Manuscript

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| **Manuscript title**Atropine penalisation versus occlusion therapies for unilateral amblyopia therapy after the critical period of visual development: a systematic review. |
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# Plain Language Summary (max. 250 words)

If sight is impaired in one eye during early life a patient may unconsciously, involuntarily, choose to use the unimpaired eye. The lack of use of one eye results in that eye not learning to see properly. This condition is sometimes called “lazy eye”; the medical term for it is *amblyopia*. We treat amblyopia by forcing the patient to use their lazy eye by penalising the good one. We do this by either covering up their good eye for a prescribed number of hours per day (occlusion therapy) or by blurring their good eye with eye drops (atropine penalisation therapy).

We measure how well the treatment is working by asking the patient how small an object they can see with their lazy eye; if our treatment is working the eye will slowly begin to see smaller and smaller objects. We use a standard test to grade how small an object an eye can see called a visual acuity test. Either one of our two treatments are normally given when a child is under the age of 8 years, and, from previous research, we know that, in terms of visual acuity outcome, the two treatments work as well as one another in this under 8 years age group.

We also know that these treatments can work for children up to 12 years of age, and they may work for children between 13 and 17-years of age too, however, we do not know if occlusion therapy is better, worse or the same as atropine penalisation therapy in children over the age of 8 years.

In this study we search the current literature to see if any studies have been done to work out if atropine penalisation therapy or occlusion therapy is better. We found 2 studies that had made this comparison, both of which concluded there was no measurable difference between the atropine penalisation and occlusion therapies for amblyopia in children over the age of 7 years. The two studies were graded as being high and moderate quality and we performed further analysis to combine the results from the two studies.

Our analysis found no difference between the atropine penalisation and occlusion therapies for the age group the studies reported on (age 7 to 20 years). Patients receiving atropine penalisation therapy may more frequently report minor eye complications such as light sensitivity compared to those having occlusion therapy, however, these minor reactions must be balanced with the benefits atropine penalisation has over occlusion therapy such as increased patient compliance with therapy.

# Keywords (min. 3, max. 10)

Amblyopia

Occlusion therapy

Atropine penalisation therapy

Paediatric ophthalmology

Visual development

# Abstract (max. 300 words)

**Introduction**Amblyopia therapy appears to be most effective when carried out on children under the age of 7 years, however, randomised control trials (RCTs) have previously shown occlusion therapy and / or atropine penalisation therapy may improve visual acuity in an older age group. Which of the two therapies is most effective with fewer adverse effects in an older age group is not agreed on.

**Methods**We systematically searched the literature for RCTs comparing atropine penalisation therapy and occlusion therapy in terms of their visual acuity outcomes and adverse events. We performed a meta-analysis on the visual acuity data and discuss the reported adverse effects and implications for clinical practice.

**Results**Two RCTs were identified, both of which conclude there is no detectable difference between the two therapies for the age groups they studied. We calculated the mean difference between atropine penalisation and occlusion therapies as -0.01 logMAR (95% confidence interval, -0.07 to 0.03 logMAR) in favour of occlusion therapy; no statistical difference between the two groups is detected (P=0.45). Neither study detected a marked difference in terms of reported adverse effects from the two interventions.

**Conclusions**We conclude there is no difference in visual acuity outcomes between atropine penalisation and occlusion therapy after 17 to 24 weeks treatment for 7 to 12-year olds. Further evidence to determine the efficacy of amblyopia therapy for a population older than this is required before studies compare atropine penalisation and occlusion therapy in this group. Atropine penalisation therapy may cause more frequent minor adverse effects such as light sensitivity but, in a clinical setting, this needs to be balanced with the potential practical benefits of twice weekly eye drops versus daily occlusion.

# Introduction

**Background**
Amblyopia describes the maldevelopment of visual function of one or both eyes in the critical period of visual development, which continues from birth through the first seven to eight years of life (1,2). Amblyopia arises secondary to any ocular pathology that disrupts the function of one or both eyes during the critical period and is characterised by an inability to resolve small letters, i.e. a reduced visual acuity.

In the case of symmetrical bilateral amblyopia, effective management of the primary ocular pathology within the critical period timeframe results in improvement of visual acuity (3). Conversely, in the case of unilateral amblyopia, visual acuity may not improve once the primary ocular pathology is managed (4). The most common primary causes of unilateral amblyopia include anisometropia, strabismus or a combination of both. Unilateral amblyopia is treated in one of two ways in the United Kingdom (UK) (5):

1. Occlusion therapy; patching the fellow, “sound” eye for a prescribed period of time per day; typically, between 2 and 6 hours depending on visual acuity at diagnosis (6).
2. Atropine penalisation; instillation of 1% atropine eye drop twice weekly into the sound eye, blurring its visual acuity.

If a patient has a moderate reduction in baseline visual acuity and treatment is started before age 7 years there is no difference between option 1 and option 2 in terms of visual acuity outcome and rate of complications (7). However, for a patient with a poor baseline visual acuity – severe amblyopia – the evidence comparing atropine penalisation and occlusion therapy is less robust (8). The most significant factor in determining visual acuity outcome is adherence to the prescribed occlusion therapy protocol (9). In a clinical setting the authors often find children reject occlusion therapy and as a result remain under review in the orthoptic department for many years before being discharged with unfavourable visual acuity outcomes (10).

Orthoptists and paediatric ophthalmologists are taught that unilateral amblyopia must be managed before the age of 7 years. The efficacy of occlusion therapy and atropine penalisation therapy in the over 7 years age group is not understood (11,12). Randomised control trials (RCTs) have explored treating unilateral amblyopia in patients older than this by comparing no treatment versus therapy (13) and found therapy for amblyopia in a post-critical period population is likely to improve visual acuity if atropine penalisation or occlusion therapies have not been tried previously (14).

There are significant differences in the way amblyopia is managed in the UK compared to German Speaking Countries (GSC), however, visual acuity outcomes are comparable (5). This study found amblyopia is more aggressively managed in the GSC compared to the UK in terms of continuing therapy into an over 7-year age group and number of hours of occlusion therapy prescribed. National guidelines for the UK and Ireland are published by the British and Irish Orthoptic Society (15) and recommend treatment of amblyopia with either occlusion or atropine penalisation but do not reference age as a factor to be considered when managing amblyopia. This guideline reflects the weak evidence for continuing amblyopia therapy into adulthood and is supported by literature narratively discussed above and explored in a Cochrane systematic review (11).

**Rationale for a systematic review**
Large, multicentre RCTs have shown atropine penalisation therapy of the sound eye using 1% atropine eye drop twice weekly has visual acuity outcomes comparable to part-time total occlusion therapy in a 7-years-and-under age group with moderate amblyopia (7,16). Studies by the same group have shown visual acuity in an over 7-years-old age group, diagnosed with isolated unilateral strabismic and/or anisometropic amblyopia, can be improved with these therapies when compared to no treatment (13). The research group have also published some work to compare part-time total occlusion therapy to twice weekly atropine penalisation therapy in a 7 to 12-years age group (14) and found no difference between atropine penalisation using atropine 1% eye drop twice weekly and occlusion therapy in the 7 to 12-year age group.

Visual development is thought to end at approximately age 7 years (17), after which amblyopia therapy is unlikely to be as effective. This theory is based on extrapolations from studies on the macaque monkey (1,2). If the theory is correct, isolated anisometropic and or strabismic amblyopia patients fall into one of two categories: 1) age 7-years-and-under whom is likely to respond to treatment and 2) one who is older than 7 years and unlikely to respond to treatment. Thus, with this review, we are interested in group 2 patients; any one over the age of 7 years diagnosed with isolated, unilateral strabismic and/or anisometropic amblyopia. We aim to compare atropine penalisation and occlusion therapies for this group of patients.

# Methods

We designed and completed a systematic review of the literature using the following methodology in concordance the PRISMA statement (18). This review is registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42018089324). This review is based on previously published studies and does not contain any studies with human participants performed by any of the authors.

**Inclusion criteria**
To be included in this review, studies had to meet the participants, intervention, comparator, outcome measure and design criteria set out in table 1.

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| **Participants** | Children with a diagnosis of anisometropic, strabismic or mixed anisometropic / strabismic amblyopia |
| **Intervention** | Atropine penalisation therapy |
| **Comparator** | Part-time total occlusion therapy |
| **Outcome measure** | Best corrected visual acuity after a period of atropine or occlusion therapy |
| **Design** | Randomised control trial (RCT) |

Table 1 - summary of criteria for included studies

**Search strategy**
We performed a search of MEDLINE, EMBASE and CENTRAL databases using keywords summarised below and a search strategy to identify randomised control trials proposed by Glanville *et al.* (19). The Boolean search strategy is available in a supplementary table. Our search was limited to publications available in English language published before 12th April 2018.

**Study screening**All studies returned from our literature search were initially screened by title. If no reason to exclude the study was found the reviewer read the abstract and if no reason to exclude was found here the full text was obtained for full text screening. Following the full text screen, the reviewer decided whether to include or exclude the study from this review. This screening process was carried out by two reviewers independently, DO and KG, and any disagreements between the two reviewers were resolved with discussion with a third reviewer, ME.

**Critical appraisal**All included studies were critically appraised by the lead author, DO. The Critical Appraisal Skills Programme (CASP) toolkit (20) was used to rate the quality of evidence for each included study “low,” “moderate” or “high.”

**Data extraction and statistical analysis**The visual acuity outcomes were narratively discussed and presented in the results section. Where appropriate a forest plot was used to determine the overall effect from the included studies. For the purposes of our statistical analysis visual acuity measures were converted into logMAR units. We used the reported mean improvement in visual acuity from baseline, the standard deviation of improvement from baseline and sample sizes to calculate a 95% confidence interval (CI) for each study. We combined the results from both studies to calculate a total mean difference and 95% CI between occlusion therapy and atropine penalisation therapy using Review Manager 5 (Cochrane, London, UK). The secondary outcome of this review, adverse reactions and adverse events, are narratively discussed.

# Results

Our search strategy returned 1043 publications, which reduced to 814 once duplicates were removed. 789 publications were excluded in the primary title and abstract screen and 23 excluded after the full text eligibility screen, leaving 2 studies for critical appraisal and qualitative and quantitative data synthesis. A summary of the screening and eligibility process is summarised in the PRISMA flowchart below (18) (figure 1) and a summary of the included studies is outline in Table 2.

**Figure 1 - PRISMA flowchart**

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| --- | --- | --- | --- | --- | --- |
| **Publication** | **Experiment design** | **Participants** | **Intervention** | **Comparator** | **Outcome Measure** |
| Scheiman *et al.* (2008) (14) | Randomised control trial (RCT)Quality of study: high | * Age 7 to 12 years
* Anisometropic and / or strabismic unilateral amblyopia
* 193 participants randomised, 172 completed full follow-up
* Visual acuity of amblyopic eye between 0.30 and 0.70 logMAR with a 0.30 interocular visual acuity difference and visual acuity in the sound eye <0.10 logMAR
* Exclusion criteria: myopia, downs syndrome
 | One drop 1% atropine sulphate instilled into non-amblyopic eye. Initial dose not specified. If a less-than-six letter visual acuity improvement was seen between two visits, 6 weeks apart, dose was increased to one drop daily. Some participants prescribed reading glasses for home and school work. | Minimum of 1-hour occlusion of the non-amblyopic eye per day with a stick-on eye patch. If a less-than-six letter improvement in visual acuity was measured from one visit to the next (six weeks apart) the daily dose of occlusion therapy was increased to 4 hours per day. | Visual acuity of the amblyopic eye after 17 weeks of therapy. |
| Menon *et al.* (2008) (21) | Randomised control trial (RCT)Quality of study: moderate | * Age 8 to 20 years
* Anisometropic amblyopia
* 63 participants randomised, 57 completed full follow-up
* ﻿Visual acuity of amblyopic eye between 0.30 and 1.00 logMAR with a ≥0.30 interocular visual acuity difference and visual acuity in the sound eye <0.20 logMAR
* Exclusion criteria: myopia, known skin reaction to eye patches or allergy to atropine
 | One drop 1% atropine sulphate instilled into non-amblyopic eye daily for 3 months then twice weekly for 3 months. | Full time occlusion of non-amblyopic eye for 6 days in every 7 using an oval of opaque paper attached over the eye with Micropore. | Visual acuity of the amblyopic eye after 6 months of therapy. |

Table 2 – summary of included publications

**Included studies and critical appraisal**
Both included studies used a robust computer randomisation process to randomly allocate participants to either an atropine penalisation therapy or an occlusion therapy group. For the Scheiman et al (2008) study, visual acuity assessors were blinded from the result of randomisation; due to the nature of the intervention it was not possible to blind the participants; the masked assessors remained masked for 97% of appointments. The Menon *et al.* (2008) study did not mask the examiners or participants. Both studies had some participants withdraw from the study prior to completion of the full follow up and primary outcome data collection visit; the attrition rate was the same for both the atropine penalisation and occlusion groups. The quality of evidence in the Scheiman *et al.* (2008) study was graded as high, and the quality of evidence in the Menon *et al.* (2008) study graded as moderate.

Both studies reported baseline characteristics of included participants in tables. There are small differences of the characteristics of the participants between the intervention and comparator groups in both studies:

* Scheiman *et al.* (2008) had more participants with anisometropic amblyopia in the patching group (46/98 in occlusion therapy group versus 31/95 in the atropine penalisation therapy group). However, anisometropic and strabismic amblyopia responded similarly to treatment.
* Menon *et al.* (2008) had a difference of the spherical equivalent refractive errors between the two groups, with the patching group being more hyperopic than the atropine group (+4.24, SD 1.66 versus +3.29, SD 1.47). This difference was statistically significant (P=0.027).

Visual acuity was measured using a variety of visual acuity testing protocols. Of these, early treatment of diabetic retinopathy vision test (ETDRS) is considered the gold standard of visual acuity assessment (22), as such it is the values from ETDRS that will be reported in this review.

Menon *et al.* (2008) excluded all participants that had had more than 2 months of amblyopia treatment within the last two years, whilst Scheiman *et al.* (2008) included participants regardless of whether or not they had had previous therapy, however they ensured visual acuity was stable without atropine penalisation or occlusion therapies for at least 4 weeks prior to starting the study for an individual; 27/95 atropine penalisation therapy and 27/98 occlusion therapy participants had had previous atropine and / or occlusion therapy for amblyopia in the past.

**Meta-analysis**We performed statistical analysis on the primary visual acuity outcome data. Both studies measured visual acuity using the ETDRS or electronic-ETDRS test charts. Scheiman *et al.* (2008), reported a mean improvement in visual acuity from baseline of 7.6 letters (0.152 logMAR) and 8.6 letters (0.172 logMAR) for atropine therapy and occlusion therapy respectively. Menon *et al.* (2008) reported a mean improvement in visual acuity from baseline of 2.34 lines (0.234 logMAR) and 2.38 lines (0.238 logMAR) for atropine and patching respectively.

In our analysis a negative number is in favour of occlusion therapy and a value of 0 represents no difference between the two intervention groups. The total mean difference between the two interventions from the two studies is calculated as -0.01 logMAR (95% CI, -0.05 to 0.02), showing no statistical difference between the two interventions (P=0.45). We used a chi-squared test for heterogeneity, which showed no statistically significant heterogeneity between the two studies (P=0.68). These results are represented in Figure 2.



Figure 2 - forest plot showing nil significant difference between occlusion and atropine penalisation therapies (CI=confidence interval)

**Adverse events and reactions**Both studies discussed adverse events from both interventions within the text and presented data within tables. Menon *et al*. (2008) asked participants about eye redness and itchiness and participants in both groups reported itchiness, however, more participants in the atropine group reported red eye (8/28 [28.6%] versus 2/29 [7.9%] for atropine and occlusion groups respectively). Scheiman *et al.* (2008) reported that no participants were diagnosed with reverse amblyopia during the course of the study, however, visual acuity of the sound eye worsened by 0.3 letters (0.006 logMAR) and 1.5 letters (0.03 logMAR) in the atropine and occlusion groups respectively (mean difference between groups adjusted for baseline, 1.3 letters; 95% CI 0.4 to 2.2 letters). The Scheiman *et al.* (2008) study also reported ocular and systemic adverse events in the atropine group as follows: 14/88 (15.9%) reported ocular adverse events, most commonly light sensitivity, 1/88 (1.1%) participant reported tachycardia, 1/88 (1.1%) dry mouth and 1/88 (1.1%) irritability and headache. The study also performed analysis on change in angle of strabismus throughout the course of the study and reported “﻿no differences between treatment groups in the number of participants who developed new-onset strabismus or had an increase or decrease in a pre-existing strabismus.” The Scheiman *et al.* (2008) study reported that no participants in either group developed any persistent, constant diplopia; Menon *et al.* (2008) did not report any cases of diplopia through the course of their study.

# Discussion

Theories derived from invasive studies on macaque monkeys (1,2) suggest that the critical period of visual development ends at approximately age 7 years, after which amblyopia therapies are unlikely to improve visual acuity in the amblyopic eye of human subjects. Scheiman *et al.* (2005) (13) robustly showed amblyopia can be treated in the 7 to 12-year age group compared to a control group and showed that treatment of an older population aged 13 to 17 years may also be possible with current occlusion and atropine penalisation therapies. Innovative studies have also shown that if, in adulthood, a unilateral amblyopia patient suffers insult to vision in their sound eye their amblyopic eye may see improvement in visual acuity, suggesting amblyopia therapies may be effective in an adult age group (23).

The two trials identified in this review (14,21) both conclude no statistical difference between atropine penalisation and occlusion therapy in the samples they studied. We used a meta-analysis statistical technique to combine the results from the two studies to form a larger sample size with greater statistical power and found that the combined results do not allow us to reject the null hypothesis. This review aimed to compare atropine penalisation and occlusion therapies’ visual acuity outcomes in a post-critical period of visual development age group. The two included studies had an age range of 7 to 20 years, and as such patients over age 20 are not represented in this review; this review identified no studies for the over 20-years-old population. Furthermore, the distribution of age in the 229 participants that completed follow up in this review are not evenly spread. The largest study in terms of sample size in this review, Scheiman *et al.* (2008), did not include participants older than 13 years of age, resulting in a large number of 7 to 13-year olds included in this review, but relatively few 14 to 20-year olds. This represents an evidence gap for amblyopia patients over 13 years of age.

The secondary outcome of this review was adverse effects and events reported by included studies. Amblyopia therapies are thought to carry a risk of causing intractable, constant, binocular diplopia when used for an older population. In total, 229 participants completed the full follow-up protocol for the respective studies with nil reports of any participant acquiring binocular diplopia throughout the course of the study. Atropine penalisation therapy appears to have more frequent minor ocular adverse events than occlusion therapy, with light sensitivity being the most common complaint for atropine penalisation therapy and periocular itchiness the main complaint for occlusion therapy.

# Conclusions

Our systematic literature search identified two studies that compared visual acuity outcomes from atropine penalisation and occlusion therapies for unilateral amblyopia in a post-critical period of visual development aged population. Both identified studies reported no detectable difference in terms of visual acuity outcomes after 17 weeks treatment and 6 months treatment. We combined results from both studies in a meta-analysis and found no difference in terms of visual acuity outcomes. However, the population of unilateral anisometropic and / or strabismic between the age of 14 and 20 years were not well represented in this review and no data for over 20-year olds was identified. As such, a gap in the evidence for atropine penalisation therapy versus occlusion therapy for unilateral amblyopia patients older than 12 years exists. Atropine penalisation therapy may result in more frequent minor adverse events, such as red eye and light sensitivity; however, due to the infrequency of these events, a larger sample size may be required to determine the likelihood of these complications.

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# Supplementary material

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| **Search strategy** |
| 1 | randomised controlled trial.pt. |
| 2 | (randomised or randomized).ab,ti. |
| 3 | placebo.ab,ti. |
| 4 | dt.fs. |
| 5 | randomly.ab,ti. |
| 6 | trial.ab,ti. |
| 7 | groups.ab,ti. |
| 8 | or/1-7 |
| 9 | exp animals/ |
| 10 | exp humans/ |
| 11 | 9 not (9 and 10) |
| 12 | 8 not 11 |
| 13 | exp amblyopia/ |
| 14 | exp refractive errors/ |
| 15 | exp anisometropia/ |
| 16 | "unilateral amblyopia".mp. |
| 17 | Strabism\*.mp. |
| 18 | or/13-17 |
| 19 | atropine.mp. |
| 20 | patch\*.mp. |
| 21 | or/19-20 |
| 22 | 18 and 21 |
| 23 | 12 and 22 |

Supplementary table 1: Boolean search strategy for MEDLINE and EMBASE