

Effects of L-DOPA Monotherapy on Psychomotor Speed and [^{11}C]Raclopride Binding in High-Risk Older Adults With Depression

Bret R. Rutherford, Mark Slifstein, Chen Chen, Anissa Abi-Dargham, Patrick J. Brown, Melanie W. Wall, Nora Vanegas-Arroyave, Yaakov Stern, Veronika Bailey, Emily Valente, and Steven P. Roose

ABSTRACT

BACKGROUND: A high-risk subgroup of older patients with depression has slowed processing and gait speeds. This study examined whether carbidopa/levodopa (L-DOPA) monotherapy increased dopamine availability, increased processing/gait speed, and relieved depressive symptoms.

METHODS: Adult outpatients with depression >59 years old underwent baseline [^{11}C]raclopride positron emission tomography followed by open L-DOPA for 3 weeks (1 week each of 150 mg, 300 mg, and 450 mg). Generalized estimating equations tested the pre- and post-L-DOPA differences in processing and gait speed measures, depressive symptoms, and reported side effects. The decrease in binding potential between the pre- and posttreatment scans indexed enhanced synaptic dopamine availability induced by L-DOPA treatment.

RESULTS: Thirty-six subjects participated (age, 75.3 ± 7.5 years; 44.4% male). Significant, dose-dependent increases in processing and gait speed were observed with L-DOPA (450-mg dose: processing speed factor score effect size = 0.41, $p = .001$; dual-task gait speed effect size = 0.43, $p = .002$). [^{11}C]raclopride decrease in binding potential was significantly different from 0 in sensorimotor ($t_{24} = -4.85$, $p < .001$) and associative striatum ($t_{24} = -2.52$, $p = .019$) but not in limbic striatum ($t_{24} = 0.265$, $p = .793$). Depressive symptoms decreased significantly on the Hamilton Rating Scale for Depression (effect size = -0.37 , $p = .002$). Dropout rate was 8.3%, and nausea was the most frequently reported side effect.

CONCLUSIONS: By enhancing availability of dopamine, L-DOPA improved processing and gait speed in older adults with depression and significantly decreased [^{11}C]raclopride binding in selected striatal subregions.

Keywords: Gait speed, Late-life depression, Levodopa, Positron emission tomography, Processing speed, Raclopride

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Depression occurring in older adults (i.e., major depressive disorder [MDD], persistent depressive disorder, and clinically significant subthreshold depressive symptoms—collectively referred to here as late-life depression [LLD]), is prevalent (1–3), disabling (4,5), and associated with high rates of completed suicide (6). LLD is among the foremost reversible risk factors for cognitive decline and the development of dementia (7,8), is frequently chronic and recurrent (9), and is often difficult to treat (10). Among the patients with LLD at highest risk of these adverse outcomes are those who manifest significant psychomotor slowing, often indexed by decreased processing speed and/or decreased gait speed. Decreased processing speed has been referred to as “the core cognitive deficit” in LLD (11) because it mediates performance on tests of nearly all cognitive domains (12), predicts poorer acute response to antidepressants (13), and increases risk for dementia (14) and dependence in activities of daily living (15).

Slowed gait speed leads to incident depression in older adults (16) and has been associated with a greater risk of falls (17), disability (18), and hospital admission (19). In older adults with depression who are otherwise healthy, the development of slowed gait speed increases mortality risk over 10-year follow-up by approximately 20% (16).

Even when treatment with antidepressant medication successfully reduces depressive symptoms, it often does not improve slowed processing speed (20) or restore cognitive functioning to normal levels of performance (21,22). No studies have investigated the effects of antidepressant treatment on older adults with depression with gait slowing. To develop urgently needed novel therapeutics, a reasonable approach is to target brain systems underlying the development and persistence of psychomotor slowing. Postmortem experiments and in vivo neuroimaging studies have implicated age-related dopaminergic decline in the development of slowing,

because aging is associated with reduced dopamine levels, decreased D_1/D_2 receptor density, and loss of dopamine transporters (23–25). Mesolimbic dopaminergic tone modulates processing speed in both humans and animal models (26), and decreased striatal dopamine transmission has been associated with decreased gait speed (27) and impaired balance (28). These age-associated declines in dopaminergic functioning are topographically distinct from the denervation pattern typical of Parkinson's disease (PD), being observed diffusely across the striatum rather than being predominantly posterior putaminal in location (29).

Multiple case series from the 1960s onward report improved depressive symptoms (particularly psychomotor retardation) with levodopa (L-DOPA) monotherapy or augmentation (30,31). L-DOPA is the immediate precursor of dopamine, is converted to dopamine in presynaptic dopaminergic nerve terminals, and enhances dopaminergic transmission in multiple brain regions. L-DOPA has been reported to relieve depressive symptoms in new-onset PD, improving symptoms in 90.3% of patients ($N = 31$) and resulting in a mean Hamilton Rating Scale for Depression (HRSD) decrease of 11.7 points in one study (32). As opposed to other dopaminergic interventions (i.e., dopamine receptor agonists and stimulants), a large amount of literature shows beneficial effects of L-DOPA on cognitive performance and gait in patients with PD (33,34), whereas the few available studies in elderly patients show minimal effects of dopamine agonists or stimulants. L-DOPA, especially at lower doses, is a safe and well-tolerated medication that is difficult to differentiate from placebo in terms of side effects (35), while adverse cardiac effects and impulsive behavior are important potential risks for stimulants and dopamine agonists, respectively.

The goal of the present combined clinical trial and positron emission tomography (PET) study was to examine whether monotherapy with L-DOPA increases dopamine release in the striatum, increases processing and gait speed, and reduces depressive symptoms in a sample of older adults with LLD and psychomotor slowing. We hypothesized that enrolled patients would demonstrate dose-dependent increases of at least moderate effect size (ES) in both processing speed and gait speed over the 3-week-duration open study. Furthermore, we anticipated that [^{11}C]raclopride binding potential (BP_{ND}) in the sensorimotor striatum measured before and after subacute L-DOPA administration would be significantly reduced owing to enhanced dopamine availability effectively competing with [^{11}C]raclopride for binding to the D_2 receptor. While the 3-week-duration study is briefer than most antidepressant trials, we were interested to determine whether significant change would occur in both rater-administered and self-reported depressive symptoms.

METHODS AND MATERIALS

Subjects

This study was conducted in the Adult and Late Life Depression Research Clinic at the New York State Psychiatric Institute and approved by the New York State Psychiatric Institute Institutional Review Board. All participants met eligibility criteria and signed informed consent for the study. Eligible subjects were adult outpatients ≥ 60 years of age who were

diagnosed with DSM-5 MDD, dysthymia, or depression not otherwise specified; had Center for Epidemiologic Studies—Depression Rating scale score ≥ 10 ; and had decreased gait speed (average walking speed over 15-foot course < 1 m/s). Subjects were excluded for substance abuse or dependence (excluding tobacco use disorder) within the past 12 months; history of psychosis, mania, or bipolar disorder; diagnosis of probable Alzheimer's disease, vascular dementia, or PD; Mini Mental Status Examination ≤ 24 , HRSD suicide item > 2 , or Clinical Global Impressions–Severity score of 7 at baseline; current treatment or treatment within the past 4 weeks with psychotropic or other medications known to affect dopamine; history of intolerance to L-DOPA; physical or intellectual disability adversely affecting ability to complete assessments; acute or severe medical illness; or mobility-limiting osteoarthritis, spine disease, or history of joint or spine surgery. Subjects undergoing neuroimaging procedures did not have contraindication to magnetic resonance imaging (MRI), inability to tolerate the scanning procedures, or history of significant radioactivity exposure.

Study Design and Assessments

At baseline, patients were screened for significant medical problems with a history and physical examination, blood tests, electrocardiogram, and urine toxicology. Vital signs were recorded at baseline and weekly thereafter. Following screening, participants who were eligible for neuroimaging procedures had pretreatment PET and MRI scans prior to a week-0 visit. Participants who were ineligible for PET and/or MRI scanning (e.g., on the basis of having MRI-incompatible metal in their body) returned 1 week after screening for week 0. Open L-DOPA treatment was initiated as described below and continued for the 3-week-duration study. For participants undergoing neuroimaging, posttreatment PET scans were scheduled to coincide with day 21 of the study insofar as was possible.

Processing and gait speed were assessed at screening, week 0, and weekly on initiation of L-DOPA treatment (i.e., weeks 1–3). Assessments were performed at approximately 1 PM to control for time-of-day effects and the duration since the last morning L-DOPA dose (anticipated to be 4 hours). Therefore, week 3 measures were performed before the midday L-DOPA dose to maintain consistency across study weeks in the timing of assessments relative to last L-DOPA dose. Multiple pre-L-DOPA assessments of processing and gait speed were conducted to control for practice effects, which generally occur between the first and second assessment and decline thereafter. Processing speed was assessed using the Digit Symbol test from the Wechsler Adult Intelligence Scale III (36) and the Pattern and Letter Comparison tests (37). A latent factor constructed from these three measures was chosen as the primary outcome measure for processing speed.

Gait speed was measured in m/s both as a single task in which study participants walked at their usual or normal speed on a 15-foot walking course, and as a dual task in which participants walked at their usual speed while naming as many animals as possible. Two trials (each, for single and dual tasks) were completed, and the final gait speed measurement was

recorded as the average of these two trials. Measuring gait speed while subjects perform one or more concurrent tasks (dual task) more accurately reflects the reality of physical functioning and may be a better predictor of fall risk than single-task measurements are (38). Thus, dual-task gait speed was chosen as the primary outcome measure for gait speed.

Other study measurements performed weekly included the 24-item HRSD, the 30-item Inventory of Depressive Symptoms—Self-Report, the Clinical Global Impressions—Severity and Improvement scales, a rating scale for treatment-emergent side effects, and weekly pill counts.

L-DOPA Administration

Taking into account L-DOPA's pharmacokinetics in the plasma as well as its pharmacodynamics in the central nervous system, we devised a dosing schedule allowing us to assess the effects and tolerability of three different L-DOPA doses (150 mg, 300 mg, and 450 mg). Subjects began taking 37.5 mg carbidopa/150 mg levodopa once daily (9 AM) at the week-0 appointment. After 1 week at this dosage, subjects were instructed to take 37.5 mg carbidopa/150 mg levodopa at 9 AM and 5 PM (twice daily). For the third week of treatment, subjects took 37.5 mg carbidopa/150 mg levodopa three times daily (9 AM, 12 PM, 5 PM). Participants were instructed to maintain the same timing of doses throughout the study. Based on published work using L-DOPA for PD, we expected effects on cognition and gait to be apparent at each dosing level within the first 24 hours of administration or dosage increase and then remain relatively stable (39,40). We allowed 1 week between dosage increases to ensure tolerability as per standard neurologic clinical practice and to permit L-DOPA effects on mood to be measured.

PET Scanning

Dynamically acquired [^{11}C]raclopride scans were performed on a Biograph mCT Flow (Siemens, Knoxville, TN), a hybrid PET-computed tomography scanner. Initially, a brief (<10-second) computed tomography scan of the head was acquired for attenuation correction. Following intravenous injection of [^{11}C]raclopride, emission data were collected in list mode for 60 minutes. List mode data were binned into a sequence of frames of increasing duration (from 20 seconds to 10 minutes) and reconstructed by filtered backprojection, with correction for attenuation, random coincidences, scatter time, and dead time, using manufacturer-provided software. High-resolution anatomical T1-weighted MRI scans were acquired for each subject, and PET data were coregistered to the MRIs using maximization of mutual information (SPM12, Wellcome Centre for Human Neuroimaging, London, UK). Regions of interest (ROIs) were applied to the MRIs and transferred to the PET emission data and included the sensorimotor striatum (SMST) (postcommissural putamen), associative striatum (AST) (whole caudate and precommissural putamen), and the limbic striatum (nucleus accumbens and the most ventral aspects of the precommissural caudate and putamen) as previously described (41). Additionally, an ROI was drawn on cerebellum as a reference tissue. ROI time activity curves were derived as the average activity in each ROI in each frame. The primary

outcome measure was BP_{ND} , the binding potential with respect to the nondisplaceable compartment (42), derived by the simplified reference tissue model (43). The effect of L-DOPA treatment was measured as the percentage difference in BP_{ND} ($\Delta\text{BP}_{\text{ND}}$) between the pre- and posttreatment scans: $\Delta\text{BP}_{\text{ND}} = 100\% \times [\text{BP}_{\text{ND}}(\text{posttreatment}) - \text{BP}_{\text{ND}}(\text{pretreatment})] / \text{BP}_{\text{ND}}(\text{pretreatment})$.

Statistical Analyses

Differences in baseline demographic and clinical characteristics between subjects receiving at least one dose of L-DOPA (i.e., the analyzed sample) and those lost to follow-up prior to taking a pill were compared using *t* tests or chi-squared tests. A latent factor analysis was conducted to create a processing speed factor from Digit Symbol, Pattern Comparison, and Letter Comparison test scores. Each outcome variable was collected at five time points (i.e., screening, week 0, and weeks 1–3) and modeled with a general linear model including a five-category fixed-effect predictor for time. Estimation was performed using generalized estimating equations to account for the correlated observations within person using an independent working correlation matrix. Dose effects were estimated and tested from this model by forming contrasts of means at each time point compared with at week 0. ESs were calculated by scaling the mean differences by the standard deviation of the measure at week 0. The 95% confidence intervals for the mean differences and the ESs and associated *p* values are presented to assess statistical significance. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC).

PET data were analyzed in the mixed model framework with ROIs as repeated measures and $\Delta\text{BP}_{\text{ND}}$ as dependent variable (SPSS version 24; IBM Corp., Armonk, NY). A critical value of $\alpha = .05$ was chosen as a significance level. To understand the relationship between changes in [^{11}C]raclopride binding and changes in processing and/or gait speed change, Spearman correlation coefficients were estimated between $\Delta\text{BP}_{\text{ND}}$ and the change in processing and gait speed tests for weeks 0 to 3.

RESULTS

Subject Disposition and Characteristics

The final CONSORT diagram for the study is shown in Supplemental Figure S1. Forty-seven subjects signed consent to participate in the study, of whom 11 were lost to follow-up prior to taking the study medication and were excluded from the analyses. As shown in Table 1, participants receiving L-DOPA had a mean age of 75.3 ± 7.5 years, were 44.4% male, and suffered from depressive symptoms at a level corresponding to syndromal MDD (i.e., mean baseline Center for Epidemiologic Studies—Depression Rating scale 22.5 ± 10.0 , where Center for Epidemiologic Studies—Depression Rating scale scores ≥ 16 are associated with the presence of MDD). Twenty-one subjects (58.3%) were diagnosed with MDD, 13 (36.1%) with depression not otherwise specified, and 2 (5.6%) with dysthymia. Most individuals suffered from chronic depression (self-reported mean duration current episode was over 10 years), and the average number of failed antidepressant medication trials in the current depressive episode was 1.4 ± 2.2 . Mean baseline processing speed as measured by

Table 1. Baseline Characteristics of Analyzed Study Subjects (*n* = 36) and Those Lost to Follow-up Before Receiving L-DOPA

Characteristic	Received L-DOPA (<i>n</i> = 36)	Did Not Receive L-DOPA (<i>n</i> = 11)	<i>p</i> Value
Age, Years	75.3 ± 7.5	72.1 ± 6.6	.21
Sex, Male	16 (44.4)	2 (18.1)	.12
Ethnicity, Hispanic	7 (19.4)	2 (18.1)	.93
Race			.53
Asian	1 (2.8)	0	
Black	14 (38.9)	3 (27.3)	
White	18 (50.0)	8 (72.7)	
Other	3 (8.3)	0	
Diagnosis			.46
Major depressive disorder	21 (58.3)	8 (72.7)	
Dysthymia	2 (5.6)	1 (9.1)	
Depression NOS	13 (36.1)	2 (18.2)	
Duration of Current Depressive Episode, Weeks	528.9 ± 854.6	702.4 ± 1040.4	.60
Prior Antidepressant Medications, Number	1.4 ± 2.2	1.2 ± 1.3	.77
Hamilton Rating Scale for Depression, 24 Items	15.5 ± 6.0	19.4 ± 4.2	.056
Inventory of Depressive Symptoms—Self-Report	26.4 ± 12.6	30.5 ± 12.4	.47
Clinical Global Impressions—Severity	3.3 ± 0.7	3.7 ± 0.8	.11
Center for Epidemiologic Studies—Depression	22.5 ± 10.0	24.9 ± 8.7	.47

Values are mean ± SD or *n* (%).

L-DOPA, levodopa; NOS, not otherwise specified.

the Digit Symbol test was 31.9 ± 9.7 , which is >1 SD below norms for individuals having similar age, sex, and education characteristics (44). Mean dual-task gait speed was 0.7 ± 0.2 , which is >1 SD below the age-adjusted norm for 74 years of age (closest published norm to the mean age of the current sample) (45). No significant differences were observed between subjects receiving L-DOPA (i.e., the analyzed sample) and those lost to follow-up during the screening process.

Effects on Psychomotor Speed and Depressive Symptoms

Significant practice effects were observed from screening to week 0 (see Supplemental Table S1) on Digit Symbol ($ES = 0.55$, 95% confidence interval [CI] = 0.35 to 0.75, $p < .001$), the composite processing factor ($ES = 0.28$, 95% CI = 0.11 to 0.45, $p = .001$), single-task gait speed ($ES = 0.46$, 95% CI = 0.18 to 0.73, $p = .001$), and dual-task gait speed ($ES = 0.22$, 95% CI = 0.03 to 0.40, $p = .022$). Consistent with the pattern of diminishing practice effects that is frequently observed with repeated testing, a smaller amount of improvement occurred from week 0 to week 1 on these measures despite the initiation of L-DOPA.

As hypothesized, L-DOPA treatment was associated with dose-dependent increases in both processing speed and gait

speed on multiple outcome measures (see Table 2). For the 450-mg L-DOPA dose, statistically significant improvements of moderate ES or greater relative to week 0 pretreatment were observed on the primary outcome measures for both processing speed (processing speed factor $ES = 0.41$, 95% CI = 0.24 to 0.58, $p < .001$) and gait speed (dual-task $ES = 0.43$, 95% CI = 0.16 to 0.70, $p = .002$). Plots depicting individual participants' change on the Digit Symbol and dual-task gait speed measures as well as means and 95% CIs at each time point are shown in Supplemental Figures S2 and S3, respectively. A significant decrease in depressive symptoms was observed from week 0 pretreatment to week 3 (450 mg) on the HRSD ($ES = -0.37$, 95% CI = -0.61 to -0.14 , $p = .002$) and Inventory of Depressive Symptoms—Self-Report ($ES = -0.54$, 95% CI = -0.74 to -0.34 , $p < .001$). Remission rate defined by final HRSD < 10 was 48.5%.

Effects on [^{11}C]Raclopride Binding

Ten subjects underwent neuroimaging procedures. One subject had to be excluded immediately after undergoing PET scanning when it became known that the subject had covertly continued taking a prohibited psychotropic medication (duloxetine) during the pretreatment PET scan and early phases of the clinical trial. There was no significant difference in injected activity between the pre- and posttreatment scans (pretreatment: 11.2 ± 2.3 mCi, posttreatment: 10.0 ± 1.5 mCi, $p = .30$). There was a small but significant difference in injected cold raclopride mass between conditions (pretreatment: 2.3 ± 0.9 μg , posttreatment: 1.5 ± 0.6 μg , $p = .04$), but all mass was within the tracer dose range. Figure 1 shows BP_{ND} and $\Delta\text{BP}_{\text{ND}}$ across the three striatal subregions. BP_{ND} was uncorrelated across ROIs ($|r| < .14$, $p > .6$ in all cases) and was significantly different from 0 in SMST ($t_{24} = -4.85$, $p < .001$) and AST ($t_{24} = -2.52$, $p = .019$) but not in limbic striatum ($t_{24} = 0.265$, $p = .793$).

Exploratory analyses examined relationships between improvements in processing and/or gait speed and [^{11}C]raclopride $\Delta\text{BP}_{\text{ND}}$ in corresponding brain regions (i.e., AST and processing speed, SMST and gait speed). These revealed that improvement on the processing speed factor was significantly correlated with reduced BP_{ND} in the AST ($r_7 = -.75$, $p = .02$), while increased single-task gait speed was correlated at a trend level with decreased BP_{ND} in the SMST ($r_7 = -.63$, $p = .07$). No significant correlations were observed between [^{11}C]raclopride $\Delta\text{BP}_{\text{ND}}$ and depressive symptoms measured by the HRSD or Inventory of Depressive Symptoms—Self-Report.

L-DOPA Adverse Effects and Attrition

The overall dropout rate was 8.3%, with 5.6% of subjects dropping out owing to adverse effects of L-DOPA. Thirty of the total 36 analyzed subjects reached the final L-DOPA dose of 450 mg. As shown in Table 3, nausea was the most frequently reported treatment-emergent side effect. The frequency of subjects reporting nausea decreased over the course of the trial, from 19.4% of subjects reported for 150-mg L-DOPA, to 17.1% for 300-mg L-DOPA, and 9.1% for 450-mg L-DOPA. The only other side effects reported by more than one subject were insomnia (150-mg/300-mg/450-mg L-DOPA: 8.3%/5.7%/3.0%) and headache (150-mg/300-mg/450-mg L-DOPA:

Table 2. Change in Slowing and Depressive Symptoms Before and After L-DOPA Treatment

Assessment	Visit	Dose	Mean $\pm$ SD	Mean Change $\pm$ SE	Mean Change, 95% CI	ES $\pm$ SE	ES, 95% CI	p Value
Processing Speed Measures								
Digit Symbol	Screening		31.86 $\pm$ 9.69					
	Week 0	Pretreatment	37.19 $\pm$ 8.73					
	Week 1	150 mg	38.89 $\pm$ 9.43	1.69 $\pm$ 0.77	0.19 to 3.20	0.19 $\pm$ 0.09	0.02, 0.37	.027
	Week 2	300 mg	41.09 $\pm$ 8.54	3.89 $\pm$ 0.88	2.17 to 5.62	0.45 $\pm$ 0.10	0.25, 0.64	<.0001
	Week 3	450 mg	41.42 $\pm$ 9.56	4.23 $\pm$ 0.94	2.38 to 6.08	0.48 $\pm$ 0.11	0.27, 0.70	<.0001
Pattern Comparison	Screening		24.72 $\pm$ 5.42					
	Week 0	Pretreatment	25.39 $\pm$ 5.57					
	Week 1	150 mg	26.89 $\pm$ 4.87	1.5 $\pm$ 0.63	0.27 to 2.73	0.27 $\pm$ 0.11	0.05, 0.49	.017
	Week 2	300 mg	27.29 $\pm$ 5.70	1.91 $\pm$ 0.69	0.55 to 3.27	0.34 $\pm$ 0.12	0.10, 0.59	.006
	Week 3	450 mg	27.61 $\pm$ 4.94	2.22 $\pm$ 0.56	1.12 to 3.32	0.40 $\pm$ 0.10	0.20, 0.60	<.0001
Letter Comparison	Screening		14.36 $\pm$ 4.73					
	Week 0	Pretreatment	15.00 $\pm$ 4.53					
	Week 1	150 mg	15.33 $\pm$ 4.64	0.33 $\pm$ 0.52	−0.69 to 1.36	0.07 $\pm$ 0.12	−0.15, 0.30	.52
	Week 2	300 mg	15.65 $\pm$ 4.66	0.65 $\pm$ 0.5	−0.33 to 1.62	0.14 $\pm$ 0.11	−0.07, 0.36	.19
	Week 3	450 mg	15.69 $\pm$ 4.54	0.69 $\pm$ 0.54	−0.37 to 1.74	0.15 $\pm$ 0.12	−0.08, 0.38	.20
Processing Factor, Composite of DS, PC, and LC	Screening		−2.87 $\pm$ 7.05					
	Week 0	Pretreatment	−0.91 $\pm$ 6.79					
	Week 1	150 mg	0.63 $\pm$ 6.33	1.53 $\pm$ 0.58	0.40 to 2.67	0.23 $\pm$ 0.09	0.06, 0.39	.008
	Week 2	300 mg	1.54 $\pm$ 6.47	2.45 $\pm$ 0.61	1.26 to 3.64	0.36 $\pm$ 0.09	0.19, 0.54	<.0001
	Week 3	450 mg	1.85 $\pm$ 6.72	2.76 $\pm$ 0.59	1.60 to 3.91	0.41 $\pm$ 0.09	0.24, 0.58	<.0001
Gait Speed Measures								
Single-Task Gait Speed	Screening		0.80 $\pm$ 0.18					
	Week 0	Pretreatment	0.88 $\pm$ 0.21					
	Week 1	150 mg	0.89 $\pm$ 0.19	0.01 $\pm$ 0.02	−0.02 to 0.05	0.07 $\pm$ 0.08	−0.09, 0.22	.41
	Week 2	300 mg	0.91 $\pm$ 0.21	0.04 $\pm$ 0.03	−0.01 to 0.09	0.18 $\pm$ 0.12	−0.06, 0.42	.15
	Week 3	450 mg	0.92 $\pm$ 0.21	0.04 $\pm$ 0.02	0.00 to 0.08	0.19 $\pm$ 0.09	0.01, 0.38	.0367
Dual-Task Gait Speed	Screening		0.69 $\pm$ 0.23					
	Week 0	Pretreatment	0.74 $\pm$ 0.20					
	Week 1	150 mg	0.74 $\pm$ 0.23	0.00 $\pm$ 0.02	−0.05 to 0.05	0 $\pm$ 0.12	−0.23, 0.23	.99
	Week 2	300 mg	0.80 $\pm$ 0.24	0.06 $\pm$ 0.03	0.01 to 0.12	0.32 $\pm$ 0.15	0.03, 0.62	.031
	Week 3	450 mg	0.82 $\pm$ 0.24	0.09 $\pm$ 0.03	0.03 to 0.14	0.43 $\pm$ 0.14	0.16, 0.70	.0018
Depression Measures								
Hamilton Rating Scale for Depression, 24 Items	Screening		15.53 $\pm$ 6.04					
	Week 0	Pretreatment	13.42 $\pm$ 6.63					
	Week 1	150 mg	11.97 $\pm$ 6.96	−1.44 $\pm$ 0.94	−3.29 to 0.40	−0.22 $\pm$ 0.14	−0.50, 0.06	.13
	Week 2	300 mg	11.06 $\pm$ 6.17	−2.36 $\pm$ 1.03	−4.37 to −0.35	−0.36 $\pm$ 0.16	−0.66, −0.05	.022
	Week 3	450 mg	10.94 $\pm$ 6.87	−2.48 $\pm$ 0.80	−4.05 to −0.90	−0.37 $\pm$ 0.12	−0.61, −0.14	.002
Inventory of Depressive Symptoms—Self-Report	Screening		26.42 $\pm$ 12.57					
	Week 0	Pretreatment	22.47 $\pm$ 13.61					
	Week 1	150 mg	19.17 $\pm$ 11.44	−3.31 $\pm$ 1.9	−7.03 to 0.42	−0.24 $\pm$ 0.14	−0.52, 0.03	.082
	Week 2	300 mg	17.57 $\pm$ 11.71	−4.9 $\pm$ 1.86	−8.55 to −1.25	−0.36 $\pm$ 0.14	−0.63, −0.09	.0084
	Week 3	450 mg	15.09 $\pm$ 10.64	−7.38 $\pm$ 1.38	−10.09 to −4.67	−0.54 $\pm$ 0.1	−0.74, −0.34	<.0001

“Screening” refers to assessments performed at screening visit, “week 0” refers to premedication baseline, and weeks 1 to 3 refer to assessments performed after 150 mg, 300 mg, and 450 mg L-DOPA, respectively. Dose effects are estimated by tests of change from pretreatment (week 0). ES is calculated by scaling the mean change by the standard deviation at week 0. The number of subjects contributing data to this table were 36 at screening, week 0, and week 1; 35 at week 2; and 33 at week 3.

CI, confidence interval; DS, Digit Symbol; ES, effect size; LC, Letter Comparison; L-DOPA, levodopa; PC, Pattern Comparison.

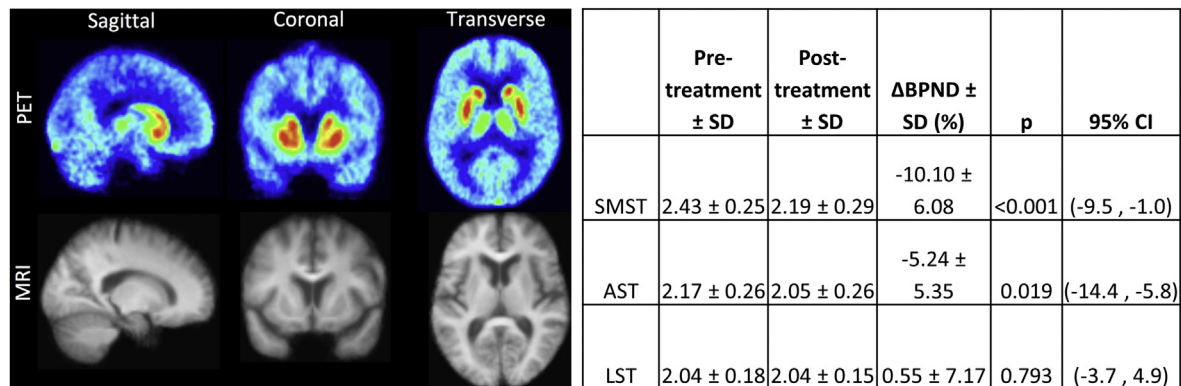


Figure 1. Baseline (week 0) and postlevodopa (week 3) mean [^{11}C]raclopride binding ($n = 10$). To the left, mean sagittal, coronal, and transverse images for [^{11}C]raclopride positron emission tomography (PET) and structural magnetic resonance imaging (MRI) are shown. Canonical striatal brain regions demonstrating [^{11}C]raclopride are evident. To the right, mean changes from pre- to postlevodopa in [^{11}C]raclopride binding potential are provided. Significantly decreased [^{11}C]raclopride was observed in sensorimotor striatum (SMST) and associative striatum (AST), but not limbic striatum (LST). CI, confidence interval; ΔBPND, difference in binding potential.

2.8%/2.9%/6.1%). The emergence of dyskinesias during L-DOPA treatment was evaluated using items 32 and 33 of the Unified Parkinson's Disease Rating Scale, and no significant change from baseline was observed on either these items. Mean scores were 0.0 at week 3 for both items.

DISCUSSION

The primary finding of this open study of L-DOPA for psychomotor slowing and depression in older adults was a dose-dependent increase in both processing and gait speed, which coincided with significantly decreased [^{11}C]raclopride binding in selected striatal subregions. While L-DOPA effects on processing and gait speed were modest ($ES = 0.41$ and 0.43 , respectively), these effects are significant given the functional disability and increased risk for adverse outcomes associated

with slowing and its lack of responsivity to standard antidepressant treatments. Though depressive symptom change was not the focus of this study, we found a significant decrease from baseline on both rater-administered (HRSD) and self-report measures of depression across this relatively brief, 3-week-duration study. L-DOPA was remarkably well tolerated in this patient sample. The most common side effect, nausea, decreased in frequency as the study progressed, and no persistent motor outcomes such as dyskinesias were observed.

While the number of individuals undergoing PET scanning in this study was relatively small, significantly decreased [^{11}C]raclopride binding following subacute L-DOPA treatment was observed, and these regionally specific BPND reductions were associated with characteristic behavioral outputs. For example, reduced AST binding was specifically

Table 3. Treatment Emergent Adverse Events Associated With L-DOPA

Variable	Week 1			Week 2			Week 3		
	Mean	SD	p Value vs. Week 0	Mean	ES vs. Week 0	p Value vs. Week 0	Mean	ES vs. Week 0	p Value vs. Week 0
Unified Parkinson's Disease Rating Scale									
Item 32	0.18	0.58	.17	0.18	0.18	.17	0.0	0.0	.32
Item 33	0.09	0.38	.09	0.09	0.09	.09	0.0	0.0	.32
Treatment-Emergent Side Effect Scale	n	%		n	%		n	%	
Nausea	7	19.4		6	17.1		3	9.1	
Insomnia	3	8.3		2	5.7		1	3.0	
Headache	1	2.8		1	2.9		2	6.1	
Drowsiness	0	0.0		1	2.9		1	3.0	
Dystonia	0	0.0		1	2.9		0	0	
Akathisia	1	2.8		0	0		0	0	
Dry mouth	0	0.0		0	0		1	3.0	
Dizziness	0	0.0		0	0		1	3.0	

Items 32 and 33 on the Unified Parkinson's Disease Rating Scale assess the presence or absence of motor side effects. The number of study subjects and proportion of the sample experiencing specific side effects are listed. All side effects experienced by at least one study subject at any time point are listed.

ES, effect size; L-DOPA, levodopa.

correlated with increased processing speed, which is consistent with prior literature linking maladaptive changes in AST (i.e., caudate) structure and function to slowed processing speed in neuropsychiatric disorders such as PD and normal aging (46,47). Similarly, the trend-level correlation between reduced SMST binding following L-DOPA and increased single-task gait speed is consistent with a large PD literature demonstrating links between putaminal dopamine release, gait speed, and responses to L-DOPA treatment (48,49). Larger samples of older adults with depression who do not have PD are needed to further examine the behavioral consequences of L-DOPA-induced changes in specific striatal subregions and how change in specific subregions interact with one another.

More generally, the conceptual framework undergirding this line of research—that novel therapeutic development for later life neuropsychiatric disorders should be guided by an understanding of the causative age-related physiologic processes—may merit broader application. Historically, treatments for disorders such as LLD have been based on pathophysiologic models of depression in younger adults and have been efficacy-tested in clinical trials mostly enrolling younger patients. As development and validation of the “vascular depression” hypothesis in the 1990s made clear (50), distinct processes (e.g., cerebrovascular aging and development of deep white matter hyperintensities) may cause and perpetuate depressive disorders in later life as compared to earlier in the life course. More recently, other processes, such as dopaminergic decline, age-related hearing loss (51), and development of the syndrome of frailty (52), have been identified as pathophysiologic routes to developing or perpetuating LLD. By developing precision interventions for these age-related disease mechanisms and testing them in etiologically homogenous patient samples, better outcomes for older adults may be achievable.

Future studies should examine more closely the relationship between slowing and depression in older adults, which is facilitated by the recent addition of a sensorimotor domain to the research domain criteria matrix. One possibility is that slowed processing and gait speed are not causally related to depression but are simply markers of a low dopamine state, which leads to the development of depressive disorders via other processes such as impaired reinforcement learning (53,54) or reduced hedonic capacity (55,56). Alternatively, slowing may reside on a causal sequence leading to depression in older adults, possibly through increased fatigability leading to alterations in effort-based decision making (57,58). It is intuitive to hypothesize that psychomotor slowing increases the effort cost of voluntary behavior, such that slowed older adults are less willing to work for rewards of a given value relative to older adults without slowing. This state may lead to reduced behavioral activation and contribute to social isolation and loneliness, all of which increase risk for depression (59).

A significant limitation to the above-presented results is the open administration of L-DOPA utilized in this study. Although some evidence suggests that older adults with depression experience diminished expectancy-based placebo effects relative to those effects in younger adults (60), a portion of the improvement observed on processing speed, gait speed, and depressive symptoms may be attributable to participants' expectation of improvement, therapeutic interactions with the

research staff, and spontaneous improvement. Given that striatal dopamine release has been shown to mediate placebo responses of various types (61), a portion of the change in [^{11}C]raclopride binding potential observed with L-DOPA treatment also may have been caused by nonspecific factors. Another limitation to be considered when interpreting results from this study is its relatively small sample size, for both the clinical and molecular effects of L-DOPA. Larger sample sizes will permit confirmation of the findings reported above and provide the requisite power for mediation analyses testing whether a greater degree of slowing improvement predicts greater reductions in depressive symptoms.

Given that this study was designed to identify L-DOPA effects on molecular and functional targets, its ability to detect change in depressive symptoms was limited. In particular, the brief treatment duration and mild depression severity of study participants pose limitations to detecting L-DOPA treatment effects as well as finding significant correlations between change in [^{11}C]raclopride binding and change in depression outcomes. In addition, there was variability in L-DOPA effects on psychomotor speed among participants in this study, which may relate to the nonspecific nature of slowed gait speed as a marker for age-associated dopaminergic decline. This limitation is mitigated by the inherently scalable and noninvasive nature of gait speed as a marker of dopamine availability in older adults, but future studies may consider how individual differences in dopamine metabolism contribute to slowing and may moderate response to L-DOPA (e.g., catechol-O-methyl-transferase genotype).

To address these limitations and focus on depression-related outcomes, a double-blind, placebo-controlled study with increased sample size and longer duration is now underway in our laboratories. However, the above data already suggest the exciting possibility that age-associated dopaminergic decline and its adverse functional consequences can be remediated in this high-risk and therapeutically challenging subgroup of LLD patients. Restoring psychomotor speed to age-appropriate norms may improve cognitive and physical functioning, relieve symptoms of depression, and reduce long-term risk for adverse health outcomes associated with slowing. Existing treatments (e.g., antidepressant medication) largely do not address the loss of dopaminergic tone hypothesized to cause psychomotor slowing in older adults, which may explain why they are often unsuccessful in achieving response or remission.

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ARTICLE INFORMATION

From the Columbia University Vagelos College of Physicians and Surgeons (BRR, CC, PJB, MWW, NV-A, YS, SPR) and New York State Psychiatric

Institute (BRR, CC, PJB, MWW, VB, EV, SPR), New York; and Stony Brook University Renaissance College of Medicine (MS, AA-D), Stony Brook, New York.

Address correspondence to Bret R. Rutherford, M.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032; E-mail: br8@cumc.columbia.edu.

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