

Few data exist for the prevalence or incidence of the various types of amblyopia. Deprivation amblyopia seems to be rare, based on the incidence of the primary causative factors such as infantile cataract (2 to 4·5 of every 10 000 births).[12,13] Many clinical studies have shown about a third of amblyopia to be caused by anisometropia, a third by strabismus, and a third by a combination of both disorder types.[14,15] Nevertheless, these data are age-dependent, since strabismic amblyopia often presents earlier than anisometropic amblyopia because of parental observation of squint. The remainder of this Seminar will focus on unilateral amblyopia caused by anisometropia, strabismus, or both.

Diagnosis of amblyopia

The diagnosis of unilateral amblyopia is made when reduced visual acuity is recorded in the presence of an amblyogenic factor, despite optimum refractive correction (ie, best-corrected visual acuity) and not explained by another ocular abnormality. Residual visual deficits after correction of any amblyogenic factor (eg, by spectacles prescription or cataract removal) are assumed to be due to amblyopia. Therefore a critical component of amblyopia diagnosis is the measurement of visual acuity.

In children younger than 2·5 years, the diagnosis of unilateral amblyopia relies on comparison of fixation preference on a light or small toy. If the child has an obvious squint, it is relatively easy to determine which eye the child prefers, but with a straight-eyed child the visual axes of the two eyes must be optically separated with the so-called induced tropia test to make this assessment.[16,17] More quantitative methods to assess visual acuity have been used in these younger children, such as preferential looking techniques (Teller acuity cards),[18] Kay pictures,[19] and Cardiff cards,[20] but assessment of grating acuity with Teller acuity cards has been shown to be relatively insensitive to amblyopia.[21]

Children aged 2·5 years or older can complete optotype visual acuity testing (identifying symbols or letters), allowing quantification of visual acuity on a Snellen or preferably a logMAR scale. Use of a non-logMAR scale, such as the classic Snellen chart, introduces errors and inefficiencies due to the non-equal increments between one level and the next. Very large increments between higher levels result in imprecise estimates of visual acuity, and smaller increments at lower levels result in increased testing time with little additional information. Picture charts have been used in children aged 2–3 years,[22] but again they seem to be insensitive to amblyopia. Children younger than 5 years can undertake a matching task, which is the basis of the Amblyopia Treatment Study (ATS) visual acuity protocol using HOTV optotypes,[9] the Glasgow cards using XVOHUY optotypes,[23] the STYCAR test using HOTVLXAUC optotypes,[24] and the Lea symbol test.[25] Children as young as 5 years can be tested with conventional adult visual-acuity charts, such as the standard Snellen charts and Early Treatment Diabetic Retinopathy Study (ETDRS) protocols.[26–28]

Most clinical visual acuity tests for amblyopia use an assessment in which isolated letters surrounded by crowding bars or letters are presented in a line of 4 or 5 letters. Visual acuity tests with single uncrowded letters seem to be insensitive to amblyopia.[21] Crowding (a reduction of visual acuity when optotypes are presented in a line or surrounded by bars) seems to be a feature of the developing visual system, which persists in amblyopia and cerebral visual impairment.[29]

One important feature of visual acuity testing to diagnose amblyopia is that there is a distribution or range of typical visual acuity in any population. This range changes with age because of neural maturational processes. With age-appropriate logMAR tests in 4-year-old children, the mean visual acuity is about 0·1 (6/7·5, 20/25) logMAR, with a typical range, as measured by 2 SDs from the mean, extending from 0·0 (6/6, 20/20) to 0·2 (6/9, 20/30) logMAR.[30] Thus, the visual system is not fully developed at this age, and therefore doctors should not use failure to reach 6/6 as a criterion to diagnose and treat amblyopia.

Screening for amblyopia: how to screen?

Since measurement of best-corrected visual acuity is a critical part of amblyopia diagnosis, it might seem intuitive that screening for amblyopia would use a measurement of visual acuity. Indeed, many screening programmes use measurement of visual acuity as the only screening method or part of a screening battery. Other screening methods rely on detection of amblyogenic factors (or amblyopiogenic, as the proper term), such as refractive error (using automated autorefractors) or strabismus (using photoscreening techniques). Other methods test other types of visual function, such as stereoacuity that could be reduced or absent in amblyopia.

In the Vision in Preschoolers study,[31] various screening methods were compared with each other and with gold standard eye examinations in an enriched population of children aged 3–5 years (over-representing children who would probably have ocular problems). For detection of amblyopia, the autorefractor methods had a higher sensitivity than visual-acuity screening methods using HOTV letters or Lea symbols, and photoscreener methods and stereoacuity screening did less well than visual acuity screening.[31]

In the UK, Williams and colleagues[32] did a randomised controlled trial to compare visual surveillance by health visitors and family practitioners with regular assessments by orthoptists (paramedical ophthalmic professionals who treat childhood eye disease and adult strabismus), and tested for visual acuity, ocular alignment, stereopsis,

and non-cycloplegic photorefraction. The researchers concluded that photorefraction (to detect refractive errors) combined with a cover test (to detect strabismus) at age 37 months would have the highest sensitivity and specificity of any of the methods they included.[32]

Who should screen?

The Vision in Preschoolers study[31] had licensed eye professionals (ophthalmologists and optometrists) as screeners to compare screening instruments. In a second phase,[33] nurses and trained lay people were used as screeners, comparing the best screening tests in phase I studies with gold standard examinations in a similar population. For detection of amblyopia, the two autorefractors continued to have a higher sensitivity than visual acuity testing, if visual acuity testing was done at the standard 10-feet testing distance. Sensitivity of visual acuity testing only became similar to that of autorefraction when the format was changed to single surrounded letters and the test distance was reduced to 5 feet.

Based on this second study,[33] autorefraction could be used by nurses or trained members of the public to screen for amblyopia. If screening with visual acuity tests is used, its sensitivity seems to depends greatly on the screener, type of test, and testing distance.

In the UK, orthoptists have been shown to be the most accurate screeners for amblyopia and orthoptic-led community screening programmes are currently in existence. In the study by Williams and co-workers,[32] orthoptists did multiple examinations between ages 8 and 31 months. Nevertheless, the availability and costs associated with the use of orthoptists for screening will be prohibitive in some countries.[34,35]

When to screen?

The controversy of when to screen is based on beliefs regarding the sensitive period for the development and treatment of amblyopia. Standard teaching has been that amblyopia caused by strabismus and anisometropia should be treated before age 7 years,[8] and the earlier the treatment, the better. This approach is supported by data from a randomised trial of screening strategies[36] and the philosophy to treat as early as possible has led to recommendations to screen for amblyopia as soon as a child can undertake a visual acuity measurement task, typically at 3 years old in many US states.[37]

Emerging data from recent randomised clinical trials[14,38–40] have led us to question whether earlier treatment does result in better outcomes, which has implications for screening. If visual acuity outcomes are similar in 3-year-old and 6-year-old children after treatment for amblyopia, then screening at school entry (age 5 years in the UK, 6 years in the USA) might be more reasonable, rather than at age 3 or 4 years as currently recommended by many authorities.[37,41,42] Nevertheless, further studies are needed to establish whether earlier screening strategies, or multiple screening strategies, would be best in decreasing the ultimate burden of amblyopia in a population.

Should amblyopia be treated?

Public-health authorities have questioned whether amblyopia should be treated at all, since individuals with amblyopia show little functional disability and treatment with patching is psychologically distressing.[43] Data for the natural history of untreated amblyopia are scarce, but they have indicated either no or minimum improvement with time.[39,44] Little work has been done so far on the degree of disability associated with unilateral amblyopia and on the degree of disability associated with the resulting reduced stereoacuity (ie, loss of depth perception).[45] Few data indicate that unilateral amblyopia greatly affects quality of life, as long as vision in the fellow eye remains good. Chua and Mitchell[46] found that amblyopia in people aged 49 years or older did not affect lifetime occupational class, but that fewer affected individuals completed university degrees than those unaffected. By contrast, Membreno and colleagues[47] calculated the effect of unilateral amblyopia on the quality of life by estimating utility values for the effect of poor vision in one eye. With a time trade-off estimation approach, treatment of amblyopia in childhood resulted in a substantial lifetime gain in quality-of-life years.

If normal vision is assumed in the fellow eye, reduced binocular visual acuity could result from the temporary or permanent loss of acuity in this eye. Temporary loss of acuity in the healthy eye could result from trauma, which might be why reduction in unilateral visual acuity precludes individuals from professions such as the fire service and armed forces.[48]

Permanent loss of acuity in the healthy eye will result in reduced quality of life. Tommila and Tarkkanen[49] found that in 1958–78, 35 patients with amblyopia lost vision in the healthy eye. For more than 50% of these individuals, the cause was traumatic. The occurrence of loss of vision in healthy eyes was 1·75 per 1000 people. During the same period, the overall blindness rate was 0·11 per 1000 in children and 0·66 per 1000 in adults. The researchers concluded that individuals with amblyopia are at increased risk of blindness. In a UK national survey of the incidence of visual loss in the healthy eye,[50] an estimated 1·2% risk of loss of vision in the healthy eye to 6/12 or less (lower than the UK driving standard) was recorded during the working lifetime of an individual with amblyopia. Even with possible partial improvement in visual acuity in the amblyopic eye in some individuals after vision loss in the healthy eye,[51,52] prevention of future disability is an important argument for the treatment of amblyopia in childhood.

Amblyopia treatment

If amblyopia can be thought of as disuse or misuse, then all treatments for the disorder can be thought of as designed to increase the use of the amblyopic eye. In

	Prescribing guidelines for children aged 2–3 years*	Spectacle requirements before entry into recent randomised trials†
Anisometropia (asymmetric refractive error)		
Hyperopic	≥1·50	≥1·00
Astigmatism	≥2·00	≥1·50
Myopic	≥–2·00	≥–1·00
Symmetric		
Hyperopia	≥4·50	>3·00
Myopia	≥–3·00	>–3·00

*Based on prescribing guidelines from the American Academy of Ophthalmology for refractive error recorded in a routine eye examination and the philosophy of preventing ambylopia.55 †Based on the minimum amount of refractive error that should be first treated with spectacles, with respect to reduced visual acuity in recent randomised trials by the Pediatric Eye Disease Investigator Group (PEDIG).14,38,54

Table 2: **Degrees of refractive error thought to induce amblyopia**

	Patching	Atropine
Effect on appearance of patient	Obtrusive	Unobtrusive
Reversibility	Immediate	Effects last up to 2 weeks
Local side-effects	Irritation and allergy	Light sensitivity and allergy
Systemic side-effects	None	Rare but dangerous (possibly more common in trisomy 21): flushing, dry mouth, hyperactivity, tachycardia, and very rare possibility of seizures
Compliance	Easy for child to remove	Compliance is assured once drop is instilled
Binocularity	Impaired during treatment	Peripheral binocularity allowed
State of child distress while treated	Could be high	Rarely more than very low

Table 3: **Comparison between atropine and patching treatments for amblyopia**

general, treatment for amblyopia consists of depriving the healthy eye of visual input by patching or by optical or pharmaceutical penalisation.

In deprivation amblyopia, the cause of the visual deprivation (eg, ptosis or cataract) needs to be addressed first and then the disorder should be treated similarly to other types of amblyopia. In anisometropic amblyopia, refractive errors need to be corrected with spectacles or contact lenses. In strabismic amblyopia, conventional wisdom states that the amblyopia should be treated first, and that correction of the strabismus will have little if any effect on the amblyopia, although the timing of surgery is controversial.[53]

Initial correction of refractive errors

Table 2[14,38,54,55] summarises the degrees of refractive error thought to induce amblyopia. Correction of lower degrees of refractive error might be needed to yield the true best-corrected visual acuity, which is especially true of low amounts of myopia. With the optimum refractive correction in place, any residual visual deficit is, by definition, due to amblyopia. Convincing evidence indicates that continued spectacle wear is therapeutic in its own right, providing a clear image to the fovea of the amblyopic eye for perhaps the first time.

Researchers[56,57] have shown a progressive improvement in acuity for up to 18 weeks in some patients after refractive correction alone, coining the term refractive adaptation. Clarke and colleagues[39] showed that refractive correction alone resulted in a significant improvement in acuity in a group of children failing preschool vision screening, compared with no treatment. Unexpectedly, improvement occurred not only in patients with pure anisometropic amblyopia but also in children with strabismic amblyopia.[57] Since most of these children with strabismus also had hyperopia, we speculate that correction of their refractive error treated a component of refractive deprivation amblyopia. Additionally, the US-based Pediatric Eye Disease Investigator Group (PEDIG)[58] will soon report the results of a similar study in which children with amblyopia were treated with refractive correction alone until they stopped improving. In all these studies, about a quarter of children with amblyopia reached equal visual acuity with refractive correction alone, and therefore did not need other treatments.

Patching versus atropine for ambloypia treatment

Patching has been used to treat amblyopia for centuries[59] whereas the use of atropine was first described for use more recently.[60,61] Atropine is used as a 1% drop to the healthy eye, blocking parasympathetic innervation of the pupil and ciliary muscle and causing pupillary dilatation and loss of accommodation. The blurring that occurs is much greater in eyes with hypermetropic refractive errors since accommodation can no longer correct blur.

Historically, patching has been more popular than atropine, based partly on a belief that patching is more effective. Atropine has often been reserved for instances when the child is intolerant of patching, which thus selects cases more likely to have unsuccessful outcomes, reinforcing a potentially erroneous belief. Table 3 lists theoretical and practical advantages of each treatment.

In a PEDIG randomised trial,[14,61] patching for at least 6 h per day was compared with a 1% atropine drop every morning in 419 children aged 3–7 years with acuities of 6/12 to 6/30. At the 6-month primary outcome, mean improvement was 3·16 lines in the patching group and 2·84 lines in the atropine group. The researchers concluded that atropine was as effective as patching, but that patching was initially faster and atropine had a somewhat higher acceptability based on a parental questionnaire.[62,63] The 6-month trial was followed by 18 months of the best possible clinical care. At 2 years of follow-up, mean improvements were 3·7 lines in the patching group and 3·6 lines in the atropine group.[61] The suggestion that atropine would result in better stereoacuity outcomes than patching was not supported by the data.[61]

Other atropine issues

With atropine therapy, the hypermetropic spectacle correction over the treated eye can be reduced to enhance the effect of atropine on visual acuity in the healthy eye. In

	Visual acuity	Age (years)	Prescribed regimens (h/day)	Actual patching (h/day)*	Duration (weeks)	Lines improved†
PEDIG (n=189)[38]	6/12–6/24	3 to <7	A: 2‡ B: 6‡	..	17	2 h: 2·4 6 h: 2·4
PEDIG (n=175)[54]	6/30–6/120	3 to <7	A: 6‡ B: All or all but 1‡		17	6 h: 4·8 Full-time: 4·7
Awan, et al (n=60)[70]	6/12–6/48	Mean 4·5	A: 0 B: 3 C: 6	A: 0 B: 1·7 C: 2·5 (NS)	12	0 h: 2·4 3 h: 2·9 6 h: 3·4
Randomised Occlusion Treatment of Amblyopia Study (ROTAS; n=82)[71]	n/a	Mean 5·5	A: 6 B: 12	A: 4·2 B: 6·2 (NS)	Weekly until no improvement	0–3 h: 1·8 >3–6 h: 2·6 >6–12 h: 3·0

n/a=not available. NS=non-significant differences between groups. *Measured with occlusion dose monitor. †None of the outcomes differed significantly between groups within each trial, apart from the ROTAS study, which was analysed by actual patching hours. ‡With 1 h of near visual activities.

Table 4: **Patching dose studies**

the PEDIG comparison of atropine with patching,[14,61] reduction of the hypermetropic spectacle correction was undertaken at an interim visit if the child had not responded. Another randomised trial is currently being done by PEDIG, comparing atropine with and without a plano spectacle lens (results expected in 2006 or 2007).

Since one dose of 1% atropine lasts up to 2 weeks, a less than daily dosing schedule might also be reasonable. PEDIG compared daily atropine with twice weekly atropine (given on Saturday and Sunday) in moderate amblyopia (6/12 to 6/24).[64] The improvement in visual acuity was 2·3 lines in each group, and the researchers concluded that weekend atropine provides an improvement in visual acuity of similar magnitude as daily atropine.

During atropine therapy, vision in the treated eye should be checked to ensure that no iatrogenic reverse amblyopia has taken place.[65] This check of visual acuity poses a difficulty, since optical aberrations caused by pupillary dilatation often result in a slight reduction of visual acuity even if accommodative factors are corrected by full hypermetropic correction. Nevertheless, the two PEDIG studies[14,64] found only one of 372 patients treated with atropine was actively treated for reverse amblyopia, and only two patients had a drop of more than one line from baseline, at last follow-up.

Another reason for previous unpopularity of atropine has been a perception that the treatment would not be effective unless fixation switched to the amblyopic eye. Consequently, atropine was thought not to be effective in severe amblyopia. PEDIG studies[64,66] have shown that fixation switch, or reduction of near visual acuity of the healthy eye beyond that of the amblyopic eye, is not needed for atropine to be effective. We speculate that atropine could be effective even without a fixation switch by blurring of higher spatial frequencies in the atropinised eye. Another PEDIG study is currently investigating atropine in severe amblyopia.

How much patching?

Until recent trials,[67,68] the amount of patching prescribed has been entirely a matter of individual preference. Some researchers have argued for full-time occlusion, recommending at least three cycles[69] of a week of full-time occlusion per year of age. Others have preferred to patch less intensively (a few h per day), recognising that treatment could take longer than expected but could be just as effective with the advantage of being less disruptive.

Patching has been investigated in several randomised trials (table 4).[38,54,70,71] Although the PEDIG studies[38,54] and the study by Awan and colleagues[70] were somewhat restricted by failure to wait for maximum improvement of visual acuity with spectacles alone, they show that many children improve with much less patching than has often been prescribed. Notably, substantial individual variability of response to patching has been recorded[72] and recent data[73] suggests that 1 h or more of actual patching per day is effective in many children. The panel summarises interpretation of data from all these recent trials and observational studies with an evidence-based approach to treating amblyopia.

Compliance issues and side-effects of patching

Occlusion dose monitors have confirmed that some children and families comply well with patching whereas

***Panel:* Current treatment recommendations for amblyopia secondary to anisometropia, strabismus, or both**

- For diagnosis and monitoring of amblyopia, measure best-corrected visual acuity with logMAR-based tests
- Prescribe refractive correction based on cycloplegic retinoscopy
- Wear spectacles full time and monitor visual acuity every 6–12 weeks until stable
- If amblyopia remains, discuss options of patching versus atropine
- If patching treatment is used, start with a low dose (eg, 1–2 h per day) and monitor visual acuity every 6–12 weeks
- If atropine treatment is given, start with twice weekly dose, and monitor visual acuity every 6–12 weeks
- If improvement stops and amblyopia remains, consider increasing treatment or switching treatment

If no further improvement occurs or amblyopia resolves, consider weaning treatment or stopping treatment, but follow for at least a year after stopping treatment, because of risk of recurrence.

others do not.[72,74,75] Parents or carers having to deal with distressed, uncomfortable, and visually-impaired children wearing the patch should be given information, convinced of the need for treatment,[76,77] and appropriately motivated to treat.[78,79] Parents or carers giving older children a role in monitoring their own treatment—eg, with the use of patching diaries with stickers—could help. Active, unreasonable toddlers pose the biggest challenge. Behavioural modification programmes might also help children and families.[80]

Patches can also be stuck onto spectacles, but this method gives the child the opportunity to look around them. Felt patches, which slide over the spectacle lens, have a side-piece that helps prevent the child looking around the patch but are cosmetically obtrusive. Translucent material such as blenderm or Bangerter filters (Fresnel Prism and Lens Co LLC, Eden Praire, MN, USA) are more cosmetically acceptable but have not been rigorously studied.

Some concerns have been raised regarding the emotional effect of amblyopia treatment,[43] but in a PEDIG study,[63] both atropine and patching treatments seemed to be well tolerated by assessment with a parental questionnaire. Additionally, several other studies[81,82] have shown minimum emotional effect from amblyopia treatment.

Effective ages at which to treat amblyopia

The duration of a sensitive period for amblyopia treatment seems to vary depending on the cause of the disorder. Causes that severely degrade the retinal image early in infancy (usually the stimulus deprivation type of amblyopia—eg, caused by congenital cataract) need early, vigorous treatment. Causes with a late onset could respond to treatment given well into late childhood and after.

In a PEDIG trial,[14] no effect of age was found at the 6-month primary outcome in children aged 3 to less than 7 years, and only a very small effect was seen at the 2-year follow-up,[61] with children aged 6–7 years having a slightly worse outcome (3·2 lines improvement) than those aged less than 4 years (3·9), 4–5 years (3·7), and 5–6 years (3·7). A similar absence of age effect was seen in a 2-h versus 6-h randomised trial;[38] however, a full-time versus part-time trial[54] did show reduced improvement in the older children. Nevertheless, these two patching regimen trials were only designed to have 4 months' follow-up, and not to indicate maximum improvement.

In a randomised trial[83] enrolling 7 to 17-year-old individuals with anisometropic and strabismic amblyopia ranging from 6/12 to 6/120, 53% of 7 to 12-year-old children responded to patching, atropine, near activities, and optical correction, whereas 25% responded to optical correction alone (response was defined as at least ten letters on the ETDRS chart—ie, two lines).[83] In 13 to 17-year-old individuals, similar proportions responded to patching-optical correction and optical correction alone (25% and 23%, respectively), although those who had not been previously treated had a higher response rate than those who had been previously treated (47% *vs* 20%). These data support previous reports[84–86] that amblyopia can be treated beyond age 7 years. What is unclear, and will be forthcoming in long-term follow-up data,[83] is whether these improvements in visual acuity are sustained, similar to the younger age group, in which 2-year follow-up data are available.[61]

Does amblyopia treatment work?

There has been some skepticism[43] about the effectiveness of amblyopia treatment, because until recently,[70,87] few studies have included untreated controls in their design. Some researchers have suggested that many instances of amblyopia are due to a congenital and permanent optic-nerve abnormality,[88,89] which would be expected to be completely resistant to any intervention. The reluctance to design studies with untreated controls has resulted from the previous feeling of urgency to treat, due to the potential closing of a window of opportunity. The failure of several trials to find any relation between treatment effect and age in 3 to 7-year-old children, and the finding of response in 7 to 12-year-old children, increases the comfort level with studies that have an untreated control group.

Of studies that have included untreated controls, Clarke and colleagues[87] showed that in a group of children (mean age 4 years) who had failed preschool screening on account of poor vision in one eye, treatment resulted in a significant improvement in acuity. Subgroup analysis showed this benefit to be confined to children with visual acuity of 6/18 or worse in the eye with reduced acuity at presentation.

Awan and co-workers[70] recorded no mean difference between 0, 3, and 6 h/day of prescribed patching in a short 12-week randomised trial, but the participants only had 6 weeks of spectacle wear before study entry, so some of the improvement in the 0-h group would have been expected to be due to continued optical treatment of amblyopia[57] and therefore potentially masked any dose-response treatment difference. In a secondary analysis, patients who actually wore the patch for 3–6 h/day had greater improvement than those who had no patching. A forthcoming PEDIG trial will report data comparing 2 h/day of patching with continued spectacle wear in children who had reached maximum visual acuity improvement with spectacle wear alone.

Why is amblyopia treatment not always successful?

Evidence from retrospective case series[90] and more recent randomised trials[61] suggests that only about 50% of children achieve normal vision in the amblyopic eye. In the past, this effect has often been assumed to be because treatment has been started too late to be

effective, but recent data indicating an absence of age effect should question this assertion.

Subtle ocular and cerebral pathology could underlie failure to respond to treatment. Optic nerve hypoplasia is easily missed on indirect ophthalmoscopy and should be specifically excluded. Inaccurate refractive correction, which inevitably occurs during periods of emmetropisation, should also be considered. Lack of compliance (concordance), as discussed earlier, is also a factor.

The approach to an individual in whom vision initially improves and then seems to plateau is far from clear. Attempts to improve compliance with a specific regimen, followed by increasing the number of hours per day, are reasonable. Nevertheless, since only 50% of children ever reach normal visual acuity, to continue patching indefinitely until visual acuity reaches 6/6 would be unreasonable. Although some investigators feel all improvement is seen in the first 12 weeks,[72] other studies suggest extended courses.[61]

Other methods of treating amblyopia

Optical penalisation

Blurring of the sound eye by use of optical means in a spectacle correction or contact lens has been reported to successfully treat amblyopia[91] but has not yet been subject to a randomised clinical trial.

Near activities while patching

Although many practitioners instruct children to do near activities or activities that need hand-eye coordination while patching, the issue has not been rigorously studied. A pilot study[92] was undertaken by PEDIG to determine whether children would stay in their assigned groups if randomised to near or distance activities, and data for visual acuity suggested a modest benefit of near activities. A full-scale randomised controlled trial is currently underway to address this issue.[92]

Levodopa and citocholine

Oral levodopa has been reported in amblyopia treatment and has shown effects seen on both visual acuity and functional MRI.[93–96] Citocholine has been reported to have similar effects.[97,98] The neuropsychiatric side-effects of these drugs render their use unlikely in routine clinical practice for amblyopia treatment, but the studies do show the potential for such an approach to treatment.

Visual stimulation

Since the use of the CAM (Cambridge) stimulator,[99] there has been interest in the use of positive visual stimulation compared with occlusion or penalisation, but this treatment has not shown to be beneficial in randomised trials. The role of near visual tasks as an adjunct to patching has been a feature of some trials,[38,54] and is currently being investigated,[92] as are other computer-based systems.[100,101]

Future developments and implications

Continuing and planned research will provide further evidence on: the role of near-activities while patching, atropine in more severe amblyopia, combined optical and atropine penalisation, atropine versus patching in older children with amblyopia, and the effectiveness of blurring filters. The past few years have heralded a new era in evidence-based treatment for amblyopia, increasing the options and reducing the burden for the child and family.

Conflict of interest statement

We declare that we have no conflict of interest with respect to the writing of this Seminar.

Acknowledgments

J M Holmes is funded by grants from the National Institutes of Health, Bethesda, MD, USA (EY015799 and EY011751); Research to Prevent Blindness Inc, New York, NY, USA (Olga Keith Weiss Scholar); and an unrestricted grant to the Department of Ophthalmology, Mayo Clinic College of Medicine.

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