

2018

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Recommended Citation

Kraus, Courtney L. and Culican, Susan M., "New advances in amblyopia therapy I: Binocular therapies and pharmacologic augmentation." *British Journal of Ophthalmology*.102,. 1492-1496. (2018).
https://digitalcommons.wustl.edu/open_access_pubs/7239

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New advances in amblyopia therapy I: binocular therapies and pharmacologic augmentation

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Received 28 February 2018

Revised 16 April 2018

Accepted 22 April 2018

Published Online First

18 May 2018

ABSTRACT

Amblyopia therapy options have traditionally been limited to penalisation of the non-amblyopic eye with either patching or pharmaceutical penalisation. Solid evidence, mostly from the Pediatric Eye Disease Investigator Group, has validated both number of hours a day of patching and days per week of atropine use. The use of glasses alone has also been established as a good first-line therapy for both anisometropic and strabismic amblyopia. Unfortunately, visual acuity equalisation or even improvement is not always attainable with these methods. Additionally, non-compliance with prescribed therapies contributes to treatment failures, with data supporting difficulty adhering to full treatment sessions. Interest in alternative therapies for amblyopia treatment has long been a topic of interest among researchers and clinicians alike. Incorporating new technology with an understanding of the biological basis of amblyopia has led to enthusiasm for binocular treatment of amblyopia. Early work on perceptual learning as well as more recent enthusiasm for iPad-based dichoptic training have each generated interesting and promising data for vision improvement in amblyopes. Use of pharmaceutical augmentation of traditional therapies has also been investigated. Several different drugs with unique mechanisms of action are thought to be able to neurosensitise the brain and enhance responsiveness to amblyopia therapy. No new treatment has emerged from currently available evidence as superior to the traditional therapies in common practice today. But ongoing investigation into the use of both new technology and the understanding of the neural basis of amblyopia promises alternate or perhaps better cures in the future.

INTRODUCTION

Amblyopia therapy has benefited significantly from the investigations of the Paediatric Eye Disease Investigator Group (PEDIG). There have been 18 completed Amblyopia Treatment Studies (ATS) as of publication of this review. In these well-designed, predominantly randomised controlled trials, there have been numerous notable conclusions that continue to shape and dictate how to care for children with amblyopia. Early studies provided solid epidemiological data on patients with amblyopia.^{1–3} Through the early studies, the equivalent efficacy of patching versus atropine penalisation was established.^{4–6} Concern that cessation of treatment would lead to a relapse in amblyopia was widely touted, but 15-year follow-up data confirmed that the amblyopia treatment effect persisted.⁷

Traditional amblyopia treatment strategies have documented improvement with spectacle correction when indicated, followed by patching or atropine penalisation of the non-amblyopic ('fellow') eye. While the majority of children show improvement with these approaches, not all children respond to traditional therapies. Even responders often have residual amblyopia. Fifty-four per cent of children treated at age <3–7 years still demonstrate some amblyopia at age 10.⁴ Older children fair even worse; 74% of children aged 7–12 years treated with patching, and 80% treated with atropine have some degree of residual amblyopia on long-term follow-up.⁵ In the teenage cohort, outcomes are even less effective with only one-quarter to one-half of children responding to combined treatment of spectacles and patching depending on whether they had previous treatment or were treatment naïve (respectively).⁶

Non-compliance contributes to treatment failures, with data supporting less than perfect adherence to prescribed regimens.⁸ However, data from use of an occlusion dose monitor confirmed that some children demonstrate excellent compliance, yet still fail to improve.^{9–10} This suggests an opportunity for novel strategies to target non-compliant patients and non-responders. In this review, we will explore the binocular therapies as an alternative to traditional amblyopia treatments, as well as pharmacologic adjuncts to standard regimens.

BINOCULAR THERAPIES

Background and rationale

The depth of amblyopia has been positively correlated to the degree of binocular imbalance.¹¹ Affected individuals show impaired stereoacuity and abnormal binocular summation.¹² Yet evidence suggests that binocular cortical communication persists in subjects with amblyopia.^{13–14} These findings are the basis for the hypothesis that activation of these persistent binocular neural circuits might be exploited to 'awaken' an amblyopic eye. Binocular therapies designed to improve amblyopia through binocular stimulation are largely broken down into perceptual learning and dichoptic training.

Perceptual learning

Perceptual learning was defined in 1963 by Eleanor Gibson as an evolution in the discernment of a stimulus array after repetitive exposure or practice with this array.¹⁵ This work is the psychophysical validation of the old adage 'Practice makes perfect'. Performance on simple visual tasks has been long known to improve with practice in adults. Application



To cite: Kraus CL, Culican SM. *Br J Ophthalmol* 2018;**102**:1492–1496.

of perceptual learning to various visual tasks has reportedly resulted in improvement in several measures, including orientation discrimination, stereoacuity and contrast sensitivity.¹⁶ A number of visual tasks have been explored as a means to apply perceptual learning, including vernier acuity, Gabor detection, positional discrimination, letter identification in noise, position discrimination in noise and contrast detection.¹⁷

Studies by Polat *et al* suggest that perceptual learning in adult amblyopes can augment visual function. Improved pretest to post-test performance and gains in visual acuity (VA) were reported when subjects participated in a learnt trial of Gabor signals in a series of 77 adult amblyopes.¹⁸ The criticism of this approach is that gains on test outcome measures in the amblyopic eye do not transfer to novel situations—improvement is only seen for the task practised.¹⁹ Advocates of perceptual learning note that the specific nature of the stimuli chosen for training tasks contributes to the capacity for generalisability of the trained discrimination.²⁰ Others cite the targeted reduction in the detrimental effect of crowding (a reduction in VA when viewing a line of linear letters more severe than when viewing letters individually).²¹ The neural basis for this is postulated to result from a reduction in lateral inhibition within the brain with training.²²

Small studies of juvenile amblyopes have demonstrated improvements. Seven participants with prior occlusion therapy had improved visual performance following completion of a positional discrimination task.²³ A second pilot study of five amblyopic children who underwent 40 hours of perceptual learning demonstrated improved scores on Snellen acuity and contrast sensitivity. There was no follow-up following completion of the treatment regimen.²⁴ In their comprehensive review of perceptual learning, Levi and Li reported on the relative effectiveness of the various types of tasks in both performance of the trained task and Snellen acuity. Five of the 12 studies reviewed showed improvement in post-test results, of which 4 employed practising contrast detection. The fifth study examined extended positional acuity learning in children.^{17 25}

Drawbacks to treatment

Perceptual learning has yet to gain widespread support. Most of the aforementioned studies contained very small numbers of participants, limiting generalisability to populations at large. Perceptual learning effects have been demonstrated to last hours to months without continued practice,²⁶ but long-term follow-up is lacking. Additionally, implementation of a successful clinical programme of treatment would require the ability to perform training at home while the aforementioned studies required perceptual learning tasks to be in a laboratory setting.

Dichoptic training

Unlike perceptual learning, where a single visual percept is administered to both eyes simultaneously or under monocular viewing conditions, dichoptic treatment presents independent stimuli to each eye (figure 1). The therapy derives its effect from unlocking binocular visual function. The treatment effect then follows from introducing a task that requires the integration of the two stimuli under binocular viewing conditions. The paradigm is customised to overcome the patient's suppression of the amblyopic eye. To do so, the image shown to the amblyopic eye must be of higher contrast than that shown to the fellow eye.^{14 27} As the patient's developing binocular function improves, the contrast difference between the two eyes is reduced, potentially to a point where no difference is required. VA gains follow improvements in binocularity and contrast sensitivity, presumably due to reduced suppression.²⁴

Early reports of dichoptic training used this concept in a clinic-based setting with the adult amblyopes.^{28–30} They demonstrated both proof-of-concept as well as the potential for amblyopia improvement outside of the critical period. Hess *et al* showed statistically significant improvements in amblyopic eye visual and stereoacuity in nine adults (four of whom had prior patching treatment).²⁸

In order to move the therapy from a clinic-based, observed task to mobile, home-based use, it was necessary to adapt the design to be more user-friendly. An iPod display with a lenticular

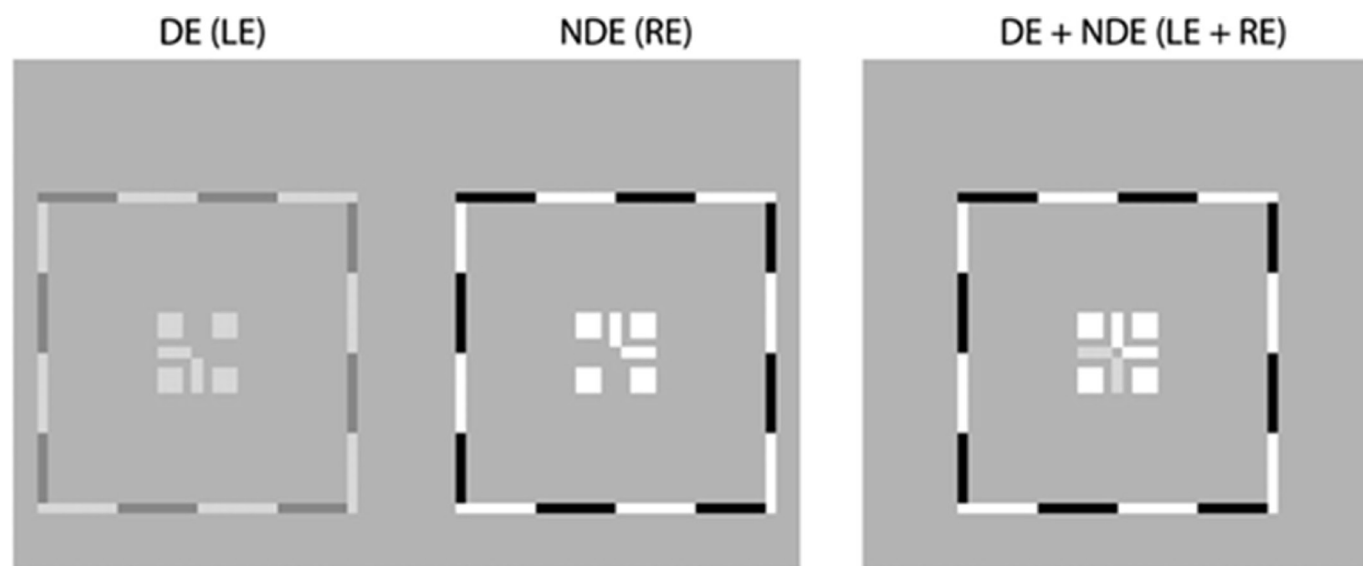


Figure 1 Dichoptic stimuli as presented to the patient with amblyopia. The stimuli are adjusted so that the dominant eye (DE), in this case the left eye (LE), has less contrast and is therefore more difficult to discriminate than the non-dominant eye (NDE). When the images are superimposed, the subject perceives a single percept with summation of elements presented to each eye separately. Over time, the contrast can be adjusted as the non-dominant eye improves with training (reproduced from Ding and Levi, figure 1A).⁶² RE, right eye.

overlay (a textured screen overlay that produces images with a perception of depth, eg, holograms) allowed for viewing the dichoptic stimuli, but required stable head positioning. While studies suggest that such method is successful, it is a challenge to use.³¹ A shift away from the lenticular design and transition to anaglyphic (red-green dichoptic) images with accompanying red-green glasses overcame this limitation and permitted utilisation of this form of therapy by young children and in unsupervised patients.^{29 32}

Binocular iPad therapy

Interest in dichoptic treatment progressed with the migration of the Hess Falling Blocks game onto an iPad. Birch and colleagues conducted a small study of children aged 4–12 playing this dichoptic iPad game using red-green anaglyphic glasses for 4 hours/week over 4 weeks and saw improvement in amblyopic eye logMAR acuity (0.47–0.39, $p < 0.001$).³³ A subsequent study looking at younger children confirmed previous work demonstrating improved amblyopic-eye acuity as well as a dose-response effect.³² Those children completing 8 total hours of game play during the 4-week study had significantly greater improvement than those playing 0–4 hours. The results of these early studies suggested promise for dichoptic training in the treatment of amblyopia.

In 2015, PEDIG conducted the first large-scale, multisite randomised controlled trial comparing the effectiveness of 1 hour/day, 7 days/week binocular game play to 2 hours/day patching in children <13 as a non-inferiority study. There was a parallel superiority study examining the same regimen in children aged 13 to <17 years. Results of the non-inferiority study in the younger cohort demonstrated improvement in both the 1 hour/day iPad game play as well as the 2 hours/day patching groups with no statistically significant difference between the groups at 16 weeks. There were no side effects of treatment, specifically diplopia, reduction in fellow eye VA or new tropia. A disappointing finding of the study was the poor overall compliance in the binocular game group.³⁴ The 13 to <17 years age group cohort results were similar; amblyopic eye VA was not better with iPad play, and was possibly worse. Compliance was similarly poor, with 13% completing >75% of prescribed treatment.³⁵

Similar work by Gao *et al* compared 1 hour of home-based, dichoptic falling-blocks video game play to a placebo game.³⁶ They recruited participants age 7 years and up, including adults 18 years and older. Results failed to show a meaningful difference in amblyopic eye 6-week VA, the primary outcome of interest. They found no significant age effect, type of amblyopia or impact of prior occlusion treatment.

Drawbacks to treatment

While initially heralded as superior to patching due to theorised improved compliance, the results of the first randomised controlled trial were underwhelming. Less than one-quarter of children in the PEDIG study completed 75% of prescribed treatment time.³⁴ Thus, ironically, non-compliance has dampened enthusiasm for binocular amblyopia treatment over traditional therapies. The theorised rationale for the high rate of non-compliance is that the Falling Blocks game was not stimulating enough to encourage a full hour of play on multiple days per week. The author's own experience included patient reports of preference for patching due to the wider range of activities that could be performed with a patch over the repetitive play on the iPad game. Similarly, poor compliance and participant

dropout was seen in weeks 4–6 in the study by Gao *et al*.³⁶ This led the authors to suggest the need for more engaging games with potential reward reinforcement as the next iteration of binocular iPad play. Use of a more stimulating Dig Rush game has shown promise³⁷ and recruitment is currently underway for a randomised controlled trial comparing play with glasses with glasses alone (NCT02983552).

Alternative technologies

While iPad-based platforms for binocular treatment of amblyopia have the most research into their use incorporating a variety of study designs and age groups, alternative technological presentations of binocular therapy have been created. Passive viewing of dichoptic movies has demonstrated success in a paediatric cohort both with compliance and vision outcomes. Study limitations included short, 2-week follow-up and lack of randomised design.³⁸ Head-mounted virtual reality displays have also shown preliminary evidence to suggest improvement in both VA and stereoacuity in adult patients³⁹ as has video game play.^{40 41} This latter study by Vedamurthy *et al* also demonstrated retention of VA and stereoacuity after a 2-month time period.⁴¹ Continuously evolving technology will likely yield additional means to deliver dichoptic stimuli in engaging, interactive platforms; hopefully, with the added benefit of effectiveness and patient compliance.

Interactive binocular treatment (I-BiT) system was developed to treat amblyopia using dichoptic stimuli presented via virtual reality game play or movie watching.⁴² The special software selectively stimulates the amblyopic eye without compromising vision in the fellow eye. Initial pilot studies showed promise improving the VA of paediatric and adult patients with amblyopia.^{43–45} Use of shutter glasses has also been paired with this technology, where the glasses lighten and darken in synchrony with the monitor, allowing an enriched image to be presented to the amblyopic eye only.^{41 46} In one study, all subjects used shutter glasses to present dichoptic stimuli but were randomised to one of three arms: active I-BiT game play, passive I-BiT DVD use or non-I-BiT game play. There was improvement in all groups in VA, with no meaningful difference found between the groups. Interestingly, the game platform that included an interactive shooter game and DVD, had >90% participant-reported satisfaction with treatments.⁴⁶ This lends further support to the notion of patient engagement in treatment success or compliance.

THE DRUG THERAPIES

Background and rationale

Amblyopia is considered to be most receptive to treatments initiated within the 'critical period', during which cortical brain plasticity allows for reversal of some or all of the visual loss in the non-dominant eye. Results of the ATS have shown that the critical period is protracted with visual improvement possible up to age 17 years. However, the response to treatment is greatest under age 7 years, with waning benefit with increasing age. Furthermore, treatment during the teen years disproportionately benefits those with no prior history of treatment.⁴⁷ The opportunity to neurosensitise a brain to allow for improvement with patching or atropine in children for whom conventional treatments have failed or after the critical period has ended is desirable. Pharmaceutical agents may offer that ability and a select few have reached human studies.

Pharmacologic options: levodopa-carbidopa

A theory has been proposed that increasing levels of dopamine may improve vision in the context of amblyopia. Some

investigators have reported that levels of retinal dopamine are decreased in deprivation amblyopia.⁴⁸ The first report of dopamine augmentation came in 1990 when Gottlob and Stangler-Zuschrott examined the effect of levodopa on adult amblyopia.⁴⁹ Levodopa is the immediate metabolic precursor of dopamine and is Food and Drug Administration approved for use in other neurological disorders.

There have been several clinical trials that have evaluated the use of levodopa across a range of patients. PEDIG investigators organised a randomised trial of levodopa for the treatment of amblyopia in an older cohort of patients (children aged 7–12 years). When prescribed daily levodopa with carbidopa in addition to continued 2 hours/day of patching, no clinically significant or meaningful improvement in VA was seen. Reassuringly, no serious adverse events were reported.⁵⁰ In a different prospective trial with a larger cohort of patients, children who had previously received spectacles but were otherwise treatment-naïve were prescribed full-time patching and then randomised to levodopa or placebo. The authors reported statistically significant visual gains sustained at 1 year of follow-up for children in the levodopa group. In this study, the levodopa dosage was three times higher than in the PEDIG study.⁵¹

Pharmacologic options: citicoline

Citicoline is a complex biomolecule involved in cellular metabolism. Its structure confers both cholinergic and neuroprotective properties.⁵² Due to its role in phospholipid metabolism, citicoline has been theorised to protect the anatomic and structural integrity of cell membranes, thereby preventing nerve cell damage. This has led to its use for the recovery from traumatic, ischaemic and degenerative insults.⁵³ It was initially trialled in ophthalmic care for the treatment of glaucoma.⁵⁴

Initial work in adult patients demonstrated improvement in VA with citicoline augmentation of patching that was not sustained following cessation of the medication.⁵⁵ Early studies in amblyopic children were promising, showing treatment effect with citicoline both alone and in addition to patching.^{56–57} A study of treatment-naïve participants randomised to added citicoline after a run-in patching phase showed a significant treatment effect at 90 days for the citicoline-augmented group.⁵⁸ However, failure to demonstrate improvement in the control group (2 hours a day of patching) was unexpected and therefore results from this study should be cautiously interpreted.

Research into the use of citicoline is arguably behind that of levodopa. Well-designed randomised controlled trials and appropriately selected treatment groups need to be initiated. At the time of this review, all the studies of citicoline failed to include follow-up periods beyond 3–6 months.

Drawbacks to medical therapy

Pharmaceutical augmentation of amblyopia therapy appears to be well tolerated. A liquid suspension of levodopa is available to facilitate use in a young patient population, although has a reportedly unpleasant bitter taste.^{59–60} Side effects of levodopa therapy are reassuringly mild, with children describing mild nausea, vomiting and headache^{31–32} and not severe enough to necessitate cessation of treatment. The addition of carbidopa to the prescribed formulation reduces these gastrointestinal side effects by inhibiting peripheral conversion of levodopa to dopamine. Because carbidopa cannot cross the blood-brain barrier, it only prevents levodopa conversion peripherally and allows more central activity of levodopa. One worrisome result from the PEDIG study was regression of treatment effect with drug

cessation.³¹ Therefore, randomised controlled trials with ample follow-up still remain necessary. Side effects of citicoline were negligible in all studies. In early use, intramuscular injection was the only means of administration; however, there is now an oral formulation.⁶¹ Medical therapy, in isolation or in addition to conventional therapy, is still in its infancy and potential agents are in the research and development stages.

SUMMARY/CONCLUSIONS

The past 15 years have been replete with well-designed, prospective controlled clinical trials to demonstrate both the efficacy and limitations of traditional amblyopia therapies. Novel approaches to this problem have met with mixed success. Perceptual learning and medical intervention have shown promise, but lack well-designed studies to suggest sustained effect outside the treatment period. Dichoptic training has extensive research suggesting effectiveness, but the most recent randomised trial failed to demonstrate non-inferiority over standard treatments. Future investigation will likely continue to modify and adapt these novel approaches to generative creative, engaging amblyopia therapies that may benefit children and adults, alike.

Contributors CLK wrote the first draft of the review. SMC edited and added relevant references and citations. Both authors approved the final version of the manuscript.

Funding This work was supported by awards to the Department of Ophthalmology and Visual Sciences at Washington University from a Research to Prevent Blindness, unrestricted grant (New York, New York), the NIH Vision Core Grant P30 EY 0268 (Bethesda, Maryland). The funding organisations had no role in the design or conduct of this research.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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