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## Review Article

## The challenges of amblyopia treatment



Gail D.E. Maconachie, Irene Gottlob\*

Ulverscroft Eye Unit, Department of Neuroscience, Psychology and Behaviour,  
University of Leicester, RKSCB, Leicester Royal Infirmary, Leicester LE2 7LX, UK



Dr. Irene Gottlob

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## ABSTRACT

The treatment of amblyopia, particularly anisometropic (difference in refractive correction) and/or strabismic (turn of one eye) amblyopia has long been a challenge for many clinicians. Achieving optimum outcomes, where the amblyopic eye reaches a visual acuity similar to the fellow eye, is often impossible in many patients. Part of this challenge has resulted from a previous lack of scientific evidence for amblyopia treatment that was highlighted by a systematic review by Snowdon et al. in 1998. Since this review, a number of publications have revealed new findings in the treatment of amblyopia. This includes the finding that less intensive occlusion treatments can be successful in treating amblyopia. A relationship between adherence to treatment and visual acuity has also been established and has been shown to be influenced by the use of intervention material. In addition, there is growing evidence of that a period of glasses wearing only can significantly improve visual acuity alone without any other modes of treatment. This review article reports findings since the Snowdon's report.

Unilateral amblyopia is a loss in visual function in one eye in comparison to the other and is often caused by other associated factors that force the visual system to prefer one eye over another [1]. The most common of these factors is a difference in refractive error between the two eyes, usually in spherical correction (anisometropic amblyopia) and/or a strabismus (strabismic amblyopia). Many other forms of unilateral amblyopia occur as a result of pathological changes in the structure in or around the eye such as unilateral cataracts or ptosis (stimulus deprivation amblyopia). A challenge in the

treatment of amblyopia is that there is often no apparent structural reason why there is a limitation of vision and yet many amblyopes, after several years of amblyopia treatment, fail to reach successful outcomes.

Since as early as the 1st century AD [2] covering of the dominant eye to increase visual acuity in the amblyopic eye, now referred to as occlusion therapy, has been suggested as the standard form of treatment in anisometropic and strabismus amblyopia. However, it was not until the Snowdon's report [3] in 1998 that it became apparent that evidence-based

\* Corresponding author. Ophthalmology Group, University of Leicester, RKSCB, Leicester Royal Infirmary, Leicester LE2 7LX, UK. Tel.: +44 (0) 116 258 6291; fax: +44 (0) 116 255 8810.

E-mail address: [Ig15@le.ac.uk](mailto:Ig15@le.ac.uk) (I. Gottlob).

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research about treatment modalities in amblyopia was lacking. As a result of these findings, there has been a significant increase in publications of randomized controlled studies in amblyopia. This review will explore the new findings since this report and discuss future areas of interest for amblyopia treatment.

## Refractive therapy

In children with amblyopia, in particular when a strabismus is present, it is recommended that full refractive correction should be prescribed [4]. However, there is some confliction within literature with regards prescribing full prescription due to its possible effects on emmetropization. In a study by Atkinson et al. [5] they found that those who were prescribed a partial correction in comparison to those who were prescribed no refractive correction the process of emmetropization was the same. In contrast, a randomized control trial (RCT) study by Ingram et al. ( $n = 287$ ) [6], showed that those who were prescribed full correction from the age of 6 months and had good adherence to glasses wear, the effect on emmetropization was significantly delayed in comparison to those who were poor compliers or were not prescribed any refractive correction. Further investigation regarding the amount of hyperopia that affects emmetropization is still required.

In 2002, Moseley et al. [7] reported the results of 13 anisometropic and strabismic amblyopes who were prescribed refractive correction only, they showed for the first time that amblyopic subjects can gain significant improvements in visual outcome with refractive correction alone. In a later study [8], 14 of 65 amblyopic subjects (interocular difference in visual acuity of  $>0.1$ ) had a resolution of their amblyopia with glasses alone, and no further treatment was required. The mean improvement in visual acuity for the 65 patients was 0.18 LogMAR with the majority of cases achieving maximum improvement within the first 18 weeks of wearing refractive correction. There was no significant difference in the level of improvement between different types of amblyopia, (anisometropic, strabismic or strabismus with anisometropia)  $p = 0.29$ . However, a recent survey of orthoptists reported 94% prescribe a period of refractive correction before implementing further treatment, although this is lower for strabismic (75%) or strabismic and anisometropic amblyopia (79%) [9]. This period of refractive correction is also commonly referred to as refractive adaptation or refractive treatment [8]. Limitations of this study include no randomized control group and the inclusion of patients with an intraocular difference of 0.1 which is not often described as amblyopia.

Since this study, a number of additional studies have confirmed that this period of refractive treatment does occur in anisometropic and/or strabismic amblyopes [10–12]. It has been also reported to have a greater effect in those with better baseline stereopsis, milder forms of anisometropic amblyopia and those with a worse baseline visual acuity in strabismus with anisometropia and strabismic patients. The least likely type of amblyopia to respond to refractive adaptation has been reported to occur in strabismus with anisometropia amblyopia. There is also a wide variance in the length of time required to achieve the maximum outcome of refractive

adaptation [12]. One of the possible factors is the influence of adherence to glasses wear. An unpublished pilot study including 26 patients [13], has revealed variable adherence to glasses wear. It has also shown a strong dose–response relationship between adherence and visual outcome ( $r = 0.76$ ,  $p = 0.0001$ ). Further work in this area with a larger cohort is needed to explore the relationships between glasses wearing, refractive adaptation and visual outcome.

When refractive adaptation is translated into a clinical setting, it has been reported that the recommended 18–22 weeks may, for some patients, delay treatment. Norris et al. [10], recommend that patients should be reassessed at 6 and 14 weeks and if there is no significant improvement they suggest prescribing other forms of treatment. This highlights the need for further research into refractive treatment for example a RCT comparing refractive adaptation and other treatment modalities for amblyopia.

## Occlusion

### How much?

The use of occlusion therapy is the most well-known and commonly practiced way of treating amblyopia. Until occlusion therapy was prescribed based on clinical experience rather than scientific based evidence. This generated a wide variance between departments on how amblyopic patients were treated clinically [14]. In 1998, the PEDIG [15] sought to review the number of hours prescribed by recruiting, moderate and severe strabismic and anisometropic amblyopes into two groups with the moderate amblyopes receiving either 6 h or 2 h of occlusion, whereas the severe amblyopes received either full time (all or all but 1 h 4/day) or 6 h of occlusion [16,17]. Their results revealed that visual outcomes with more intensive occlusion, 6 h for moderate amblyopes and full time for severe amblyopes, were similar to the lower amount of prescription 2 h and 6 h respectively. In addition, their findings revealed no significant difference between cause of amblyopia and improvement in visual acuity ( $p = 0.85$ ). Guidelines from the American Academy of Ophthalmologist [18] and the Royal College of Ophthalmologist [19] have changed as a result of these findings so that now both advise the use of 6 h for severe amblyopia and 2 h for moderates. Although at present there is still a wide variance in the number of hours of occlusion prescribed by those treating amblyopia.

### Adherence to occlusion

There is some concern with basing guidelines on the PEDIG studies because adherence to occlusion therapy is less than optimal. Therefore, the results shown by the PEDIG group have been challenged by the work objectively exploring compliance in amblyopia treatment with the use of occlusion dose monitors (ODMs) [20,21]. In one study, it was shown that patients who were prescribed 6 h or 3 h a day only adhered to half of their prescribed amount, average 2 h 33 min and 1 h 45 min respectively, leading to there being no significant difference in the total amount of occlusion therapy undertaken

between the two groups [21]. This finding has been supported by another study [11].

Dose response relationships between hours of effective patching measured by ODMs and visual outcome revealed a strong correlation up to 6 h in a study including 52 participants ( $F = 17.1$ ,  $p = 0.00013$ ,  $r = 0.50$ ) [21]. However, in a study with more participants ( $n = 97$ ), where refractive adaptation was prescribed prior to occlusion, dose response relationship plateaued around 4 h particularly in children <4 years [11]. Older children (older than 6 years) required a higher average of 5.55 (4.45–6.45) h/day of occlusion although this was not significantly different to the amount necessary for <4 years. Similarly, patients with strabismic amblyopia required more hours of occlusion therapy than anisometropic amblyopes (5.79 and 5.19 respectively) but again this was not significant. A limitation of this study was the inclusion of patients with a difference in visual acuity between the eyes of 0.1, which is lower than the usually defined difference of 0.2 or even 0.3 as used in the PEDIG studies. Recently, in unpublished work where participants did not have prolonged refractive adaptation, a significant dose response relationship was found up to 10 h for strabismic and strabismus with anisometropia amblyopes but not in anisometropes [22]. Further evidence is required to explore the possibility of differing treatment based on the type of amblyopia.

Studies have also begun exploring reasons for poor adherence to occlusion therapy in order to produce better compliance. In 2006, Dixon-Wood et al. [23] interviewed 25 parents of children who underwent occlusion therapy in order to find reasons for reduced compliance. A number of key themes were highlighted including parents being unsure about the benefits of treatment, difficulties with distress in the child who was patching and relationship pressures particularly in the early stages of treatment. Parents were also asked for suggestions that could help compliance. Many recommended the use of rewards, establishing routine, decoration of the patch or educational cartoons [24]. From this advice, many research groups have initiated the development of intervention material. Tjiam et al. [25] reported using several intervention materials in low-socioeconomic groups, including cartoons, reward calendars and parent information leaflets. The result showed that cartoons produce a significant improvement in compliance in comparison to a control group. In another study by Pradeep et al. [26], two groups of patients, a control group and an intervention group, were prescribed 10 h/day of occlusion therapy and were reviewed 12 weeks later. Although the overall compliance between the two groups was similar, the intervention material significantly reduced the number of drop-outs and reduced the number of poorly compliant patients.

Additional studies have explored ways of improving visual outcomes through increasing the stimulation of the amblyopic eye during occlusion. In a pilot RCT study published by the PEDIG group [27], which included 64 children, with various types of amblyopia, aged 3 to <7 years, showed that 2 h of occlusion with advised near tasks did suggest an increase in visual outcome in comparison to those who were not advised to undertake near activities while patching. Later with a larger number of amblyopes ( $n = 425$ ) and longer follow-up (up to 17 weeks), the same authors reported that occlusion with near task was insignificant [28]. Another group reported subjects who underwent 3 h or 6 h occlusion therapy with near tasks

and again showed undertaking near tasks while patching significantly improved visual outcomes [29]; however, greater numbers are needed to compare to the larger PEDIG study.

Partial occlusion therapy has also been suggested to help with compliance in the form of Bangerter foils, semi-opaque foils that can be attached to the glasses. However, in a RCT comparing Bangerter foils to glasses alone or occlusion, there was no significant difference in visual outcome for any cause of amblyopia [30]. It is suggested however that in comparison to occlusion, Bangerter foils do provide less distress for the patient and therefore could be considered as a possible alternative.

### Recurrence

A challenge of amblyopia treatment is recurrence of amblyopia on cessation of treatment. It is reported that 13–24% of patients decrease by 2 or more LogMAR lines within the 1st year of completing treatment [31–34]. A number of factors have been associated with this recurrence including better vision at the end of treatment, greater improvement during treatment, history of recurrence and a combination of strabismus with and without anisometropia or microtropia, a small angled strabismus with abnormal binocular functions. An additional inverse relationship has also been found between recurrence and age [31]. In a clinical setting, it has been suggested that patients should undergo a period of maintenance or weaned occlusion. Initial research suggests that moderate patching treatment (6–8 h of occlusion) should undergo a period of weaning [32]. However, in the only reported RCT of 20 patients who underwent full-time occlusion, there was no significant difference between the number of patients in which amblyopia recurred, with and without weaning treatment [34]. A larger RCT is required to re-affirm this finding.

### Critical period

Recent reports have challenged the clinical perception that amblyopes cannot be treated beyond the critical period, suggested to be around the age of 8 years of age. A large multicenter study by PEDIG in 2005 [35] revealed that 50% of children aged between 7 and 12 years of age who underwent a period of amblyopia treatment, such as occlusion or atropine, had a significant improvement in visual outcome in comparison to a control group who were only prescribed glasses. The findings however were not significant for >12 years, but there was a suggestion that children who had not yet undergone treatment could also improve. Type of amblyopia, either anisometropic and/or strabismic was found not to be a predictor of visual outcome.

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### Atropine

With the increasing knowledge of poor compliance during patching and the potential cause of social deprivation as result of occlusion therapy [36], atropine is often used in clinic as an alternative to occlusion. The role of atropine is to blur the vision in the nonamblyopic eye by paralyzing the ciliary muscles that control accommodation and constriction of the pupil. Although this treatment has been recommended since

before the Snowdon's report, again similar to occlusion therapy, there were no previous RCTs. Large multicenter RCT have revealed a number of previously unknown benefits including the use of atropine being instilled only at the weekends producing similar visual outcomes to weekday instillation and the finding that severe amblyopes can also be treated effectively [37]. The final point, however, is surprising as it has been reported that atropine can only blur visual acuity to a maximum of 20/100 in the nonamblyopic eye [38]. The treatment of severe amblyopia with atropine still requires further investigation as at present this is limited to an RCT comparing the effects of 2 h of occlusion therapy and atropine in children 7–12 years. This does not accurately reflect the amount of occlusion suggested for severe amblyopia particularly in this older age group [39].

A greater amount of research has been undertaken investigating the treatment of moderate amblyopes with atropine in comparison to occlusion. Comparisons between occlusion and atropine at long-term outcomes are reported to have a similar visual outcome in moderate amblyopes. Occlusion therapy (minimum 6 h a day to maximum 10 h a day) was revealed to have a quicker initial, although not significant, improvement in vision in comparison to the atropine group [40–42]. Subgroup analysis of type of amblyopia has no effect on long-term visual outcomes ( $p = 0.83$ ). Despite the equivalent outcomes between occlusion and atropine, atropine is still commonly only used as a secondary option after occlusion has been unsuccessful, usually as a result of poor compliance [9]. Even though atropine is reported to be better tolerated and a less emotional experience than occlusion therapy [43], it is not clear whether occlusion therapy could achieve better visual outcomes than atropine, especially if adherence to occlusion is optimized with the use of intervention.

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## Perceptual learning

The idea of perceptual learning was first defined by Eleanor Gibson (1963) and involved training patients on perceptual tasks with the Cambridge Visual Stimulator (CAM) a system that used high contrast rotating sine-wave gratings [44]. The use of CAM significantly decreased when little benefit in comparison to occlusion therapy was found [45]. With the availability and improvements of computers, perceptual learning has begun to regain increasing interest, particularly in patients beyond the critical period. During perceptual learning, patients are often trained on contrast sensitivity tasks while nonamblyopic eye is occluded [46,47]. More recent game play formats have also been used to increase stimulation of the amblyopic eye [48,49]. Initial results report a significant improvement in visual outcome in the amblyopic eye [48–50]. The limitation of many perceptual learning studies is the lack of large scale, RCTs with long term follow-up. Two studies have followed-up subjects after monocular and binocular treatment. Both studies show a decline in visual outcomes after 8–10 weeks although less significant in the binocular group [49,51]. In addition, due to low study number, sub-analysis of amblyopia cause has not yet been undertaken. Moreover, very few studies report the size of the strabismic deviation except Li et al. [50] who recruited 3/10 strabismic subjects of a deviation greater than 10 prism dioptres.

An adaption of perceptual learning is to use stimulation to both eyes to treat amblyopia [51]. During treatment, an image is presented to both eyes, the dominant eye is presented with a low contrast eye while the amblyopic eye is given a high contrast eye. If subjects are successful in completing the game, the image in the dominant eye is slowly increased until the contrast in both eyes is equal. Patients are trained using a dichoptic game format, usually Tetris. This game requires the use of both eyes by presenting only half the blocks to each eye. Pilot data show promising results with improvements in visual outcome and stereopsis in the majority of patients. The stereopsis outcomes have also been reported to be enhanced using transcranial direct current stimulation [52]. However, due to the current sample size in both studies, no analysis was undertaken to explore the effects of the cause of amblyopia on visual outcome. Moreover, the size of strabismic deviations in strabismic subjects was also not reported. Further analysis with greater number of subjects would help to establish suitable subtypes of amblyopia that would benefit from this form of treatment.

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## Pharmacological treatment

Levodopa is the most commonly reported medical drug used in amblyopia treatment and is a precursor to dopamine. Dopamine is a neurotransmitter present within the visual pathway which has been shown, with the use of animal model [53], to be reduced in amblyopia. In 1990, Gottlob and Stangler-Zuschrott [54] first described the use of levodopa in severe strabismic and strabismic with anisometropia amblyopia and reported a significant improvement in suppression scotomas and contrast sensitivity outcomes when treated with levodopa. Improvements in other visual functions, including visual acuity, have been reported in a number of studies [55,56] and are enhanced by the use of occlusion therapy and carbidoopa, which increases levodopa uptake into the blood–brain barrier [57]. Regression of VA outcomes after ceasing levodopa are high although more sustained in those who receive full-time occlusion and are younger (3–7 years) [58–60]. In all studies except one, all forms of amblyopia were recruited into the study. Due to the sample sizes, no analysis based on type of amblyopia was performed. Side effects from levodopa are commonly reported in literature and limit its use in a clinical setting however further work, suggested by the PEDIG group, in the form of a placebo-control trial is warranted.

Recent discoveries in mice have shown that the *lynx1* gene codes for a protein that suppresses acetylcholine receptor signaling in the brain and regulates plasticity of the mature brain [61]. Cholinesterase inhibitors may prevent the expression of *lynx1* allowing for plasticity in the brain beyond the critical period that would be beneficial in amblyopia treatment and has already begun to form the basis of future research.

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## Acupuncture

The use of acupuncture for the treatment of medical conditions has long been discussed in the literature but has only relatively recently been applied to amblyopia treatment.



Acupuncture has been shown, using fMRI, to improve blood flow in the visual cortex through accurate stimulation using the correct acupoints [62]. Currently, two RCT using acupuncture in amblyopia treatment have been reported. The initial study reported the results of two groups of anisometropic amblyopes aged 7–12 years. The first group received acupuncture while the second group (control groups) received 2 h of occlusion therapy. At 15 weeks, follow-up subjects in the acupuncture group were found to have significantly greater improvements in visual acuity in comparison to the control group (2.27 lines and 1.83 lines respectively) [63].

More recently, Lam et al. [64] reported the effects of acupuncture on anisometropic children aged 3–7-year-old who were undergoing refractive adaptation. Using a randomized cross-over trial method, they found significantly greater improvements in visual acuity in the phases that corresponded with the use of acupuncture. Although both studies revealed a benefit of acupuncture a significant limitation was absence of a control group to assess for placebo effect. An additional limitation in the first study was that the acupuncture group required more clinical visits than the occlusion group leading to a possible Hawthorne effect (positive attention bias). These limitations would need to be further addressed before implementation into clinical practice particularly in areas where acupuncture is not a common treatment in any medical condition.

### Other treatments

Several other suggestions have been reported as an alternative to the conventional treatment for amblyopia. Many have developed in order to address the issue with poor compliance to either glasses or occlusion therapy [65–67]. Very few have been translated into clinical practice although significant improvements have been noted in refractive surgery and occlusive contact lenses treatment. The main concern is the increased risk that many of these suggested treatments have in comparison to occlusion therapy. Although refractive surgery has proven successful in adults, it is not clear what long-term effects it has on young children particularly when the eye is still continuing to develop. An additional difficulty is compliance with maintenance issues particularly with contact lenses where good hygiene practice is required [67].

Other more controversial nonrandomized prospective trials have reported the use of sutured occluders or silicone lid closures to promote the use of the weaker eye [68,69]. With high-risk of reversal amblyopia, lasting long-term effects and no control group, it is difficult to warrant their merit in comparison to occlusion.

### Conclusion

Since the Snowdon's report, amblyopia research has advanced significantly particularly with the use of randomized controlled trials. However, while revealing that refractive adaptation, occlusion and penalization can improve visual acuity in amblyopia this has led to the raising of additional questions that require further investigation. Compliance issues remain a

significant problem, although studies have positively addressed this by increasing the amount of information provided to families. With the increasing knowledge of the role occlusion and glasses plays individually in the improvement of the amblyopic eye, research should continue to find more specific treatment protocols for the various types of amblyopia. Further, RCTs are required to investigate these relationships.

Additional research could also help to provide more reliable treatment options. With the growing public interest in binocularity and computer systems, treating amblyopes with game-play could potentially initiate a new form of amblyopia treatment. It is, however, important that these treatment methods undergo robust clinical trials so that further clarification of the types of amblyopia that will benefit with game-play treatments can be established. RCTs between binocular treatments and occlusion therapy are also still warranted.

In conclusion, although advancements have been made, further research is still required to help those treating amblyopia particularly in regards to improvement and maintaining compliance to treatment. Research in the area of refractive correction compliance, binocular treatment and more education on atropine is also needed. However, since the Snowdon's report, we now have reliable scientific evidence to show that prescribing refractive correction and atropine or occlusion with additional interventional material should optimize visual outcomes in amblyopic patients with minimal side effects.

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None declared.

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