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# Pharmacological therapy for amblyopia

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## Abstract:

Amblyopia is the most common cause of preventable blindness in children and young adults. Most of the amblyopic visual loss is reversible if detected and treated at appropriate time. It affects 1.0 to 5.0% of the general population. Various treatment modalities have been tried like refractive correction, patching (both full time and part time), penalization and pharmacological therapy. Refractive correction alone improves visual acuity in one third of patients with anisometropic amblyopia. Various drugs have also been tried of which carbidopa & levodopa have been popular. Most of these agents are still in experimental stage, though levodopa-carbidopa combination therapy has been widely studied in human amblyopes with good outcomes. Levodopa therapy may be considered in cases with residual amblyopia, although occlusion therapy remains the initial treatment choice. Regression of effect after stoppage of therapy remains a concern. Further studies are therefore needed to evaluate the full efficacy and side effect profile of these agents.

## Keywords:

Amblyopia, levodopa, pharmacological therapy for amblyopia

## Introduction

Amblyopia is defined as unilateral or bilateral dimness of vision caused by form vision deprivation and/or abnormal binocular interaction.<sup>[1]</sup> This is the most common cause of preventable monocular blindness in children and young adults.<sup>[2]</sup> Amblyopic visual loss is reversible with timely detection and appropriate intervention in almost all cases.<sup>[3]</sup> Various treatment modalities such as refractive correction,<sup>[4-8]</sup> patching,<sup>[9-21]</sup> penalization,<sup>[22-32]</sup> and pharmacological therapy<sup>[33-42]</sup> have been tried till date.

Various drugs have been tried, of which carbidopa and levodopa have been popular. The past efforts to treat amblyopia medically have experimented with substances such as oxygen, strychnine, alcohol, propranolol, bicuculline, and exogenous nerve growth factor (NGF), but none were successful in terms of clinical applicability and effectiveness.

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## Pharmacological Therapy

The conventional occlusion therapy for amblyopia is often found incomplete as many patients are left with some amount of permanent reduction in visual acuity (VA) despite maintaining adequate compliance.<sup>[43-46]</sup> In view of this suboptimal response, alternative treatment options are being tried such as levodopa-carbidopa combination, antidepressants such as fluoxetine, GABA antagonists, and cytidine 5'-diphosphocholine (CDP).

### Levodopa-carbidopa combination therapy

It is a well-known theory that amblyopia is a consequence of competition between individual eye's input to the visual cortical cells. This phenomenon of binocular competition, besides age, has been shown to be dependent on the presence of certain neurotransmitters and neuromodulators in the brain.<sup>[47-50]</sup>

Kasamatsu and Pettigrew<sup>[49]</sup> in an animal study showed that even older amblyopic

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animals could recover some function if their brain is flooded with a dopaminergic drug. The study also found that the adverse effects of occlusion could be prevented, if a neurotoxin such as 6-hydroxydopamine is administered to destroy the dopaminergic terminals, suggesting that dopaminergic drugs may influence visual cortical plasticity and hence visual recovery in the amblyopes.

Oral levodopa is used to supplement dopamine deficiency in adults with Parkinson's disease and children with dopamine-responsive dystonias. Levodopa-carbidopa combination therapy has been used for the treatment of amblyopia since 1993.<sup>[51,52]</sup> Dopamine has been known to play an important role in retinal function and in central visual processing.<sup>[43-53]</sup> Dopamine cannot be administered as such since it is unable to cross blood-brain barrier. Levodopa is a precursor of dopamine, and easily crosses blood-brain barrier. Carbidopa is a peripheral decarboxylase inhibitor which prevents peripheral conversion of levodopa to dopamine, thereby increasing the availability of levodopa in the central nervous system and allowing for reduction in the dose by about 75%.<sup>[52-54]</sup>

Levodopa has been shown to improve VA and visual-evoked potential (VEP) amplitudes in various studies in amblyopic patients [Table 1]. Various doses of levodopa have been tried for different durations: single-dose,<sup>[38]</sup> 1-week,<sup>[55]</sup> 3-week,<sup>[51]</sup> and 7-week course.<sup>[56-58]</sup> Some studies used lower doses – 1.5 mg/kg/day<sup>[39,56-58]</sup> and 30 mg/day<sup>[51]</sup> of levodopa – while others used higher ones – 6–13 mg/kg/day.<sup>[38,55,59]</sup> Levodopa has also been used for management of residual amblyopia after failure of other therapies and in older age group up to 46 years.<sup>[60-63]</sup> Despite initial improvement in VA, partial regression has been seen to occur after stopping the medication.<sup>[38,55,64]</sup>

Levodopa is usually administered along with carbidopa in a 4:1 dose ratio, either in the form of oral tablets or as oral suspension. Liquid suspensions have been shown to be stable for around 28 days when stored at 25°C and for 42 days, when stored at 4°C.<sup>[65]</sup> The drug is bitter in taste and therefore advised to use it with a protein drink.<sup>[66,67]</sup> Overall, levodopa has been shown to be well tolerated in children.<sup>[47]</sup> Leguire *et al.*<sup>[60]</sup> found that continuous use of levodopa/carbidopa therapy (1.02/0.25 mg/kg body weight) lowered oral body temperature by 1.2°F over a 7-week period. Hence, it has been suggested that longitudinal oral dosing with levodopa should be <1.02 mg/kg body weight three times daily, to prevent change in body temperature. Other commonly reported side effects include headache, nausea, dry mouth, and abdominal cramps.<sup>[43,46]</sup>

## Effects of levodopa administration

### *Increased endogenous expression of nerve growth factor*

Li *et al.*<sup>[67]</sup> assessed the anatomic and physiologic effects of L-DOPA methyl ester administration on visual cortex area 17 in a feline model with stimulus deprivation amblyopia. The structural changes and the expression of NGF were studied using immunohistochemical staining and Western blot. The study found significantly increased the density of NGF-immunoreactive cells and elevated expression of endogenous NGF in the visual cortex following drug administration.

### *Expression of N-methyl-D-aspartate receptor-1-subunit in the visual cortex*

Zhao and Shi showed the importance of glutamate and its receptor N-methyl-D-aspartate receptor-1-subunit (NMDAR1) in the pathogenesis of amblyopia.<sup>[68]</sup> NMDAR1 is known to improve the permeability of nerve cells for calcium ions leading to intracellular physiological changes. NMDAR1 regulates the plasticity during the critical and adult period.<sup>[69]</sup> Studies have shown reduced expression of NMDAR1 in visual cortical neurons in amblyopic animals compared to the controls.<sup>[70,71]</sup> In another study by Sun and Zhang,<sup>[72]</sup> the expression of NMDAR1 in the visual cortex of monocularly deprived rats was studied before and after administering levodopa. The study found increased expression of NMDAR1 protein and mRNA in the group that received levodopa, suggesting that NMDAR1 could be related to the plasticity of visual development and levodopa might reverse its expression in the visual cortex.

### *Improved visual-evoked potential response*

Den *et al.*<sup>[73]</sup> evaluated the effects of single dose of levodopa administration on pattern VEP (PVEP) in cases with unilateral amblyopia. The study found decreased latency of N1 and P1 in the amblyopic eye and increased amplitude of N1P1 and P1N2 in the sound eye. In another study done by Basmak *et al.*,<sup>[56]</sup> the efficacy of levodopa administration, thrice a day for 1 week, was studied in 32 amblyopic children, aged 4 and 17 years with central fixation. After 1 week, a significant but transient improvement in VA and PVEP amplitudes was noted.

### *Visual field changes*

Gottlob *et al.*<sup>[74]</sup> studied VA and visual field changes at 3 weeks, 1 month, and 2 months of daily administration of levodopa/carbidopa combination therapy. The study found a significant increase in VA and a decrease in fixation point scotomas, which persisted for around 2 months after completion of treatment.

**Table 1: Outcomes of oral levodopa/carbidopa combination therapy for the management of amblyopia**

Author	Study design	Intervention	Study group	n	Results	Conclusions
Orge <i>et al.</i> , 2015	Case report	Oral levodopa along with full-time occlusion over 16 weeks	46-year-old male with glaucomatous right eye with no light perception leading to full-time occlusion of the same	1	On 3-month follow-up, his left eye improved two lines and stabilized at 6 months	Oral levodopa can be of benefit in the treatment of amblyopia in older age group
Repka, <i>et al.</i> , 2015 (PEDIG <sup>a</sup> group)	RCT <sup>b</sup>	Oral levodopa (0.76 mg/kg with carbidopa 0.17 mg/kg 3 times/day for 16 weeks) versus placebo as an adjunct to patching (2 h/day)	7-12 years old age with residual strabismic/ anisometropic amblyopia (VA range-20/50-20/400)	139	VA improved by an average of 5.2 letters in levodopa group and by 3.8 letters in the placebo group at 18 weeks ( $P=0.06$ )  Frequency of headaches was more with levodopa, although not significant	Oral levodopa with patching provides no additional benefit over placebo therapy
Kothari, 2014	Case report	Oral Levodopa/ carbidopa (2.5/0.6 mg/kg three times daily) with part-time occlusion	6-year-old child with anisometropic amblyopia	1	Occlusion amblyopia noted after 5 months of levodopa use, which reversed on stopping occlusion therapy alone  No signs and symptoms of systemic toxicity seen	Oral levodopa should be combined with occlusion therapy only for residual amblyopias (nonimprovement in vision after 6 months of patching)  If necessary, the dose should be reduced to <2 mg/kg/ dose especially, for younger children and if needed for a longer duration
Rashad, <i>et al.</i> , 2012	P <sup>c</sup>	Oral levodopa as an adjunct to occlusion	Occlusion group ( $n=35$ ) PE group ( $n=28$ )	63	Significant improvement in mean LogMAR seen in both groups  Greater improvement in mean LogMAR noted in the subgroup older than 12 years of age and in patients with dense amblyopia in the PE group	Levodopa may be added to occlusion therapy in older patients and in patients with severe amblyopia
Yang, <i>et al.</i> , 2012	M <sup>d</sup>	Levodopa versus placebo	6 RCTs included in analysis	-	Pooled mean difference of endpoint LogMAR of levodopa versus placebo was found to be -0.11 ( $P=0.01$ )  No increased frequency of adverse events seen with levodopa compared to placebo	Levodopa may be considered as a first-line treatment option for amblyopia in view of its safety and efficacy
Dadeya <i>et al.</i> , 2009	RCT	Oral levodopa/carbidopa (0.50 mg+1.25 mg/kg three times/day) versus placebo	Strabismic amblyopia (3-12 years of age) Group A ( $n=15$ ): Levodopa/carbidopa + full-time occlusion Group B ( $n=15$ ): placebo + full-time occlusion	30	Improvement in VA was greater in the levodopa group compared to placebo ( $P<0.005$ )  Patients younger than 8 years of age had greater improvement compared to older children ( $P=0.0026$ )  No regression of effect up to 6 months follow-up	Improvement in VA with levodopa is maintained, especially in patients younger than 8 years age

Contd...

**Table 1: Contd...**

Author	Study design	Intervention	Study group	n	Results	Conclusions
Leguire, <i>et al.</i> , 2002	P	Levodopa-carbidopa (for 7 weeks) with part-time occlusion	Refractory amblyopia Study group: Levodopa + occlusion Control group: Occlusion Few patients received only levodopa	30	Similar amount of regression seen in study and control groups Subjects receiving only levodopa regressed more compared to the study and control groups	L-DOPA may be used for long-term visual improvement in cases not responding to occlusion therapy
Pandey, <i>et al.</i> , 2002	RCT	Levodopa-carbidopa for 3 weeks	Two different dosing schedules given to adults and children	88	Patients receiving higher dose of levodopa showed better response Effects sustained till 9 weeks after stopping treatment	Oral levodopa may be considered as an adjunct to conventional therapy for improving patient compliance to occlusion, by improving VA in the amblyopic eye
Bhartiya, <i>et al.</i> , 2002	P	Levodopa/carbidopa (average dose 1.86 mg/kg/day in 3 divided doses for 4 weeks) versus a placebo with full-time occlusion	6-18 years age children with strabismic (n=19)/ anisometropic (n=21) amblyopia	40	Contrast sensitivity decreased in the levodopa group at the end of 1 <sup>st</sup> month, but later recovered by the 3-month follow-up Both groups showed significant improvement in visual function in the amblyopic eye (P<0.001) Strabismic and anisometropic amblyopes behaved similarly	Levodopa supplementation does not offer any advantage over occlusion alone Risk of occlusion amblyopia remains an issue
Mohan <i>et al.</i> , 2001	P	Levodopa/carbidopa (0.50 mg/kg body weight three times orally for 7 weeks) versus occlusion	Group A: Levodopa Group B: Levodopa + part-time occlusion (3 h/day) Group C: Levodopa+full-time occlusion	72	74% (n=53) showed improvement in VA after treatment 44/53 completed 1-year posttreatment follow-up out of which 52% (n=23) had a regression in VA	Addition of full-time occlusion therapy to levodopa helps to maintain VA for a longer period compared to levodopa alone or combined with part-time occlusion
Wu <i>et al.</i> , 1999	P	Oral levodopa/carbidopa (1.5/0.38 mg/kg) for 3 months	4.5-14 years of age with refractory amblyopia; VA stable for 6 months	36	88.89% experienced improvement in VA by an average of 2.27±1.26 lines at 3 months follow up Significant increase in retinal light sensitivity noted 19 eyes noted complete disappearance of scotomas and 6 noted contraction	Levodopa is a safe and effective drug for improving visual functions in children with refractory amblyopia
Leguire <i>et al.</i> , 1998	P	Levodopa/carbidopa versus part-time occlusion	Group 1: Levodopa/ carbidopa (1.02/0.25 mg/kg three times daily for 7 weeks) + part-time occlusion (3 h/day) Group 2: Levodopa/ carbidopa only	13	Addition of occlusion therapy improves significantly improves VA and mean log contrast sensitivity in amblyopic eyes (P=0.01) Effects maintained for 4 weeks after stopping treatment	Addition of occlusion therapy with levodopa improves visual functions more than drug therapy alone

<sup>a</sup>Pediatric Eye Disease Investigator Group, <sup>b</sup>Randomized controlled trial, <sup>c</sup>Prospective study, <sup>d</sup>Meta-analysis. VA = Visual acuity, LogMAR = Logarithm of the minimum angle of resolution

### Functional magnetic resonance imaging changes

Algaze *et al.*<sup>[75]</sup> used functional magnetic resonance imaging (fMRI) to assess differences between amblyopic and normal adults. They found that the level and

extent of activation of occipital visual cortex elicited by stimulation of the amblyopic eye was less than that of the dominant eye. The area of activation driven by monocular stimulation of the amblyopic eye was about

50% less than that of the dominant eye. Amblyopes exhibited a significantly larger interocular difference in activation compared to normals. The study found fMRI, a potential tool for the assessment of human amblyopia.

In another randomized study by Rogers,<sup>[47]</sup> the effects of single dose of levodopa administration (2 mg/kg body weight) on visual cortex and visual functions were studied using fMRI and psychophysical tests, in 6 amblyopic and 9 normal subjects at baseline and at 90 min the administration. The parameters analyzed were the area and level of activation and a summed score (area × level). At baseline, the area of activation and summed score were significantly less in the amblyopic eyes compared to the dominant ones. Following levodopa ingestion, VA showed significant improvement along with a decrease in the area and level of activation with levodopa administration suggesting only a weak correlation between VA and fMRI changes in amblyopia.

Outcomes of oral levodopa/carbidopa combination therapy for management of amblyopia in various studies are summarized Table 1.

### Fluoxetine

Fluoxetine is a selective serotonin reuptake inhibitor, used as antidepressant. It acts by altering the cortical expression of various heat shock proteins and neurofilaments which are important for synaptic functions. Guest *et al.* demonstrated an increase in the percentage of synapses with split postsynaptic densities, a phenomenon characteristic of activity-dependent synaptic rearrangement on electron microscopic analysis.<sup>[76]</sup> Maya Vetencourt *et al.* showed that chronic administration of fluoxetine promotes the recovery of visual functions in adult amblyopic animals by reducing the intracortical inhibition and increasing the expression of brain-derived neurotrophic factor in the visual cortex, both of which are prevented by cortical administration of diazepam.<sup>[77]</sup>

Fluoxetine can have various side effects such as irritability, behavioral changes, restlessness, and agitation. This drug should be prescribed with caution in patients with impaired liver and renal function, in case of diabetes and bipolar disorders.

### GABA antagonists

Monocularly deprived experimental animals have been shown to have lack of responsiveness to visual stimulation of the deprived eye. Various experimental studies have been conducted to establish the possible etiology.

Duffy *et al.*<sup>[78]</sup> evaluated various agents to reverse the effects of monocular deprivation including GABA

antagonists such as bicuculline, picrotoxin, and naloxone, glycine antagonist such as strychnine, chloride channel blockers such as ammonium ion and cholinesterase inhibitor, physostigmine. The drugs were administered through intravenous route. The study found that drugs with GABA antagonistic action were effective in restoring neuronal responsiveness in the deprived eye. Bicuculline restored binocularity in 50% of the visual cortical neurons tested and naloxone in up to 36% neurons. The receptive fields of both eyes were found normal after the drug administration. Ammonium ion also restored binocularity in 27% of neurons tested, but with grossly abnormal receptive fields. Other agents including strychnine and physostigmine failed to restore binocularity. The study concluded that GABA inhibition may contribute to the cortical effects since only the drugs with GABA antagonistic activity were able to restore binocularity.

In another experimental study done by Burchfiel and Duffy,<sup>[79]</sup> involving 4 monocularly deprived cats, GABA antagonist, bicuculline was administered microiontophoretically in the cells present in the visual cortex at 5 months of age. The study found that bicuculline was able to restore input in 42% of cells in the deprived eye.

Mower *et al.*<sup>[80]</sup> also studied the role of microiontophoretic application of bicuculline in rearing cats with surgically induced strabismus and found that the agent was able to restore binocular responses in over 50% of monocularly deprived cells.

Various side effects are reported with this group of drugs. For example, bicuculline can cause behavioral changes, and ammonium ions can impair renal and hepatic function. Further, naloxone can be associated with severe allergic reaction and opioid withdrawal symptoms such as nausea, vomiting, diarrhea, running nose, tremor, shivering, and tachycardia. Physostigmine can cause seizure, cardiovascular collapse, bradycardia, bronchospasm, dyspnea, diaphoresis, diarrhea, hyperperistalsis, and hallucinations.

### Cytidine 5'-diphosphocholine, CDP-choline, or citicoline

Citicoline is an intermediate by-product involved in the biosynthesis of cell membrane phospholipids. Following systemic administration, it gets degraded into its constituents, cytidine and choline. Citicoline, once absorbed, crosses the blood-brain barrier and gets incorporated into the cell membrane phospholipids. It has been shown to increase the levels of norepinephrine and dopamine levels in CNS, offering neuroprotection in hypoxic and ischemic conditions. In addition, citicoline has been shown to restore the activity of



mitochondrial ATPase and membrane Na<sup>+</sup>/K<sup>+</sup> ATPase, thereby accelerating resorption of cerebral edema in various experimental models. It has been shown to inhibit apoptosis in neurodegenerative models, thereby potentiating neuroplasticity. Based on these neuromodulatory properties, it may prove beneficial in ocular conditions such as amblyopia and glaucoma. Organic brain disorders such as cerebral vascular disease, head trauma, cognitive disorders, posttraumatic coma and neurological deficits, postconcussional syndrome, acute ischemic cerebral vascular disease, senile cognitive impairment secondary to degenerative diseases and chronic cerebral vascular diseases, Parkinson disease, and drug addictions might also benefit from the chronic use of this drug. The drug is well tolerated with no significant systemic cholinergic effects.<sup>[81]</sup> However, some patients can have side effects such as insomnia, headache, diarrhea, low or high blood pressure, and nausea.

Porciatti *et al.*<sup>[82]</sup> measured contrast sensitivity and VEPs in amblyopic patients before and after the administration of CDP-choline (1 g/day intramuscular injection for 15 days) and the day after stopping treatment. The study found improvement in VA, contrast sensitivity, and VEP amplitudes in both normal and amblyopic eyes. Campos *et al.*<sup>[83]</sup> also reported a statistically significant improvement in VA following treatment with citicoline (1000 mg intramuscular administration, daily for 15 days) in older children, and found that significant visual improvement occurred in both amblyopic and sound eye, which remained stable for at least 4 months after stopping the treatment.

## Conclusion

The inadequacy of conventional occlusion treatment therapy and noncompliance of patients led to an insight into the role of pharmacological therapy for the management of amblyopia. Various studies have shown improvement in VA and VEP amplitudes with these agents in amblyopic children. Most of these agents are still in experimental stage though levodopa-carbidopa combination therapy has been widely studied in human amblyopes with good outcomes.

Although occlusion of the dominant eye is the best treatment modality for amblyopia, its efficacy decreases after 6 years of age. That's why, levodopa/carbidopa has been explored as an adjunct to conventional therapy and has been shown to have an immediate impact on VA; especially, in older age group, several studies to date have shown mixed results on the benefit of supplementing occlusion therapy with levodopa/carbidopa, although they have primarily studied children.

Levodopa may be considered as an adjunct to conventional occlusion therapy in cases with residual amblyopia and in older age group. Regression of effect after stoppage of therapy and occlusion amblyopia in younger patients ( $\leq 8$  years) remain matters of concern. Further studies are therefore needed to evaluate the full efficacy and side effect profile of these agents.

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## Conflicts of interest

The authors have no any conflicts of interest to declare.

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