

PEER REVIEWED

Diagnosis and Management of Residual Amblyopia in a Non-compliant Patient

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Abstract

Amblyopia is a common neurodevelopmental visual disorder for which there are well-established evidence-based treatment paradigms involving appropriate refractive correction followed by occlusion and/or atropine penalization. Nevertheless, evidence is limited for when to cease therapy, particularly for patients with poor compliance, if visual acuity (VA) plateaus at a sub-optimal level. This teaching case report illustrates the clinical dilemma of determining when to cease therapy in a child with residual amblyopia. Although the patient described in the case showed substantial initial VA improvements, amblyopia therapy was prolonged because of reluctance to cease when VA failed to improve beyond 0.4 logMAR.

Key Words: *amblyopia, anisometropia, patching, atropine, occlusion therapy*

Introduction

Amblyopia, a prevalent neurodevelopmental visual disorder, carries a significant risk of serious bilateral visual impairment and disability later in life.¹ The prevalence of amblyopia is estimated to be 1-3%²⁻⁴ of the population and the condition is the leading cause of uncorrectable vision loss in children and adults under the age of 60.⁵ Refractive correction, occlusion therapy and atropine penalization are the mainstays of amblyopia treatment in children, and well-established clinical management paradigms for unilateral amblyopia now exist.¹ Although amblyopia is potentially reversible if detected and treated early, amblyopic eye visual acuity (VA) remains subnormal in 15-50% of children despite extended periods of occlusion therapy.⁶

We present a case of an 8-year-old girl, referred for anisometropic amblyopia and managed using current evidence-based guidelines.¹ Despite appropriate refractive correction and lengthy periods of prescribed occlusion and atropine penalization, the amblyopic eye VA plateaued at a suboptimal level. This case illustrates the characteristics of, and risk factors for, residual amblyopia in a patient for whom patching and atropine therapies were prolonged despite static VA. We evaluate current evidence and discuss factors that may help clinicians make the difficult decision to stop amblyopia therapy in children unresponsive to treatment, particularly those with poor compliance. This case report is intended for optometry students in their final 2 years of study and eyecare providers in clinical practice, particularly those interested in children's vision.

Case Description

A community-based optometrist referred an 8-year-old girl to the local hospital eye department after diagnosing left amblyopia and prescribing glasses of right eye +0.50DS and left eye +0.75/-0.75x8. The patient had no significant ocular, medical or family history. Unaided VAs were: right eye 0.10 logMAR

(Snellen equivalent 20/25) and left eye 1.20 logMAR (1.00 logMAR with pinhole; Snellen equivalent 20/200) with the crowded Keeler logMAR test. Cover test and ocular health were unremarkable in both eyes. Cycloplegic refraction, with 1% cyclopentolate, found right eye +1.75DS and left eye +9.00/-1.50×180. The patient was diagnosed with anisometropic amblyopia, prescribed glasses of right eye +0.75DS and left eye +8.00/-1.50×180, and advised to start occlusion of her right eye as much as possible. (The prescription was based on the Pediatric Eye Disease Investigator Group (PEDIG) studies, which recommend determination of refractive error based on cycloplegic refraction using 1% cyclopentolate and that astigmatism and anisometropia are fully corrected and hyperopia is either fully corrected or under-corrected by no more than 1.50D.)

Management and outcome

Figure 1 shows visual acuities, patient-reported compliance and the management plan for all clinic visits, which occurred over an extended period of time. At all visits, the need for compliance was reinforced with both the patient and her parents.



Figure 1. Clinical timeline: 8-year-old Caucasian female diagnosed and treated for anisometropic amblyopia. (OD = right eye; OS = left eye)

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Figure 2. Left Y axis: change in visual acuity (logMAR) for both the amblyopic left eye (red dashed line) and fellow right eye (black solid line). Right Y axis: change in stereosensitivity (inverse of stereoacuity) over the course of treatment. Unmeasurable stereoacuity has a value of 0.0 stereosensitivity.

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The patient and her parents reported good compliance with full-time spectacle wear but poor adherence to the prescribed occlusion and atropine regimens except for short periods during school holidays. The cycloplegic refraction was repeated 10 months after the initial examination and the patient's spectacle prescription was updated to right eye plano and left eye +7.50/-1.00×180, as the patient's hyperopia had reduced. The cycloplegic refraction was repeated 5 months later, 15 months after initial diagnosis, as the patient had broken her glasses, and no clinically significant change in refractive error was found.

The patient's VA improved by 0.175 logMAR in the right eye and 0.750 logMAR in the left eye (**Figure 2**). During the first 5 months of treatment, VA improved significantly despite poor compliance with occlusion, which was most likely due to refractive adaptation, full-time spectacle wear and appropriate correction of her anisometropia. Stereopsis was measured at each visit and first detected 18 months after the initiation of treatment (1200" of arc with the Frisby stereotest). Stereoacuity eventually improved to a maximum of 55" of arc.

Educator's Guide

Key concepts

1. Diagnosing amblyopia
2. Identifying residual amblyopia
3. Evidence-based treatment regimens for amblyopia including the importance of appropriate refractive correction and the efficacy of occlusion and atropine therapies
4. The importance of compliance in amblyopia therapy
5. Deciding when to cease therapy in cases of residual amblyopia

Learning objectives

By the end of this case study, learners should be able to:

1. Correctly identify amblyopia risk factors and how these can be used to make the diagnosis of amblyopia
2. Identify and describe the risk factors for residual amblyopia
3. Differentiate amblyopia from other childhood ocular conditions
4. Formulate an evidence-based management plan for children with amblyopia
5. Construct an appropriate follow-up schedule
6. Evaluate clinical test results to decide when further therapy is not warranted in cases of residual amblyopia

Assessment of learning objectives

- a. Case-based discussions on diagnosis and management of amblyopia particularly in patients at risk of residual amblyopia
- b. Clinical thinking skills and knowledge base of the clinical signs of amblyopia could be assessed in a small-group setting, e.g., seminar, with an academic staff member mediating the discussion to cover all the appropriate points. The material could also be reviewed as a Grand Rounds case and assessed as part of a written exam
- c. Students should be evaluated on their knowledge of different amblyopia therapies and be able to create a child-specific treatment plan
- d. Practical assessment of clinical tests that are commonly used in the diagnosis of amblyopia e.g., pediatric visual acuity tests, cover test and stereoacuity tests can be used in a practical or clinical proficiency examination. Practice with cycloplegic retinoscopy could also be included as part of the practical assessment
- e. Role-playing simulations on managing non-compliance in patients
- f. Written communication skills can be assessed by writing an information brochure for parents and/or children on amblyopia therapy (patching and atropine regimens)
- g. Literature review on evidence-based amblyopia management could be written up as a dissertation

Discussion Points

Amblyopia is defined as a reduction in VA in one or both eyes while wearing optimal refractive correction, in the presence of an amblyopia risk factor such as anisometropia, strabismus or media opacification, and in the absence of ocular pathology.⁷ The functional deficits associated with amblyopia are widespread and include impairment in VA, stereopsis,⁸ motion processing⁹ and visual motor integration¹⁰ as well as abnormal fixational and saccadic eye movements,¹¹ contrast sensitivity¹² and contour integration.¹³

The natural history of amblyopia is poorly understood as it is unethical to withhold treatment. However, it is widely acknowledged that spontaneous recovery is unlikely. In one small study of 18 children, who were age 4-6 and non-compliant with amblyopia therapy, VA was either unchanged or reduced when the patients were re-tested 12 months after screening.¹⁴ It is well understood that amblyopia therapy leads to significantly better patient outcomes both in terms of visual function (most notably visual acuity and stereoacuity) and quality of life.¹⁵ Furthermore, people with untreated amblyopia have nearly double the risk of bilateral visual impairment compared with the general population.¹⁶ Therefore, effective treatment in childhood can prevent blindness later in life. While there is increasing evidence that amblyopia therapy can be effective in older children¹⁷ and adults,^{18,19} the efficacy of amblyopia therapy is related to age at the commencement of treatment.²⁰

Making the diagnosis of amblyopia – structuring the clinical examination

Assessment of amblyopia should include a comprehensive patient history, an ocular health examination, refraction and measurement of binocular function and VA using age-appropriate methods. Commonly, 'crowded' VA is measured because amblyopia is associated with impaired contour interaction. However, it is important to note the critical spacing is proportional to letter size and maximal impairment occurs when crowding bars (or equivalent) are within 0.25 diameter away from an optotype, and no impairment occurs when crowding bars are \geq one optotype spacing away.²¹ Furthermore, the detrimental effect of crowding on acuity measurement is most pronounced in strabismic (and mixed) amblyopes when compared with anisometric amblyopes.²²

Therefore to diagnose amblyopia, a clinician must:

1. Perform an age-appropriate refractive examination, which will typically include the use of cycloplegia
2. Re-measure visual acuity with the optimal refractive correction in place and compare to age-appropriate norms²³
3. Undertake a thorough ocular health assessment, including ocular imaging where required, to rule out anterior or posterior segment pathology
4. Identify at least one amblyopia risk factor, for example anisometropia (in one or both principal meridians), high bilateral refractive error, strabismus or media opacities. In patients with anisometric amblyopia associated with hyperopia, the degree of visual impairment should be well-correlated.^{24,25} The relationship between degree of anisometropia and depth of amblyopia is less clear in patients with unilateral myopia and visual impairment may be associated with changes in retinal structure and function²⁶



Table 1. [Click to enlarge](#)

The exact association between magnitude of refractive error and risk of amblyopia development has not been fully elucidated due to the limited number of participants with amblyopia included in most epidemiological studies. Various odds ratios and guidelines exist, which are summarized in **Table 1**. Previously, it was assumed that moderate to high levels of unilateral myopia were required before amblyopia developed, however; the Vision in Preschoolers study found that children with unilateral myopia \geq 0.50 D to $<$ 2.00 D also had an increased risk of amblyopia development (odds ratio 1.74; 95% confidence intervals 1.08-2.80; $p = 0.02$).²⁷ Other studies showed a dose-dependent association between magnitude of ametropia and amblyopia development and a higher risk of amblyopia development with esotropia compared with exotropia.^{27,28}

Differential diagnoses

Clinicians should be aware of other potential causes of monocular or binocular vision loss in children when making the diagnosis of amblyopia. Ocular pathology including retinal diseases and dystrophies²⁹ should be excluded as potential causes of impaired VA. Congenital optic nerve anomalies and toxic optic neuropathies from tobacco, alcohol³⁰ or pharmaceutical agents³¹ should also be excluded. It is also imperative to rule out orbital or visual pathway tumors as a cause of vision loss in children.³² Accidental or non-accidental traumatic brain injury can result in profound deficits in visual function³³ and cerebral visual impairment (CVI) can cause impairments similar to those in amblyopia including reduced visual acuity, contrast sensitivity and abnormal eye movements.³⁴ Much like amblyopia, CVI is a diagnosis of exclusion but a thorough history-taking is likely to elicit a history of perinatal asphyxia/hypoxia, non-accidental injury, prematurity or neonatal trauma, infection or seizures.³⁵

How should amblyopia be managed?

Current amblyopia treatment regimens focus on improving monocular visual acuity, typically by penalizing the fellow (“good”) eye. Treatment entails several steps (**Table 2**) generally commencing with the elimination of any visual obstruction such as refractive error to provide both eyes with clear foveal images.



Table 2. [Click to enlarge](#)

Amblyopia treatment plans should be considered in consultation with both the patient and the parent(s)/caregiver(s) and take into account the age of the patient³⁶ and likely compliance with different treatment modalities, as well as the psychosocial impact on the patient and their family.³⁷

The typical starting point for amblyopia therapy is full-time refractive correction (“optical treatment”) to provide retinal images of equal size, clarity and accommodative demand. When prescribing optical treatment for children with amblyopia, the clinician should correct the full amount of myopia and astigmatism as well as the full anisometric difference.¹⁷ Hyperopia can either be fully corrected or symmetrically under-corrected to allow for adaptation to the spectacle prescription. Over three-quarters of patients show improvement in VA with optical treatment alone, and these improvements may continue for up to 30 weeks.³⁸ The patient described in this case study was not prescribed her full anisometric prescription by the community optometrist prior to referral to the hospital eye department. It is unclear whether this was due to the failure to detect the high degree of hyperopia in the left eye, or whether this was prescribed as a “balance” lens.

In general, children should be prescribed refractive correction alone until VA ceases to improve. Optical treatment results in resolution of amblyopia in approximately 25% of children^{38,39} and potentially improves compliance with later patching due to improved acuity in the amblyopic eye in those children with residual amblyopia. In this case study, the patient’s age, as well as poor VA at presentation, were deciding factors for starting occlusion immediately. The Pediatric Eye Disease Investigator Group (PEDIG) found a decreasing treatment response to amblyopia therapy with increasing age, particularly in children with severe amblyopia.⁴⁰ In older children, optical therapy augmented with occlusion or atropine penalization was more effective than refractive correction alone for moderate and severe amblyopia.⁴⁰ Despite augmented therapy, VA improved less (on average 2.2 lines) than in younger children.¹

Patching, atropine penalization or other amblyopia treatments typically begin when VA has stabilized, i.e., when there is no improvement from the previous examination despite good compliance. However, in non-compliant patients, determining VA stability and visual potential is more difficult. Chen et al. found a linear improvement in VA between four and 12 weeks after initial spectacle wear followed by an acuity plateau until week 20 after which VA continued to improve again although at a reduced rate.⁴¹ The authors suggested that refractive adaptation should be considered for up to 4 months, after which patching or atropine penalization could be instituted if there is no further improvement in VA with spectacle wear alone.

PEDIG found no difference in final visual acuity in children with mild to moderate amblyopia who had been prescribed two hours patching vs. six hours patching.⁴² Likewise, in children with severe amblyopia (worse than 20/120), there was no difference between six hours per day patching vs. full-time patching.⁴³ However, in both PEDIG and Chen et al., compliance wasn’t controlled or monitored and objectively measured compliance with patching was estimated to be as low as 44-57%⁴⁴ with large inter-individual variability (0-100%).⁴⁵ Furthermore, compliance typically reduces with increasing treatment duration and reduces to approximately 20% after 5 months of treatment.⁴⁴ Therefore, one of the reasons why the PEDIG studies may have shown no difference between two hours vs. six hours of daily patching is that children prescribed longer daily patching regimens may have in fact done no more patching than the

shorter patching group.

The Monitored Occlusion for the Treatment of Amblyopia Study (MOTAS) found VA improved during the first 12 weeks of patching⁴⁵ and most children achieved maximum VA within 150-250 cumulative hours of therapy.³⁶ While more than 1,000 hours of patching were prescribed for the patient in this case study, we estimate that she only completed approximately 150 hours. Obstacles to patching include the child's personality, tiredness and physical health as well as parental belief in the efficacy of treatment.⁴⁶ While VA gain is similar in patching and atropine, many patients find atropine more socially acceptable,¹ thus pharmacological penalization may be more appropriate for older children where social stigma limits patching.⁴⁶

Traditionally, atropine penalization was reserved for children with mild-moderate amblyopia who were poorly compliant with patching due to concerns about photophobia as a result of pupillary dilation, questions regarding the efficacy of atropine in severe amblyopia, and the potential for development of iatrogenic amblyopia in the penalized eye. However, results from PEDIG studies show that after 6 months of treatment, atropine was as effective as patching as an initial therapy for amblyopia and that the patient's age, initial acuity and cause of amblyopia did not affect treatment efficacy.⁴⁷ In children with mild-moderate amblyopia, weekend atropine was as effective as daily atropine with 53% of children in the weekend atropine group achieving a final visual acuity of 0.1 logMAR (Snellen equivalent 20/25) vs. 47% in the daily atropine group.⁴⁸ Concerns have been raised about the use of atropine penalization in children with severe amblyopia (VA worse than 0.8 logMAR or 20/125) as atropine may not blur the "good" eye enough. However, even in children with severe amblyopia, weekend atropine improved VA by 4.5 lines in children 3-6 years of age and 1.5-2.3 lines in older children,^{49,50} similar to results seen with patching. Self-reported compliance is generally high in studies involving atropine penalization with 59-94% of parents reporting "excellent" compliance with therapy.⁴⁴ This is assumed to be because pharmacological therapy is easier to manage for parents, less disruptive to the child's daily life, and has a lower psychosocial impact.⁴⁴

Other potential therapies for patients not responding to patching and/or atropine penalization include Bangerter Filters, binocular therapy and non-invasive brain stimulation. Bangerter filters are transparent filters that adhere to a spectacle lens and cause a diffuse blurring of the retinal image in the non-amblyopic eye. PEDIG found no clinically significant difference in VA improvement in children treated with full-time Bangerter filters compared with children undergoing two hours of daily patching, with better compliance in children prescribed Bangerter filters as these tend to be less obvious to observers than patching.⁵¹

Over the past decade a number of novel therapies have been developed for the treatment of amblyopia, which include dichoptic training (binocular therapy), perceptual learning and video gaming. A meta-analysis of 24 published studies investigating these novel therapies found that there was a mean VA improvement of 0.17 logMAR in the amblyopic eye, which is marginally larger than the test-retest variability of VA measures.⁵² Dichoptic training typically involves some form of contrast balancing so that the non-amblyopic eye receives a lower contrast image, which promotes sensory input from the amblyopic eye and binocular summation.⁵³ The aim of many of these treatments is to reduce or eliminate suppression of the amblyopic eye by modulating the input from the fellow (good) eye to create a "binocularly balanced" image.⁵³ Initial trials of a falling blocks game (Tetris) found statistically and clinically significant improvements in amblyopic eye VA,^{54,55} however, larger clinical trials have found more modest results. In a recent randomized controlled trial of 115 children and adults, there was no significant change in amblyopic eye acuity between the active home-based video treatment group and the placebo group.⁵⁶ Likewise, a multi-center study of 385 children, 5-13 years of age, found a one-line improvement in acuity after 16 weeks of video game play.⁵⁷ Despite the theoretical appeal of video game play as a treatment option, adherence to therapy was problematic with less than a quarter of participants

performing >75% of the prescribed treatment hours.

How frequently should patients undergoing amblyopia therapy be monitored?

In this case study, the frequency of review appointments was somewhat sporadic. This was a result of not only the public health setting in which this patient was seen, with waiting lists affecting frequency of follow-up appointments, but also the number of visits missed or rescheduled by the patient and her parents. The MOTAS study assessed children at 6-weekly intervals during the refractive adaptation phase of amblyopia treatment and fortnightly during the occlusion phase.⁵⁸ Some participants attended more or less frequently, and the MOTAS results suggested that there was a positive correlation between frequency of clinic visits and compliance with occlusion therapy possibly due to parental understanding of the importance of treatment.⁵⁸ Other authors have suggested more frequent visits initially (every 1-4 weeks) to document and encourage compliance, with later visits extended to every 4-6 months to prevent discouragement as later VA changes are likely to be more modest.⁵⁹ A study of levodopa for older children with amblyopic deficits not ameliorated by patching or pharmacological penalization scheduled in-office visits at weeks 4, 10 and 16 with phone calls at 2, 7 and 13 weeks to encourage compliance.⁶⁰ Evidence-based guidelines for amblyopia review schedules are yet to be developed and this is an area for future research to optimize both patient compliance and health-delivery costs.

Residual amblyopia

While VA improves in 73-90% of amblyopic children, complete resolution occurs in only 25% of patients.⁶¹ The remaining children fail to achieve normal vision despite extended periods of amblyopia therapy. Thus residual amblyopia, typically defined as VA of 0.2 logMAR (Snellen equivalent 20/32) or worse in the amblyopic eye or an interocular difference of at least two logMAR lines despite lengthy amblyopia therapy, is common.⁶ Nevertheless, the exact pathophysiological reasons for residual amblyopia remain largely unexplained although late diagnosis, poor compliance and high anisometropia may impede resolution of amblyopia.⁶ Despite its obvious significance, the timing of therapy cessation remains a neglected area in amblyopia research and clinicians require clear guidelines to aid in making the decision to stop treatment.⁶²

Residual amblyopia is challenging to manage and various studies in 3- 7-year-old children have trialed increasing patching dosage, adding a plano lens to atropine treatment, and combining patching and atropine penalization prior to ceasing therapy in cases where VA has plateaued. However, most of these interventions are unsuccessful and, even in children who do improve, VA gains are typically small (0.07 logMAR or less).¹ Despite the high prevalence of residual amblyopia, the decision to stop treatment is complicated by a lack of evidence-based guidelines and our limited ability to identify children likely to recover from persistent visual deficits.⁶³

Risk factors for residual amblyopia

Several risk factors for a poor prognosis were identified in our patient: delayed diagnosis and late onset of treatment, high refractive error, absent stereopsis at presentation and poor compliance. High hyperopia⁴⁰ and large degrees of anisometropia are strong risk factors for persistent amblyopia.⁶ Anisometropia can induce both defocus and aniseikonia, and spectacle correction can actually increase the image size difference between the eyes. Eyecare professionals rarely measure aniseikonia in clinical practice. However, aniseikonia may act as a barrier to neural plasticity, restricting visual recovery and resulting in variable treatment outcomes likely through suppression of the amblyopic eye.^{64,65} Anisometropic patients have greater suppression in glasses than in contact lenses due to a larger image size difference between the eyes with spectacle lenses.⁶⁶ Fitting contact lenses or prescribing iseikonic lenses to minimize interocular retinal image size differences may be appropriate in cases where amblyopic eye VA is static despite good compliance with prescribed therapy.⁶⁴

Suppression plays a key role in the development of visual deficits in amblyopic children and absent stereopsis, a further indicator of suppression, is independently associated with residual amblyopia.⁶ Bosworth and Birch found that previously treated amblyopic children with no measurable stereopsis had larger discrepancies between their optotype and grating acuities, which the authors proposed was due to under-sampling of binocular cortical cells which in turn results in poorer outcomes.⁶⁷ Binocular amblyopia therapies aim to improve binocular cell neural connectivity⁸ by increasing the signal to noise ratio of the amblyopic to fellow eye and these therapies have led to improvements in both stereoacuity and visual acuity in some groups of patients.⁵² Initially our patient had no measurable stereoacuity. Stereopsis was first detected after 18 months of treatment and continued to improve to 55" of arc by the end of therapy. Most studies suggest a linear correlation between improvement in VA and stereoacuity,⁶⁸ however, our patient's stereopsis continued to improve despite stable VA, probably due to poor compliance with occlusion and atropine regimens which meant maximal VA was never achieved.

Compliance with amblyopia therapy

For any treatment to succeed, compliance is essential but many patients with amblyopia are non-compliant with prescribed therapies.⁷ In one small pilot study of 31 children, more than 50% of children were non-compliant with the prescribed patching regimen by parental report.⁶⁹ Improvement in amblyopic eye VA was strongly correlated with compliance with patching, and parents cited lack of cooperation from their child as the main barrier to patching. Less than 50 cumulative hours of occlusion and/or less than 30 minutes per day of patching are known risk factors for residual amblyopia.⁷⁰ Compliance has been identified as particularly problematic in children 8 years and older and has been identified as one of the primary reasons for treatment failure in older children.⁷¹ Compliance is influenced both by the patient's initial amblyopic eye VA^{71,72} and parental factors including language skills, level of education and country of origin.⁷² Parents' perceived self-efficacy (the parents' belief in their ability to perform patching) is positively associated with compliance while parental belief that patching limits their child's activities is negatively associated with patching compliance.⁷³ Therefore, encouraging children to engage in activities while patching such as coloring,⁷² initiating peer-led support groups and improving parent knowledge about amblyopia therapy⁷³ may assist in improving patching compliance. Compliance with pharmacological penalization tends to be better than with patching⁷⁴ due to reduced social stigma as children are not required to wear a physical patch.⁷⁵ Combined optical and pharmacological penalization, whereby the non-amblyopic eye is prescribed a plano spectacle lens and daily atropine 1% eye drops, has an overall success rate of 76% with high compliance (83%). A recent meta-analysis identified parent education as an important element in improving compliance in amblyopia therapy, although in general all types of interventions had positive effects to some extent.⁷⁶ Providing written information, tailored for both the child and the parent, may also help improve compliance as parents find it difficult to comprehend and retain much of the verbal information provided.⁶⁹ For our patient, we recommended both occlusion and atropine, separately and in combination, due to our patient's age, poor compliance with individual therapy regimes and poor initial VA in the amblyopic eye. Nonetheless, our patient was only compliant with optical correction and short periods of intense treatment in school holiday periods.

Conclusion

This case describes an 8-year-old patient with residual amblyopia resulting from late diagnosis, high anisometropia and poor compliance with therapy. Nevertheless, her VA and stereoacuity improved significantly following optical treatment with full-time spectacle wear. Clinicians should be aware of the risk factors for residual amblyopia and be prepared to cease therapy when there are no further gains in visual function. Further research is needed to give clinicians clear evidence-based guidelines to assist in making the decision to stop treatment.

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