## CHAPTER 5: A RANDOMIZED TRIAL OF ORAL AND TRANSDERMAL RIVASTIGMINE FOR POSTURAL INSTABILITY IN PARKINSON'S DISEASE DEMENTIA

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### Résumé

**Objectifs:** Comparer la rivastigmine sous forme orale et forme transdermique pour l'instabilité posturale chez les patients atteints de la démence de la maladie de Parkinson.



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La principale variable de l'étude était le changement de vitesse moyenne du centre de pression en position debout après 6 mois. **Méthodes:** Les patients ont été randomisés (1:1) à la rivastigmine orale ou transdermique. Les variables étaient évaluées au départ et après 6 mois. **Résultats:** Dix-neuf patients ont complété l'étude (n=8 orale; n=11 transdermique). Le groupe transdermique a démontré une réduction de la vitesse moyenne à 15.8% (p <0,05; orale: réduction de 10,0%, p=0,16) lors de la condition d'équilibre la plus difficile. Des améliorations significatives ont été observées au niveau de la durée moyenne des pics (timbre) et de la distance entre les pics (orale) dans la même condition. **Conclusions:** La rivastigmine pourrait améliorer le contrôle postural, spécifiquement sous des conditions difficiles.

**Abstract**

**Objectives:** To compare the efficacy and safety of oral and transdermal rivastigmine for postural instability in patients with Parkinson's disease dementia (PDD) who were candidates for a cholinesterase inhibitor. The primary outcome was the change in mean velocity of the centre of pressure (CoP) after 6 months. Secondary outcomes included structural parameters of dynamic posturography, clinical rating scales and adverse events requiring dose reduction. **Methods:** Patients with PDD were randomized in a 1:1 ratio to oral or transdermal rivastigmine with target doses of 6 mg twice daily and 9.5 mg/10 $cm^2$ daily, respectively. Outcomes were assessed at baseline and 6 months. Results were compared within and between groups. **Results:** Nineteen patients completed the study (n=8 oral, n=11 transdermal). Mean daily doses of 9.4 mg (± 1.5 mg) and 16.4 mg (± 3.6 mg) were achieved in the oral and transdermal groups, respectively. The transdermal group demonstrated a significant 15.8% decrease in mean velocity of CoP (patch: p <0.05; oral: 10.0% decrease, p=0.16) in the most difficult scenario (eyes closed with sway-referenced support). There was no difference between groups (p=0.27). For structural parameters, significant improvements were seen in the mean duration of peaks (patch) and inter-peak distance (oral) in the most difficult condition. No changes were observed in clinical rating scales. Six patients experienced non-serious adverse events requiring dose reduction (n= 5 oral; n=1 transdermal). **Conclusions:** Rivastigmine may

improve certain elements of postural control, notably the mean velocity of CoP. Benefits appear to be more obvious under more taxing sensory conditions.

## Introduction

Postural instability is a cardinal feature of Parkinson's disease (PD) that typically presents late in the course of illness. Along with other axial symptoms, it is a major determinant of disability and poor quality of life in patients with PD (Muslimovi et al., 2008). As a result of this instability, falls are frequent and often accompanied by a debilitating fear of falling, contributing significantly to disease morbidity (Adkin et al., 2003). The underlying pathophysiologic mechanisms are poorly understood.

Unfortunately, dopaminergic therapies are largely ineffective for postural symptoms in advanced disease (Benatru et al., 2008). Neuronal degeneration in the substantia nigra, while highly correlated with bradykinesia, is minimally associated with postural instability (Vingerhoets, Schulzer, Calne, & Snow, 1997). It is likely that non-dopaminergic dysfunction, including deficiencies in adrenergic and cholinergic systems, contributes to the late postural instability observed in PD.

The cholinergic pedunculopontine nucleus (PPN) and nucleus basalis of Meynert (nBM) are of particular interest as they supply most of the cholinergic input to the central nervous system (Perry et al., 1999). The PPN provides cholinergic input to the thalamus, cerebellum, multiple brainstem nuclei, the basal ganglia and spinal cord (Martinez-Gonzalez, Bolam, & Mena-Segovia, 2011) whereas the nBM provides most of the cholinergic input to the cerebral cortex. Cholinergic neurons of the PPN that innervate the thalamus, including sensory afferent and cerebellar relay nuclei, mediate important aspects of sensory integration for postural control which requires the integration and re-weighting of visual, vestibular and proprioceptive information in order to maintain balance (F. B. Horak, 2006). Reduced thalamic acetylcholinesterase activity, as a surrogate marker of PPN function, has been correlated with falls and postural sway in PD (N. Bohnen et al., 2009; Müller & Bohnen, 2013).

Similar observations have been made correlating reduced cortical acetylcholinesterase activity and falls (N. Bohnen et al., 2009). However, this likely relates to defecits in attention and executive functioning, rather than sensory integration. The frontoparietal attention network, supplied by the nBM, mediates spatial attention and may be essential for shifting attention among sensory systems for postural control (Scolari, Seidl-Rathkopf, & Kastner, 2015). Indeed, balance may be significantly impaired in the presence of cognitive dysfunction (F. B. Horak, 2006) and patients with impaired executive functioning display an increased risk of falling (Smulders, Esselink, Cools, & Bloem, 2014) especially in dual task conditions.

As one may see, postural control is a complex process requiring simultaneous integration of reflexive and controlled processes. Patients with Parkinson's disease dementia (PDD) represent a special case in that they display both aberrant anticipatory and reactive postural adjustments to obstacles and dynamic imbalances along with specific cognitive dysfunction (Kim et al., 2013). Patients with PDD experience attention deficits and visuospatial and executive dysfunction, which may also be related to cholinergic degeneration in the nBM and PPN (Yarnall et al., 2011).

Promisingly, detriments in attentional tasks and consciousness appear to improve with acetylcholinesterase inhibitors in PDD (Emre et al., 2004; Wesnes et al., 2005) and therefore these agents have the potential to improve balance through cognitive mechanisms or via a direct effect on postural control. Preliminary evidence suggests that acetylcholinesterase inhibitors may reduce fall frequency in PD with postural instability (Chung et al., 2010; E. J. Henderson et al., 2016; Hiller, Nutt, Mancini, Horak, & Kareus, 2015). However, these initial observations have not been replicated in patients with PDD. Rivastigmine is currently the only cholinesterase inhibitor approved in Canada for PDD.

Therefore, the purpose of the current study was to compare the effects of 6 months of oral or transdermal rivastigmine on postural instability in PDD patients who were candidates for cholinesterase inhibitor therapy. It was hypothesized that treatment with rivastigmine would result in postural improvements at 6 months, rather than the expected deterioration associated with the natural history of the disease, and that those in the transdermal group

would display similar benefits compared to the oral group. If any differences were to be found, it was hypothesized that the transdermal group would outperform the oral group, owing to a potential for increased tolerance to a higher dose. Postural changes would be scored with dynamic posturography.

**Materials & Methods**

Participants for the current posturographic study were recruited from a concurrent clinical trial being conducted at the site (Emre et al., 2014). Males or females (not of childbearing potential) between 50-85 years of age were eligible for inclusion. Patients were required to have a diagnosis of idiopathic PD according to the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria (Hughes, Daniel, Kilford, & Lees, 1992), PDD as defined by the DSM-IV (First & Tasman, 2004) with an onset ≥ 1 year after the diagnosis of PD, and MMSE (Folstein, Folstein, & McHugh, 1975) ≥ 10 and ≤ 26. Patients were community dwelling and were living with or in regular contact with a caregiver. In all cases, the caregiver assumed responsibility for supervising treatment adherence and study procedures.

Exclusion criteria included any contraindication to rivastigmine, an explanation for dementia other than PD, advanced, progressive or unstable disease, Hoehn & Yahr (Hoehn & Yahr, 1967) stage more than 3 in "on" state, and the use of cholinesterase inhibitors or cholinergic drugs within 4 weeks prior to randomization. Subjects were required to provide written informed consent for both the parent trial comparing the effects of oral and transdermal rivastigmine on cognition and the current posturographic arm. If incompetent, consent was obtained from their legal representative and caregiver. An independent ethics review board approved the study protocol. Data were collected at the Québec Memory and Motor Skills Disorders Research Centre (Clinique Sainte Anne, Québec City, Canada).

Eligible patients were randomized in a 1:1 ratio to either oral or transdermal rivastigmine (Novartis Pharmaceuticals Canada Inc., Dorval, Québec, Canada) using an interactive voice randomization system. Patients in the oral group were initiated at a dose of 1.5 mg

twice daily with increases every 4 weeks to a target of 6 mg twice daily, if tolerated. Patients receiving transdermal patches were initiated at 4.6 mg/5 $cm^2$ with escalation to a target of 9.5 mg/10 $cm^2$ at 4 weeks, if tolerated. All assessors were blinded to treatment allocation at all points during the study. Dose adjustments and temporary interruptions were permitted if any safety or tolerability issues arose during the first 3 months of study.

Subjects performed computerized dynamic posturography (Pro Balance Master, NeuroCom International Inc., Clackamas, Oregon, USA) at baseline and after six months of treatment. This includes forceplates that allow measurement of the displacement of the centre of pressure (CoP), defined as the application point of the force vector that is equal to the sum of the forces acting between the foot and the platform. The CoP is an indirect measure of body sway and is proportional to ankle torque, which is a combination of descending motor commands and muscle activity around the ankle used to keep the whole body centre of gravity within the base of support (Baratto et al., 2002; J. E. Visser et al., 2008). Data was recorded under the following conditions: eyes open with static support surface, eyes open with sway-referenced support surface, eyes closed with static support surface, eyes closed with sway-referenced support surface. The study of body sway (particularly when sway is unpredictable and backward) is highly appropriate to study sensitivity to imbalance in retropulsion, which has the smallest stability margin in PD (F. B. Horak, Dimitrova, & Nutt, 2005). Three trials of 20 seconds each were conducted for each condition. All patients were tested in the "ON" state.

The primary outcome of this study was the change in mean CoP velocity, defined as the total distance travelled by the CoP (i.e. the total sway path) divided by the duration of the sampling period. This velocity (cm/s) is indicative of the amount of activity or effort required to control balance; the greater the velocity of the CoP, the more compensatory adjustments required to maintain stability (Maki et al., 1990). The mean velocity of the CoP is a validated measure of postural stability and fall risk (Maki et al., 1990). Furthermore, time structure of the CoP may reveal pathological postural specificities. Thus, structural posturographic parameters were calculated by means of a sway density plot method (Baratto et al., 2002). The sway density plot is computed by totaling the number of consecutive samples during which the postural oscillations remain inside a 2.5

mm radius. The sway density curve was digitally filtered with a fourth-order Butterworth filter (2.5 Hz low pass cut-off frequency with dual-pass to remove phase shift) to improve peak extraction of the three structural parameters. The mean value (duration) of all peaks, the mean of all distances between one peak and the successive peak (spatial distance) and the mean time distance between peaks (time distance) were derived from the sway density curve. The peaks of the sway density curve relate to periods of relative CoP stability (postural stabilization), whereas troughs indicate periods where the CoP is rapidly shifting in order to maintain balance (postural adjustment control) (Baratto et al., 2002; Corbeil et al., 2004). The peak duration reflects the amount of time spent in a stable position (with respect to ankle torque and associated motor commands). The spatial distance corresponds to the amount of effort (postural commands) required to resume a stable position, whereas the time distance represents the amount of time required to resume a stable position or rather the rate of production of postural commands (Baratto et al., 2002). The number of falls during posturographic trials was also recorded at each visit. A score of "0" or a "fall" is automatically assigned by the system if a patient's sway exceeds the limits of stability, takes a step, grasps the handrail, or the patient or operator stops the trial due to safety concerns. As the patient wears a safety harness throughout the study, true falls did not occur.

Secondary clinical outcomes included UPDRS III global motor and axial subscore |(Fahn, 1987), Mattis Dementia Rating Scale (MDRS) global and attention subscores (Mattis, 1976), and Neuropsychiatric Inventory (NPI) global and anxiety and depression subscores (Cummings, 1994). Secondary safety outcomes included patient or caregiver-reported adverse events. Examinations were conducted by trained research professionals at baseline and 6 months.

*Statistical Analysis*

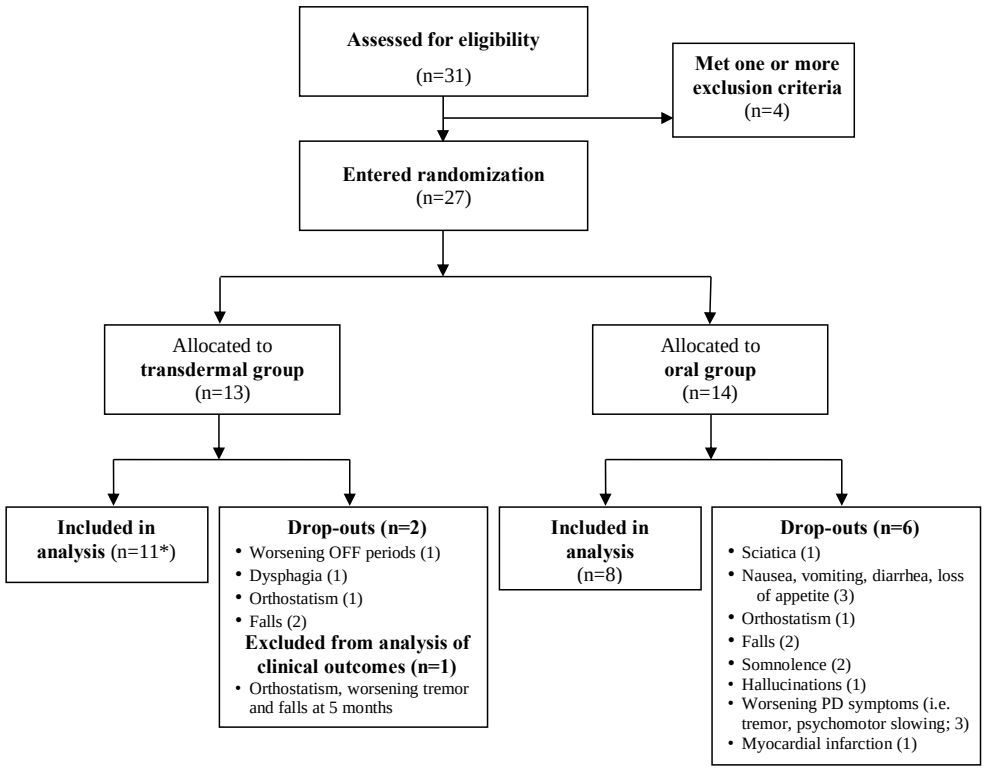
All analyses were carried out using Statistical Package for the Social Sciences (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) with $\alpha = 0.05$. To test for normality and equivalence of variances, the Shapiro-Wilk test and the Levene test were used, respectively. Baseline posturographic

performance and demographic variables were compared between treatment groups using the Mann-Whitney U test. Within group comparisons of posturographic outcomes and changes in UPDRS III, MDRS and NPI scores before and after treatment, with each subject serving as their own control, were conducted using the Wilcoxon signed-rank test; between group comparisons were conducted using the Mann-Whitney U test. Effect sizes were calculated using $r = z/\sqrt{N}$, where N represents the total number of samples (Fritz, Morris, & Richler, 2012). Effect sizes may be defined according to Cohen (Cohen, 1988) as small (0.1), medium (0.3) or large (0.5).

## Results

Between March of 2008 and April of 2009, a total of 31 subjects were screened into this initial study (Figure 2).

**Figure 2:** Flow diagram outlining patient recruitment



Note that one patient in the transdermal group withdrew due to orthostatism, falls and worsening tremor at 5 months; however, posturography was available and therefore the patient was included in the posturographic analysis, but not the analysis of clinical outcomes.

The remaining 19 patients were included in the current postural study. Follow-up was completed by October 2010. One patient in the transdermal patch group was excluded from the analysis of the most difficult condition (eyes-closed with sway-referenced support) as they fell in all 6 trials at follow-up; their data was included in the remainder of the analysis.

**Table 2:** Baseline demographics

| | Mean | SD | Median | Min | Max | p-value (between) |
|---|---|---|---|---|---|---|
| **Age (year)** | | | | | | |
| Patch | 72.9 | 5.0 | 75.0 | 62.0 | 78.0 | 0.90 |
| Oral | 73.1 | 5.7 | 72.5 | 66.0 | 81.0 | |
| **Weight (kg)** | | | | | | |
| Patch | 74.4 | 16.4 | 75.0 | 50.0 | 107.0 | 0.66 |
| Oral | 76.0 | 11.5 | 77.5 | 55.0 | 89.0 | |
| **Height (cm)** | | | | | | |
| Patch | 164.6 | 12.2 | 163.0 | 147.0 | 183.0 | 0.13 |
| Oral | 172.3 | 8.0 | 171.5 | 163.0 | 183.0 | |
| **BMI ($kg/m^2$)** | | | | | | |
| Patch | 27.2 | 3.4 | 27.5 | 20.3 | 32.4 | 0.31 |
| Oral | 25.6 | 3.4 | 26.2 | 20.7 | 30.9 | |
| **Duration of illness (year)** | | | | | | |
| Patch | 5.2 | 4.0 | 6.0 | 1.0 | 15.0 | 0.90 |
| Oral | 4.5 | 3.2 | 3.5 | 2.0 | 10.0 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Stage (H&Y)** | | | | | | |
| Patch | 2.4 | 0.4 | 2.5 | 2.0 | 3.0 | 0.49 |
| Oral | 2.3 | 0.4 | 2.0 | 2.0 | 3.0 | |
| **MMSE** | | | | | | |
| Patch | 21.6 | 2.2 | 22.0 | 18.0 | 24.0 | 0.90 |
| Oral | 21.4 | 2.1 | 21.0 | 19.0 | 24.0 | |

SD: standard deviation; Min: minimal value; Max: maximal value; BMI: body mass index (kg/m2); H&Y: Hoehn & Yahr staging of Parkinson's disease; MMSE: mini-mental state examination.

The two treatment groups were well matched with respect to baseline demographics (Table 2), however there were more males in the oral group compared to the transdermal group (7/8 (87.5%) vs. 5/11 (45.5%). All patients were taking levodopa at the time of study. In the oral group, 3 patients were taking levodopa alone, 3 were also taking a dopamine agonist and 2 were taking entacapone in addition to levodopa. In the transdermal group, 8 were taking levodopa alone, 2 were taking levodopa and a dopamine agonist and 1 patient was using entacapone and levodopa. Use of potentially confounding medications was more common in the patch group where 6 of 11 patients used benzodiazepines at bedtime, compared to only 1 of 8 in the oral group. One patient in each group was using a urinary anticholinergic. Use of other medications was similar across groups. The mean daily dose of rivastigmine achieved for patients assigned to the patch was 16.4 mg (± 3.6 mg); only one patient was unable to tolerate the 10 $cm^2$ dose. Patients assigned to oral capsules achieved a mean daily dose of 9.4 mg (± 1.5 mg). In the first 3 months of the study period, a total of 6 patients temporarily discontinued and resumed therapy at a lower dose for non-serious adverse events (n= 5 oral; n=1 transdermal).

*Global Parameters*

As presented in Table 3, improvement in the primary outcome of mean velocity of CoP was seen under the most difficult condition (eyes closed with sway-referenced support



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surface). Patients in the transdermal, but not oral, group experienced a significant 15.8% decrease in mean velocity of CoP at 6 months (patch: $p < 0.05$; oral: 10.0% decrease, $p=0.16$); there was no difference between groups ($p=0.27$). There were no significant differences within or between groups under the remaining conditions (within ps $\geq 0.33$; between ps $\geq 0.24$), namely eyes open with static support surface (patch: 1.26 cm/s (pre) vs. 1.24 cm/s (post); oral: 1.24 cm/s (pre) vs. 1.29 cm/s (post)), eyes open with sway-referenced support surface (patch: 2.91cm/s vs. 2.95 cm/s; oral: 3.69 cm/s vs. 3.52 cm/s), eyes closed with static support surface (patch: 1.90 cm/s vs. 2.05 cm/s; oral: 2.21 cm/s vs. 3.13 cm/s). There were no differences within or between groups in terms of sway area. For the hardest condition, there was no observable trend towards increased improvement in those with higher initial mean velocities compared to those with lower initial mean velocities. Of patients who improved more than 20% from baseline (a clinically significant difference; n=6), the range of baseline mean velocities was 3.43 cm/s to 7.68 cm/s. This is compared to a range of 2.03 cm/s to 10.47 cm/s in baseline mean velocities for those who improved less than 20% or who worsened.

**Table 3:** Results for global and structural parameters and number of falls observed during dynamic posturography performed with eyes closed on sway-referenced surface

| | Baseline | | Post-treatment | | Within | | Between | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | p-value | Effect size | p-value | Effect size |
| *Global parameters* | | | | | | | | |
| **Mean velocity (cm/s)** | | | | | | | | |
| Patch | 6.28 | 2.36 | 5.29 | 1.92 | **0.02*** | 0.73 | 0.27 | 0.27 |
| Oral | 6.88 | 2.47 | 6.20 | 3.06 | 0.16 | 0.49 | | |
| **Surface ($cm^2$)** | | | | | | | | |
| Patch | 20.13 | 12.89 | 15.19 | 8.19 | 0.24 | 0.37 | 0.63 | 0.13 |
| Oral | 18.31 | 8.04 | 17.02 | 9.78 | 0.48 | 0.25 | | |
| **ML SD (cm)** | | | | | | | | |
| Patch | 0.47 | 0.19 | 0.43 | 0.19 | 0.29 | 0.34 | 1.00 | 0.00 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Oral | 0.46 | 0.12 | 0.44 | 0.16 | 0.58 | 0.20 | | |
| **AP SD (cm)** | | | | | | | | |
| Patch | 2.16 | 0.65 | 1.89 | 0.49 | 0.20 | 0.40 | 0.36 | 0.23 |
| Oral | 2.16 | 0.81 | 2.03 | 0.60 | 0.58 | 0.20 | | |
| *Structural parameters (sway density plots)* | | | | | | | | |
| **Mean duration of peaks (s)** | | | | | | | | |
| Patch | 0.23 | 0.06 | 0.26 | 0.07 | **0.05*** | 0.63 | 0.83 | 0.06 |
| Oral | 0.21 | 0.07 | 0.24 | 0.09 | 0.07 | 0.64 | | |
| **Inter-peak spatial distance (mm)** | | | | | | | | |
| Patch | 17.5 | 6.3 | 16.2 | 4.6 | 0.20 | 0.40 | 0.90 | 0.04 |
| Oral | 16.2 | 4.9 | 14.4 | 4.7 | **0.04*** | 0.74 | | |
| **Time distance (s)** | | | | | | | | |
| Patch | 0.54 | 0.03 | 0.56 | 0.04 | 0.45 | 0.24 | 0.83 | 0.06 |
| Oral | 0.55 | 0.03 | 0.55 | 0.03 | 0.89 | 0.05 | | |
| **Number of falls** | | | | | | | | |
| Patch | 10 | | 4 | | | | | |
| Oral | 2 | | 2 | | | | | |

SD: standard deviation; ML: mediolateral direction; AP: anteroposterior direction; *p<0.05

*Structural Parameters*

As per Table 3, significant improvements were seen in at least one group for both the mean duration of peaks (patch group) and inter-peak distance (oral group) under the most difficult condition. As well, the same tendencies in the same direction were observed in the opposing groups for each of these variables. The pre-post difference in the mean duration of peaks in the oral group, albeit non-significant, was + 0.03 seconds; the same as in the transdermal group. The pre-post difference in inter-peak distance, which was

again non-significant, was -1.3 mm in the transdermal group (compared to -1.8 mm in the oral group).

No significant differences in peak duration within or between groups were observed in any of the 3 easiest conditions (within ps ≥ 0.16; between ps ≥ 0.31), namely eyes open with static support surface (patch: 1.76 s (pre) vs. 1.49 s (post); oral: 1.46 s (pre) vs. 1.31 s (post)), eyes open with sway-referenced support surface (patch: 0.56 s vs. 0.51 s; oral: 0.37 s vs. 0.43 s), and eyes closed with static support surface (patch: 1.01 s vs. 0.88 s; oral: 0.75 s vs. 0.58 s). The same held true for inter-peak distance (within ps ≥ 0.12; between ps ≥ 0.09), namely eyes open with static support surface (patch: 3.4 mm (pre) vs. 3.2 mm (post); oral: 2.7 mm (pre) vs. 3.4 mm (post)), eyes open with sway-referenced support surface (patch: 8.7 mm vs. 8.6 mm; oral: 9.9 mm vs. 9.1 mm), and eyes closed with static support surface (patch: 5.1 mm vs. 5.4 mm; oral: 5.5 mm vs. 7.0 mm). Clinically, these results translate to longer periods of relative stability.

*Falls*

The greatest number of falls was observed with eyes-closed and a sway-referenced support surface. No falls occurred in either condition with static support. There were more fallers in the patch group (5/11) than in the oral group (2/8) at baseline. It is important to note that benzodiazepine use was not different in fallers (n=3) and non-fallers (n=4). Considering more males participated in the study, proportionally more females fell in comparison (4/6 females vs. 4/13 males). One male and one female fell more often on treatment and one male fell the same number of times. Otherwise, all patients had fewer falls on treatment and fewer patients fell (2 of 11 patch patients and 1 of 8 oral patients).

*Secondary Clinical Outcomes*

Regarding the secondary clinical outcomes, all observations were non-significant with only a trend towards significance for oral patients on the global MDRS score (pre 114.9 vs. post 121.9; p = 0.09) and the attention subscore (pre 32.3 vs. post 34.0; p = 0.07). Data are reported in Table 4.

**Table 4:** Secondary clinical outcomes

| | Baseline | | Post treatment | | Within | | Between | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | p-value | Effect size | p-value | Effect size |
| **UPDRS III axial** | | | | | | | | |
| Patch | 3.7 | 2.2 | 3.7 | 2.0 | 0.89 | 0.04 | 0.76 | 0.09 |
| Oral | 3.1 | 3.3 | 3.1 | 3.5 | 1.00 | 0.00 | | |
| **UPDRS III global** | | | | | | | | |
| Patch | 23.5 | 6.6 | 23.1 | 8.3 | 0.86 | 0.05 | 0.36 | 0.23 |
| Oral | 20.0 | 8.9 | 22.0 | 11.2 | 0.44 | 0.27 | | |
| MDRS **attention** | | | | | | | | |
| Patch | 33.1 | 3.0 | 33.2 | 2.0 | 1.00 | 0.00 | 0.15 | 0.35 |
| Oral | 32.3 | 3.1 | 34.0 | 2.4 | 0.07 | 0.64 | | |
| MDRS **global** | | | | | | | | |
| Patch | 106.6 | 15.6 | 112.6 | 19.9 | 0.26 | 0.34 | 0.63 | 0.12 |
| Oral | 114.9 | 13.0 | 121.9 | 15.2 | 0.09 | 0.59 | | |
| **NPI anxiety and depression** | | | | | | | | |
| Patch | 1.9 | 1.3 | 3.6 | 4.1 | 0.26 | 0.34 | 0.41 | 0.20 |
| Oral | 1.8 | 1.8 | 1.6 | 2.0 | 0.71 | 0.13 | | |
| **NPI global** | | | | | | | | |
| Patch | 9.4 | 9.1 | 8.5 | 7.1 | 0.72 | 0.11 | 0.57 | 0.13 |
| Oral | 6.1 | 4.2 | 5.9 | 5.3 | 0.92 | 0.04 | | |

## Discussion

The current study provides objective evidence that cholinesterase inhibitors may confer postural benefits in PDD, especially under taxing conditions. Patients in the patch group experienced an improvement in mean CoP velocity under the most difficult sensory condition, indicating global postural improvement.

In terms of structural parameters, patients were able to maintain longer periods of stability and were able to regain stability more efficiently when on treatment. Interestingly, others have shown that the ability of these two structural parameters, together with the mean CoP velocity, to distinguish among sensory and pathological conditions in postural control may be synergistic (Baratto et al., 2002). Therefore, the significant observations noted in both of these structural parameters and the mean CoP velocity are worth exploring.

It is likely that the exclusive significance of the results for eyes closed- dynamic support was an artifact of the sensitivity of this more difficult condition for detecting instability. This phenomenon has been observed previously; Nardone & Schieppati (Nardone & Schieppati, 2006) were also unable to detect any postural differences between PD fallers and non-fallers until the most difficult condition. It has been demonstrated that patients with PD rely heavily on visual flow (Schubert, Prokop, Brocke, & Berger, 2005) to compensate for demonstrated neurosensory deficits in the sole of the foot and an impaired ability to process and appropriately integrate proprioceptive information (Abbruzzese & Berardelli, 2003). Therefore, in an eyes-open scenario, deficits in proprioceptive processing may be masked by visual compensation. Furthermore, it has been proposed that dopaminergic, rather than cholinergic, mechanisms may contribute more significantly to the visuospatial aspects of postural control (Cham, Perera, Studenski, & Bohnen, 2007). The absence of a significant modulation of dynamic balance by cholinergic agents under easier conditions is not necessarily discouraging as dynamic conditions are typically more reflective of activities of daily living and therefore more indicative of fall risk.

Patients were also followed over a relatively long duration and natural disease progression may have affected balance control in the direction of a mild deterioration over six months. Thus, even the slight improvement in postural performance observed in this study is promising, considering the progressive nature of PDD.

With respect to falls, patients in the patch group did fall more frequently. This difference between groups is likely a chance observation as most falls occurred prior to treatment. Although, this may have been a signal that patients assigned to the patch group had slightly more advanced disease at baseline, despite a lack of significant difference between groups in terms of duration of illness, disease stage and MMSE at enrolment. Randomization was not stratified by fall history or stage of disease, therefore this could partly explain the significant finding of improved mean velocity in the patch group. Others, such as Chung et al. (Chung et al., 2010), have shown an enriched benefit of cholinesterase inhibitors in frequent fallers. Their randomized, placebo-controlled trial of 23 patients with PD and frequent falls showed that 6 weeks of donepezil significantly decreased fall frequency. Group assignment aside, 5 of 8 fallers showed improvement in the number of falls. Only 2 of the 19 patients fell more frequently after 6 months; one of which fell in 3 and 6 trials at baseline and 6 months, respectively. Notably, this patient showed extreme oscillations relative to other participants, even in the easiest condition, but also had the longest duration of illness of all participants at 15 years. With the exception of this fall pattern, there was no clear indication, in the most difficult condition, that those with the lowest levels of baseline postural performance fared any better on-treatment than those who performed better at baseline.

The achievement of a significant outcome was inconsistent with respect to treatment allocation, which may be explained by our sample size as similar trends were observed in both groups. Heterogeneity of the two groups for co-medication and sex at baseline was previously mentioned. There were more patients in the patch group using benzodiazepines, which are known to impair balance and increase fall-risk (Cutson, Gray, Hughes, Carson, & Hanlon, 1997; Ray, Thapa, & Gideon, 2000). Indeed, patch users fell

more frequently at baseline. However, they were the only group to show significant improvement in mean CoP and most fallers demonstrated improvement in the number of falls on treatment. These observations could suggest that cholinergic therapies may help overcome the balance perturbing effects of benzodiazepines and certainly deserves further study. Another possible explanation for the inconsistency could be that the patch group had proportionally more females than the transdermal group. Sex-related differences in PD pathophysiology and symptomatology are recognized (Gillies, Pienaar, Vohra, & Qamhawi, 2014; Lubomski, Rushworth, Lee, Bertram, & Williams, 2014), including a predilection for women to experience greater visuospatial deficits compared to men (Miller & Cronin Golomb, 2010), which is supported by our observation that a larger proportion of female participants fell prior to treatment. Therefore, the current study suggests that potential confounders such as sex, medication use (e.g. benzodiazepines), disease progression, cognitive and physical functioning may have precluded the emergence of any observable patterns between groups.

Although, none of the posturographic outcomes were significantly different between treatment groups, this is to be expected, as comparative studies have shown little to no difference between oral and transdermal rivastigmine for cognition in Alzheimer's disease (Winblad, Cummings, et al., 2007). However, as expected, more patients were able to consistently tolerate the transdermal patch as this route of administration minimizes gastrointestinal adverse effects associated with oral administration (Kurz, Farlow, & Lefevre, 2009) and promotes compliance (Winblad, Kawata, et al., 2007).

No significant differences were observed for any of the cognitive outcomes under study, nor were there any observable patterns of improved cognition associated with improved balance at the individual level. Similarly, Henderson et al. (E. J. Henderson et al., 2016), despite a significant improvement in step-time variability with rivastigmine, were also unable to demonstrate an improvement in secondary cognitive measures. Chung et al. (Chung et al., 2010), in their aforementioned study, were also unable to suggest an etiology of the observed reduction in fall frequency as no improvement in clinical

measures of balance, PD symptoms or mental status were observed. Indeed, larger populations were needed to demonstrate a cognitive benefit of rivastigmine in PDD.

Therefore, while preliminary pathophysiologic and posturographic evidence favours a cholinergic mechanism with a potential role for cholinesterase inhibitors, more research into cognitive correlates of postural instability is required.

*Limitations*

As mentioned, the trial is limited by its small sample and was surely underpowered to detect any subtle differences between dosage forms as well as improvements in the less challenging postural conditions.

Some limitation also exists in that comparator group in the current trial also received active treatment. However, as rivastigmine has previously established benefits in PDD (Emre et al., 2004; Wesnes et al., 2005), a placebo group in a population of patients with dementia would have been unethical.

**Conclusions**

This study offers preliminary evidence that rivastigmine may improve certain elements of postural control, notably the mean velocity of the CoP, a validated measure of fall-risk. Benefits appear to be more obvious under more taxing sensory conditions and in frequent fallers, where room for improvement is greatest. Along with previous results showing benefits in frequent fallers, those at the highest risk of postural instability, such as women and benzodiazepine users as suggested in the current study, may benefit the most. At the very least these results suggest that balance would not be adversely affected with rivastigmine. Therefore, rivastigmine may be considered on a case-by-case basis for PDD patients at high risk of falling. There is a need for larger randomized controlled trials to

further clarify the role of cholinesterase inhibitors in postural instability in PD patients both with and without dementia.

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