

# Pharmacological enhancement of treatment for amblyopia

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**Background:** The purpose of this study was to compare a weight-adjusted dose of carbidopa-levodopa as treatment adjunctive to occlusion therapy with occlusion therapy alone in children and adults with different types of amblyopia.

**Methods:** This prospective study included 63 patients with amblyopia classified into two groups, ie, an occlusion group which included 35 patients who received occlusion therapy only and a pharmacological enhancement group which included 28 patients who received oral carbidopa-levodopa together with occlusion therapy for 6 weeks.

**Results:** The mean logarithm of the minimal angle of resolution (logMAR) of the eyes with amblyopia was not significantly different in the occlusion group (0.52, 0.52, and 0.51) than in the pharmacological enhancement group (0.58, 0.49, and 0.56) at three follow-up visits (at months 1, 3, and 12, respectively). There was a highly significant improvement in mean logMAR of amblyopic eyes compared with baseline in both occlusion groups (from 0.68 to 0.52, from 0.68 to 0.52, and from 0.68 to 0.51) and in the pharmacological enhancement group (from 0.81 to 0.58, from 0.81 to 0.49, and from 0.81 to 0.56) at the month 1, 3, and 12 visits ( $P = 0.01$ ,  $P = 0.01$ , and  $P = 0.001$ , respectively). The improvement of mean logMAR in the subgroup of patients older than 12 years was greater in the pharmacological enhancement group (42.5%) than in the occlusion group (30%). The improvement of mean logMAR in the subgroup of patients with severe amblyopia was greater in the pharmacological enhancement group (34.3%) than in the occlusion group (22%).

**Conclusion:** Significant improvement was reported in both groups at all follow-up visits over 1 year. Regardless of the etiology of amblyopia, levodopa-carbidopa may be added to part-time occlusion in older patients as a means of increasing the plasticity of the visual cortex. Levodopa may add to the effect of occlusion in severe amblyopia and bilateral amblyopia.

**Keywords:** amblyopia, levodopa, carbidopa, occlusion

## Introduction

Amblyopia describes decreased vision, usually from one eye but occasionally from both eyes, despite correction of refractive errors, which cannot be attributed to coexisting eye or visual pathway disease. Amblyopia is the most common cause of monocular visual loss in children and in young and old children.<sup>1</sup> In one study of 250 amblyopes who lost vision in their nonamblyopic eye over 2 years from 1997, 25% were left severely visually impaired, 25% were unable to drive, and 50% of those in paid employment were unable to continue working.<sup>2</sup> Occlusion and atropine are accepted modalities of treatment. However, many older children and teenagers with amblyopia fail to achieve near normal visual acuity. Only 23% (severe amblyopia) to 36% (moderate amblyopia) of children aged 7–13 years achieve visual acuity 20/40 or better.<sup>1</sup>

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Carbidopa-levodopa has been described for the treatment of amblyopia since 1993.<sup>3</sup> Levodopa is a catecholamine precursor used to treat adults with Parkinson's disease and children with dopamine-responsive dystonia. Dopamine is a neurotransmitter that does not cross the blood–brain barrier. Levodopa is an intermediate in the biosynthesis of dopamine that can cross the blood–brain barrier where it is converted to dopamine. Carbidopa is a peripheral decarboxylase inhibitor that prevents peripheral conversion of levodopa to catecholamine metabolites, thus allowing more levodopa to cross the blood–brain barrier. This allows reduction in the dose of levodopa required for the desired effect by about 75%.<sup>4</sup> Adults with Parkinson's disease can tolerate a levodopa dose of up to 30 mg/kg body weight.<sup>5</sup> Levodopa has been also used for many years in children to treat dopamine-responsive dystonia. Chronic dosing is 4–5 mg/kg in divided doses, although up to 20 mg/kg/day may be needed.<sup>6</sup> Many studies have been performed to evaluate the role of levodopa in the treatment of amblyopia. Some of these studies used levodopa at a relatively high dose (6 mg/kg/day<sup>7,8</sup> to 13 mg/kg/day<sup>9</sup>), but for short durations (1 day<sup>9</sup> to 1 week<sup>7</sup>). Other studies used much lower doses of 1.5 mg/kg/day<sup>10–14</sup> for a longer duration (7 weeks), and one as yet unpublished randomized trial of levodopa as treatment for residual amblyopia used two doses (0.51 mg/kg versus 0.76 mg/kg, each given three times daily) for 8 weeks.<sup>15</sup> Another study used low doses for shorter durations, ie, 30 mg/day for 3 weeks.<sup>16</sup> Further studies used levodopa at a relatively high dose (6–9 mg/kg/day) for a relatively short duration (3 weeks)<sup>17</sup> or lower doses (1.86 mg/kg/day and 2.36 mg/kg/day) for a longer duration (4 weeks).<sup>18</sup> In addition, some of these studies<sup>7,15,17</sup> compared two different doses of levodopa without a control group. Some of these trials used levodopa only for residual amblyopia after use of other treatments.<sup>10,15,19</sup>

In mild to moderate amblyopia (visual acuity better than 0.2) a similar treatment response was seen at 2 hours and 4 hours of occlusion, and the effect then plateaued with additional patching.<sup>20</sup> In severe amblyopia (visual acuity 0.2 or worse), occlusion for 6 hours has been found to be as effective as full-time occlusion.<sup>21</sup> Some of the previous studies of levodopa used the drug without occlusion<sup>8,11</sup> in some patients. Some studies used only 2–3 hours of occlusion<sup>7,11,15</sup> and other studies used full-time occlusion.<sup>14,17</sup>

The present study used occlusion graded according to the severity of amblyopia, and evaluated higher doses (6.25–8.3 mg/kg/day) of levodopa for a longer duration (6 weeks) in cases not treated previously for amblyopia.

## Materials and methods

This prospective interventional study included 63 patients aged 3–24 years with amblyopia.

Exclusion criteria were previous amblyopia treatment, previous refractive surgery, side effects related to levodopa treatment reported as being intolerable by patient or parents, and amblyopic eyes with improper or incomplete causal treatment.

The subjects comprised 26 males (41.3%) and 37 females (58.7%). There were 16 patients (25.4%) aged younger than 7 years, 28 patients (44.4%) aged 7–12 years, and 19 patients (30%) aged 13 years or older. There were 33 patients (52.4%) with anisometropic/ametropic amblyopia, seven patients (11.1%) with strabismic amblyopia, 20 patients (31.7%) with mixed etiology (ametropic-strabismic) amblyopia, and three patients (4.8%) with relative amblyopia.

There were 27 patients (42.8%) with mild to moderate amblyopia (visual acuity better than 0.2) and 36 patients (57.2%) with severe amblyopia (visual acuity 0.2 or worse). This classification considered patients with bilateral amblyopia and having one eye affected by severe amblyopia as severe cases. There were 15 patients with bilateral amblyopia.

All patients underwent a detailed ophthalmological examination, including cycloplegic refraction. Best corrected distance visual acuity was recorded using a Snellen's distance visual acuity chart and converted to a logarithm of the minimal angle of resolution (logMAR) equivalent. Any significant error of refraction was corrected with glasses or contact lens. Any significant angle of deviation was surgically corrected.

Patients were distributed into two groups. Group 1 included 35 patients (55.6%) who received occlusion therapy alone (occlusion group), and Group 2 included 28 patients (44.4%) who received occlusion therapy with levodopa-carbidopa (pharmacological enhancement group). Occlusion was part-time in both groups, and performed for 2–4 hours in patients with moderate amblyopia and for 6 hours in those with severe amblyopia.

Carbidopa-levodopa 25/250 (1:10) combination tablets (Sinemet<sup>®</sup>, Merck and Co, Inc, Whitehouse Station, NJ) were administered orally in a dose range of 6.25 to 8.3 mg/kg (0.5–2.0 tablets per day). The dose was adjusted according to patient weight (Table 1).

All patients were supplied with enough doses for 6 weeks. Patients were informed about potential side effects of the drug, such as nausea, vomiting, headache, dry mouth, dizziness, fatigue, and sleep disorders. They were also informed about the potential benefit and possible treatment alternatives.

**Table 1** Dose adjustment of levodopa according to patient weight

Levodopa dose	Sinemet®	Weight (kg)	Dose (mg/kg)
125 mg	1/2 tablet/day	15	8.3
125 mg	1/2 tablet/day	20	6.25
250 mg	1 tablet/day	30	8.3
250 mg	1 tablet/day	40	6.25
375 mg	1.5 tablet/day	50	7.5
500 mg	2 tablets/day	60	8.3

Watching for signs of overdose, such as facial muscle twitches, sleep disorders, and repeated vomiting, were especially reinforced. Phone calls were used to monitor for potential side effects of carbidopa-levodopa. If intolerable side effects were reported by the patient or parents, the patient was excluded from the study.

Visual acuity was followed up at regular intervals for 12 months. In both groups, any decrease of visual acuity in the amblyopic eye necessitated reocclusion of the dominant eye to prevent recurrence. Also, any decrease in visual acuity in the dominant eye necessitated discontinuation of occlusion to prevent reverse amblyopia. Recordings of visual acuity and logMAR equivalents were made at months 1, 3, and 12 after intervention. The data were analyzed using Student's unpaired and paired *t*-tests and the Chi-square test ( $\chi^2$ ).

## Results

There were significantly more patients aged younger than 7 years in the occlusion group. Also, there were significantly more patients in the pharmacological enhancement group aged older than 12 years. There was no significant difference in patient numbers between the groups for patients aged 7–12 years (Table 2). There was also a higher percentage of patients with severe amblyopia in the pharmacological enhancement group than in the occlusion group, but the difference was not statistically significant (Table 2). There was a higher percentage of patients with strabismic amblyopia in the pharmacological enhancement group than in the occlusion group, and a higher percentage of amblyopia of mixed etiology in the occlusion group. The difference was not statistically significant (Table 2). The number of bilateral amblyopia cases was higher in the pharmacological enhancement group (11/15). The mean baseline (preintervention) logMAR in the amblyopic eye was 0.68 (6/24 equivalent) in Group 1 (occlusion group) and 0.81 (6/36 equivalent) in Group 2 (pharmacological enhancement group). The difference was not statistically significant.

The mean baseline logMAR in the dominant eye was similar in both groups (Table 3). The mean logMAR at the

**Table 2** Comparison between the two study groups with regard to age, severity, and causes of amblyopia

	Group 1 (n = 35) Occlusion, n (%)	Group 2, Pharmacological enhancement, n = 28 n (%)	$\chi^2$	P value
<b>Age (years)</b>				
<7	13 (37.1%)	3 (10.7%)	8.7	0.01*
7–12	16 (45.7%)	12 (42.9%)		
>12	6 (17.1%)	13 (46.4%)		
<b>Severity</b>				
Mild to moderate (VA > 0.2)	18 (51.4%)	9 (32.1%)	2.3	0.1
Severe (VA ≤ 0.2)	17 (48.6%)	19 (67.9%)		
<b>Causes</b>				
Strabismus	2 (5.7%)	5 (17.9%)	4.1	0.2
Anisometropia	17 (48.6%)	16 (57.1%)		
Mixed	14 (40.0%)	6 (21.4%)		
Relative	2 (5.7%)	1 (3.6%)		

**Note:** \* $P < 0.05$ , statistically significant difference.

**Abbreviation:** VA, visual acuity.

first follow-up visit for the amblyopic eyes was similar in the occlusion group at 0.52 (6/18 equivalent) and the pharmacological enhancement group at 0.58 (6/24 equivalent). The mean logMAR at the first follow-up visit for the dominant eye was 0.1 (6/7.5 equivalent) in the occlusion group and 0.06 (6/6 equivalent) in the pharmacological enhancement group (Table 3). The mean logMAR at the second follow-up visit for the amblyopic eye was similar between the occlusion group at 0.52 (6/18 equivalent) and the pharmacological enhancement group at 0.49 (6/18 equivalent). The mean logMAR for the dominant eye at the second follow-up visit was similar between the occlusion group 0.07 (6/6 equivalent) and the pharmacological enhancement group 0.06 (6/6 equivalent, Table 3). The mean logMAR at the third follow-up visit in the amblyopic eye was similar in the occlusion group at 0.51 (6/18 equivalent) and at 0.56 (6/12 to 6/18) in the pharmacological enhancement group. The mean logMAR at the third follow-up visit was similar (0.07) in both study groups (Table 3).

## Improvement in amblyopic eyes

There was a highly significant improvement in mean logMAR for the amblyopic eyes at the first follow-up visit (month 1) compared with baseline in both groups. Also, there was a highly significant improvement in mean logMAR at the second follow-up visit (month 3) compared with baseline in both groups. The same highly significant improvement was found in mean logMAR at the third follow-up visit compared with baseline in both groups (Table 4).

**Table 3** Comparison between the two study groups regarding mean logMAR in both amblyopic and dominant eyes at baseline and at month 1, 3, and 12 follow-up visits

Follow-up visit	LogMAR	Group 1 Occlusion, n = 35 Mean ± SD	Group 2 Pharmacological enhancement, n = 28 Mean ± SD	Paired t	P value
Baseline	Amblyopic eye	0.68 ± 0.4	0.81 ± 0.4	1	0.3
	Dominant eye	0.12 ± 0.1	0.1 ± 0.2	0.2	0.7
First follow-up (month 1)	Amblyopic eye	0.52 ± 0.4	0.58 ± 0.4	0.5	0.5
	Dominant eye	0.10 ± 0.1	0.06 ± 0.1	1.1	0.2
Second follow-up (month 3)	Amblyopic eye	0.52 ± 0.5	0.49 ± 0.4	0.1	0.8
	Dominant eye	0.07 ± 0.1	0.06 ± 0.06	0.4	0.6
Third follow-up (month 12)	Amblyopic eye	0.51 ± 0.5	0.56 ± 0.5	0.1	0.8
	Dominant eye	0.07 ± 0.1	0.07 ± 0.1	0.4	0.7

**Abbreviation:** logMAR, logarithm of the minimal angle of resolution.

### Improvement in dominant eyes

In the occlusion group, there was no statistically significant difference in the dominant eye at the first follow-up visit (month 1) for the mean log MAR compared with the baseline logMAR (0.12 logMAR and 0.10 logMAR at the first visit). In the pharmacological enhancement group, there was a statistically significant improvement in mean logMAR for the dominant eye at the first follow-up visit (month 1) compared with baseline (0.1 logMAR at baseline and 0.062 logMAR at the first visit, Table 5).

In the occlusion group, there was a statistically significant improvement in mean logMAR for the dominant eye at the second and third visits compared with baseline (0.11 mean logMAR at baseline and 0.07 mean log MAR at the second and third visits). In the pharmacological enhancement group, there was a significant improvement in mean logMAR for the dominant eye at the second and third visits compared with the logMAR at baseline (Table 5).

In the subgroup analysis of patients older than 12 years in each group, there was an improvement in mean logMAR from 0.6 at baseline to 0.42 at final follow-up (30%) in the occlusion group. In the pharmacological enhancement group, there was a greater improvement from mean baseline logMAR of 0.87 to 0.50 at the final follow-up (42.5%; Table 6). In the subgroup analysis of patients with severe amblyopia in each group, there was an improvement in mean logMAR from 1.09 at baseline to 0.85 at the final visit (22%) in the occlusion group. In the pharmacological enhancement group, there was greater improvement from 1.02 at baseline to 0.67 at the final visit (34.3%; Table 7). Tolerable side effects of levodopa were nausea with or without vomiting, and sleep disorders were reported by 4/28 patients (14%).

### Discussion

Some previous studies of carbidopa-levodopa have used this treatment for a short time (1 week or less),<sup>7-9</sup> while

**Table 4** Effect of treatment. Comparison between logMAR for amblyopic eyes at baseline and at month 1, 3, and 12 follow-up visits

Log MAR	Baseline Mean ± SD	Follow-up visit (1) 1 month Mean ± SD	Follow-up visit (2) 3 months Mean ± SD	Follow-up visit (3) 12 months Mean ± SD	Paired t	P value
Group 1 (n = 35)	0.68 ± 0.4	0.52 ± 0.4			2.7	0.009**
Group 2 (n = 28)	0.81 ± 0.4	0.58 ± 0.4			5.9	0.000**
Group 1 (n = 35)	0.68 ± 0.4		0.52 ± 0.5		3.9	0.000**
Group 2 (n = 28)	0.81 ± 0.4		0.49 ± 0.4		6.5	0.000**
Group 1 (n = 35)	0.68 ± 0.4			0.51 ± 0.5	3.8	0.000**
Group 2 (n = 28)	0.81 ± 0.4			0.56 ± 0.4	6.6	0.000**

**Note:** \*\*P < 0.01, highly statistically significant difference.

**Abbreviation:** logMAR, logarithm of the minimal angle of resolution.

**Table 5** Effect of treatment. Comparison between mean logMAR for dominant eye at baseline and at month 1, 3, and 12 follow-up visits

LogMAR	Baseline Mean $\pm$ SD	Follow-up visit 1 (3 months) Mean $\pm$ SD	Follow-up visits 2 and 3 (6 and 12 months) Mean $\pm$ SD	Paired t	P value
Group 1 (n = 35)	0.12 $\pm$ 0.1	0.10 $\pm$ 0.1		1.2	0.2
Group 2 (n = 28)	0.10 $\pm$ 0.2	0.062 $\pm$ 0.1		2.3	0.02*
Group 1 (n = 35)	0.11 $\pm$ 0.1		0.07 $\pm$ 0.1	2.3	0.02*
Group 2 (n = 28)	0.11 $\pm$ 0.2		0.06 $\pm$ 0.1	2.2	0.03*

**Note:** \*P < 0.05, statistically significant.

**Abbreviation:** logMAR, logarithm of the minimal angle of resolution.

other studies have used it at low doses.<sup>10–15</sup> The present study used the drug for a longer duration (6 weeks) and at relatively higher doses. Because occlusion of all visual input to the better seeing eye represents an established treatment approach for amblyopia,<sup>20</sup> the present study used occlusion in all amblyopic patients as a standard treatment. The purpose of this approach was to evaluate the value of pharmacological enhancement by levodopa. Preintervention characteristics, including mean baseline logMAR in amblyopic eyes, degree of amblyopia, and demographic data, were not significantly different between the groups. Mean logMAR at the three follow-up visits (months 1, 3, and 12) was similar in the occlusion group and the pharmacological enhancement group. This is contrary to a report by Dadeya et al<sup>14</sup> who described more improvement of visual acuity in a levodopa-occlusion group than in a placebo-occlusion group. This may be explained by the different statistical methods used in the analysis of these studies. Dadeya et al observed eyes with at least two lines of visual acuity improvement to be greater at 15/15 (100%) in the levodopa group than at 9/15 (60%) in the occlusion group. These statistical methods may have led to bias, but are suitable for their small sample size.

Further, the present study findings are different from those reported by Leguire et al,<sup>12</sup> who found that levodopa combined with part-time occlusion was more effective

than levodopa without occlusion in amblyopic eyes. Again, this may be due to the small sample size of the study (only 13 patients) and inclusion of only one age group (7–12 years), whereas the present study included different age groups. Further, there was no detailed description of the severity of amblyopia, whereas the present study subgroup analysis classified patients according to severity of amblyopia. A detailed description of the results of our study according to preintervention characteristics, including age, severity, and type and laterality of amblyopia, can be helpful in outcome analysis.

## Patient age

Patients aged older than 12 years in both groups showed improvement in baseline logMAR, which was found to be greater in the pharmacological enhancement group (42.5%) than in the occlusion group (30%). Although the difference was not significant, it may be explained by the fact that addition of levodopa to occlusion is a way to expand the patient age range for treatment of amblyopia, while keeping the response similar to that in younger patients. Mohan et al<sup>11</sup> found that patient age had no significant effect on mean improvement in visual acuity. The levodopa dose was adjusted for body weight in the present study (6.25–8.3 mg/kg), and was higher than the dose of 0.5 mg/kg used by Mohan et al.<sup>11</sup>

**Table 6** Effect of treatment. Comparison between mean baseline logMAR and logMAR at the final visit in the subgroup of patients older than 12 years in each group

Mean logMAR Patients > 12 years	Baseline Mean $\pm$ SD	Final visit Mean $\pm$ SD
Occlusion group n = 6	0.60 $\pm$ 0.4	0.42 $\pm$ 0.5
Pharmacological group n = 13	0.87 $\pm$ 0.3	0.50 $\pm$ 0.4
Paired t	1.4	0.3
P value	0.2	0.7

**Abbreviations:** SD, standard deviation; logMAR, logarithm of the minimal angle of resolution.

**Table 7** Effect of treatment. Comparison between baseline logMAR and final visit logMAR in subgroup of patients with severe amblyopia

Mean logMAR Patients with severe amblyopia	Baseline Mean $\pm$ SD	Final visit Mean $\pm$ SD
Occlusion group n = 6	1.09 $\pm$ 0.3	0.85 $\pm$ 0.4
Pharmacological group n = 13	1.02 $\pm$ 0.3	0.67 $\pm$ 0.4
Paired t	0.5	1.1
P value	0.5	0.2

**Abbreviations:** SD, standard deviation; logMAR, logarithm of the minimal angle of resolution.



Further, the similar outcome in the younger and older age groups in the present study was different from that reported by Dadeya et al,<sup>14</sup> who reported that levodopa improved visual acuity significantly only in patients younger than 8 years. This difference may be explained by the smaller sample size (only 15 patients in each group) and/or smaller dose of levodopa (0.5 mg/kg) in the Dadeya et al<sup>14</sup> study than in our work. The statistical methods used included the percentage of eyes achieving at least two lines of improvement, and found them to be 100% in patients younger than 8 years and 60% in patients older than 8 years. The present study used the mean logMAR for group comparison. Treatment success was similarly reported by Scheiman et al for strabismic and anisometropic patients who were older than the usual age for therapeutic success.<sup>22</sup>

The effect of levodopa on older amblyopes in the present study can be supported experimentally. Levodopa as a catecholamine precursor can affect visual function in older children. Depletion of catecholamines by a neurotoxin (6-hydroxydopamine) halts the plasticity of the visual cortex in young kittens. Plasticity can be re-established by infusion of exogenous catecholamines into the brain or by direct electrical stimulation of a locus which projects catecholamine fibers to the visual cortex.<sup>23</sup> Further support of a cortical origin for amblyopia is demonstrated by Phillipson et al.<sup>24</sup> They found dopaminergic innervation from the ventral tegmental area to striate cortex laminae I, V, and VI. Also, they found that lamina VI sent afferents to lamina IV, and neurons arising from lamina IV give rise to the dendritic tree of lamina VI. This feedback loop within the cortical laminae is in part controlled by dopaminergic innervation. Further support for the re-establishment of cortical plasticity is the significant spontaneous improvement in visual acuity of the amblyopic eye a few days after loss of vision in the dominant eye in 10% of adult amblyopic patients, as reported by Chua and Mitchell.<sup>32</sup>

## Severity of amblyopia

In the present study, a subgroup of patients with severe amblyopia in each group showed improvement in baseline logMAR. This was found to be greater in the pharmacological enhancement group (34.3%) than in the occlusion group (22%). The difference was not statistically significant. Also, the mean preintervention logMAR denoted that visual acuity was worse in the pharmacological enhancement group. However, the mean logMAR was similar in both groups at the follow-up visits, suggesting that addition of levodopa to occlusion can lead to a visual outcome of severe amblyopia similar to that of mild to moderate amblyopia.

Mohan et al<sup>11</sup> reported that there was no correlation between baseline visual acuity and treatment effect. They did not conclude advantage for levodopa over occlusion. This can be explained by their subgroup distribution. They included the levodopa alone group and the levodopa with occlusion group. They did not include a subgroup of occlusion alone.

The present study results showing more improvement of severe amblyopia in the pharmacological enhancement group can be explained by better patient co-operation with levodopa-occlusion. This finding is supported by that of Awan et al,<sup>25</sup> who reported poor compliance with patching in patients with poor initial visual acuity.

## Types of amblyopia

There was a higher percentage of strabismic amblyopia in the pharmacological enhancement group. However, there was a higher percentage of mixed etiology amblyopia in the occlusion group, comprising a mixture of strabismus and anisometropia, so our study cannot explain a greater response of certain types of amblyopia to pharmacological enhancement by levodopa. This finding is similar to the results reported by Mohan et al,<sup>11</sup> who found no significant difference in mean improvement of visual acuity among strabismic, ametropic, and mixed types of amblyopia. Similarly, Attebo et al<sup>26</sup> reported that anisometropic amblyopia tends to be diagnosed later than strabismic amblyopia or when strabismus appears (ie, mixed etiology) because the anisometropic child has only a mononuclear vision problem that is difficult to detect.

## Laterality of amblyopia

Levodopa was significantly more effective in the dominant eye at the first follow-up visit. Also, there was a greater number of bilateral amblyopia cases in the pharmacological enhancement group. However, the mean logMAR in the dominant eye was similar in both groups at the second and third follow-up visits, being nearly 6/6 equivalent in both groups. This means that levodopa adds to the effect of occlusion in bilateral cases, especially in improvement of visual acuity in dominant eyes. This may decrease the risk of reverse amblyopia in patients with bilateral amblyopia. This is similar to the conclusion reached by Wali et al,<sup>27</sup> who stated that the normal eye in amblyopes is not actually normal and exhibits various degrees of visual loss, so is better referred to as the dominant eye. The same observation is made by Leguire et al,<sup>12</sup> who stated that simultaneous use of levodopa and occlusion interacts to achieve significant improvement in visual function, and to a greater extent than sequential combination of levodopa with occlusion alone.

The results of the present study can be explained by the fact that the major metabolite of levodopa is dopamine. Dopamine constricts the receptive field size of horizontal cells, thus increasing the spatial frequency of the retina. Change in the retinal receptive field increases visual acuity in both amblyopic and dominant eyes.<sup>28</sup> This is further supported by the finding in Parkinson's disease of reduced retinal function that is improved by levodopa.<sup>24</sup> Thus, in amblyopia, as in Parkinson's disease, levodopa improves visual function by increasing retinal dopamine levels and decreasing receptive field size. Levodopa probably acts on dopamine receptors (D<sub>1</sub> and D<sub>2</sub>) widely present in the retinal pigment epithelium, photoreceptors, and amacrine and horizontal cells.<sup>28</sup>

Demer et al<sup>29</sup> have reported reduced glucose metabolism in the visual cortex of amblyopes using positron emission tomography. Using functional magnetic resonance imaging, Sireteanu et al<sup>30</sup> found a normal striate cortex and an adversely affected extrastriate cortex. Further, Von Noorden and Crawford<sup>31</sup> found that layers supplied by amblyopic eyes were shrunken in the ipsilateral geniculate body. Because the greatest input (80%) to the ipsilateral geniculate body is from the visual cortex, changes in the ipsilateral geniculate body would be secondary to influences from the cortex rather than primary ones. These studies support the role of the cortex in amblyopia and therefore a role for levodopa at the cortical level.

Carbidopa-levodopa therapy was stopped in the present study after 6 weeks. However, the effect of improvement was still present until the final follow-up visit at 1 year. This effect was maintained in both groups. Further, occlusion was maintained in both groups as long as there was a difference in visual acuity between the eyes. This may explain the role of occlusion in inducing a plateau effect, even in the pharmacological enhancement group, and also explains maintenance of the treatment effect during 1 year of follow-up. This is different from the findings reported by Mohan et al,<sup>11</sup> who described statistically significant regression of visual acuity in patients aged older than 10 years, but included only 16 patients in this age group and assessment was acknowledged to be unreliable. Also, details of occlusion duration and reuse of occlusion were not mentioned. The sustained effect of levodopa seen in this study may be due to a higher dose (6.25–8.3 mg/kg) compared with the 0.5 mg/kg dose used by Mohan et al.<sup>11</sup> The sustained improvement in visual function after cessation of treatment in the present study can be explained by restoration of cortical plasticity, achieved by increasing brain catecholamine levels. However, this would predict return of visual acuity to baseline levels after

cessation of the drug unless the improvement was maintained by occlusion.

## Conclusion

Higher weight-adjusted doses of levodopa may represent a tool additional to occlusion for expanding both the age limit for treatment beyond 12 years and the range of severity of amblyopia that can be treated successfully, but in this study could not be shown to be more beneficial in certain types of amblyopia. Occlusion is the gold standard for treatment of amblyopia. Levodopa may be helpful for bilateral cases and for avoiding reverse amblyopia. Maintained occlusion is helpful to maintain the long-term outcome.

## Disclosure

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