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Does levodopa improve vision in albinism? Results of a randomized, controlled clinical trial

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Abstract

Background—Dopamine is an intermediate product in the biosynthesis of melanin pigment, which is absent or reduced in albinism. Animal research has shown that supplying a precursor to dopamine, levodopa, may improve visual acuity in albinism by enhancing neural networks. This study examines the safety and effectiveness of levodopa on best-corrected visual acuity in human subjects with albinism.

Design—Prospective, randomized, placebo-controlled, double-masked randomized clinical trial conducted at the University of Minnesota

Participants—45 subjects with albinism

Methods—Subjects with albinism were randomly assigned to one of three treatment arms: levodopa 0.76 mg/kg with 25% carbidopa, levodopa 0.51 mg/kg with 25% carbidopa, or placebo and followed for 20 weeks, with best-corrected visual acuity measured at enrollment, and at weeks 5, 10, 15, and 20 after enrollment. Side effects were recorded with a symptom survey. Blood was drawn for genotyping.

Main Outcome Measures—Side effects and best-corrected visual acuity 20 weeks after enrollment.

Results—All subjects had at least one mutation found in a gene known to cause albinism. Mean age was 14.5 years (range: 3.5 to 57.8 years). Follow-up was 100% and compliance was good. Minor side effects were reported; there were no serious adverse events. There was no statistically

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significant improvement in best-corrected visual acuity after 20 weeks with either dose of levodopa.

Conclusions—Levodopa, in the doses used in this trial and for the time course of administration, did not improve visual acuity in subjects with albinism.

Keywords

albinism; levodopa; visual acuity; randomized controlled trial

Introduction

Oculocutaneous albinism (OCA) is an inherited disorder of melanin biosynthesis caused by mutations in genes that result in absent or reduced melanin pigment in the skin, hair, and eyes. Ocular features common to all types of OCA include reduced visual acuity, abnormal refractive errors, reduced or absent stereoacuity, nystagmus, iris transillumination, abnormal optic disc morphology, and foveal hypoplasia. Melanin biosynthesis is required for normal vision. The cause(s) of the spectrum of reduced visual acuity is incompletely understood, but is likely related to foveal morphology (McAllister et al), nystagmus (Kumar et al 2011; Hertle 2013),[1-3] mild optic nerve hypoplasia,[4] absent or reduced melanin pigment in the retinal pigment epithelium,[5,6] and misrouting of the retinostriate fibers.[7] Reduced visual acuity, improved somewhat with best refractive correction[8] and/or extraocular muscle surgery,[9-11] remains one of the most disabling aspects of the disorder. Vision loss results in difficulties in education, personal interactions with peers and family, and inability to drive.[12] Improving visual acuity by even a small amount has potential for substantial improvement in quality of life in these individuals with albinism.

OCA is associated with absent or severely reduced melanin biosynthesis in all melanocytes, whereas, individuals with ocular albinism (OA1), often produce more melanin pigment. The OA1 gene has been identified[13] and encodes a G-protein coupled receptor that was hypothesized to play a role in membrane trafficking and melanosome biogenesis.[14,15] DOPA is an intermediate product in the biosynthesis of melanin, reduction of which is speculated to account for the structural abnormalities in albinism.[16] The OA1 gene (GPR143) has been shown to be a ligand for L-DOPA,[17] leading to the hypothesis that DOPA signaling through GPR143 normally regulates retinal development and leads to normal vision. OA1 activation leads to increased Pigment Epithelium-Derived Factor (PEDF) secretion by the retinal pigment epithelium. In the absence of tyrosinase (as in OCA1A), there is reduced PEDF.[17] Therefore, PEDF secretion in the retina in vivo appears to be controlled by the OA1 receptor. Research[18] has shown that, in mice with absent tyrosinase, PEDF is reduced in culture. In vivo, PEDF is barely detectable in albino animals. In addition, data have shown that levodopa (L-DOPA) significantly enhances the number of retinal ganglia cells and outer nuclear layer in OA1 mice treated in utero (unpublished data). Furthermore, when L-DOPA provided to pregnant albino mice, L-DOPA accumulates in the retinal pigment epithelium of the murine fetuses; L-DOPA is normally absent in the embryonic murine albino retina and greatly reduced in the postnatal albino retina compared to pigmented retina.[19] While humans with OA1 would have a mutation in GPR143, those with OCA should have a normal GPR143 receptor. Levodopa (dihydroxyphenalanine) is a

precursor to dopamine and crosses the blood-brain barrier, whereas dopamine does not. Dopamine is normally present in the human amacrine and interplexiform cells,[20] and also in the visual cortex.[21] Such has led to the speculation that providing L-DOPA to individuals with OCA may lead to enhanced development or communication among neural networks.

We hypothesize that a key signal in neural networks is one of the chemical intermediaries in melanin biosynthesis, L-DOPA, the ligand for the GPR143 receptor. We designed a prospective, randomized clinical trial to determine if individuals with OCA who were treated with oral L-DOPA would tolerate the drug and show improvement in their best-corrected visual acuity (BCVA). This FDA-approved project is designed to prospectively evaluate the safety and efficacy of two doses of levodopa in improving BCVA of individuals with albinism, using a randomized, placebo-controlled, double-masked clinical trial at a single center.

Methods

This research followed the tenets of the Declaration of Helsinki. Written informed consent and Health Information Portability and Accountability (HIPAA) forms were signed by adult subjects and parents/guardians of subjects < age 18 after explanation of the study, potential side effects, and consequences. In addition, subjects age 8 and <18 signed assents after the study was discussed with them. The study was approved by the Institutional Review Board (IRB) at the University of Minnesota. Use of levodopa in the setting of this clinical trial is an off-label use of the medication, and was approved by the Food and Drug Administration (FDA; IND #106348). This study was registered on www.ClinicalTrials.gov (NCT01176435) prior to enrollment.

Study Design

Subjects aged 3 to 60 years with a clinical diagnosis of OCA were recruited from the Minnesota Lions Children's Eye Clinic at the University of Minnesota, Minneapolis, MN. Exclusion criteria included a diagnosis of OA1, plans to have extraocular surgery or to begin contact lens wear during the study, ongoing vision therapy, history of narrow angle glaucoma (or findings to suggest increased risk), known allergy to levodopa or carbidopa, history of dystonia, known liver or gastrointestinal disease, history of melanoma, psychological problems, plans to move so study participation could not be completed, previous treatment with levodopa, pregnancy, lactation, or plans to become pregnant during the study, ocular abnormalities other than those associated with albinism, no access to a telephone, medication for attention deficit disorder, attention deficient and hyperactivity disorder, or concurrent use of medications interfering with levodopa: oral iron supplements or vitamins with iron, anti-depressants, antihypertensives, phenothiazines, butyrophenones, risperidone, isoniazid, and non-specific monoamine oxidase inhibitors.

To determine sample size, test-retest reliability was assumed to be 0.04 logMAR (equivalent of approximately 2 letters), and standard deviation for a difference between baseline and 20 weeks of 0.56 logMAR (approximately 3 letters). Comparisons between the two drug doses were planned, in addition to placebo. Therefore, the Bonferroni-adjusted two-sided significance level is 0.05/3 = 0.0167. Fourteen subjects would be required in each of the

three groups to detect a one-line improvement in BCVA with 90% power. We chose to enroll 15 for each group to take potential drop-out into account.

In this single center clinical trial, subjects were randomly assigned to receive one of two oral doses of levodopa in solution (levodopa 0.76 mg/kg and 25% carbidopa given TID in the “high dose” group; levodopa 0.51 mg/kg and 25% carbidopa given TID in the “low dose” group) or placebo (solution given TID at a defined dose) and followed for 20 weeks. Carbidopa was added to levodopa to decrease potential levodopa-related side effects, as it reduces the peripheral metabolism of levodopa, lowering the amount of levodopa required for a treatment effect.[22] Because the stability of the levodopa/carbidopa solution could only be confirmed for 6 weeks, drug was re-supplied at each visit. Randomization was accomplished by the Investigational Drug Service at the University of Minnesota using the first (and original) generator, which randomizes each subject to a single treatment using the method of randomly permutated blocks with equal probability to one of two doses of levodopa or placebo. All subjects, parents/guardians, and examiners were masked to the treatment assignment. The treatment assignment was known only by the compounding pharmacy until all subjects had completed their final visit in the trial.

Each subject wore best refraction, determined by previous cycloplegic refraction, and binocular visual acuity was measured with the electronic Early Treatment for Diabetic Retinopathy Study method[23-25] by experienced testers who were certified by the Pediatric Eye Disease Investigator Group (PEDIG) for other studies; subjects were permitted to use their preferred head posture. Letters were preferred, but if a young subject could not match letters, the LEA symbols were allowed. Binocular acuity was used to avoid degradation of visual acuity with monocular occlusion or fogging that frequently occurs in individuals with nystagmus. Visits were scheduled at 5, 10, 15, and 20 weeks (+/- 1 week, at the same time of day, +/- one hour) after enrollment. Weight and vital signs were recorded at each visit, and menstruating females performed a pregnancy test at each visit. The assigned drug was gradually increased over week 1 and was tapered over one week following the 20 week visit. Subjects were instructed to refrigerate their study medication and to avoid taking it within 30 minutes of dairy products. Examination findings included the presence or absence of granular macular melanin pigment in the retinal pigment epithelium, as assessed with direct ophthalmoscopy or inspection of fundus photographs.[5,6]

If molecular testing had not been performed, blood was drawn for molecular testing, and DNA was isolated from blood at Marshfield Clinic Research Foundation for genetic analysis. Based on phenotype, patients were evaluated for mutations in the *TYR*, *OCA2*, *TYRP1*,*SLC45A2* (OCA1, OCA2, OCA3, and OCA4, respectively) by Sanger sequencing.[26-29] In addition, patients of African descent were screened for the previously identified 2.7 kb *OCA2* deletion.[30] DNA sequences were aligned and analyzed for mutations using DNASTAR Lasergene software (DNASTAR Inc., Madison, WI). Identified mutations were compared to the Albinism Database (http://albinismdb.med.umn.edu/) to determine novelty.

Compliance

Subjects (or parents/guardians) were required to keep a calendar which indicated if the assigned dose was given three times each day. In addition, subjects were instructed to return their bottle(s) of medicine at each visit. Residual volume in the bottle was measured to corroborate compliance recorded on the calendar. If the residual volume was within 10% of the expected amount (taking into account spillage, slight measurement errors, etc.) based on the doses recorded as given on the calendar, we arbitrarily concluded that the calendar was a reasonable estimate of compliance.

Safety and Efficacy Analyses

At each visit and at phone calls performed at weeks 1, 3, 7, 9, 13, 17, and 19, subjects (or parents/guardians) were queried regarding possible side effects with a symptom survey. Adverse events (dyskinesia, neuroleptic malignant syndrome, and any other untoward medical event, regardless of etiology) required report to the IRB and FDA.

This trial was designed to evaluate whether one or both doses of levodopa improved BCVA in individuals with albinism, compared to placebo dosing. The log of the minimum angle of resolution (logMAR) was computed, based on visual acuities measured with the electronic vision tester. The logMAR was assessed at the time of enrollment (Visit 0) and at visits 1, 2, 3, and 4. The change in LogMAR from baseline to visit 4 (primary outcome) was computed as logMAR(4:0) = logMAR(Visit 4) – logMAR(Visit 0). The ‘best’ value of logMAR in follow-up was computed as the minimum of logMAR(Visit 1), logMAR(Visit 2), logMAR(Visit 3), and logMAR(Visit 4), and the ‘best’ change was computed as logMAR(best:0) = logMAR(best) – logMAR(Visit 0). A positive value for logMAR outcomes corresponded to an increase in the mean angle of resolution, i.e., a worsening of the visual acuity. Conversely a visual acuity improvement from the enrollment visit to Visit 4 corresponded to a negative value for logMAR outcomes. The primary analysis of LogMAR(4:0) was a one-way analysis of variance, with treatment group as the factor of interest. A secondary analysis with logMAR(best:0) as the outcome variable was also evaluated. Additional analyses were conducted using analysis of covariance, with treatment group as the factor of interest, but also including the baseline covariates of gender, age in years, type of albinism, macular melanin, and pigmenting types of albinism (OCA1B, OCA2, and HPS-1 were considered pigmenting). Interactions of these covariates with treatment group were also examined. Lastly, a post-hoc analysis with analysis of covariance was made for age at enrollment of ≤14 years of age vs. >14 years of age. The effects of compliance (a post-randomization covariate) were analyzed as well. Results were considered significant if the associated p-values were less than 0.05. In the various secondary analyses, no adjustments were made for multiple comparisons.

Results

The 45 subjects with albinism completed all study visits within the protocol-defined window for each exam between November 2010 and June 2013. No data were missing. All wore refractive correction. All but one subject (who had BCVA tested with LEA symbols) had BCVA measured with letters (2 with HOTV, remainder with Sloan letters). Mean age was

14.5 years (range: 3.6 - 57.8 years) and 23 (51%) were female. Forty were white, 3 were Asian, and 2 were Black/African American. Study group characteristics are shown in Table 1 and Table 2 shows the characteristics of each group by randomization assignment. All subjects had at least one mutation in a gene known to cause albinism (Supporting Information - Table S1 lists these mutations). Table 3 shows the reported side effects. More symptoms were recorded in the first few weeks after enrollment. There were no serious adverse events and no subject withdrew from the study. Mean compliance rate was 96.4% (range 90.7-100%), based on calendar entries. Of recorded doses, 88% were corroborated to be within 10% of calculated usage based on residual volume. Of the 12% not corroborated as noted, half (n=9) were taking placebo, 22% (=4) were taking low dose, and 28% (n=5) were taking high dose levodopa/carbidopa.

Means and 95% confidence intervals for logMARs at each visit were displayed graphically by treatment group (Figure). We found no statistically significant difference in BCVA at enrollment to visit 4 (20 weeks) among the three treatment groups that included high and low doses of levodopa/carbidopa and placebo (Table 4). No significant differences were found from enrollment to best BCVA during the 20-week study (Table 5).

Discussion

Levodopa, a metabolic precursor to dopamine, is a neurotransmitter or neuromodulator known to be active at both retinal and central levels.[20, 21, 31] It is an accepted medical treatment for movement disorders, including Parkinson's disease, as it crosses the blood brain barrier, providing the neurotransmitter, dopamine, to the depleted stores in the corpus striatum. Levodopa is typically combined with carbidopa, a peripheral decarboxylase inhibitor, to reduce the peripheral metabolism of levodopa and increase the half-life.[22] Carbidopa reduces the required dose of levodopa to produce a treatment effect, also reducing side effects when larger doses are used. Levodopa and levodopa/carbidopa have also been used off-label in combination with patching therapy to treat amblyopia in the doses used in this clinical trial.[32-35] Both cortical and retinal mechanisms of action have been proposed for improvement in visual acuity, contrast sensitivity, scotomas, and pattern visual evoked potentials with levodopa administration.[31-33,36-39] We are not aware of other reports of the use of levodopa in individuals with albinism. Based on the research in mice indicating that levodopa administration provides an intermediary in melanin biosynthesis, we conducted a single center prospective, randomized, placebo controlled clinical trial using oral levodopa/carbidopa in a fixed ratio in subjects with albinism, in an attempt to improve BCVA. Two doses of levodopa were used, to determine efficacy and tolerability to side effects, and the trial was double masked. Both doses of levodopa were tolerated well with only minor side effects noted. The most common side effects were headache, loss of appetite, postural dizziness, dry mouth, and nausea, similar to studies of levodopa in individuals with amblyopia.[33,40,41] However, this trial failed to show a significant improvement in BCVA for subjects taking the higher or lower dose of levodopa/carbidopa. Animal research suggests that providing levodopa to pregnant animals may be the route to increase levodopa in the offspring.[19] However, because of placental transmission, caution has been advised in treating pregnant women with levodopa/carbidopa.[42]

There are several considerations for explaining the failure to find significant improvement in BCVA in individuals with albinism who were treated with levodopa in this clinical trial. Follow-up was excellent and compliance was good, likely not affecting outcome. While type of albinism and gender might not influence outcome of treatment, there is some suggestion that age might be related to successful treatment and it would have been desirable to have less age discordance across the studied groups. There was some selection bias in terms of type of albinism, gender, and age for each of the three arms of the study, as subjects with albinism were enrolled as a group and randomly assigned treatment without regard to these characteristics. For example, 67% in the high dose group had OCA1B, 53% in the low dose group had OCA2, and 47% in the placebo group had OCA1A. Similar findings were noted for gender and age. Children younger than age 3 were not enrolled due to the lack of available literature to predict safety when using levodopa. The mean BCVA at enrollment for the high dose group was .714 logMAR (~20/105), whereas it was .599 logMAR (~20/80) for the low dose group and .601 (~20/80) for the placebo group, indicating roughly equivalent enrollment acuities in the 3 studied groups. Other possibilities for lack of an effect beyond an absent effectiveness are dose of medication and sample size that is too small to detect a statistically significant effect.

The strengths of this study include the dosing based on body weight, standardized data collection, a motivated group of participants who complied with dosage prescribed and schedule of visits, a diagnosis of albinism confirmed by genotype, visits conducted at the same time of day to avoid bias, and good recruitment efforts within a single center for a disorder that occurs with a frequency of 1 in 18,000 individuals in the United States. The side effects reported were similar to previous studies using levodopa or levodopa/carbidopa for treatment of amblyopia.[33,40,41,43] Limitations of this trial are insufficient sample size, insufficient dosing, and/or distribution of ages of subjects enrolled, which included those with mature visual development, to detect an effect of levodopa, if present. Levodopa doses up to 3 mg/kg TID have been reported in studies of amblyopia in adults,[37] and single doses up to 4 mg/kg in children aged 4.67 to 14.92 years.[38,43,44] Interestingly, the initial studies of the effect of levodopa on Parkinson's disease[45,46] did not show a positive treatment effect until the dose of levodopa was increased.[47] Lastly, the normal maturation of vision in albinism[48] and test-retest variability need to be taken into account when judging the effect of treatment on a young population.

In conclusion, this randomized, controlled clinical trial with excellent follow-up found that both doses of levodopa were safe for both children and adults. Side effects were minor. The trial failed to show significant improvement in BCVA with treatment with either the higher or lower dose over 20 weeks in individuals with albinism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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This study is registered on www.ClinicalTrials.gov (NCT01176435).

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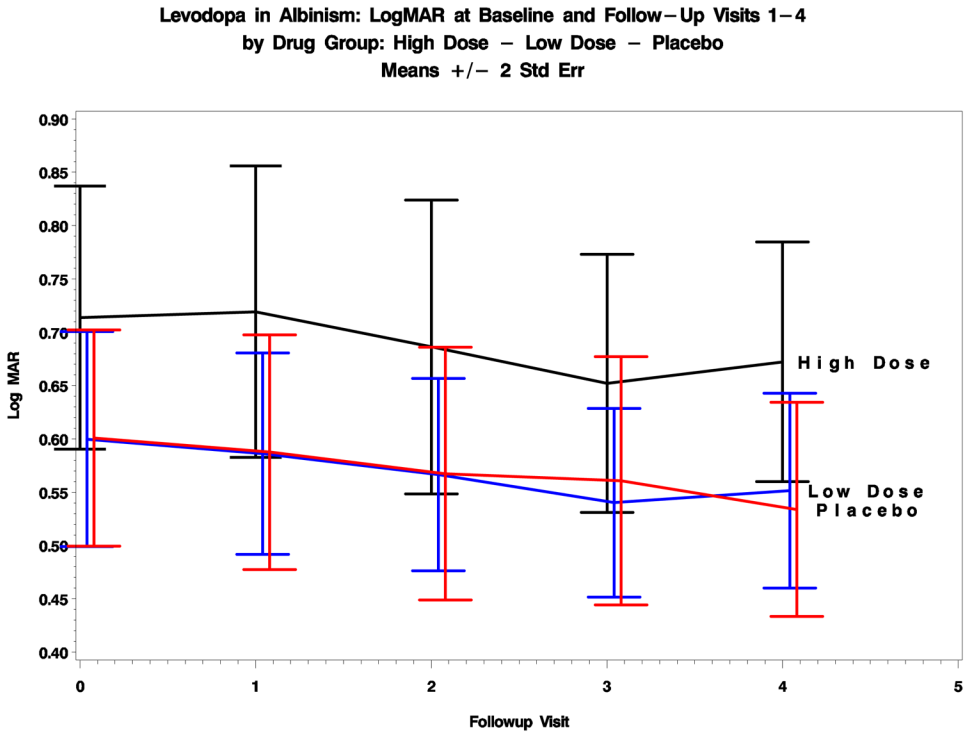

Figure 1.

Graphs shows mean BCVA at enrollment and at each of the following study visits, distributed over 20 weeks, for each of the study groups. The overlap of the error bars (2 standard errors) supports the lack of a statistically significant effect of levodopa on BCVA in albinism.

Table 1
Characteristics of clinical trial participants

Type of OCA[†] **n (%)**	**OCA1A 12 (26.7%)**	**OCA1B 18 (40%)**	**OCA2 14 (31.1%)**	**HPS-1 1 (2.2%)**
BCVA [‡] mean (range)				
BCVA at enrollment	20/106 (20/80-20/160)	20/85 (20/32-20/200)	20/75 (20/32-320)	20/100 20/100
BCVA at final visit	20/96 (20/63-20/160)	20/77 (20/32-20/160)	20/64 (20/32-20/250)	20/80 20/80
Best BCVA during trial	20/91 (20/63-20/160)	20/69 (20/25-20/160)	20/62 (20/32-20/250)	20/32 (20/32)
Genotype				
2 mutations	11	7	7	1
1 mutation	1	10	8	0
No mutations	0	0	0	0
Age yrs (range)	19.4 (6.3-57)	8.9 (3.5-26.7)	16.3 (3.96-49.3)	13.0
Gender (% Female)	58%	50%	43%	100%

[†]Oculocutaneous albinism

[‡]Best-corrected visual acuity

Table 2

Characteristics of clinical trial groups

Drug Assignment n (%)	**High Dose (0.76 mg/kg levodopa + 25% carbidopa) 15 (33.3%)**	**Low Dose (0.51 mg/kg levodopa + 25% carbidopa) 15 (33.3%)**	**Placebo (no drug) 15 (33.3%)**
Mean BCVA[†] at enrollment	20/103 (20/32-20/320)	20/87 (20/32-20/160)	20/87 (20/32-160)
Mean BCVA at final visit	20/94 (20/32-20/250)	20/71 (20/32-20/150)	20/68 (20/32-20/160)
Mean best BCVA during trial	20/85 (20/32-20/250)	20/66 (20/32-20/100)	20/67 (20/25-20/160)
Genotype			
2 mutations	8	9	9
1 mutation	7	6	6
Age yrs (range)	12.5 (3.5-57)	19.7 (4.0-49.3)	10.6 (4.0-18.1)
Gender	73% female	47% female	33% female
Type of OCA[‡] n (%)			
OCA1A	2 (13%)	3 (20%)	7 (47%)
OCA1B	10 (67%)	4 (27%)	4 (27%)
OCA2	2 (13%)	8 (53%)	4 (27%)
HPS-1	1 (7%)	0 (0%)	0 (0%)

[†]Best-corrected visual acuity

[‡]Oculocutaneous albinism

Table 3

Side effects by drug assignment

Symptom	High Dose (0.76 mg/kg levodopa + 25% carbidopa)	Low Dose (0.51 mg/kg levodopa + 25% carbidopa)	Placebo (0.76 (no drug)
Headache	9.1%	9.7%	0.6%
Loss of appetite	8.5%	1.8%	2.4%
Dizzy when stand up quickly	7.3%	0.6%	1.8%
Dry mouth	6.0%	1.2%	0.6%
Nausea	5.5%	1.2%	0.6%
Sleepiness	4.2%	1.2%	1.2%
Thirsty	3.6%	0	0.6%
Rash	2.4%	3.6%	1.2%
Fatigue	1.8%	1.2%	0.6%
Swelling of hand	0.6%	NR	NR
Hyperactivity	NR	NR	1.2%
Twitch/tremor	NR	NR	1.2%

Each parent/subject was queried a total of 11 times (with phone call or at office visit) about these specific side effects since the last query for each of the subjects over the 20 weeks in the study. The percent represents the number of times that a positive response was given. NR=not reported by any parent/subject. Additional symptoms in the query that were not reported by any parent/subject included blepharospasm, depression/feeling “down,” swelling of feet, and bizarre behavior.

Table 4

Results of regression analyses: outcome: baseline to visit 4 change in LogMAR

Model/Predictors		Coefficient	Std Error	p-value
Model 1:	$R^2 = 0.0255$			
	High-dose Levodopa	0.0256	0.2532	0.3177
	Low-dose Levodopa	0.0189	0.2532	0.4600
	(Default:Placebo)			
Model 2:	$R^2 = 0.0714$			
	High-dose Levodopa	0.0325	0.0278	0.2490
	Low-dose Levodopa	0.0283	0.0266	0.2941
	(Default: Placebo)			
	OCA1A	0.0353	0.0282	0.2183
	OCA1B	0.0226	0.0263	0.3946
	(Default: OCA2; HSP-1 omitted)			
Model 3:	$R^2 = 0.0391$			
	High-dose Levodopa	0.0323	0.0269	0.2368
	Low-dose Levodopa	0.0222	0.0258	0.3941
	(Default: Placebo)			
	Female Gender	-0.0168	0.0220	0.4500
Model 4:	$R^2 = 0.0816$			
	High-dose Levodopa	0.0231	0.0249	0.3593
	Low-dose Levodopa	0.0068	0.0260	0.7953
	(Default: Placebo)			
	Age, years	0.0013	0.0008	0.1213
Model 5:	$R^2 = 0.0612$			
	High-dose Levodopa	0.0274	0.0252	0.2829
	Low-dose Levodopa	0.0134	0.0255	0.6013
	(Default: Placebo)			
	Age <14	-0.0272	0.0218	0.2193

Table 5

Results of regression analyses: outcome: baseline to best logmar at any follow-up visit

Model/Predictors		Coefficient	Std Error	p-value
Model 1:	$R^2 = 0.0076$			
	High-dose Levodopa	-0.0132	0.0233	0.5750
	Low-dose Levodopa	-0.0055	0.0233	0.8128
	(Default: Placebo)			
Model 2:	$R^2 = 0.0233$			
	High-dose Levodopa	-0.0052	0.0261	0.8443
	Low-dose Levodopa	-0.0017	0.0250	0.9446
	(Default: Placebo)			
	OCA1A	0.0143	0.0265	0.5937
	OCA1B	-0.0072	0.0246	0.7713
	(Default: OCA2; HPS-1 omitted)			
Model 3:	$R^2 = 0.0707$			
	High-dose Levodopa	0.0000	0.0241	0.9992
	Low-dose Levodopa	.0010	0.0231	0.9643
	(Default: Placebo)			
	Female Gender	-0.0033	0.0197	0.1028
Model 4:	$R^2 = 0.0469$			
	High-dose Levodopa	0.0151	0.0231	0.5188
	Low-dose Levodopa	-0.0148	0.0241	0.5443
	(Default: Placebo)			
	Age, years	0.0010	0.0008	0.2007
Model 5:	$R^2 = 0.0426$			
	High-dose Levodopa	0.0115	0.0232	0.6219
	Low-dose Levodopa	0.0146	0.0235	0.6585
	(Default: Placebo)			
	Age <14	-0.0255	0.0200	0.2277