

RESEARCH LETTERS

Pilot Study of Levodopa Dose as Treatment for Residual Amblyopia in Children Aged 8 Years to Younger Than 18 Years

Prior studies have evaluated levodopa as an adjunct to occlusion therapy in the treatment of amblyopia.¹⁻⁹ Improvement in visual acuity after completion of a course of levodopa has been reported; however, regression has occurred in several studies after stopping the medication.^{4,6} Reported adverse effects of levodopa were mild. They have included nausea, headache, fatigue, mood changes, emesis, dizziness, dry mouth, decreased appetite, and nightmares.

In preparation for conducting a phase 3 randomized trial, we conducted a prospective randomized pilot study to provide a preliminary assessment of the efficacy and safety of 2 doses of levodopa combined with daily occlusion therapy of the fellow eye in older children and teenagers with residual amblyopia from strabismus, anisometropia, or both.

Methods. Institutional review boards approved the study and written consent was obtained from parents. Eligibility criteria included age of 8 years to younger than 18 years, best-corrected visual acuity between 67 and 18 letters inclusive (approximately 20/50-20/400) in the amblyopic eye measured with the electronic Early Treatment Diabetic Reti-

nopathy Study method,¹⁰ best-corrected visual acuity of 78 letters or better (approximately $\geq 20/25$) in the fellow eye, and the presence or history of strabismus and/or anisometropia. At the time of enrollment, subjects were required to have been treated with daily patching for at least 2 hours per day and while on that regimen to have had stable visual acuity (defined as < 5 letters or 1 logMAR line of improvement since a previous visit ≥ 8 weeks earlier).

The study intervention consisted of continuing daily patching for 2 hours per day plus the addition of levodopa in 1 of 2 doses randomly assigned with equal probability (0.51 or 0.76 mg/kg 3 times a day, referred to as lower dose and higher dose, respectively). The lower dose has been used in most prior studies. The study medication was administered for 8 weeks with 1 additional week for tapering of treatment. Levodopa was prepared in capsules combined with carbidopa, 0.17 mg/kg 3 times a day. Carbidopa was combined with levodopa to reduce adverse effects associated with levodopa alone.

Follow-up visits occurred at 4 ± 1 weeks from randomization, 9 ± 1 weeks from starting levodopa treatment as the primary outcome, and 10 ± 2 weeks after stopping levodopa treatment. The assigned levodopa-carbidopa dose was continued until 1 week prior to the visit at 9 weeks, at which time it was tapered over 1 week. Following the visit at 9 weeks, patching alone was continued for 10 ± 2 weeks. At each visit, visual acuity was measured using the electronic Early Treatment Diabetic Retinopathy Study method.

Information about adverse effects of treatment was solicited during telephone calls conducted after 1, 2, and

Table. Best-Corrected Visual Acuity in the Amblyopic Eye

Visual Acuity in the Amblyopic Eye	No. (%)							
	Baseline, Randomization		Visit 1 ^a		Visit 2 ^a		Visit 3 ^a	
	Lower-Dose Group (n=16)	Higher-Dose Group (n=17)	Lower-Dose Group (n=16)	Higher-Dose Group (n=17)	Lower-Dose Group (n=16)	Higher-Dose Group (n=17)	Lower-Dose Group (n=15)	Higher-Dose Group (n=17)
Acuity score								
<20/100, or <47 letters	2 (13)	5 (30)	2 (13)	4 (24)	2 (13)	5 (30)	2 (13)	5 (30)
20/100, or 47-52 letters	2 (13)	0	2 (13)	1 (6)	2 (13)	0	0	1 (6)
20/80, or 53-57 letters	4 (25)	6 (35)	1 (6)	3 (18)	1 (6)	1 (6)	3 (20)	2 (12)
20/63, or 58-62 letters	4 (25)	5 (29)	4 (25)	5 (29)	3 (19)	5 (29)	4 (27)	3 (18)
20/50, or 63-67 letters	4 (25)	1 (6)	4 (25)	3 (18)	4 (25)	3 (18)	2 (13)	6 (35)
20/40, or 68-72 letters	0	0	3 (19)	1 (6)	3 (19)	2 (12)	1 (7)	0
20/32, or 73-77 letters	NA	NA	0	0	1 (6)	1 (6)	3 (20)	0
Letter score								
Mean (SD)	56.2 (8.8)	50.5 (12.2)	59.1 (9.2)	54.3 (12.9)	59.9 (9.7)	56.5 (12.7)	60.6 (11.1)	53.9 (11.4)
Approximate Snellen equivalent	20/80	20/100	20/63	20/80	20/63	20/80	20/63	20/80
Change from baseline								
≥ 15 letters worse			0	0	0	0	0	0
10-14 letters worse			0	0	0	0	0	0
5-9 letters worse			0	0	0	1 (6)	0	1 (6)
Within ± 4 letters			11 (69)	9 (53)	9 (56)	5 (29)	7 (47)	8 (47)
5-9 letters better			5 (31)	7 (41)	5 (31)	6 (35)	6 (40)	7 (41)
10-14 letters better			0	1 (6)	2 (13)	4 (24)	2 (13)	1 (6)
≥ 15 letters better			0	0	0	1 (6)	0	0
Letter change, mean (SD)			2.9 (2.8)	3.8 (3.6)	3.8 (3.5)	6.1 (5.6)	4.9 (3.7)	3.5 (4.7)
95% Confidence interval			1.4-4.4	2.0-5.7	1.9-5.6	3.2-8.9	2.9-7.0	1.1-5.9

Abbreviation: NA, not applicable.

^aVisit 1 took place 4 ± 1 weeks after starting levodopa; visit 2 took place 9 ± 1 weeks after starting levodopa; and visit 3 took place 10 ± 2 weeks after stopping levodopa.

Investigators and Clinical Sites Participating in This Protocol

Sites are listed in order by number of patients enrolled in the study. Personnel are listed as investigator (I), coordinator (C), and visual acuity examiner (V).

Don L. Bremer (I), David L. Rogers (I), Rae R. Fellows (C), Amy J. Wagner (C), and Laura J. Shenberger (V), Pediatric Ophthalmology Associates, Inc, Columbus, Ohio (5 patients); Maynard B. Wheeler (I) and Caroline C. Fang (C), Concord Eye Care, PC, Concord, New Hampshire (5 patients); Nicholas A. Sala (I) and Rhonda M. Hodde (C), Pediatric Ophthalmology of Erie, Erie, Pennsylvania (4 patients)*; Patricia L. Davis (I) and Katie R. Hulett (C), Progressive Eye Care, Lisle, Illinois (4 patients); Darren L. Hoover (I) and Pamela A. Huston (C), Everett and Hurite Ophthalmic Association, Cranberry Township, Pennsylvania (3 patients); Darron A. Bacal (I), Donna Martin (C), Kelly D. Moran (C), and Jennifer A. Coyne (V), Eye Physicians & Surgeons, PC, Milford, Connecticut (3 patients); Donny W. Suh (I), Autumn Swallow (C), Amy J. Dix (C), Lisa M. Fergus (V), Rhonda J. Countryman (V), and Susan K. Hayes (V), Wolfe Clinic, West Des Moines, Iowa (3 patients); Daniel M. Laby (I), Beth G. Harper (C), and Ricky Laby (C), Daniel M. Laby, MD, Sharon, Massachusetts (2 patients); David G. Morrison (I) and Lisa A. Fraine (C), Vanderbilt Eye Center, Nashville, Tennessee (1 patient); Matthew D. Gearing (I), Doreen M. Francis (C), Lynne M. Addams (V), and Dan A. Castillo (V), University of Rochester Eye Institute, Rochester, New York (1 patient)*; Stephen R. Glaser (I), Monica Pacheco (I), Tracey L. Coussens (C), and Noga Senderowitsch (C), Stephen R. Glaser, MD, PC, Rockville, Maryland (1 patient); and C. Scott Atkinson (I), Pearlana K. Hamlet (C), and Crystal L. Trythall (C), St John's Clinic—Eye Specialists, Springfield, Missouri (1 patient).

*Center received support for this project from an unrestricted grant from Research to Prevent Blindness Inc, New York, New York.

PEDIG Coordinating Center

Raymond T. Kraker (director), Roy W. Beck, Nicole M. Boyle, Christina M. Cagnina-Morales, Debora A. Cagnina, Danielle L. Chandler, Laura E. Clark, Elise R. Diamond, Quayleen Donahue, Brooke P. Fimbel, Nicole C. Foster, Heidi A. Gillespie, Brett M. Kaminski, Elizabeth L. Lazar, Stephanie V. Lee, Lee Anne Lester, B. Michele Melia, Pamela S. Moke, Michael J. Phillips, Diana E. Rojas, and Sydney L. Shrader.

National Eye Institute, Bethesda, Maryland

Donald F. Everett.

PEDIG Executive Committee

Jonathan M. Holmes (chair), Darron A. Bacal (2009), Roy W. Beck, Eileen E. Birch, Stephen P. Christiansen, Susan A. Cotter, Donald F. Everett, Darren L. Hoover, Pamela A. Huston, Raymond T. Kraker, Katherine A. Lee (2008-2009), Noelle S. Matta (2008-2009), David G. Morrison, Michael X. Repka, Robert P. Rutstein (2009), Nicholas A. Sala (2009), Mitchell M. Scheiman (2008), and David K. Wallace.

PEDIG Data and Safety Monitoring Committee

Marie Diener-West (chair), John D. Baker, Barry R. Davis, Velma Dobson, Donald F. Everett, Dale L. Phelps, Stephen W. Poff, Richard A. Saunders, and Lawrence Tychsen.

6 weeks and at each visit during treatment. An adverse event was defined as any untoward medical occurrence in a study subject and was reported even if it was considered unrelated to the study treatment. Subjects and study personnel were masked to treatment assignment. The entire protocol is available at <http://www.pedig.net>.

Results. Thirty-three subjects were randomized, with 16 assigned to the lower-dose group and 17 assigned to the higher-dose group. The mean (SD) age was 11 (2) years, with 22 subjects (67%) younger than 12 years; 19 subjects (58%) were female and 31 (94%) were white. The mean (SD) best-corrected visual acuity in the amblyopic eye was 56 (9) letters in the lower-dose group (about 20/80) and 51 (12) letters in the higher-dose group (about 20/100). Further details on the baseline characteristics appear in eTable 1 (<http://www.archophthalmol.com>).

The visits at 4 and 9 weeks were completed by all subjects. The mean time after starting levodopa treatment to completion of the primary outcome visit was 8.4 weeks (range, 6.3-13.4 weeks). The long-term outcome visit 10 weeks after stopping levodopa treatment was completed by all but 1 subject in the lower-dose group. The

mean time from stopping levodopa treatment was 9.8 weeks (range, 8.0-13.6 weeks).

Adherence to the medication regimen was evaluated by counting capsules in the returned medication bottles; 14 of 16 subjects (88%) in the lower-dose group and 15 of 17 subjects (88%) in the higher-dose group had taken 90% or more of the prescribed doses. Eleven of 16 subjects (69%) in the lower-dose group and 15 of 17 subjects (88%) in the higher-dose group were judged by the investigator to have adhered to the prescribed patching regimen. Three of the 4 subjects not compliant with at least 90% of prescribed doses were also judged to not be compliant with patching. However, the small number of subjects precludes any further analysis.

The mean improvement in visual acuity in the amblyopic eye from baseline to the primary outcome visit at 9 weeks was +4 (±4) letters in the 16 subjects in the lower-dose group and +6 (±6) letters in the 17 subjects in the higher-dose group (mean difference between groups, -2 letters; 95% confidence interval, -6 to +1) (**Table**). An improvement of 10 or more letters was noted in 2 (13%) and 5 (29%) of the subjects in the lower- and higher-dose groups, respectively. At the outcome examination at 9 weeks, on average the fellow eye improved 0

letters in the higher-dose group and 1 letter in the lower-dose group.

At the visit 10±2 weeks after stopping the levodopa treatment, the mean change in visual acuity in the amblyopic eye from baseline was +5 (±4) letters in the lower-dose group and +4 (±5) letters in the higher-dose group.

Levodopa-carbidopa was not discontinued by any subject during the 9-week dosing regimen. Adverse events were reported for 8 of 16 subjects (29 events) in the lower-dose group and 11 of 17 subjects (26 events) in the higher-dose group (eTable 2). No adverse events were considered serious. Headaches were reported by 6 subjects; a cold, upper respiratory tract infection, and cough were reported by 6; rash was reported by 4; and nausea and vomiting were reported by 3.

Comment. We enrolled a small cohort to gain experience with the drug, define the treatment dose for a future trial, and develop study procedures. The results suggested that levodopa-carbidopa therapy for residual amblyopia in older children and teenagers is well tolerated and may improve visual acuity. There was a suggestion of partial regression of the improvement in visual acuity after treatment was discontinued. No serious adverse effects were noted. Headache and nausea were infrequent. Without a patching-only control group, no conclusions about the efficacy, safety, or frequency of adverse effects associated with this treatment can be made. A placebo-controlled trial is necessary to determine whether levodopa can successfully augment occlusion therapy in the treatment of amblyopia.

Michael X. Repka, MD
Raymond T. Kraker, MSPH
Roy W. Beck, MD, PhD
C. Scott Atkinson, MD
Darron A. Bacal, MD
Don L. Bremer, MD
Patricia L. Davis, MD
Matthew D. Gearinger, MD
Stephen R. Glaser, MD
Darren L. Hoover, MD
Daniel M. Laby, MD
David G. Morrison, MD
David L. Rogers, MD
Nicholas A. Sala, DO
Donny W. Suh, MD
Maynard B. Wheeler, MD

for the Pediatric Eye Disease Investigator Group

Author Affiliations: Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore (Dr Repka) and Stephen R. Glaser, MD, PC, Rockville (Dr Glaser), Maryland; Jaeb Center for Health Research, Tampa, Florida (Mr Kraker and Dr Beck); St John's Clinic—Eye Specialists, Springfield, Missouri (Dr Atkinson); Eye Physicians & Surgeons, PC, Milford, Connecticut (Dr Bacal); Pediatric Ophthalmology Associates, Inc, Columbus, Ohio (Drs Bremer and Rogers); Progressive Eye Care, Lisle, Illinois (Dr Davis); University of Rochester Eye Institute, Rochester, New York (Dr Gearinger); Everett and Hurite Ophthalmic Association, Cranberry Township (Dr

Hoover) and Pediatric Ophthalmology of Erie, Erie (Dr Sala), Pennsylvania; Daniel M. Laby, MD, Sharon, Massachusetts (Dr Laby); Vanderbilt Eye Center, Nashville, Tennessee (Dr Morrison); Wolfe Clinic, West Des Moines, Iowa (Dr Suh); and Concord Eye Care, PC, Concord, New Hampshire (Dr Wheeler).

Correspondence: Dr Repka, c/o Jaeb Center for Health Research, 15310 Amberly Dr, Ste 350, Tampa, FL 33647 (pedig@jaeb.org).

Group Members: The members of the Pediatric Eye Disease Investigator Group (PEDIG) participating in the study are listed on page 1216.

Financial Disclosure: None reported.

Funding/Support: This study was supported through cooperative agreement EY11751 from the National Eye Institute.

Trial Registration: clinicaltrials.gov Identifier: NCT00789672

Online-Only Material: The eTables are available at <http://www.archophthalmol.com>.

Additional Information: This study was conducted under Investigational New Drug registration 103617 from the US Food and Drug Administration.

1. Leguire LE, Walson PD, Rogers GL, Bremer DL, McGregor ML. Longitudinal study of levodopa/carbidopa for childhood amblyopia. *J Pediatr Ophthalmol Strabismus*. 1993;30(6):354-360.
2. Leguire LE, Walson PD, Rogers GL, Bremer DL, McGregor ML. Levodopa/carbidopa treatment for amblyopia in older children. *J Pediatr Ophthalmol Strabismus*. 1995;32(3):143-151.
3. Leguire LE, Narius TM, Rogers GL, Bremer DL, McGregor ML. Long-term follow-up L-dopa treated amblyopic children. *Invest Ophthalmol Vis Sci*. 1996;37(3):S941.
4. Leguire LE, Komaromy KL, Narius TM, Rogers GL. Long-term follow-up of L-dopa treatment in children with amblyopia. *J Pediatr Ophthalmol Strabismus*. 2002;39(6):326-330.
5. Gottlob I, Wizov SS, Reinecke RD. Visual acuities and scotomas after 3 weeks' levodopa administration in adult amblyopia. *Graefes Arch Clin Exp Ophthalmol*. 1995;233(7):407-413.
6. Mohan K, Dhankar V, Sharma A. Visual acuities after levodopa administration in amblyopia. *J Pediatr Ophthalmol Strabismus*. 2001;38(2):62-67.
7. Procianny E, Fuchs FD, Procianny L, Procianny F. The effect of increasing doses of levodopa on children with strabismic amblyopia. *J AAPOS*. 1999;3(6):337-340.
8. Leguire LE, Rogers GL, Walson PD, Bremer DL, McGregor ML. Occlusion and levodopa-carbidopa treatment for childhood amblyopia. *J AAPOS*. 1999;2(5):257-264.
9. Bhartiya P, Sharma P, Biswas NR, Tandon R, Khokhar SK. Levodopa-carbidopa with occlusion in older children with amblyopia. *J AAPOS*. 2002;6(6):368-372.
10. Beck RW, Moke PS, Turpin AH, et al. A computerized method of visual acuity testing: adaptation of the early treatment of diabetic retinopathy study testing protocol. *Am J Ophthalmol*. 2003;135(2):194-205.

Plus Disease in Retinopathy of Prematurity: Quantitative Analysis of Standard Published Photograph

Plus disease is defined as abnormality of the posterior retinal vessels in which the arterial tortuosity and venous dilation meet or exceed those of a standard photograph selected by expert consensus in the 1980s.^{1,2} This method has limitations, and studies have suggested that interexpert agreement in plus disease diagnosis is variable.³ Magnification of the standard photograph is larger than that of indirect ophthalmoscopy, and peripheral vessels are not visible in the narrow field of view. It is also unclear which vessels cli-