Br Ir Orthopt J 2010; **7:** 3–7

Review of amblyopia treatment: Are we overtreating children with amblyopia?

MICHAEL P. CLARKE

Newcastle upon Tyne NHS Foundation Trust and Institute of Neuroscience, Newcastle University, Newcastle upon Tyne

Abstract

Aim: **Amblyopia is a common reason for outpatient treatment in childhood. This review aims to provide an overview of recent research on amblyopia treatment.**
Methods: **A literature-based review was carried out of evidence available on amblyopia management with additional personal comments on some issues.**
Results: **Recent research evidence has shown that: refractive adaptation is a significant component of the therapeutic response, compliance with patching is problematic, most of the response to patching occurs within 6–8 weeks, and recurrence after cessation of treatment is less frequent if patching is weaned. However, this evidence from clinical trials has yet to be fully incorporated into practice: we are overtreating children.**
Conclusions: **Utilising information gleaned from recent research will enable clinicians to reduce the amount of patching which children being treated for amblyopia receive, with benefits to compliance with treatment and use of health service resources.**

Key words: Amblyopia, Atropine, Randomised controlled trials, Treatment

Background

In 2007/8 there were almost 500,000 consultations in UK eye clinics and orthoptic departments for children aged 9 years and under, accounting for 14% of all attendances for this age group (http://www.hesonline.nhs.uk). It is thought that 90% of this workload relates to the treatment of amblyopia and strabismus.[1] Amblyopia treatment is therefore one of the commonest reasons for NHS outpatient treatment.

It has long been assumed that almost all amblyopia is fully treatable, given compliance or concordance with the regime recommended by health professionals, and there has been some evidence to support this.[2] What has become apparent, however, from many recent large clinical trials, is that a significant proportion of children do not regain normal visual function, or even driving vision, following amblyopia treatment.

Patching the preferred eye of a child who has amblyopia in the other eye, renders the child visually impaired, and is not a treatment to be undertaken lightly. Treatment-induced visual impairment is a major reason for lack of compliance with treatment, and a major reason for loss of children to follow-up. It is a particular problem for those children whose vision remains poor despite treatment.

There is currently no way to accurately predict the outcome of amblyopia treatment at presentation, except perhaps in those cases where there are significant anatomical abnormalities. One of the challenges facing clinicians treating amblyopia is to identify those children who are not responding to treatment, and to have the courage to abandon treatment if alternative strategies are exhausted. This is not done often enough; and children either suffer ineffectual treatment which impairs their vision, or appear on statistics of patients who have failed to attend their appointments.

The purpose of this article is to indicate to clinicians how to achieve the best possible visual acuity for children being treated for amblyopia while causing a minimum of disruption to the child.

Correspondence and offprint requests to: Michael Clarke, Consultant Paediatric Ophthalmologist, Claremont Wing Eye Department, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP. e-mail: m.p.clarke@ncl.ac.uk

Definitions

The original meaning of amblyopia is ‘dull sight’, and so originally the term covered all forms of impaired vision. This has led to the distinction in the orthoptic literature between ‘organic’ amblyopia, in which poor vision is associated with disease of the eye, and ‘functional’ amblyopia, in which it is not. The term ‘organic amblyopia’ is not used in medical, as opposed to orthoptic, practice and the term ‘functional’ amblyopia does not distinguish between the various causes of cerebral visual impairment, of which amblyopia is one. This way of subdividing amblyopia should be abandoned.

The term amblyopia, as currently used, refers to a condition in which visual development is disrupted, in one or both eyes, because of the absence of a focused image on the fovea, with consequent failure of normal stimulation of the developing visual cortex and associated brain areas. This leads to a failure of formation of

normal cerebral visual neuronal connectivity. In other words, so-called functional amblyopia is caused by an organic problem, but that problem is in the brain rather than in the eye.[3]

Unlike most forms of cerebral visual impairment, amblyopia is potentially reversible, at least in part, provided the disorder causing the degradation of the foveal image is rectified at a sufficiently early stage.

Diagnosis

Amblyopia is often defined as a two-line difference in corrected visual acuity, in the absence of ocular pathology (although amblyopia can complicate structural ocular abnormalities). While this definition may be adequate (although arbitrary) for prevalence studies in adults, it is not adequate for children. In order to know that a measured reduction in corrected visual acuity is significant, age-related normal values for the test used have to be known, and it is only recently that these have begun to be defined.[4] Furthermore, a cause for degradation of the foveal image has to be present. These causes are classified as stimulus deprivation (cataract, ptosis, etc.), refractive, strabismic (which is always unilateral), and mixed.

It is important to understand that visual screening of children does not specifically detect amblyopia, but rather identifies a visual deficit which may be due to refractive error alone[5] or other abnormality.

It is easy to assume, because amblyopia is common and other causes of visual impairment in children are relatively rare, that all visual loss in children is due to amblyopia. It is not uncommon to see children with undiagnosed cataract or retinal dystrophy who are being treated for 'amblyopia'.

Rationale for amblyopia treatment

It seems obvious that amblyopia should be treated; however, this is not as straightforward a matter as it would first appear. Not only is amblyopia treatment not uniformly successful, but also, with the exception of pure refractive correction, amblyopia treatment renders the child visually impaired for the duration of therapy. This leads to high rates of non-concordance with treatment.[6]

There is little evidence that monocular developmental visual impairment causes significant functional disability or impact on quality of life, as opposed to measurable deficits on psychophysical tests.[7] Apart from a general desire to maximise visual function, two reasons are commonly given for treating amblyopia: maximising employment prospects and lowering the risk of bilateral visual impairment resulting from injury to the non-amblyopic eye.

Various visual standards apply to different forms of employment, from the lifeboat service to heavy goods vehicle driving.[8] None of these standards are evidence-based, all are potentially subject to challenge under disability discrimination legislation, and all are likely to change in the UK with the introduction of new European legislation.

Individuals with monocular amblyopia are clearly more at risk of visual impairment following ocular trauma and pathology, as they do not have a normal 'spare eye', although most ocular pathology, as opposed to trauma, affects both eyes anyway.[9]

Improvement in the vision of amblyopic eyes following loss of vision in the normal eye is well documented in some adult, even elderly, individuals. Rahi *et al*. identified 254 individuals aged 11 years or older with unilateral amblyopia who were visually impaired after loss of vision in their non-amblyopic eye but had no other disorder affecting their amblyopic eye. Twenty-five (10%) of these had improved visual acuity in their amblyopic eye.[10]

One unresolved question is whether amblyopia treatment should cease once the maximum visual acuity has been reached, as opposed to being recommenced if acuity subsequently deteriorates. If the goal of amblyopia treatment is to maximise the vision in the amblyopic eye in the event of deterioration of vision in the normal eye, then it may be that the maximum potential vision may be represented by the best acuity seen during treatment, as opposed to the vision at some arbitrary age of discharge from follow-up (typically 5–7 years).

How is amblyopia treated?

The initial phase of amblyopia treatment is to correct the cause of degradation of the retinal image, for example by removal of cataract or correction of refractive error.

The details of treatment of sensory deprivation are beyond the scope of this article, but it is instructive to note that for unilateral complete congenital cataract, there is evidence to show that visual results deteriorate if surgery is delayed beyond the age of 4–8 weeks.[11–16] Following unilateral cataract removal, there is a continuing amblyogenic stimulus from aphakia or pseudophakia with lack of accommodation. While limited patching may suffice in the first year of life subsequent to unilateral cataract removal (with benefit on the development of binocular vision),[14] beyond the first year, $\geq$6 hours a day of patching are required, depending on acuity, up to at least the age of 5 years, in order to obtain good visual results.[15] These onerous amounts of patching often affect the vision of the normal eye.[16]

Refractive correction

The absence of a significant degree of bilateral refractive error or anisometropia should raise the suspicion that the cause of the visual loss is not refractive amblyopia. The degree of anisometropia should also be consistent with the acuity: for example, anisometropia of 0.75D would be consistent with a corrected acuity of 0.3 logMAR in the worse eye, but an acuity of 1.0 logMAR should be viewed with some suspicion. It is easy to generate apparent refractive errors in eyes with poor vision which do not fix well, leading to off-axis retinoscopy.

Assuming the visual loss is consistent with the refractive error, then correcting the refractive error becomes the first treatment.

The major advance in amblyopia treatment in recent years has been the demonstration that correction of refractive error alone has a prolonged treatment effect in amblyopia.[17–19] Following correction of refractive error

in children with refractive and strabismic amblyopia, patching or atropine treatment should be deferred for up to 24 weeks, assuming continued improvement during that period.[20,21]

Patching

Patching the normal eye of a small child with amblyopia is challenging, as anybody who has tried to do it will tell you. Failure to comply with recommended patching treatment is not evidence of moral deficiency on the part of the parents or the child. Before commencing treatment there should be a discussion with the parents concerning the intended goals of treatment, and in the absence of any accurate way to predict the outcome of treatment, an undertaking should be given to the parents that treatment will be abandoned at an early stage if it is proving ineffective.

How can we make patching easier for parents? The most effective way is to reduce the amount of patching they need to do. This includes reducing the amount done per day (and evidence from studies where patching has been monitored suggests most parents cannot manage more than 3–4 hours per day of patching anyway); reducing the duration of patching treatment; and abandoning patching which is demonstrably having no significant effect on vision. Fortunately, there are recent studies which provide evidence that reducing the daily dose of patching does not adversely affect the outcome. Many of these have been carried out by the US Pediatric Eye Disease Investigator Group (PEDIG). PEDIG studies have demonstrated that, for children <7 years with amblyopia of 20/40 to 20/80 (0.3–0.6 logMAR), 2 hours of patching per day is as effective as 6 hours per day.[22] A further study showed that for children <7 years with amblyopia of 20/100 to 20/400 (0.7–1.3 logMAR), 6 hours of patching per day is as effective as 'full time' (all but 1 hour per day) patching.[23] It is worth noting that approximately 50% of patients in both groups in this latter study failed to improve beyond 20/50 (0.4 logMAR).

Supportive evidence that 6 hours of patching per day is as effective as 12 hours per day comes from the Randomized Occlusion Treatment for Amblyopia Study (ROTAS).[24] This study monitored the actual dose of patching received by children in the study and demonstrated that actual occlusion doses were substantially less than those prescribed.

In a separate series of studies from the same group, it was shown that the bulk of treatment effect from patching was achieved with a cumulative dose of between 150 and 250 hours.[25] Specific patient characteristics (especially age) modified the steepness of this function: for example, a 0.20 logMAR gain in visual acuity required a cumulative dose of 170 hours for children at age 48 months and 236 hours at age 72 months. They also showed that visual improvement was correlated with >1 hour per day of patching.[26]

The implication of this is that, for strabismic and refractive amblyopia, there is little point in patching children for 3 hours per day (assuming this is achieved) for longer than around 80 days – say 12 weeks. However, local review of our own practice shows some children undergoing patching for years, and this is likely to be the case in other departments too. Partly this is due to a reluctance to accept that no further significant improvements in vision are occurring, a situation complicated by the test/test variability of quantitative visual acuity measurements in small children, which is greater at lower levels of acuity.

Atropine

Atropine used to be reserved for children who could not tolerate patching at all and so ended up being used for a selected group of patients who were likely to have a poor outcome (as one of the reasons patching was not tolerated was that visual acuity was poor and not improving). It does, however, have advantages as an amblyopia treatment compared with patching in that it cannot be reversed by the patient, and it allows some use of the better seeing eye. It would seem intuitive that atropine would not work for children who have a worse acuity in the amblyopic eye than they do in their atropinised normal eye; however, it has been shown that atropine is equally as effective as patching for acuities from 20/40 to 20/100 (0.3 to 0.7 logMAR),[27] and atropine given only at weekends is an effective treatment for severe amblyopia (0.75–1.3 logMAR).[28]

There are concerns about systemic side-effects of topical atropine; however, it appears to be extremely safe, particularly when used once or twice per week only. Drops or ointment and 1% or 0.5% concentrations are equally effective and safe. Atropine is therefore a particularly useful treatment for toddlers, who are likely to remove their patches. The usefulness of atropine for sensory deprivation amblyopia has not been formally tested.

Visual stimulation

Treatment of amblyopia by attempting to stimulate development of vision in the amblyopic eye has a long history. The CAM stimulator, a rotating grating pattern, was popular for a time in the 1960s but unfortunately was shown to be ineffective in one of the first randomised controlled trials in this area. Near activities are often recommended during amblyopia treatment but their effectiveness is not clear. More recently, an interactive computer system has been developed which has shown some promise and is the subject of further investigation.[29,30] For the time being, however, these methods remain investigational.

Stopping treatment: abruptly or gradually?

There is some evidence that regression from maximum acuity following cessation of treatment is more likely to occur if treatment is stopped abruptly rather than weaned,[31] is more common in children with mixed strabismic and refractive amblyopia,[32] and is more likely to occur in those children in whom treatment had been most successful.[33]

Treatment of children over 7 years

Traditionally, it has been assumed that amblyopia treatment is only possible in children under the age of

7 years, as beyond this age there was no potential for cortical plasticity. This is clearly an oversimplification, and a proportion of children will show a treatment response beyond the age of 7.[34] The age at which there is potential for treatment depends, amongst other things, on the age of onset and type of amblyopia. For example, plasticity in a case of unilateral complete congenital cataract lasts for 2 months following birth. It is possible that some adults with amblyopia would show visual improvement if they were patched; however, the induced visual impairment which would result would be unlikely to be tolerated.

Outcomes

In my view, the major issue confronting clinicians treating children with amblyopia is when to stop treatment. Most children currently undergo far more than the 150–250 hours of patching beyond which, studies suggest, little further improvement occurs.[25,35] This is partly due to uncertainties about visual acuity measurements in children under 4 years, such as whether normal visual acuity measurements on single optotype tests will translate into normal acuities on crowded tests. For children over 4 years, however, these considerations should not apply. For these children, the difficulty is usually in accepting a subnormal level of acuity as the most which can be achieved with treatment. It is important to point out, though, that a subnormal level of acuity is the norm following treatment for many children.

In 1994, Woodruff *et al*. demonstrated in a multicentre UK study that only 48% of children treated for amblyopia achieved an acuity of 6/9 or better in the treated eye.[36] While this appeared to reflect a poor standard of practice in the UK compared with Scandanavia,[2] Woodruff's findings have been confirmed, although not highlighted, by more recent studies. For example, in the PEDIG study ATS1 (atropine versus patching) 37% of children in the patching group and 47% in the atropine group had visual acuities $\leq$20/40 at outcome.[27] This pattern is reflected across other trials, and is greater in trials of treatment of children over 7 years of age.[37,38]

Why do some children not achieve normal visual acuity following treatment?

There are a number of reasons why children might not achieve normal visual acuity following amblyopia treatment. Some children may have structural abnormalities of the retina, optic nerve or central visual apparatus which are either not sought, or are not readily apparent with current imaging techniques.[39] Others may have developed amblyopia at an early age and reversal of the changes which have occurred may no longer be possible by the time of diagnosis.

Key points

- The terms organic and functional amblyopia should be abandoned.
- Amblyopia should only be diagnosed when:
  - acuity falls below the age-related normal range;
  - an amblyogenic stimulus consistent with the measured acuity is present.
- Patching or atropine treatment should be deferred for up to 24 weeks following correction of refractive error in refractive and strabismic amblyopia, assuming continued improvement.
- Patching is challenging: Do not recommend more than is required to obtain the maximum predicted acuity – which is usually not 0.0 logMAR.
- If there has been no significant change in acuity following 6–8 weeks of treatment with atropine or patching, stop treatment and reassess.
- Total achieved doses of patching over 250 hours (3 hours per day for 12 weeks or 6 hours per day for 6 weeks) are unlikely to produce significant further improvements in acuity in strabismus and refractive amblyopia.
- Deterioration of acuity following cessation of treatment occurs in some patients and may be less frequent if treatment is weaned.
- Whether the acuity regained in an amblyopic eye is the maximum achieved during treatment or the acuity at age 7 years is not known.

References

1. Stewart CE, Moseley MJ, Stephens DA, Fielder AR. Treatment dose-response in amblyopia therapy: the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). *Invest Ophthalmol Vis Sci* 2004; **45:** 3048–3054.
2. Lithander J, Sjøstrand J. Anisometropic and strabismic amblyopia in the age group 2 years and above: a prospective study of the results of treatment. *Br J Ophthalmol* 1991; **75:** 111–116.
3. Holmes JM, Clarke MP. Amblyopia. *Lancet* 2006; **367:** 1343–1351.
4. Stewart CE. Comparison of Snellen and log based acuity scores for school aged children. *Br Orthopt J* 2000; **57:** 32–38.
5. Clarke MP, Wright CM, Hrisos S, Anderson JD, Henderson J, Richardson SR. Randomised controlled trial of treatment of unilateral visual impairment detected at preschool vision screening. *Br Med J* 2003; **327:** 1251–1256.
6. Loudon SE, Passchier J, Chaker L, *et al*. Psychological causes of non-compliance with electronically monitored occlusion therapy for amblyopia. *Br J Ophthalmol* 2009; **93:** 1499–1503.
7. Rahi JS, Cumberland PM, Peckham CS. Does amblyopia affect educational, health, and social outcomes? Findings from 1958 British birth cohort. *Br Med J* 2006; **332:** 820–825.
8. Adams GG, Karas MP. Effect of amblyopia on employment prospects.[letter]. *Br J Ophthalmol* 1999; **83:** 380.
9. Rahi J, Logan S, Timms C, Eggitt IR, Taylor DSI. Risk, causes, and outcomes of visual impairment after loss of vision in the non-amblyopic eye: a population based study. *Lancet* 2002; **360:** 597–602.
10. Rahi JS, Logan S, Borja MC, Timms C, Russell-Eggitt I, Taylor D. Prediction of improved vision in the amblyopic eye after visual loss in the non-amblyopic eye. *Lancet* 2002; **360:** 621–622.
11. Birch EE, Cheng C, Stager DR Jr, Weakley DR Jr, Stager DR Sr. The critical period for surgical treatment of dense congenital bilateral cataracts. *J AAPOS* 2009; **13:** 67–71.
12. Lloyd IC, Ashworth J, Biswas S, Abadi RV. Advances in the management of congenital and infantile cataract. *Eye* 2007; **21:** 1301–1309.
13. Lambert SR, Plager DA, Lynn MJ, Wilson ME. Visual outcome following the reduction or cessation of patching therapy after early unilateral cataract surgery. *Arch Ophthalmol* 2008; **126:** 1071–1074.
14. Taylor D, Wright KW, Amaya L, *et al*. Should we aggressively treat unilateral congenital cataracts? *Br J Ophthalmol* 2001; **85:** 1120–1126.
15. Wright KW, Matsumoto E, Edelman PM. Binocular fusion and stereopsis associated with early surgery for monocular congenital cataracts. *Arch Ophthalmol* 1992; **110:** 1607–1609.
16. Lewis TL, Maurer D, Tytla ME, Bowering ER, Brent HP. Vision in the 'good' eye of children treated for unilateral congenital cataract. *Ophthalmology* 1992; **99:** 1013–1017.
17. Moseley MJ, Neufeld M, McCarry B, *et al*. Remediation of

refractive amblyopia by optical correction. *Ophthalmol Physiol Opt* 2002; **22:** 296–299.
18. Stewart CE, Moseley MJ, Fielder AR, Stephens DA, MOTAS Cooperative. Refractive adaptation in amblyopia: quantification of effect and implications for practice. *Br J Ophthalmol* 2004; **88:** 1552–1556.
19. Cotter SA, Edwards AR, Arnold RW, *et al*. Treatment of strabismic amblyopia with refractive correction. *Am J Ophthalmol* 2007; **143:** 1060–1063.
20. Shotton K, Powell C, Voros G, Hatt SR. Interventions for unilateral refractive amblyopia. *Cochrane Database Syst Rev* 2008; CD005137.
21. Moseley MJ, Fielder AR, Stewart CE. The optical treatment of amblyopia. *Optom Vis Sci* 2009; **86:** 629–633.
22. Pediatric Eye Disease Investigator Group. A randomized trial of patching regimens for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2003; **121:** 603–611.
23. Holmes JM, Kraker RT, Beck RW, *et al*. A randomized trial of prescribed patching regimens for treatment of severe amblyopia in children. *Ophthalmology* 2003; **110:** 2075–2087.
24. Stewart CE, Stephens DA, Fielder AR, Moseley MJ. Objectively monitored patching regimens for treatment of amblyopia: randomised trial. *Br Med J* 2007; **335:** 707.
25. Stewart CE, Stephens DA, Fielder AR, Moseley MJ. Modeling dose-response in amblyopia: toward a child-specific treatment plan. *Invest Ophthalmol Vis Sci* 2007; **48:** 2589–2594.
26. Stewart CE, Fielder AR, Stephens DA, Moseley MJ. Treatment of unilateral amblyopia: factors influencing visual outcome. *Invest Ophthalmol Vis Sci* 2005; **46:** 3152–3160.
27. Pediatric Eye Disease Investigator Group. A randomized controlled trial of atropine vs patching for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2002; **120:** 268–278.
28. Repka MX, Kraker RT, Beck RW, *et al*. Treatment of severe amblyopia with weekend atropine: results from 2 randomized clinical trials. *J AAPOS* 2009; **13:** 258–263.
29. Waddingham PE, Butler TKH, Cobb SV, *et al*. Preliminary results from the use of the novel Interactive Binocular Treatment (I-Bit) system, in the treatment of strabismic and anisometropic amblyopia. *Eye* 2006; **20:** 375–378.
30. Eastgate RM, Griffiths GD, Waddingham PE, *et al*. Modified virtual reality technology for treatment of amblyopia. *Eye* 2006; **20:** 370–374.
31. Holmes JM, Beck RW, Kraker RT, *et al*. Risk of amblyopia recurrence after cessation of treatment. *J AAPOS* 2004; **8:** 420–428.
32. Tacagni DJ, Stewart CE, Moseley MJ, Fielder AR. Factors affecting the stability of visual function following cessation of occlusion therapy for amblyopia. *Graefes Arch Clin Exp Ophthalmol* 2007; **245:** 811–816.
33. Holmes JM, Melia M, Bradfield YS, Cruz OA, Forbes B. Factors associated with recurrence of amblyopia on cessation of patching. *Ophthalmology* 2007; **114:** 1427–1432.
34. Pediatric Eye Disease Investigator Group. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. *Arch Ophthalmol* 2005; **123:** 437–447.
35. Cleary M. Efficacy of occlusion for strabismic amblyopia: can an optimal duration be identified? *Br J Ophthalmol* 2000; **84:** 572–578.
36. Woodruff G, Hiscox F, Thompson JR, *et al*. Factors affecting the outcome of children treated for amblyopia. *Eye* 1994; **8:** 627–631.
37. Repka MX, Kraker RT, Beck RW, *et al*. A randomized trial of atropine vs patching for treatment of moderate amblyopia: follow-up at age 10 years. *Arch Ophthalmol* 2008; **126:** 1039–1044.
38. Scheiman MM, Hertle RW, Kraker RT, *et al*. Patching vs atropine to treat amblyopia in children aged 7 to 12 years: a randomized trial. *Arch Ophthalmol* 2008; **126:** 1634–1642.
39. Barrett BT, Rowan Candy T, McGraw PV, Bradley A. Probing the causes of visual acuity loss in patients diagnosed with functional amblyopia. *Ophthalmic Physiol Opt* 2005; **25:** 175–178.