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Effects of augmenting cholinergic neurotransmission on balance in Parkinson's disease

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ABSTRACT

Introduction: Degeneration of cholinergic systems may contribute to impairments of balance and gait in Parkinson's disease (PD) and phase 2 clinical trials have suggested that centrally acting cholinesterase inhibitors reduce falls. Here, we examined the effects of augmenting cholinergic neurotransmission on static and dynamic balance, indices of fall risk.

Methods: A single-site, randomized, double-blind, crossover trial examined the effect of donepezil in patients with PD. Forty-nine participants with idiopathic PD were randomized and 45 completed the trial. Each treatment period was 6 weeks with a 6-week washout between treatments. Donepezil in 2.5 mg capsules, or identical appearing placebo capsules, was increased from two per day (5 mg) to four capsules (10 mg) after 3 weeks. The primary outcome measures were the range of the medio-lateral sway when standing (static balance) and the variability of the stride duration when walking (dynamic balance). A linear mixed model was used to investigate whether the change in outcomes between weeks 0 and 6 differed between phases.

Results: There were no significant differences in treatment effects between placebo and donepezil for medio-lateral sway range during quiet standing ($p = 0.28$), nor in gait variability ($p = 0.31$). None of the secondary outcome measures or exploratory analyses were significant although one secondary measure of static balance was increased by donepezil.

Conclusions: Contrary to our hypothesis, cholinergic augmentation with donepezil at 10 mg/day for 6 weeks did not affect measures of static or dynamic balance in people with PD. These results are compared with other phase 2 trials of cholinesterase inhibitors and considerations for future trials are discussed.

1. Introduction

Impaired balance and gait impacts quality of life in Parkinson's disease (PD). Over a quarter of the questions in the Parkinson's disease quality of life scale, PDQ-39, questions are mobility items. Loss of mobility in the home and community affects tasks required for independent living and participation in family and community affairs [1,2]. Falls cause minor to major trauma; the injuries restrict a person's activities and add to the fear of falling which further reduces mobility [3]. Levodopa, the mainstay for treatment of PD, may improve some aspects of balance and gait but is ineffective for the more severe problems with balance and may even worsen some aspects of balance [4].

In addition to degeneration of the dopaminergic system, the cholinergic system also degenerates in PD [5]. The basal forebrain cholinergic nuclei that project to all aspects of the cortex degenerate as do the upper brainstem pedunculopontine and dorsolateral tegmental nuclei that project to thalamus and basal ganglia as well as to other targets [5]. Chemical lesions of the nigrostriatal dopaminergic neurons and the pedunculopontine cholinergic neurons produce imbalance in the non-human primate model of parkinsonism that is not corrected by dopaminergic stimulation [6].

In humans, PET studies demonstrate that reduction of basal forebrain cholinergic projections to cortical areas is associated with slower gait [7]. Degeneration of brainstem cholinergic projections to the thalamus is associated with falls [8]. In addition, using surrogate measures of cholinergic activity as measured by short-latency afferent inhibition (SAI) [9], an association between gait speed and cholinergic dysfunction has been found in mild-to-moderate participants with PD [9]. These observations have led to 3 randomized clinical trials to examine the effects of augmenting cholinergic activity with cholinesterase

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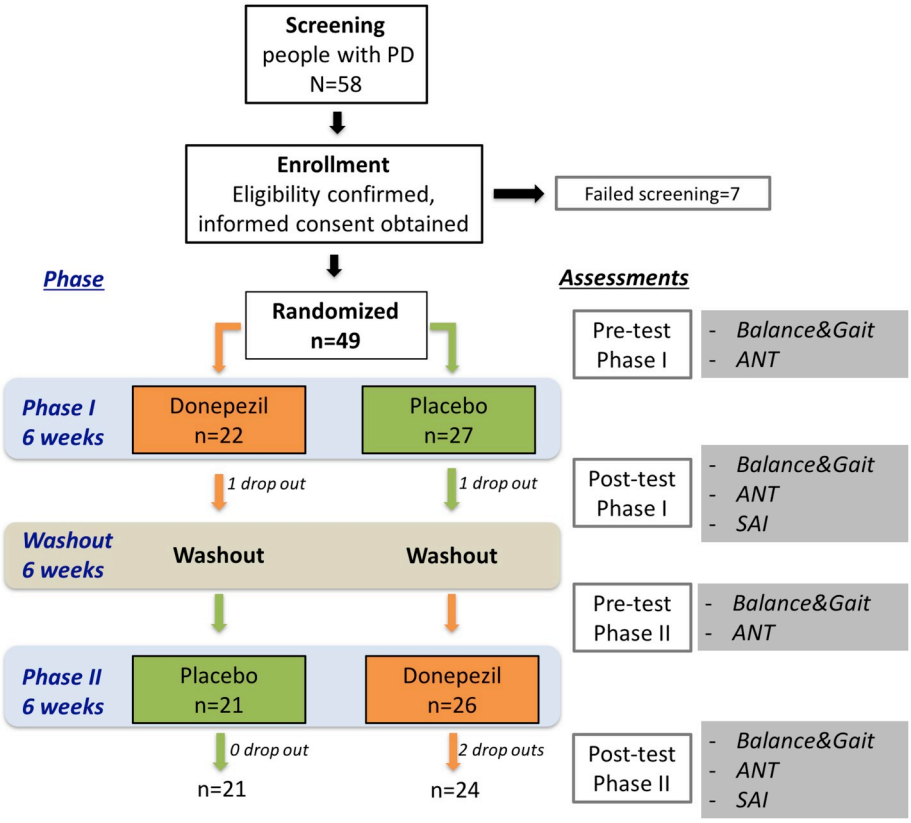

Fig. 1. Study consort diagram.

inhibitors [10–12]. In a small, double-blind crossover study, we found that the cholinesterase inhibitor, donepezil, reduced falls in frequent fallers [11]. A larger study on participants falling weekly would be very difficult because few patients who fall this frequently are sufficiently stable to carry out a study for several months.

Therefore, we postulated that measures of standing balance and dynamic balance, both argued to be predictors of falls [13–18] would reveal the effects of donepezil in people with mild-to moderately-severe PD. Specifically, we selected an objective measure of quiet standing, as outcome of standing balance because: 1) it predicts falls in elderly people [19], 2) it is sensitive to PD [4], and 3) it changes significantly with exercise [20]. In addition, as measure of dynamic balance, we selected an objective measure of gait variability because of its use in the previous literature as surrogate for fall risk [21,22] and sensitivity to PD [23].

The effects of manipulation of the cholinergic system could be mediated by at least two general mechanisms: attention, through alteration of the cortical and subcortical cholinergic system, or directly on balance, via effects on brainstem-cortical locomotor cholinergic circuits. Therefore, we used the attention network test (ANT) to determine if changes in gait and balance were associated with changes in attention. SAI, a physiological index of central cholinergic function, was used to determine if the deficits in balance and gait correlated with abnormalities of the SAI and if SAI was altered by donepezil as a measure of drug efficacy.

2. Methods

2.1. Participants and study design

We carried out this randomized, double-blinded, cross-over trial at the Oregon Health & Science University (OHSU). The study protocol was published previously [24]. Patients were eligible if they: i) were 30 years or older, ii) had idiopathic PD as determined from history and exam and lack of history or physical findings that would suggest another diagnosis or a parkinsonism-plus syndrome, iii) were Hoehn and Yahr (H&Y) stages II to IV, and iv) able to stand unassisted for 1 min and to walk continuously for 2 min without assistance or assistive devices. In addition, participants had a Montreal Cognitive Assessment (MoCA) of 23 or above and were judged to be able to appreciate the purpose of the research, give informed consent to participate, be able to cooperate with the testing and be compliant with taking the experimental medications.

Exclusion criteria were other factors affecting gait such as musculoskeletal disorders, uncorrected vision disturbance, vestibular problems or any other health problems judged to interfere with participation. Medical problems that might be worsened by donepezil (tachycardia, bradycardia, arrhythmias, and peptic ulcer disease) were exclusion criteria. Finally, use of anticholinergics for parkinsonism, urinary urgency or depression (tricyclics) were contraindications as was concurrent use of cholinesterase inhibitors for cognitive impairment.

Participants were randomized in a 1:1 ratio to start with donepezil or placebo. The Research Pharmacy at OHSU was responsible for purchasing study medication and creating blinded capsules for each subject, maintaining and storing drug, randomizing to maintain blinding and dispensing medication. Compliance was checked by returned capsule count. This trial was registered at clinical trials.gov (NCT02206620) and the OHSU IRB approved all aspects of the study.

The adverse events were collected weekly and unexpected or serious adverse events were reported immediately to the IRB. An independent neurologist, Safety Monitoring Officer, reviewed the reported adverse events each six months and made recommendations to the trial leadership as well as the IRB about advisability of continuation of the trial, changing the protocol or other safety concerns.

Table 1
Participants demographics at baseline.

N = 45	Mean	SD
Age at baseline	69	(7)
Symptoms (years)	9	(6)
Diagnosis (years)	7	(5)
Medications (year)	5	(4)
BMI	27	(5)
PDQ (total)	80	(27)
MoCA (total)	26	(3)
ABC	72	(22)
MDS-UPDRS Part III	43	(12)
	%	***N***
Freezing of gait	38	(17)
Any anticholinergic medication	6	(3)
Deep brain stimulator implant	11	(5)
Right side most affected	55	(24)

2.2. Procedures

Briefly, all people who were eligible per phone screening came into the clinic for the informed consent process and the screening visit. Participants completed 4 visits, each of which included a clinical assessment and an instrumented assessments of mobility (Fig. 1). Participants received the first study phase medications from the research pharmacy at the end of the baseline testing. At 6 weeks, the subject returned to the clinic for repeat testing with the measures captured at baseline. The participants then entered the 6-week washout period. At the conclusion of the 6 weeks, the participants return to the clinic for repeat testing and to have medications dispensed for the final 6-week phase of the protocol, conducted exactly as was the first six-week phase. A research assistant called participants weekly to ask about falls, adverse events or problems with complying with the protocol.

Donepezil was started at 5 mg per day and the dose increased to 10 mg/day after 3 weeks because this titration was well tolerated in a previous study [11,25]. For each visit, participants came in “OFF”, having held levodopa medications overnight.

The clinical assessment consisted of: 1) MDS revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS); 2) the MoCA; 3) the Activities of Balance Confidence (ABC) and 4) the PDQ-39.

The instrumented assessment of mobility was recorded by wireless, body-worn, inertial sensors (Opals, by APDM) recording triaxial acceleration, angular velocity and magnetic field. The sensors were placed bilaterally on the feet, wrists as well as on the sternum and sacrum with Velcro straps. Inertial data were wirelessly transmitted to a laptop that controls the protocol, and stores raw data for further offline analysis. Postural sway was measured while participants were standing with feet together looking straight-ahead at a fixed point with eyes open. To characterize gait, participants were instructed to walk for 2-min at their comfortable pace down a 20-m long hallway, turn around at each end and continue walking back and forth. Details are described in the protocol publication [24].

2.3. Outcome measures

The primary measure of balance was the medio-lateral postural sway range (detected from the sensor on the lower back) during the eyes open, quiet stance trial. Secondary balance measures were: sway dispersion (measured as root mean square, i.e. variability around the mean position) and jerkiness of sway (measured by differentiating the acceleration values of sway).

The primary measure of dynamic stability was the coefficient variability of stride duration (time) during a 2-min walk. Secondary gait measures included stride length, gait speed, cadence, double support time, arm swing amplitude, and mean trunk rotation.

The secondary outcome measures were the ANT and the SAI. Attention was tested with the ANT, a 15-min, computerized test that examines the effects of cues and targets within a single reaction time task to provide a means of exploring the efficiency of the alerting, orienting, and executive control networks involved in attention. SAI was employed to measure brain cortical cholinergic activity, using transcutaneous magnetic stimulation, with a protocol previously described [9,26]. A full description of our SAI methodology can be found in our protocol paper [24]. In addition, a power analysis was carried out for the chosen sample size, as detailed in our protocol publication [24].

2.4. Statistical analysis

We hypothesized that the change in outcomes between weeks 0 and 6 would differ between the donepezil and placebo phases. The four observations for each participant contained their measurements at weeks 0 and 6 under the different treatment conditions (donepezil/placebo). To estimate each of the “differences in differences”, we used a linear mixed model that included an indicator of treatment, an indicator of week 0 vs 6, and their interaction. This interaction term reflected the main focus of the study, namely to determine whether the effect of donepezil differs from placebo. We also included terms to assess possible period or carryover effects and random effects for patients within treatments. Because we had two primary outcomes, we tested each with a significance threshold of 0.025. Observations that were ± 3 SD outside the mean were considered outliers, results of the main analysis are presented both with and without outliers. Many of the primary and secondary outcome measures showed extreme skew. We used Tukey's ladder of powers to identify a transformation for each variable to better approximate normality, when needed. Both primary outcomes were modelled on the natural log scale for significance testing. Associations between the baseline primary outcome measures and clinical measures of severity were tested with Spearman rho.

3. Results

Between October 2014 to July 2017, we randomized 49 participants with PD, into the protocol illustrated in Fig. 1. Baseline demographics and clinical characteristics of the 45 participants completing the trial are reported in Table 1.

3.1. Primary outcome measures of balance and gait

The placebo first and donepezil first groups had similar baseline values for medio-lateral sway range ($p = 0.64$), see Fig. 2A and Table 2. Using all available data from complete cases, we found a trend towards a larger increase in medio-lateral sway range of 0.17 units, on the natural log scale, with donepezil compared to placebo ($p = 0.050$). These findings were driven by two extreme observations; when these outliers were omitted, the increase was only 0.07 units ($p = 0.34$). Similarly to medio-lateral sway range, medio-lateral sway dispersion (RMS) showed an increase of 0.18 units, on the natural log scale, with donepezil increasing sway more than placebo ($p = 0.004$). When the two extreme observations were omitted, the increase in medio-lateral sway dispersion with donepezil compared to placebo was still significant ($p = 0.016$). Jerk was not affected by donezepil.

Baseline values were similar between placebo first and donepezil first groups for the variability (CoV) of stride duration while walking ($p = 0.96$), see Fig. 2B and Table 2. Variability of stride duration did not change during donepezil and placebo phases ($p = 0.78$). There were no carryover effects for either outcome measure. Similar results were found for the gait secondary outcome measures, Table 2 and example for gait speed in Fig. 3A.

Table 2
Summary of findings. Means and standard deviations (SDs) of primary and secondary sway and gait outcomes at each baseline and changes at six weeks for complete cases in a two-arm crossover trial.

	Primary	Donepezil				Placebo				Paired difference:						
		Baseline		Change at 6 weeks: Δ_D		Baseline		Change at 6 weeks: Δ_C		Donepezil - Placebo (Δ_D - Δ_C)						
		Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	p*	Standardized β (95% CI)		p**	p if outliers omitted
(1)	Sway: Medio-lateral range	0.382	(0.37)	−0.012	(0.33)	0.346	(0.11)	0.088	(0.22)	0.100	(0.38)	0.33	0.33	(-0.05, 0.72)	0.050	0.180
(2)	Gait: Stride time CoV	8.10	(5.88)	−0.07	(4.17)	7.62	(4.93)	−0.25	(4.09)	−0.18	(4.93)	0.77	−0.08	(-0.35, 0.19)	0.78	
	Secondary															
(3)	Sway: Medio-lateral dispersion (root mean squared acceleration)	0.058	(0.028)	−0.001	(0.023)	0.057	(0.015)	0.012	(0.025)	0.013	(0.029)	0.005	0.49	(0.14, 0.84)	0.004	0.016
(4)	Gait: Stride length (m)	0.925	(0.204)	−0.006	(0.076)	0.911	(0.200)	0.010	(0.073)	0.015	(0.098)	0.45	0.08	(-0.05, 0.22)	0.23	
(5)	Gait: Cadence (steps/minute)	111.6	(13.2)	0.5	(7.2)	109.9	(12.8)	0.6	(6.3)	0.04	(9.5)	0.80	0.03	(-0.17, 0.24)	0.76	
(6)	Gait: Double support (% of gait cycle in which both feet are on the ground)	24.3	(5.7)	0.1	(2.3)	24.8	(4.9)	0.0	(2.5)	−0.2	(2.9)	0.91	−0.05	(-0.21, 0.11)	0.39	
(7)	Gait: Arm range of motion (RoM; degrees/second)	26.9	(11.8)	−0.2	(5.1)	26.1	(12.2)	−1.6	(6.1)	−1.4	(9.0)	0.50	−0.09	(-0.31, 0.13)	0.45	
(8)	Gait: Trunk RoM (degrees/second)	4.2	(1.6)	0.0	(0.6)	4.3	(1.5)	0.2	(0.8)	0.1	(1.0)	0.90	0.07	(-0.11, 0.24)	0.74	
(9)	Gait: Dual-task cost	0.14	(0.37)	−0.01	(0.47)	0.16	(0.53)	−0.02	(0.66)	−0.01	(0.83)	0.77	0.11	(-0.44, 0.66)	0.64	
(10)	Attention Network Task (ANT)	238	(77)	−17	(82)	226	(69)	−1	(65)	16	(118)	0.23	0.11	(-0.37, 0.58)	0.97	
(11)	Short-latency afferent inhibition (SAI)									0.19	(34)	0.85	−0.06	(-0.46, 0.35)	0.82	
(12)	UPDRS Part III	43	(13)	−4	(12)	43	(14)	−1	(14)	3	(18)	0.16	0.21	(-0.18, 0.6)	0.30	
(13)	Quality of life: PDQ-39 (0–100 possible; lower = better)	77	(26)	−3	(13)	76	(24)	2	(13)	5	(20)	0.16	0.18	(-0.05, 0.42)	0.10	
(14)	Activities-Specific Balance Confidence (ABC) Scale (0–100 possible; higher = more confident)	74	(20)	0	(12)	71	(23)	1	(12)	1	(13)	0.95	0.002	(-0.18, 0.18)	0.78	

p*: p-value from Wilcoxon matched-pairs signed-ranks test on complete cases.
p**: p-value from mixed model on all available data controlling for sequence and period; sway outcomes log-transformed for modeling. **Standardized β** obtained by standardizing outcome values to baseline before modeling.

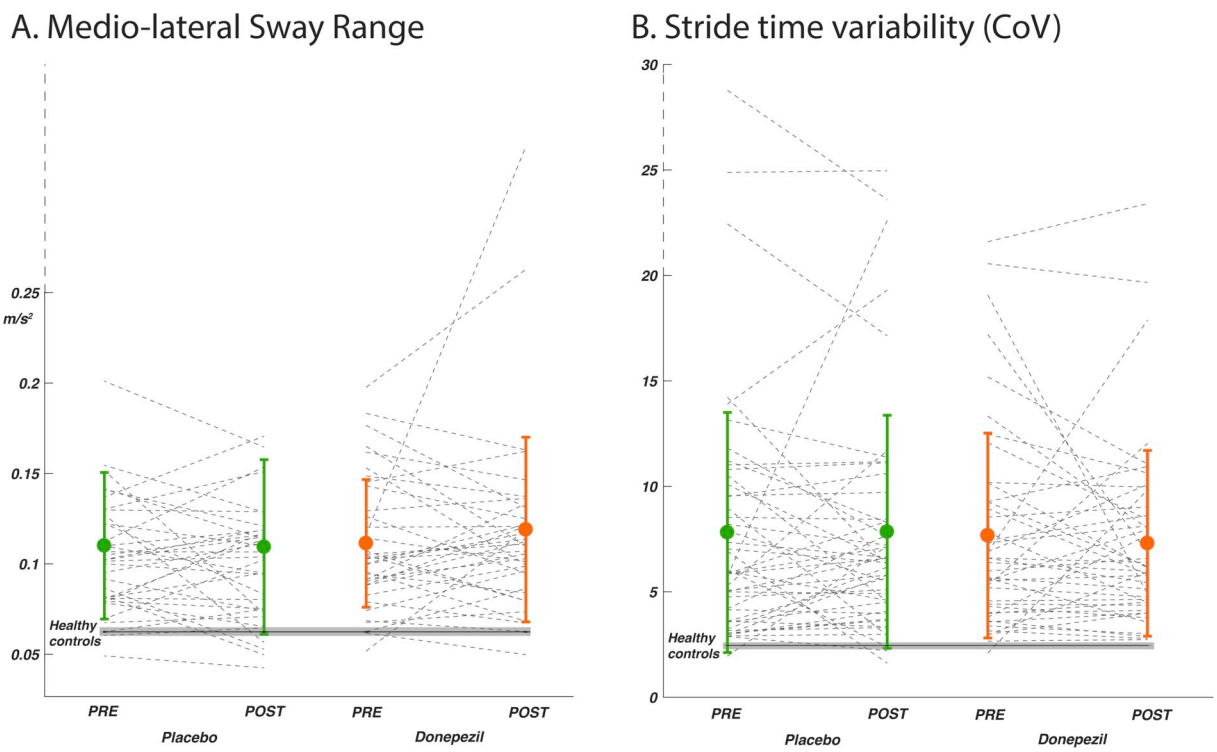

Fig. 2. Mean ± SD, and individual individual plots for participants for the primary outcome measures of A) static and B) dynamic balance. The grey shaded area represents normative value for healthy controls of similar age.

3.2. Secondary measures of attention and cholinergic activity

There were no significant changes in the three domains of the ANT nor their sum with donepezil or placebo (p = 0.97 for sum) (see Table 2). SAI was also not different between visits after each treatment phase (p = 0.82), Fig. 3B.

3.3. Association analysis

At baseline, dynamic balance (gait variability) was associated with disease severity, measured by MDS-UPDRS III (rho = 0.4, p = 0.006), PDQ-10 (rho = -0.58, p < 0.0001), and ABC (rho = -0.6, p < 0.0001), Fig. 4. Static balance (medio-lateral sway) did not correlate with measures of parkinsonian severity.

3.4. Unplanned subgroup analysis

Exploratory analyses examined the effects of donepezil in the following subgroups: participants with Rapid Eye Movement sleep behavior disorder (RBD), participants reporting freezing of gait, participants with history of previous falls, participants with a slow gait speed (< .8 m/s) at baseline and participants with reduced SAI. None of these analyses showed significant effects of donepezil.

3.5. Compliance and adverse events

Compliance was calculated from returned pills. The counts revealed 94% adherence with donepezil and 93% with placebo. There were a total of44 88 adverse events with donepezil,2222 45 with placebo and3

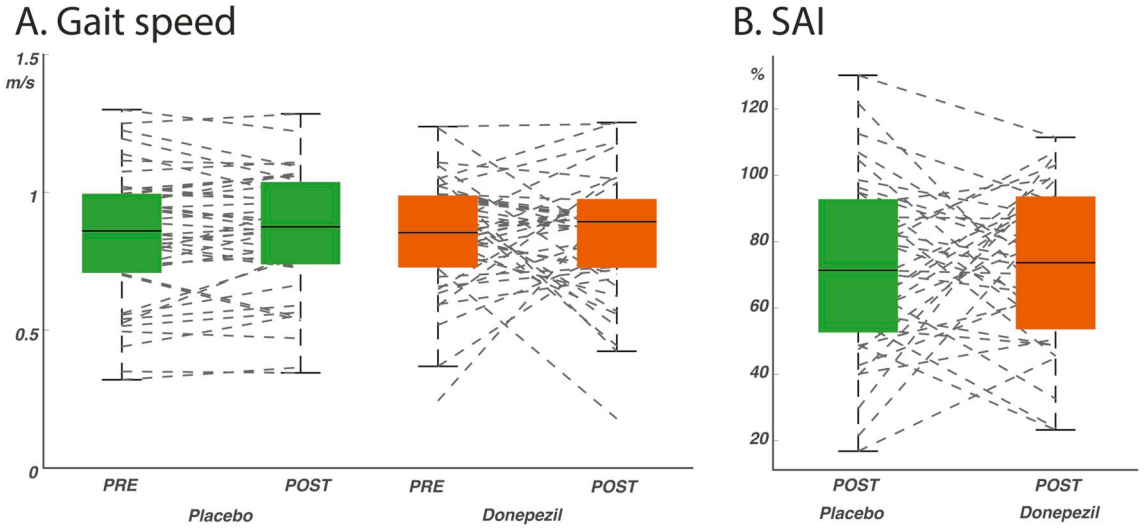

Fig. 3. Boxplot with median, 25th and 75th percentiles, and single participants for A) gait speed and B) SAI.

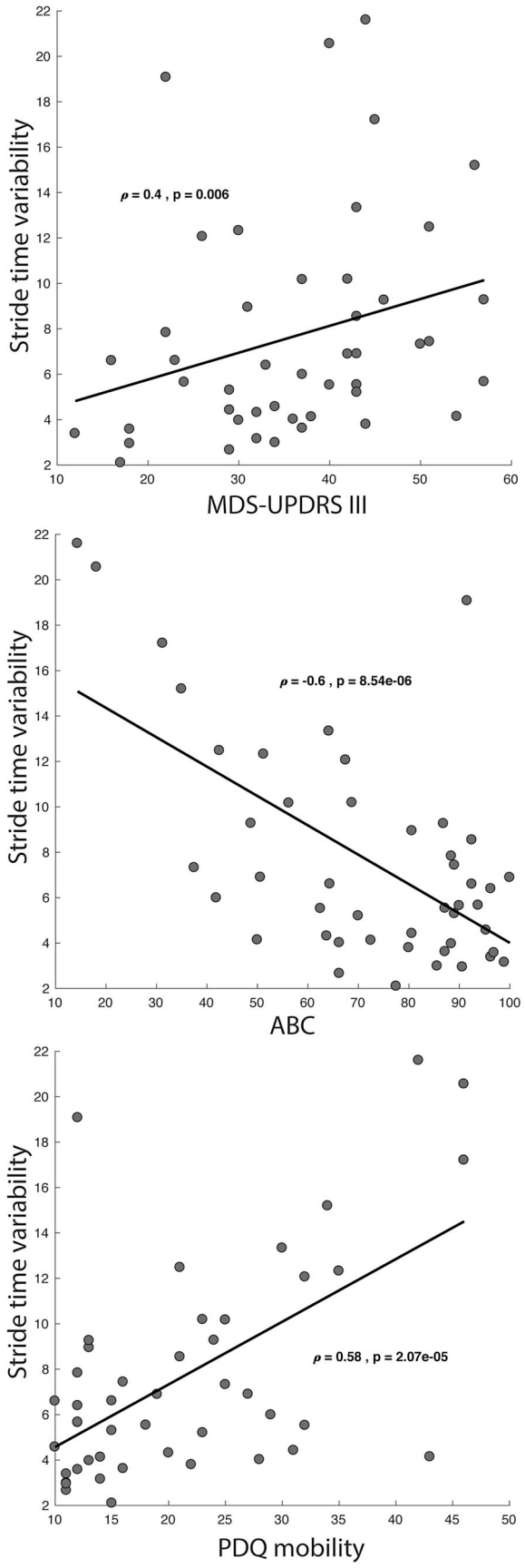

Fig. 4. Association of dynamic balance and MDS-UPDRS, PDQ-39 and ABC at the baseline assessment.

15 during the open washout phase. Donepezil had more gastrointestinal adverse events (26 versus 9), and more muscle cramps (8 versus 4). One serious adverse event (pulmonary embolus) occurred during the washout phase.

4. Discussion

Donepezil, 10 mg/day for 6 weeks did not affect our primary outcome measures of static and dynamic balance in a cohort of people with PD with no or limited fall history and intact cognition. SAI and ANT, two secondary outcome measures, were also not affected by donepezil. Exploratory post hoc analyses examining subgroups defined by slower gait speed, presence of REM sleep behavior disorders, previous falls, freezing of gait and decreased SAI did not detect any effect of donepezil. The lack of efficacy of donepezil in our trial stands in contrast to positive outcomes with donepezil [11,25] and with rivastigmine [12,27]. We review the differences between our study and these phase II trials in order to identify a trial design and subset of people with PD who could potentially benefit from cholinergic therapy.

Inclusion criteria for enrolled participants is an important consideration. Chung et al. [11] chose participants who were falling on average, once per week and it was only the participants that were falling almost daily that were improved by donepezil. In Hiller et al. [25], we chose more severely affected participants with abnormal dynamic posturography on screening with a composite score of 70 or less. Henderson et al. [12] entered participants who were falling an average of 5 times per year prior to entering the study. Furthermore, 65–74% were freezing, indicating more advanced PD. Li et al. [27] included a full range (H&Y stages 1–5) of participants with over 60% in H&Y stages 1 and 2 at entry to the trial, but 53–58% were falling before entering the trial. Our participants were, on average, milder, ranging from H&Y stage 2–4 on the Hoehn and Yahr scale and only 16 of the 45 participants reported previous falls. In addition, the average MoCA of the included participants was 26, indicating intact cognition in this group; thus, our participants may have had less impairment of cholinergic systems than the participants in the other studies [5,28]. In addition, a secondary static balance measure, medio-lateral sway dispersion was increased by donepezil.

A more definitive method of selecting suitable participants for phase 2 studies of cholinergic agents would be to quantify cortical cholinergic deficits. We used SAI to assess cortical cholinergic activity, as it as been shown to be reduced in PD [29] and related to gait speed in early PD [9]. However, we did not find that participants with decreased SAI following the placebo phase were more responsive after the donepezil phase. Nor were we able to document an increase in SAI in response to donepezil. Treatment status (“On” or “Off” levodopa) at the time of SAI testing may be important [29]; our participants’ SAI were tested off levodopa overnight when less difference in SAI between PD and controls have been found [24]. But, it should be noted that changes in SAI in PD, “on” and “off” levodopa are not consistent in the literature nor has test-retest validity of SAI been established. Thus the use of SAI as a probe of cholinergic function needs to be further validated. An even more accurate method to select participants may be evidence of cholinergic deficits documented with PET. Decreased thalamic cholinergic markers with PET was associated with falls in PD [28]. Conversely, RBD and the presence of falls has been found to be predictor for combined thalamic and cortical cholinergic deficits documented with PET while slow gait and cognitive dysfunction (MoCA < 24) predicted isolated cortical cholinergic denervation [28].

Another potential factor to explain absent changes in balance primary measures, attention and SAI is the drug concentrations achieved at the appropriate cholinergic receptors for sufficient time. One indication that donepezil can raise cortical acetylcholine concentrations comes from the observations that a 10 mg dose of donepezil for 3 months in participants with Alzheimer's disease inhibited cortical acetylcholinesterase 19–39% as shown with PET studies using a marker

for cholinesterase inhibition [30,31]. This level of inhibition of acetylcholine esterase has a modest but significant effect on cognition in Alzheimer's disease [32] and it may enhance functional networks detected by resting-state MRI [33]. Six weeks of donepezil should produce steady state plasma levels and has been effective in other studies of donepezil on balance. However, the number of cholinergic receptors is large; there are 5 muscarinic receptor subtypes and multiple nicotinic receptor subtypes made from combinations of 12 different nicotinic receptor subunits [34]. Which specific cholinergic receptor(s) might affect balance and falling is unknown but it is possible that selective cholinergic drugs and drugs with less gastrointestinal side-effects may be more effective than a modest elevation of acetylcholine with cholinesterase inhibition. Support for this suggestion comes from a recent reanalysis of a study with nicotine bitartrate which found that nicotine was associated with a reduction of falls and freezing measured by two questions from section II of the MDS-UPDRS and an improvement in the pull test of section III, [35]. It is important to note that we found an increase in postural sway, in a secondary outcome measure, during static balance could represent an improvement in balance confidence because more confident people sway closer to their limits of stability [36], or, on the contrary, an increase in postural sway could indicate an increased risk for falls. In conclusion, at this point we do not know whether specific cholinergic receptors should be targeted nor which physiological effects of cholinergic stimulation might improve balance, gait and falls.

Lastly, although falls are clinically important, falls are a difficult outcome measure. Nevertheless, it is falls that all the previous, positive phase 2 cholinesterase inhibitors studies found to be significantly reduced. We postulated that quantitative measures of balance and gait stability that tightly correlate with falls would be superior to quantifying falls and might be evident even before falls were occurring. Laboratory testing of balance and gait, however, brings up the question of whether participants should be tested “off” or “on.” It is known that levodopa can improve some aspects of balance and gait while worsening others [4]. We chose to test people “off” to look at the effects of donepezil on parkinsonism uncomplicated by acute levodopa therapy. This difference in timing of testing may explain why we did not find a reduction in sway during quiet standing or stride time variability during walking. In contrast, Hiller et al. [25] reported a reduction in mediolateral sway with donepezil in participants that were “on.” Levodopa increases mediolateral sway and conceivably donepezil suppressed this effect [2]. Henderson et al. [12], using a single sensor on the belt, reported reduced variability of step time asymmetry with rivastigmine when “on”, in a larger group of people. However, this methodology for measuring gait variability is considered to be of poor to moderate validity in healthy individuals and people with PD [37].

Because falls have multiple environmental, social, emotional and physical contributors, it is unlikely that any one physiologic measure will capture all people that will fall. Further, measuring balance and gait in the clinic probably yields the participants best performance and is also dependent upon the pharmacological state at the time of measurement and would require larger sample size. Monitoring mobility in people throughout the day in the home, especially if falls could also be documented, would be a superior method to assess the effects of manipulating the cholinergic system on balance and gait. However, falls are infrequent, sporadic events so would need to be monitored for at least 6 months, not only the 6-week period of our study.

Finally, although we have explored potential reasons we failed to find an effect of donepezil on balance measures, does it indicate that our study design was inadequate? In fact, our results are consistent with two large studies with acetylcholinesterase inhibitors in PD participants, 362 participants treated with rivastigmine and 377 participants treated with donepezil that found no difference in the fall rates for the acetylcholinesterase inhibitor and placebo treatments [38,39]. But, it should be noted that the participants in these trials were not selected for gait or balance difficulties but for cognitive impairment. In addition, falls were collected by adverse events reports at clinic visits and not by fall diaries. Lastly, due to the relatively small sample size, the possibility of at type II error is important to consider, in fact, although the results of this study point to the absence of a major treatment effect, small-to-moderate treatment effects cannot be ruled out. However, most of the effects we observed were too small to be clinically meaningful.

In conclusion, this double-blind, randomized trial of cholinergic augmentation with donepezil at 10 mg/day for 6 weeks did not affect measures of static or dynamic balance in participants with PD without a history of falls and intact cognitive function.

Acknowledgment

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Appendix. Summary of findings.

	PRIMARY	Baseline placebo		Donepezil group difference from placebo group at baseline			Placebo effect			Diff btw donepezil and placebo			Sequence			Phase			N
		β_0	Std. err.	β_1	Std. err.	p	β_2	Std. err.	p	β_{12}	Std. err.	p	β_3	Std. err.	p	β_4	Std. err.	p	
(1a)	Sway, range (ln)	−1.1	0.09	−0.03	0.07	0.64	0.04	0.06	0.48	0.17	0.09	0.050	0.06	0.09	0.48	−0.09	0.06	0.12	170
(1b)	Sway, range (ln) 2 obs omitted	−1.1	0.08	0.01	0.06	0.89	0.08	0.05	0.15	0.10	0.07	0.18	0.02	0.09	0.80	−0.08	0.05	0.12	166
(2)	Gait, Stride time CoV	1.9	0.12	0.00	0.06	0.96	0.01	0.08	0.87	−0.03	0.11	0.78	−0.01	0.15	0.93	−0.02	0.04	0.62	176
	SECONDARY																		
(3a)	Sway, RMS (ln)	−2.9	0.09	−0.01	0.06	0.82	0.00	0.05	0.94	0.18	0.06	**0.004**	0.05	0.09	0.54	−0.06	0.05	0.17	170
(3b)	Sway, RMS (ln) 2 obs omitted	−2.9	0.08	0.01	0.05	0.80	0.01	0.05	0.77	0.14	0.06	**0.016**	0.02	0.08	0.77	−0.06	0.04	0.18	166
(4)	Gait stride length	1.0	0.04	−0.01	0.01	0.27	0.00	0.01	0.75	0.02	0.01	0.23	−0.05	0.06	0.39	0.00	0.01	0.85	176
(5)	Gait, cadence	112	3.1	−2.01	1.03	0.051	0.47	1.05	0.66	0.44	1.43	0.76	−0.19	3.75	0.96	0.05	0.68	0.94	175
(6)	Gait, Double support	3.1	0.05	0.03	0.02	0.07	0.01	0.01	0.54	−0.02	0.02	0.39	0.05	0.06	0.39	0.00	0.01	0.87	175

(7)	Gait, Arm ROM	27	2.4	−1.0	1.0	0.30	−0.1	0.7	0.87	−1.0	1.4	0.45	0.1	3.4	0.98	−0.3	0.6	0.65	176
(8)	Gait, Trunk ROM	2.1	0.07	0.01	0.02	0.71	0.03	0.02	0.23	0.01	0.03	0.74	−0.11	0.12	0.35	0.05	0.02	0.016	174
(9)	Gait, DT cost	0.2	0.07	0.00	0.07	0.98	−0.04	0.07	0.54	0.06	0.12	0.64	−0.04	0.07	0.60	−0.14	0.05	0.006	170
(10)	ANT	226	13.9	−8.2	16.1	0.61	−6.6	14.0	0.64	0.8	20.6	0.97	31	16	0.06	−7.9	12.1	0.52	173
(11)	SAI	70	6.4							−1.2	5.3	0.82	3.2	6.1	0.60	5.2	5.3	0.32	78
(12)	UPDRS Part III	43	2.9	0.3	1.2	0.83	−4.0	1.8	0.02	2.8	2.7	0.30	0.8	3.5	0.82	−0.8	1.4	0.56	180
(13)	PDQ-39	77	5.0	−0.8	2.0	0.70	−3.4	1.9	0.08	4.9	2.9	0.10	4.4	6.5	0.49	−4.9	1.3	0.00	180
(14)	ABC	77	4.0	−3.3	1.4	0.02	0.4	1.7	0.83	0.6	2.0	0.78	−5.5	5.6	0.33	0.6	1.2	0.63	180

2 obs omitted: Model re-run without potential outliers, where both pre and post obs under one condition are left out (2*2 data points when pre/post considered).
Model: Outcome $= \beta_0 + \beta_1 txB + \beta_2 pst + \beta_{12}(txB * pst) + \beta_3 BAorder + \beta_4 Phase + b_i$.
β_0: mean for treatment A at start. β_1: difference between A and B at start. β_2: treatment effect of A (pst = post). β_{12}: difference between treatment effects of A & B. β_3: controls for AB or BA sequence. β_4: controls for Phase I or Phase I. b_i: random effect for participant; handles correlation.
$p < 0.05$. Note that β_1 is the coefficient of an indicator for treatment B, so that a positive value indicates a higher mean for B than A. SAI was measured only at the 'post' visits, so the value in the β_{12} column is actually not an interaction term, but was moved there for comparison with other outcomes. All estimates rounded to 2 or 3 significant digits, depending on scale. P-values rounded to 2 digits if > 0.1, 3 if ≤ 0.1.

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