

'It's too late'. Is it really? Considerations for amblyopia treatment in older children

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Abstract: In recent years, media coverage has demonstrated instances in which families of children aged 7 and older, newly diagnosed with strabismic and/or anisometropic amblyopia through community eyecare services, were told it was 'too late' for their child to effectively respond to conventional amblyopia treatment (occlusion or atropine penalisation). Formal guidance pertaining to binocular vision anomalies from eyecare professional bodies does not specifically make reference to a child's age, beyond stating the importance of early diagnosis and treatment of strabismus/amblyopia. However, there have been many changes in the way we view the recovery period for amblyopia, and it is well demonstrated both within literature and clinical practice that conventional treatment can improve amblyopic eye visual acuity in children beyond the age of 7 years. The occurrence of these media described cases within the community eyecare sphere would suggest it is worthwhile revisiting the literature on the subject of amblyopia treatment in older children (aged 7+ years), to address misconceptions and place in the spotlight current considerations facing clinicians when treating newly diagnosed amblyopia within this age group. This perspective review provides an evidence-based update covering the various considerations associated with treatment of amblyopia in older children, along with recent amblyopia treatment advances that could have an impact on treatment prospects for this patient group. Considerations include the risks, benefits and efficacy of treating newly diagnosed amblyopia in older children, monitoring density of suppression to mitigate intractable diplopia risk, and recent findings regarding binocular treatments for amblyopia.

Keywords: amblyopia, atropine penalisation, density of suppression, occlusion therapy, older children perceptual learning

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Preamble

Media coverage of amblyopia treatment has highlighted instances where children aged between 7 and older,^{1–3} newly diagnosed with amblyopia through community eyecare services, were deemed 'too old' to effectively respond to conventional amblyopia treatment beyond refractive error correction. Conventional amblyopia treatment usually comprises this correction followed by a 18-week refractive adaptation period,⁴ then engagement with occlusion or atropine/optical penalisation to treat any residual amblyopia.⁵ While isolated cases, at odds with Royal College of Ophthalmologists recommendations⁶ and College

of Optometrists information materials^{3,7} regarding amblyopia treatment, they do highlight that formal guidance from these professional bodies about binocular vision anomalies^{8,9} does not specifically make reference to a child's age beyond stating the importance of early diagnosis and treatment of strabismus/amblyopia. Such cases occurring within the community eyecare sphere would suggest that it is worth revisiting the literature on the subject of amblyopia treatment in older children (aged 7 and above, as defined by media coverage^{1–3} and classification by seminal Paediatric Eye Disease Investigator Group (PEDIG) research^{10–12} or other work),^{13,14} to address such misconceptions.

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How often is amblyopia newly diagnosed in older children?

There is little data on the incidence of late diagnosis of amblyopia in the United Kingdom, as well as limited data on amblyopia prevalence in older children aged 7 and above.¹⁵ However, some degree of inference can be made using primary vision screening audit data from the British and Irish Orthoptic Society,¹⁶ which suggests that from 42 screening sites across the United Kingdom and Northern Ireland, 7% of children eligible for screening failed to attend in the 2016–2017 school year ($n = 12,539$ of 175,407) and from 38 of these sites, 29% of children, on average, fail vision screening but then do not attend for follow-up (mean $n = 3182$ of 10,974, non-attendance range 5–73%). Based on prevalence of past/present amblyopia at age 7 from a UK regional birth cohort of 7825 children (3.6%),¹⁵ a rather crude estimate is that up to 578 children across these 42 sites each year may present at a community eyecare service in future with untreated amblyopia of some degree, although it is impossible to determine if/when this presentation will occur, and therefore a diagnosis rate. This assumes 16,056 children not attending initial screening or failed screening follow-ups¹⁶ and tallies against some dated regional UK studies identifying that 0.28–3%^{17,18} of children having a vision assessment after age 7 may be newly diagnosed with amblyopia. A similar level was reported in Australia among 12-year-old children (0.21%).¹⁹ While a dearth of literature in this area limits accuracy of these inferences, and sociodemographic factors influencing amblyopia risk¹⁵ and uptake of vision screening^{20,21} or UK National Health Service-funded optometric sight tests^{20–22} should be considered, it is reasonable to suggest that a relatively low number of older children (7 and above) may be newly diagnosed with amblyopia in the United Kingdom each year.

Given this posited low figure, it is hardly surprising that optometry practice patterns regarding advice given to families of an older child newly diagnosed with amblyopia appear to vary, and at times contradict guidance from professional bodies. Indeed, Shah and colleagues²³ point out that it is difficult for the practicing optometrist to gain experience in paediatric optometry generally, due to the infrequent attendance of young children within practice.²⁴ It is therefore important to consider the impact of such contradictions against existing guidance.

What happens if amblyopia is not treated?

Untreated amblyopia in school-aged children can impact in a number of ways, from fine visuomotor task difficulties associated with reduced/absent binocular vision,^{25–27} to lower self-esteem or self-perception^{28,29} and other psychosocial domains,³⁰ to limitations on educational attainment^{28,31,32} (although for an earlier birth cohort this was not the case).³³ In adulthood, lifelong bilateral visual impairment risk is increased by 1.2–3.3% where dense amblyopia is present.³⁴ The numbers quoted above for older children newly diagnosed with amblyopia may seem small when considering orthoptic throughput of younger children, but current evidence and the practice guidelines drawing upon it emphasises the importance of, at a minimum, initiating treatment in older children to reduce these impacts. Optical correction alone, while thought to produce some degree of improvement in amblyopic eye visual acuity, appears to be insufficient to resolve the full amblyopic visual acuity defect in older children,^{12,35,36} and while occlusion treatment is not without psychosocial impacts of its own,^{29,37–40} it can be seen that there are more benefits to treatment than just improvement of visual acuity and binocular function. However, conventional amblyopia treatment (occlusion, atropine) for this group may not be without risk, which should also be considered.

What are the risks associated with treating amblyopia using occlusion or atropine in older children?

Clinically, the primary reason for some degree of nervousness when treating amblyopia in older children is the risk of intractable diplopia. Intractable diplopia has a significant impact on visual function and wellbeing^{41–43} and is difficult to remedy in older children,⁴⁴ remaining a highly undesirable complication of amblyopia treatment. This can arise through alteration of corticoretinal suppression during treatment, and it is recommended that density of this suppression be monitored when treating strabismic and mixed strabismic/anisometric amblyopia in children over 5 years of age, as a measure of intractable diplopia risk.⁴⁵ Incidence of intractable diplopia following amblyopia treatment with occlusion or atropine remains extremely low in the United Kingdom,^{46,47} perhaps because of our highly conservative approach to amblyopia treatment in older children,⁴⁶ but is the evidence base for this approach valid?

Concerns regarding intractable diplopia can affect treatment approaches for older children. A survey of UK orthoptists found they were less likely to use atropine penalisation with this age group,⁴⁸ with risk of systemic side effects or intractable diplopia highlighted as key concerns. This is despite reported side effects being few within the survey, systemic retention of atropine being thought to reduce with age,⁴⁹ and the absence of nationwide yearly incidence data for systemic atropine side effects or intractable diplopia to evidence such concerns.

Furthermore, major question marks hang over the test–retest reliability of the tools we use to measure suppression density,^{50–53} and the validity of the rather arbitrary suppression density cutoffs used in practice to aid clinical decision-making about stopping treatment due to unacceptable diplopia risk.^{46,52} In addition, no studies currently demonstrate a relationship between age and density of suppression in amblyopia,^{50,52,53} nor reinforce the idea that density of suppression is more easily disrupted in older children. In fact, suppression in recent years has been painted as the ‘enemy of successful amblyopia treatment’,⁵⁴ and a widely cited PEDIG study exploring amblyopia treatment with occlusion and atropine for older children did not measure suppression density,¹² reporting incidents of diplopia were infrequent and short-lived. It is therefore difficult to argue whether treating newly diagnosed amblyopia in older children carries significantly elevated risk of intractable diplopia.

Should we continue to rely on density of suppression measurements for intractable diplopia risk assessment and clinical decision-making during amblyopia treatment for older children? Without comparable incidence data on intractable diplopia in other parts of the world, it is difficult to determine whether the UK’s virtually non-existent incidence of intractable diplopia post-amblyopia treatment⁴⁷ originates purely from our zealous monitoring of suppression density. With a lack of evidence generally on the nature of changes in suppression density for older children during both occlusion and atropine penalisation treatments for amblyopia, discontinuing the practice is as difficult to justify as continuing it.

More research in these areas, as well as audit data on incidence of early termination of amblyopia treatment due to suppression changes, could stabilise the foundations for density of suppression

monitoring practices when embarking upon amblyopia treatment for older children, to maximise treatment benefit. Importantly, current evidence shows there is no clinical justification for refusing to offer treatment to a newly diagnosed older child, provided appropriate monitoring is employed. However, visual acuity and binocular function gains for older children during amblyopia treatment may be more limited. This is an issue warranting further examination.

How effective is amblyopia treatment for older children?

It is widely accepted that treatment for moderate and severe strabismic and/or anisometric amblyopia can produce better visual outcomes when it is the first treatment attempt with occlusion or atropine, compared to instances where treatment has been attempted in the past.^{10–12} In addition, it is acknowledged that treatment effectiveness can reduce with age for both treated¹⁰ and untreated amblyopia,^{10,13,55} although not all of these studies included children treated with atropine penalisation.^{13,55} These findings have influenced amblyopia treatment guidelines from both the College of Optometrists and the Royal College of Ophthalmologists, which state that treatment is more effective when initiated earlier.

However, many seminal studies from the PEDIG cited here are affected by restrictive inclusion criteria and definition of treatment responder, and a fixed occlusion dosage for duration of treatment prior to being defined as a responder/non-responder. Furthermore, comparisons between the treatment and control groups in key papers focusing on older children were affected by use of optical correction as the control condition, now known to produce a treatment effect.⁵⁶ These aspects of older Amblyopia Treatment Study protocols limit applicability of findings to a rather specific set of instances not always reflective of clinical practice, and PEDIG authors have recommended in other papers to always attempt treatment in older children regardless of previous treatment history.^{10,56–58} Indeed, recent studies from Fronius and colleagues⁵⁵ suggest interocular acuity difference improvements with occlusion of 43% on average for untreated amblyopes aged 7 and above. A later PEDIG study also found increasing occlusion dosage produced further acuity improvements in a sample of children with residual amblyopia that included 38 children aged 7+ years.⁵⁷ Further study of the impact of

applying a stepped conventional treatment approach for strabismic and/or anisometric amblyopia (including atropine as well as occlusion) in older children could therefore be beneficial.

Overall, the literature would seem to indicate that with good compliance, appropriate monitoring of suppression density, and suitable tailoring of occlusion dosage, initiating treatment for strabismic and/or anisometric amblyopia should theoretically maximise the acuity of the amblyopic eye. However, even with good compliance, there are instances where amblyopia does not fully resolve, and a residual interocular acuity difference remains. Patient characteristics that differentiate responders and non-responders to conventional amblyopia treatment are still not well understood, but current evidence demonstrates that age at start of treatment is not a sole dictat for either occlusion^{10–13,55} or atropine.^{10–12} This raises the question of whether we are yet to identify the most effective combination of amblyopia treatment approaches for this group, and whether newer amblyopia therapies may have potential to minimise or address a residual interocular acuity deficit.

Will newer, binocular treatments for amblyopia be more effective in older children?

More recently, amblyopia has come to be regarded as a binocular condition, due to the known deficits occurring in the fellow eye^{59–67} and the role of defective binocular vision as an amblyogenic factor.⁶⁸ Emerging amblyopia treatments have embraced this, utilising stereoscopic presentation techniques and luminance/contrast matching to promote binocular combination of the amblyopic and fellow eye.^{69,70} Some of the most well-known studies demonstrating the use of these emerging treatments with older children and adults are the works of Levi, Li and colleagues, who successfully employed monocular or binocular perceptual learning techniques to reduce interocular acuity difference in children^{71–73} and adults^{74–76} aged 7–17 years.

The majority of participants in these studies has a history of previous amblyopia treatment or at a minimum have undergone refractive adaptation, and it has proved difficult to explain individual differences in treatment outcomes and dose–response curves between participants.^{77,78} The efficacy of

such binocular treatments as a first-line amblyopia therapy is yet to be established, although trials are underway. However, given existing evidence suggests better conventional treatment outcomes (atropine/occlusion) in children with no history of previous amblyopia treatment, it seems reasonable to suggest emerging, binocular amblyopia treatment approaches could have a similar enhanced impact where used as a first-line treatment. Whether these techniques are more effective at resolving an interocular acuity difference for newly diagnosed older children, in comparison to conventional treatment approaches, is also an area worth exploring.

Despite being designed to circumnavigate conventional suppression mechanisms to promote binocular combination, these emerging therapies have not resulted in instances of intractable diplopia^{79–81} and appear not to disrupt suppression,⁸² but it is important to note that treatment durations were limited to 1 h a day, compliance in many of these trials has been limited,^{79,82} and suppression measures used may not necessarily correlate with conventional density of suppression measurement techniques such as the Bagolini Filter Bar, and as such may not tap into the same mechanisms of suppression.⁸³

Our own randomised controlled trial,⁸⁴ involving children with residual amblyopia aged 5–14 years, compared contrast-balanced binocular amblyopia treatment with monocular and non-contrast-balanced binocular approaches, using a stereoscopic child-friendly first-person shooter paradigm⁸⁵ to promote replayability. Although the trial terminated prematurely due to limited recruitment associated with use of an office-based treatment paradigm, we found changes in density of suppression as measured with the Bagolini Filter Bar during the treatment period. This resulted in termination of treatment before the end of the 10-day treatment period for 4 of 14 children, scattered across all three viewing modalities (contrast-balanced, monocular, non-contrast balanced), with reduction in suppression from baseline ranging from four to nine filters.

While these numbers are small and preclude formal analysis, they demonstrate that suppression density as measured clinically can change during stereoscopically administered amblyopia treatment paradigms. When interpreting data regarding diplopia risk in association with binocular amblyopia treatments, that utilise stereoscopic

viewing for differential presentation, some degree of caution may be required. As research in this new area continues, more evidence is likely to emerge regarding the nature of any changes in suppression that may occur with this treatment, and whether first-line deployment of these therapies for older children carries the same risks (if any) as conventional amblyopia treatment. If not, this could open up an important access avenue for older children newly diagnosed with amblyopia, which practitioners in the community need to be aware of.

Conclusion

Current conventional amblyopia treatment guidelines stating better outcomes can be achieved in younger children are based on up to date literature and standard treatment approaches, defined previously as refractive error correction, refractive adaptation and use of occlusion or atropine penalisation to treat residual amblyopia. It is not possible to conclude from existing evidence that a newly diagnosed older child is as likely to have a good visual outcome from conventional amblyopia treatments as a child who is younger, even when considering the differential effects of compliance and previous amblyopia treatment history.

However, a growing body of evidence supports the efficacy of many emerging binocular amblyopia therapies, where compliance is good. Due to the relatively small numbers of older children diagnosed with amblyopia each year, it would be logistically challenging to evaluate and compare first-line treatment effects for these emerging therapies against conventional treatments. Yet work in this area, even if conducted over a protracted period of time, could be informative in determining which patient groups maximally benefit from these approaches, and whether they carry the same perceived risks as conventional treatment approaches with regard to changes in density of suppression.

Nonetheless, the evidence does show that it is always worth attempting amblyopia treatment for older children as many can and will experience an improvement in visual function. Essentially, the words 'It's too late' should not be something parents have to hear as part of receiving an amblyopia diagnosis for their older child. The authors hope this article will equip eyecare professionals to have a balanced discussion with parents about

the risks and benefits of amblyopia treatment for older children and take an evidence-based approach to managing amblyopia arising in this group.

Conflict of interest statement

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