Investigating the effect of rivastigmine on postural control in Parkinson's disease dementia

Mémoire

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RÉSUMÉ

Objectifs : Comparer l'efficacité et l'aspect sécuritaire de la rivastigmine sous forme orale et transdermique destinée au traitement des symptômes liés aux instabilités posturales de patients atteints de la démence de la maladie de Parkinson (PDD) et qui sont des candidats pour un inhibiteur de l'acétylcholinestérase. La principale variable de l'étude était le changement de vitesse moyenne du centre de pression (CoP) en position debout après 6 mois de traitement. Les variables secondaires étaient les paramètres structuraux de posturographie dynamique, des échelles d'évaluation cliniques et les effets secondaires nécessitant une réduction de la dose. **Méthodes:** Des patients avec PDD ont été randomisé dans un ratio de 1 :1 impliquant une prise de rivastigmine orale ou transdermique avec des doses cibles de 6 mg deux fois par jour et 9,5 mg/10 cm^2 par jour, respectivement. Les variables dépendantes ont été comparées au départ de l'étude et après 6 mois (comparaisons intra-groupes), de même qu'entre les groupes. **Résultats:** Dix-neuf patients ont complété l'étude (n=8 orale; n=11 transdermique). Des doses quotidiennes moyennes de 9,4 mg (± 1,5 mg) et 16,4 mg (± 3,6 mg) ont été administrées aux groupes oral et transdermique, respectivement. Le groupe transdermique a démontré une réduction significative de la vitesse moyenne du CoP de 15.8% (timbre: p=0,02; orale: réduction de 10,0%, p=0,16) lors de la condition d'équilibre la plus difficile (yeux fermés en maintenant l'équilibre sur une plateforme mobile synchronisée avec les déplacements du corps). Aucune différence n'a été trouvée entre les groupes (p=0,27). Concernant les paramètres structuraux, des améliorations significatives ont été observées au niveau de la durée moyenne des pics de stabilité de l'équilibre (timbre) et de la distance entre les pics de stabilité (orale) dans la condition d'équilibre la plus difficile. Aucun changement n'a été observé par rapport aux échelles cliniques. Six patients ont eu des effets secondaires mineurs nécessitant une réduction de dose (n=5 orale; n=1 transdermique). **Conclusions:** La rivastigmine pourrait améliorer certains éléments du contrôle postural de patients atteints de PDD, notamment la vitesse moyenne du CoP en position debout. Les bienfaits sont plus évidents sous les conditions qui challengent davantage l'équilibre.

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.

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ACh : acetylcholine
AChE : acetylcholinesterase
AChEI : acetylcholinesterase inhibitor
AD: Alzheimer's disease
ADHD : attention deficit hyperactivity disorder
AOS : accessory optic system
AP : anteroposterior
APA : automatic postural adjustment
APR : automatic postural reaction
BBB : blood-brain barrier
BMI : Body mass index
CNS : central nervous system
CoG : centre of gravity
CoM : centre of mass
CoP : centre of pressure
CPAS : consecutive or compensatory postural adjustments
DBS : deep brain stimulation
DRT : dopamine replacement therapy
DSM-IV: diagnostic and statistical manual IV
EMG : eletromyogram
FDOPA : ^{18}F-fluorodopa
fMRI : functional magnetic resonance imaging
GABA : gamma-aminobutyric acid
GI : gastrointestinal
H&Y: Hoehn & Yahr
HAM-D Hamilton depression scale
MDRS: Mattis Dementia Rating Scale
ML: mediolateral
MMSE: mini-mental status exam
MP4A: N-[^{11}C]-methyl-4-piperidyl acetate
MPH : methylphenidate
nBM : nucleus basalis of Meynert
NMS : non-motor symptoms
NPI : Neuropsychiatric Inventory
PD: Parkinson's disease
PDD: Parkinson's disease dementia
PET : positron emission tomography
PIGD : postural instability and gait disorder
PPN : pedunculopontine nucleaus
PSP : progressive supranuclear palsy
SD : standard deviation
SOT : sensory organization test
SPSS : Statistical Package for the Social Sciences
UPDRS : Unified Parkinson's Disease Rating Scale
VNC : vestibular nuclear complex
VOR : vestibulo-ocular reflex

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First and foremost, I would like to thank Dr. Philippe Corbeil for without him this would not have been possible. His patience has been endless and has spanned the nearly 9 years it has taken me to complete this project. Not once did he express any doubt that I would not finish. He pushed me to be a better student and to extend my boundaries beyond pharmacology and into the unknown of human kinetics and postural control.

I must also thank Dr. Emmanuelle Pourcher who is responsible for much of the higher-level thinking that went into the design and conception of this study. Her professionalism and attitude towards her patients has inspired me to be a better researcher and clinician. Her support of my professional and personal endeavors has been unending. She is an admirable woman and one I aspire to emulate. I thank her for her teaching moments and for allowing me to be a part of caring for her patients. It is an experience that I will carry with me throughout my career.

Thank you to Mr. Charles Garneau for his logistical support and his generosity for allowing me to be a part of the Clinique Ste-Anne and the current research. His guidance was instrumental in the success of this project. I also owe a debt to Mr. Garneau who was instrumental in helping me achieve any sort of competency in the French language.

Thank you to Alexandra Nadeau and Yoann Dessery who helped with data collection and analysis while I was galavanting around the country completing my PharmD. Without their support, I could not have achieved the academic career I am thankful for today.

I would like to thank my husband, Mathieu, for his much-needed French-language support. His love has given me the stability I needed to make the final push towards completing this project. I would also like to thank my daughter, Madelyn, who has inspired me to be an example for her and finish what I have started.

FOREWORD

This project was supervised by Dr. Philippe Corbeil. Dr. Corbeil completed a Master's degree in Physical Activity followed by a Doctor of Philosophy in Kinesiology at Laval University. He completed post-doctoral studies in aging and postural control in Toronto. His research interests include the evaluation of motor control in man, notably the effects of aging on motor processes. His research objectives include the development of physical interventions to help delay the effects of aging and other disease pathologies on motor capabilities that are essential to the autonomy of patients.

Dr. Emmanuelle Pourcher, neurologist and movement disorders specialist associated with the Faculty of Medicine at Laval University, graciously co-supervised this project and oversaw the design and completion of data collection at the Clinique Ste-Anne in Québec, QC.

The current thesis was not the original intent of my studies. Before pursuing the current area of study, with the help of Dr. Pourcher and Dr. Corbeil, I designed and implemented a randomized, placebo-controlled clinical trial of methylphenidate for the treatment of postural instability and non-motor symptoms in Parkinson's disease. However, owing to difficulties in recruitment and unfavorable interim analyses, the study was halted after 6 patients. While unproductive from the point of view of dissemination and publication, this study taught me the intricacies of designing a clinical trial, the Health Canada and ethics committee approval processes, patient recruitment and informed consent, data collection and analysis, as well as using professional judgement to end the study in the best interest of the participants.

Therefore, it was decided that I would pursue an orphaned study conducted previously at the Clinique Ste-Anne. While the design, data collection and a portion of the analysis had already taken place, the synthesis and interpretation was left to me – the piece of my experience missing from my first attempt at a clinical trial.

The case study outlined in Chapter 5 of this thesis was published in the *Journal of Neurological Sciences* on June 1, 2017 (McDonald, Corbeil, & Pourcher, 2012). It has been inserted in this thesis without modification to content. The order of content has been changed to facilitate readability. I was listed as the first author of this study as I completed the data collection and also contributed to the analysis in collaboration with Dr. Philippe Corbeil. I authored the article which was reviewed and revised by my co-authors, Dr. Emmanuelle Pourcher and Dr. Philippe Corbeil. Dr. Pourcher was the treating physician of the included patient and was responsible for conception of the treatment plan and outcome analysis.

The main study outlined in Chapter 6 of this thesis was accepted without modification to *Clinical Neuropharmacology* in November of 2017 and is awaiting publication. It is presented in its published format without modification to content. I am listed as the first author along with Emmanuelle Pourcher, Alexandra Nadeau and Philippe Corbeil, respectively. Our contributions were as follows:
Conception and design: EP

Collection and assembly of data: AN, EP

Analysis and interpretation of data: JM, EP, AN, PC

Critical revision of the article for important intellectual content: JM, EP, PC

Final approval of article: JM, EP, AN, PC

CHAPTER 1: INTRODUCTION

In its simplest form, posture may be considered as the maintenance of an upright body position that counters the effects of gravity. The control of posture is a constant process and must be maintained both under static conditions and in motion. In humans, the process is invariably complex and represents the culmination and coordination of various functions. To complicate matters, age and disease often have undesirable effects on posture and ultimately fall-risk.

In the case of Parkinson's disease (PD), both age and postural instability are the most important risk factors for falling (Hiorth et al., 2017). Unlike the cardinal motor features of PD, which include resting tremor, bradykinesia and rigidity, postural instability is a late feature of PD which rarely presents early in the course of illness (Postuma et al., 2015). While the cardinal motor features of PD are thought to be mostly related to nigrostriatal dopamine loss, postural instability in PD is likely due to extra-dopaminergic neurodegeneration (Kim, Allen, Canning, & Fung, 2013). Postural instability in PD manifests itself as a progressive loss of postural reflexes, however the underlying pathophysiologic mechanisms are complex, involving both the underlying disease process and compensatory mechanisms (Benatru, Vaugoyeau, & Azulay, 2008). Postural instability is extremely debilitating for PD patients, increasing the risk of falls and their associated morbidity, and drastically reduces quality of life (Muslimovi et al., 2008).

Like postural instability, Parkinson's disease dementia (PDD) is one of the later complications of PD. Nearly 30% of patients with PD have dementia and at least three-quarters of PD patients surviving for more than 10 years will develop dementia as a complication of their illness (Aarsland & Kurz, 2010). The clinical picture of PDD may include, among other symptoms, executive dysfunction, impaired recognition memory, deficits in attention and visual perception, hallucinations and cognitive fluctuations (rather than impairment) as well as behavioural features such as apathy, personality or mood changes, hallucinations, delusions or excessive daytime sleepiness (Emre et al., 2007). The constellation of motor and cognitive deficits unique to PDD has synergistic

effects on posture in that these patients display both aberrant postural adjustments as well as cognitive dysfunction (Kim et al., 2013), which on its own is known to impair the sensory integration and re-weighting essential for postural control (F. B. Horak, 2006). Unfortunately, the discussion of postural instability in PDD involves some extrapolation as little research is available to characterize the pathology and clinical picture of postural instability in PDD specifically.

While postural instability itself is not a diagnostic criterion for PDD, a subtype characterized by postural-instability and gait difficulty represents 88% of these patients; it is more than twice as common in patients with PDD than in those with PD alone (Burn et al., 2003). As well, transition to this subtype of PD has been associated with incident dementia, suggesting that postural instability and PDD may share a neuropathologic etiology (Alves, Larsen, Emre, Wentzel‐Larsen, & Aarsland, 2006).

The most likely common denominator, from a neurotransmitter perspective, is acetylcholine (ACh); neuroimaging and clinical trials alike have supported this hypothesis. The cholinergic pedunculopontine nucleus (PPN) is heavily involved in postural control and cholinergic systems exhibit significant pathology in PDD (Hilker et al., 2005). Clinical trials of acetylcholinesterase inhibitors (AChEIs) have demonstrated their ability to reduce fall-risk in PD populations (Chung, Lobb, Nutt, & Horak, 2010; E. J. Henderson et al., 2016), however there are no studies of AChEIs for postural instability or falls in patients with PDD.

Therefore, the objective of the current research is to conduct a randomized trial of rivastigimine, an AChEI already approved for PDD in Canada, for postural instability in PDD. Participants with PDD will be randomized to rivastigmine transdermal patches or oral capsules at therapeutic doses and will be assessed using dynamic posturography for markers of fall-risk prior to and after 6 weeks of therapy. In support of the primary hypothesis that pharmacologic enhancement of cholinergic pathways will have beneficial effects on elements of postural control, this document presents a case study of donepezil

in progressive supranuclear palsy (PSP), a Parkinsonian disorder sharing some pathology and symptomatology with PD, notably in its propensity for postural instability and falls.

Following this introduction, in order to gain an understanding of how human systems function to maintain an upright body posture, an outline of the anatomy and physiology of various systems involved in postural control will be presented in Chapter 1. As both the peripheral and central nervous systems are intricately involved in the gathering and processing of sensory information, particular attention will be paid to neuroanatomy and neurotransmission. Where important, various neurotransmitter systems will be highlighted to guide the understanding of how posture may be influenced by age and disease-related deficits and in turn, how they may be treated with pharmacologic therapy.

Following a description of the neurologic mechanisms of postural control, Chapter 2 will discuss various disease states and their relevant neurologic pathology. The discussion is based largely upon the thesis that cholinergic neurotransmission is intricately involved in postural control and that in disease states such as PD and PDD, deficits in cholinergic pathways result in symptoms of postural instability and falls.

In Chapter 3, a review of the published literature regarding the pharmacologic treatment, in particular the utility of cholinesterase inhibitors, of various dimensions of postural instability and falls will clarify the state of our current knowledge and suggest directions for future study.

Finally, Chapters 4 and 5 consist of the research articles comprising this thesis in their published and accepted forms, respectively. A general conclusion closes the document.

CHAPTER 1: ANATOMICAL AND PHYSIOLOGICAL ASPECTS OF POSTURAL CONTROL

The control of posture in healthy individuals involves the integration of multiple sensorimotor processes. The central nervous system receives input from several sensory systems, including the vestibular, visual and somatosensory systems. In order to maintain postural equilibrium, these inputs are integrated and various compensatory strategies are initiated to stabilize the centre of mass (CoM), maintain gaze, head and body posture as well as control static and dynamic balance. Both sensory orientation and the maintenance of equilibrium will be discussed in detail.

The Vestibular System

The main function of the vestibular system is to perceive movement and body (head) position relative to objects in space and to the body. Information from the vestibular system is integrated with input from other sensory systems, primarily the visual and somatosensory systems, to coordinate centrally mediated and reflexive motor responses that help maintain balance and equilibrium.

Peripheral Vestibular Anatomy

The peripheral vestibular system is located in the inner ear, which consists of the cochlea, the vestibule and the semicircular canals. The cochlea is involved in hearing with the latter two structures comprising the vestibular system. This system consists of two anatomical components; the semicircular canals and the otoliths. Each component is paired across the head with its counterpart (i.e. left and right semicircular canals) with each pair working in tandem to convey information regarding head position to the brain.

With respect to the detection of rotational movement, the three semicircular canals project posteriorly from the vestibule and correspond to each of the three dimensional anatomical planes; the sagittal, frontal and horizontal planes. Movement of fluid

contained within these semicircular canals corresponds to rotational accelerations in the direction of the corresponding anatomical plane. The *crista ampullaris*, which is situated at the end of each canal, contains mechanoreceptors known as hair cells (Springhouse, 2002). Hair cells transduce mechanical movement, in this case the fluid within the canals, into electrical impulses. Mechanical stimulation in one direction results in depolarization of the hair cell and neurotransmitters are released from the base of the hair cell, resulting in increased neural discharge in the selected primary afferent neurons. Alternatively, if the hair cells are sheared in the opposite direction, hypopolarization of the hair cell ensues, resulting in decreased neurotransmitter release and decreased neuronal firing (Jones, Jones, Mills, & Gaines, 2009). When one side is activated by head motion, the opposite side is inhibited. This selective firing of primary afferent neurons allows information regarding the direction of movement to be relayed to the vestibular nuclei. Relative activation and inhibition will be discussed further under "Vestibulo-Ocular Reflex."

The otolithic organs, the utricule and the saccule, are membranous sacs suspended by a fluid contained in the vestibule of the inner ear. The hair cells of these organs detect linear and angular accelerations as well as gravitational changes (Springhouse, 2002). Essentially, these organs are responsible for providing information regarding the orientation of the head in space, both at rest and during movement.

Central Vestibular Anatomy

Vestibular nerves located at the base of hair cells in the otoliths and semicircular canals converge at the vestibular ganglion. From here, their axons travel in the vestibular portion of the VIIIth cranial nerve and enter the brain stem between the pons and the medulla. Most of these primary afferents synapse at second order neurons in one of the four vestibular nuclei (superior, lateral, medial and inferior), referred to as the vestibular nuclear complex (VNC). There is both a left and right VNC, which receives input from its respective peripheral organs. Some nerves, however, do travel directly to the cerebellum. Projections from the four vestibular nuclei extend to 1) the extraocular motor

nuclei, which control eye movements;2) the spinal cord, which controls head and body position; 3) the thalamus, which in turn extends to the cortex for conscious perception of movement; and 4) the cerebellum, which coordinates postural adjustments (Baloh & Kerber, 2010).

Vestibular Neurotransmission

The primary neurotransmitter of hair cell afferent synapses is glutamate, an excitatory neurotransmitter (Soto & Vega, 2010). Glutamate is also released where these primary afferent neurons synapse with secondary neurons of the vestibular nuclei.

The neurons of the vestibular nuclei extend glutamatergic, cholinergic and gamma-Aminobutyric acid (GABA)-ergic projections to various parts of the central nervous system (CNS) as discussed above. Acetylcholine (ACh) is likely the primary neurotransmitter in vestibulocerebellar pathways (Balaban & Porter, 1998; de Lacalle, Hersh, & Saper, 1993) and is also involved in thalamic neurotransmission (McCormick & Prince, 1986). Acetylcholinesterase (AChE), which is the enzyme responsible for the metabolism of ACh and is often used as a surrogate marker for cholinergic activity, is also found in cerebellum and the thalamus (de Lacalle et al., 1993).

Conversely to afferent vestibular neurotransmission, efferent neuronal synapses (i.e. neurons transmitting impulses from the central nervous system to the vestibular periphery) release ACh as the primary neurotransmitter (Soto & Vega, 2010). These efferent neurons originate in the brainstem and innervate hair cells and vestibular afferents to exert central control over vestibular responses based on the movement programming of the subject (Bridgeman, Hoffman, Wackym, Micevych, & Popper, 1996; Soto & Vega, 2010).

The Visual System

Simply put, the visual system is fundamental in providing information regarding the layout of the surrounding environment that is then used to develop appropriate motor responses (i.e. stepping onto a curb or avoiding an obstacle). It also serves as a reference point for other sensory and cortical functions that use visual cues to orient the body in space.

Like the peripheral vestibular system, the visual system also delivers its information to the vestibular nuclei, among other locations, for integration. More specifically, visual information is relayed from the retina to the accessory optic system (AOS) nuclei, which project to the vestibular nuclei. The main role of the AOS in maintaining posture is, with help from the vestibular system, to help distinguish between movements in the environment from movement of the body (Soto & Vega, 2010). In addition to their connections to the vestibular nuclei, the AOS nuclei have efferent connections to the cerebellum and midbrain. In turn, the vestibular nuclei receive afferent input from the visual cortex, which is responsible for processing visual information (Giolli, Blanks, & Lui, 2006).

Vestibulo-Ocular Reflex (VOR)

A reflex occurs relatively rapidly in response to sensory stimuli. The VOR is an example of a polysynaptic reflex (i.e. more than one synapse is involved). Alternatively, most peripheral muscle reflexes such as the "knee-jerk reflex" are monosynaptic (i.e. only one synapse is involved at the level of the spinal cord) (Barrett, 2010). This VOR serves to maintain a fixed image on the retina while the head is in motion. The VOR produces compensatory eye movements in the opposite direction of head movement. This is achieved when vestibular afferent neurons are activated on one side and subdued on the other, for example when the head turns to one side. To simplify, when the respective VNC is activated, signals travel through second order neurons to the IIIrd cranial (oculomotor) nerve on the same side. This nerve then crosses over to the opposite side, activating the opposite abducens nucleus (VIth cranial nerve). While these neurons are being activated on one side, they are being inhibited on the other. The neurons from the

abducens nucleus activate the lateral rectus muscle, which pulls the eye in the opposite direction of the movement (i.e. if the head turns right, the eye moves left). Motor neurons from the opposite oculomotor nucleus will contract the medial rectus muscle of the other eye to pull this eye in the same direction (opposite to the movement). The opposing muscles in each eye will relax as they have been inhibited by their respective motor nuclei (Jones et al., 2009). This reflex plays an important role in the complex sensorimotor integration that maintains balance. Nystagmus, which is the presence of compensatory eye movements in the absence of head movement, can in some instances cause blurred vision, postural imbalance, ataxia and gait disturbances (Jahn & Dieterich, 2011).

Ocular Neurotransmission

Most of the neurotransmitter pathways of the AOS utilize GABA, however other transmitters may be involved. However, as they are motor neurons, the medial rectus and abducens motoneurons, responsible for activating the muscles that turn the eyes horizontally as described above, utilize ACh (Leigh & Ramat, 1999).

ACh activity is also prevalent in the visual cortex and is purported to reduce "noise" signals during the processing of visual inputs (Gu, 2003). ACh may also be involved in neuroplasticity within the visual cortex (Maya-Vetencourt & Origlia, 2012).

The Somatosensory System

The main function of the somatosensory system may be drawn from its name, that is to say, somatic sensation. This complex arrangement of neurologic connections is omnipresent throughout the body with receptors on the skin, bones, muscles, joints, and internal organs. These receptors are responsible for detecting pressure, pain, hot and cold as well as chemical and osmotic stimuli. For the purposes of postural control, the most relevant receptor types are mechanoreceptors and proprioceptors, responsible for

detecting pressure and body positions (relative to other body parts and the environment), respectively.

For example, plantar mechanoreceptors (located in the skin) provide information regarding contact pressures on the sole of the foot, making them capable of detecting changes in body orientation relative to the ground (MacLellan & Patla, 2006). These receptors are divided into two subtypes, rapidly or slowly adapting. Rapidly adapting mechanoreceptors detect the rate and degree of change in the pressure exerted on the foot and slowly adapting mechanoreceptors provide constant information on how pressure is spatially and consecutively applied (Kavounoudias, Roll, & Roll, 1998).

Alternatively, proprioceptors are located in the joints, muscles and tendons. They provide sensory information regarding joint angle, muscle length, and muscle tension, which is used to detect the position of the limb in space. Muscles spindles are proprioceptors located parallel to muscle fibers and activate a primary sensory afferent neuron when the muscle is stretched. Alternatively, the Golgi tendon organ is located in tendons, in series with muscle fibers, and activates primary sensory afferent neurons when the attached muscle contracts (Purves et al., 2001).

When neurons carrying proprioceptive information reach the level of the spinal cord, most form synapses with interneurons that relay the information to higher levels of the CNS. Interestingly, the brainstem and cortex are able to exert descending control over these neurons that also allows them to filter the ascending information. Most proprioceptive information travels through the dorsal lateral tracts or the spinocerebellar tracts of the spinal cord. The dorsal lateral tracts, thought to carry most of the information that is consciously perceived, travel from the dorsal root ganglia to thalamic nuclei and then on to the somatosensory cortex. The somatosensory cortex is located in the parietal lobe, where central processing occurs. Conversely, the spinocerebellar tracts travel to the cerebellum, where the signals are integrated with descending information and input from other afferent tracts. It is hypothesized that the spinocerebellar tracts are involved in transmitting unconscious proprioceptive information, such as limb position or muscle

length, which is used for local reflexes as well as automatic and voluntary movement (Riemann & Lephart, 2002; Warren, Yezierski, & Capra, 1997).

Somatosensory information is translated into motor commands and responses via complicated interconnections with the primary motor cortex, which is beyond the scope of this discussion. The motor portion of the sensorimotor system consists of a central axis and "associate" areas. The central axis is comprised of the spinal cord, brainstem, and cerebral cortex. The associate areas include the cerebellum and basal ganglia, which coordinate the motor commands (Matthews, 1997).

Briefly, the spinal cord is responsible for the transmission of information to and from the central nervous system as well as local reflexes and the cerebral cortex (sensorimotor cortex and supplementary motor area) is involved in sensory integration, initiating various motor commands and performing executive functions related to maintaining gait, posture and balance. The cerebellum is responsible for timing and fine-tuning motor output and the basal ganglia, which will be discussed further in subsequent sections, are responsible for learning, planning, initiating, executing, and terminating motor programs. The mesencephalon (midbrain) is an important brainstem structure containing the substantia nigra and is closely linked to motor pathways of the basal ganglia. The substantia nigra will also be discussed in subsequent sections (Sousa, Silva, & Tavares, 2012).

Somatosensory Neurotransmission

With respect to the somatosensory cortex, there is animal evidence that ACh is released in large quantities following mechanical sensory stimulation(Kurosawa, Sato, & Sato, 1992). There is also evidence that following sensory stimulation (visual, tactile, olfactory, auditory), large amounts of ACh are released in the hippocampus and frontal cortex, linking cholinergic mechanisms with attention and arousal following sensory stimuli (Inglis & Fibiger, 1995).

The Stretch Reflex

The stretch reflex, or the myotatic reflex, is a reflex involving a sensory neuron and a motor neuron and is essential in the involuntary control of posture (Shemmell, Krutky, & Perreault, 2010). The most commonly known example of the stretch reflex is the "knee-jerk" reflex, but stretch reflexes also occur in postural muscles of the spine as well as in destabilizing and stabilizing muscles involved in responses to postural perturbations. If a muscle is stretched, the muscle spindle (described previously) is stretched and neuronal output is increased, thereby increasing alpha motor neuron activity. This causes the muscle fibers to contract and oppose the stretch. The opposing muscle also relaxes to accommodate this contraction (Yessis, 2000).

Stretch reflex responses have divided according to their onset latencies on electromyogram (EMG) into short- and medium- and long-latency components. Both short and long latency responses are considered involuntary as they occur before even the most rapid voluntary reaction to a stimulus, however they can be modulated under certain situations (Shemmell et al., 2010). The relative roles and timing of these responses are debated however, it is thought that the short-latency reflex is involved in regulating muscle stiffness, or rather compensating for transient decreases in muscle stiffness following joint perturbation, thereby reducing muscle yielding following the perturbation (Cronin, Carty, & Barrett, 2011). These short-latency responses occur in the stretched muscle. Medium-latency responses are deemed to be destabilizing and also occur in the stretched muscle (i.e. in the triceps surae following a toes-up platform rotation) and long-latency responses are considered stabilizing and occur in the antagonist muscle (i.e. the tibialis anterior following a toes-up platform rotation). As demonstrated in an EMG study of 33 PD patients undergoing 4-degree toes-up platform rotations, the latencies of EMG responses in these muscles are usually normal in PD patients, with the exception of an increased short-latency response (Scholz et al., 1987) in the triceps surae muscle. However, the amplitude and duration of certain of these responses are affected in PD, which will be discussed in subsequent sections.

The following excerpt from an article published by Bloem and colleagues (Bloem et al., 1996) aptly describes the role of these responses in the control of upright stance following toes up platform rotations:

"[Medium latency] stretch responses induced by toe-up rotations are functionally destabilizing since their plantar flexion force aggravates the posterior body sway induced by the toe-up rotational perturbation. In contrast, the dorsiflexion force of [long-latency] responses is functionally stabilizing."

Cholinergic Projections

ACh is a critical neurotransmitter in the central nervous system where it plays a role in arousal, attention, executive functioning and neural plasticity (Yarnall, Rochester, & Burn, 2011). The striatum is supplied with ACh via cholinergic interneurons that make up 1-2% of intrinsic striatal neurons (Zhou, Wilson, & Dani, 2002). The nucleus basalis of Meynert (nbM) is responsible for providing most of the cholinergic input to the cerebral cortex and appears to be important for several aspects of cognition, including attention (Sarter, Gehring, & Kozak, 2006). However, the PPN is responsible for providing most of the cholinergic input to the subcortical systems including the thalamus as well as the brain stem and cerebellum(Perry, Walker, Grace, & Perry, 1999). The PPN also possesses connections with the basal ganglia, notably the substantia nigra, subthalamic nucleus, globus pallidus, and extends directly to the spinal cord and the cerebral cortex (Jenkinson et al., 2009)The role of both the basal ganglia and the PPN in the pathophysiology of PD will be discussed in following sections.

Role of Cognitive Processing

Sensory Integration

Postural control relies on the integration of information from several systems and the selection of an appropriate motor program to deal with both expected and unexpected

perturbations. Neural integration of information from multiple sensory, motor and cognitive systems occurs in the VNC (Jones et al., 2009). The vestibular nuclei receive input from the three sensory systems (vestibular, visual and proprioceptive) and transmit this information to the spinal cord for postural stabilization. Interestingly, some hypothesize that abnormal activation or dysfunction in the vestibule-spinal pathways are a cause of postural imbalance and ataxia. Information is also relayed from the vestibular nuclei to the vestibular thalamus and cortex (for spatial orientation, perception of movement and sensorimotor transformation), as well as the brainstem and cerebellum (for the vestibulo-ocular reflex) (Dieterich, 2004).

Sensory Reweighting

Under normal conditions, healthy adults rely mostly on somatosensory (70%) information, but vision (10%) and vestibular (20%) information are also important (Peterka, 2002). Because sensory information is not always available (i.e. in a dark room) or reliable (i.e. compliant support surface), the dependence on each system must be re-weighted in order to accommodate. For example, when standing on an unstable support surface, reliance on visual and vestibular input increases while plantar and ankle proprioceptive information is minimized (Peterka, 2002) as it is unreliable or conflicting. The ability to re-weight sensory information is important to adapt to changing environments (i.e. changes in lighting) or sensory deficits (i.e. neuropathy). Persons with deficits in any or several of the sensory systems involved in postural control are at an increased risk of falling as their ability to re-weight dependence to that system is limited. It also appears that sensory re-weighting is limited in individuals with CNS or cognitive dysfunction (i.e. Alzheimer's disease (AD)) as the ability and rapidity of sensory re-weighting is reduced, even if peripheral input is adequate and reliable (F. B. Horak, 2006).

Attention

Balance control requires a certain level of attention on behalf of the subject and the attention required increases with the difficulty of the task at hand. For example, it has been shown that standing requires more attention than sitting and walking more attention than standing (Lajoie, Teasdale, Bard, & Fleury, 1993). In their experiment, Lajoie and colleagues demonstrated that reaction times were significantly increased when subjects were in the single-support phase compared to the double-support phase of straightforward gait. Because the base of support is smaller during the single-support phase, this represents a more difficult postural task. In this instance, balance was maintained at the expense of the subject's reaction time. Because attentional performance deteriorated under a more difficult postural condition, this study represents a good example of the involvement of attention in the maintenance of balance.

Dual Tasking

The experiment cited above by Lajoie and colleagues employed the use of a dual-task to demonstrate the involvement of attention in balance control. The theory behind dual tasking is that postural stability is not simply an automatic spinal reflex, but as previously mentioned, a task that also requires cognitive control. By dividing attention between a cognitive and postural task, one should observe a deterioration of one, the other or both tasks, depending on the difficulty of the task and the priorities, capacities or focus of the individual (Siu, Chou, Mayr, van Donkelaar, & Woollacott, 2008).

The concept of dual tasking in an experimental setting is important to consider as performing two tasks simultaneously is common in daily life (i.e. walking and talking on a cell phone). Including dual-tasks in study design allows extrapolation of experimental data to more real-life settings.

Functional magnetic resonance imaging (fMRI) evidence has shown that the cerebellum plays an important role in processing dual motor and cognitive tasks. In a study combining a motor task (finger tapping) with a counting task (counting the number of times a certain letter was displayed on a screen), various cerebellar regions were activated

on fMRI (Wu, Liu, Hallett, Zheng, & Chan, 2013). These cerebellar regions had extensive connections with motor and cognitive regions of the brain including the sensorimotor cortex, the supplementary motor area, the premotor cortex, the parietal cortex and the thalamus. Training resulted in less activation in several areas, however it increased connectivity between the cerebellum and some of the motor and cognitive areas, providing evidence that a learning effect or habituation may occur. Others have shown, again with fMRI, that dual cognitive tasks rely mostly upon the prefrontal cortex (Szameitat, Schubert, Müller, & Von Cramon, 2002), however it is unknown if the cerebellum is also heavily involved in the performance of dual motor tasks (i.e. reaching while walking).

Strategies to Maintain Postural Equilibrium

Various voluntary and involuntary as well as anticipatory and compensatory strategies are involved in postural control and will be discussed in the following sections. Evidence exists supporting a cortical role in postural responses (Jacobs & Horak, 2007). However, it is clear that not all postural responses are cognitive in nature as humans can walk and remain upright without conscious effort. Therefore, postural control is simultaneously a complex cortical and subcortical function.

Biomechanical Considerations

In order to maintain balance under static and dynamic conditions, the CoM, which represents the centre of gravity of the whole body, must remain within the limits of stability. The limits of stability are three-dimensional (in the shape of a cone) and represent the distance the CoM can travel before a loss of balance occurs. The CNS creates an internal representation of this cone of stability to determine appropriate movements to maintain upright equilibrium. The magnitude of these limits is determined by the size and integrity of the base of support, in this case the feet. Any physiological or external constraint (i.e. pain, foot size, support surface) will affect these limits and the subsequent risk of falling. When the CoM travels outside of the limits of stability,

balance is lost and a reaction must occur (i.e. taking a step or grabbing an object) to prevent a fall (F. B. Horak, 2006).

Movement Strategies

A number of movement strategies are in place to maintain the CoM within the limits of stability. These movement strategies are implemented to maintain and reestablish postural equilibrium, depending on the nature of the disturbance. These strategies can be divided into three categories: ankle, hip and stepping or reaching strategies (F. B. Horak, 2006).

In the ankle strategy, the body moves around the ankle as an inverted pendulum. This type of movement is usually adequate to account for small degrees of postural disturbance or sway, particularly when standing on a firm surface. Alternatively, the hip strategy involves an exertion of torque (or bend) at the hips and is employed when the CoM must be relocated quickly or to a larger degree. The hip strategy is commonly used when the support surface is variable or ankle torque is ineffective. When the disturbance is large and the CoM travels outside the limits of stability, a step or a reach must occur to prevent a fall. Selecting a movement largely depends on the individual's expectations and experience and in general, those at a lower risk of falling employ the ankle strategy, with those at higher risks of falling (i.e. the elderly) employing hip and stepping strategies more frequently (F. B. Horak, 2006). These strategies may be anticipatory, voluntary or compensatory. Automatic postural reactions (APRs) represent responses to sensory (visual, vestibular and somatosensory) input, which signal postural disturbances in relation to movement. Anticipatory postural adjustments (APAs) occur prior to the initiation of voluntary movements and serve to counteract the disturbance that movement will impose on balance (Kim et al., 2013).

Anticipatory Postural Adjustments (APAs)

The main function of APAs is to compensate for the destabilizing forces associated with moving a limb. The subsequent disturbance, be it internal or external, is predicted by the CNS and select muscles are activated to maintain the CoM within the limits of stability. It is hypothesized that APAs may originate from the supplementary motor area (Massion, 1992).

Therefore, these APAs occur prior to, or in anticipation of, voluntary movements, such as before taking a step. In the instance of stepping, the centre of pressure (CoP), which is the projection on the ground plane of the vertical ground reaction force distribution under the base of support (Iqbal, 2011), is shifted via selective joint repositioning and muscle contraction (in this case the tibialis anterior) backward and towards the swing leg before the movement is initiated. This helps neutralize the induced interaction torque caused by lifting the leg to take a step (Hyodo et al., 2012; Iqbal, 2011). However, APAs are also scalable to the magnitude (velocity and size) of the perturbation, usually based on preconceptions regarding the difficulty or the resources required to complete a task. This brings attention to the observation that APAs, and all postural adjustments for that matter, are learned, individualized and dependent on the task.

Interestingly, APAs are smaller when an individual is unstable, which results in further destabilization following movement of a limb owing to inadequate preparation (Aruin, Forrest, & Latash, 1998). APAs are also smaller or absent when visual or proprioceptive information is unreliable (i.e. vision is impaired and the subject is required to catch a falling object), confirming the anticipatory nature of these adjustments and supporting a feed-forward theory of postural control (Mohapatra, Krishnan, & Aruin, 2012a, 2012b).

Voluntary Movements

Centrally-mediated voluntary movements may be performed to maintain equilibrium in response to identified disturbances (i.e. stepping around an object), however, balance must also be maintained during all types of voluntary movements, whether the effort to remain upright is conscious or not. Therefore, voluntary movements inherently render

balance control more difficult. The simultaneous conduction of a voluntary movement and stabilization of balance is determined by the sum of the internal (i.e. voluntary movement of an arm) and external forces (i.e. gravity) acting on the body (Bouisset & Do, 2008). To successfully neutralize destabilizing forces and perform voluntary movements, postural adjustments occur before (APAs), during (synchronous postural adjustments) and after the movement (consecutive or compensatory postural adjustments; CPAS) (Bouisset & Do, 2008). Clearly, the relative difficulty of voluntary movements can differ greatly depending on the task (i.e. waving an arm versus getting out of a chair). However, tasks involving multiple body segments (i.e. walking) and an unstable, rather than stable, base of support are generally more challenging in terms of postural control (F. B. Horak, 2006).

Automatic Postural Reactions (APRs)

Compensatory, or reactive, strategies help stabilize the body following inappropriate or absent anticipation of movement or following external perturbations. These responses are triggered automatically, unlike APAs, which precede voluntary internal perturbations (Jacobs & Horak, 2007). If a perturbation were self-initiated (i.e. moving an arm) an APA would precede the movement, helping to maintain stability. If the perturbation was recognized in advance (i.e. an object obstructing the path), a voluntary movement could also be employed to avoid destabilization. However, it is when APAs are insufficient or perturbations are not predicted that reactive strategies must be used. These reactive postural responses occur secondary to sensory information from the visual, vestibular and somatosensory systems regarding movement. In these instances, a mechanical and then neuromuscular response occurs following the perturbation. For example, when a subject receives an unexpected perturbation during straightforward gait, the tendons and ligaments surrounding the ankle, knee and hip are stretched in sequence, which is rapidly followed by a neuromuscular adjustment in the muscles that control and stabilize the joint. The muscles surrounding the hip are likely the most important owing to the unexpected nature of the perturbation and the magnitude of compensation that is required (Ferber, Osternig, Woollacott, Wasielewski, & Lee, 2002).

However, in some cases compensatory adjustments are not sufficient to prevent destabilization. For example, APAs may be minimal during compensatory stepping and therefore the CoM tends to travel toward the swing leg side during, rather than before, the step causing a lateral instability and a subsequent risk of falling (Hyodo et al., 2012).

There is evidence that postural adjustments are under cortical control (Jacobs & Horak, 2007); therefore one can imagine that any decline in cortical function would be detrimental to postural control. Indeed, it has been shown that when performing a simultaneous cognitive math task, the response latency and amplitude of tibialis anterior and gastrocnemius muscle activity following standing platform perturbation is reduced (Rankin, Woollacott, Shumway-Cook, & Brown, 2000). This is known as the dual-task paradigm, discussed previously.

However, divergent to these processes which typically occur in a predictable environment, there appears to be a "first-pass" effect in terms of APRs in that subjects will rapidly develop adaptation or habituation following a first-time or unexpected balance perturbation. Therefore, the hierarchal organization of subsequent responses (as described above) is naturally different than the first. Both repetition and, to a lesser extent, instruction appear to induce a learning effect with respect to CoP responses to balance perturbations (Maki & Whitelaw, 1993). In fact, the learning response observed with computerized dynamic posturograhy appears to be so marked that some have suggested its utility as physical therapy for patients with PD (Rossi-Izquierdo et al., 2009). With respect to data analysis, however, it appears that analyzing first trials or pooled data from multiple trials makes no difference (J. Visser et al., 2010).

It is also likely that these "first-pass" reactions are not universal or generic and that significant inter-personal variability exists. This is particularly important to consider when analyzing the studies found in Chapters 4 and 5 as multiple trials were conducted in sequence and, in Chapter 5, across several patients. Corbeil et al. (Corbeil, Bloem, van Meel, & Maki, 2013) were able to demonstrate said occurrences by focusing solely on

first-trial arm reactions evoked by small perturbations (that would ideally not require the use of arms for stabilization) to balance using a motor-driven platform. Their hypothesis was that responses would not be stereotypical across subjects and would alternatively be modulated according to the direction of the balance perturbation and the presence or absence of environmental factors (e.g. handrail). In their study of 12 healthy adults, they found that most subjects initiated active movement of both arms in response to the provocation. This response influenced by the perturbation direction (rightward or forward platform movement), which suggests a functional strategy rather than a reflexive or stereotyped response. The handrail also modulated responses in the speed of arm reaction. There was large inter-subject variation with respect to amplitude, velocity and timing of these movements. The results were statistically significant despite a small sample and together are inconsistent with a generic or stereotypical reaction.

The Centre of Pressure (CoP)

A commonly employed measure of postural sway is the centre of pressure. Referred to commonly as the CoP, it may be defined as the application point of the force vector that is equal to the sum of the forces acting between the foot and support surface. 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 (or the CoM) within the base of support (Baratto, Morasso, Re, & Spada, 2002; J. E. Visser, Carpenter, van der Kooij, & Bloem, 2008). The CoP is usually described in terms of its displacement (amplitude and frequency) in the medial-lateral and anterior-posterior directions which is thought to be independently controlled by the CNS and represents the overall neuromuscular response required to maintain control of the CoM within the limits of stability (Pasman, Murnaghan, Bloem, & Carpenter, 2011; Winter, Prince, Frank, Powell, & Zabjek, 1996).

By measuring the change in mean CoP velocity, which is defined as the total distance travelled by the CoP (i.e. the total sway path) divided by the duration of the sampling period (cm/s), one can estimate 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, Holliday, & Fernie, 1990). As a dependent variable in quantitative research, the mean velocity of the CoP is a validated measure of postural stability and fall-risk (Maki et al., 1990). Studies have shown that the velocity of CoP displacements is indeed higher in PD than controls (Rocchi, Chiari, & Horak, 2002).

Posturographic Analysis

Posturography can be a useful clinical tool for detecting and characterizing balance problems. Data collection is typically achieved through the use of force plates to quantify the CoP. The most widely accepted measure involves computerized dynamic posturography, which employs the use of moveable (sway-referenced to the subject's postural sway) force plates to measure displacement of the CoP under various sensory conditions. The sensory organization test (SOT) typically uses up to six conditions to isolate the effects of vision, proprioception and vestibular input during upright balance by selectively limiting or altering sensory input. The most commonly used SOT protocol measures standing balance on a 1) static support with eyes open; 2) static support with eyes closed; 3) sway-referenced support with eyes open and 4) sway-referenced support with eyes closed. This allows the clinician to elucidate the etiology of balance problems using various outcome variables.

In addition, the mean velocity of the CoP as described above, the time structure of the CoP may reveal pathological postural specificities. Thus, structural posturographic parameters may be 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 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) are then 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, Blouin, & Teasdale, 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). Together these variables can aid in the diagnosis of balance problems, however they must always be interpreted in the context of an individual patient.

CHAPTER 2: PARKINSON'S DISEASE AND ITS DEMENTIA: PATHOLOGY AND CONSIDERATIONS IN POSTURAL CONTROL

Parkinson's Disease

Epidemiology and Clinical Characteristics

PD is the second most common neurodegenerative disorder, behind AD. The incidence of PD varies according to age group, with some estimates placing the incidence rate at a median of 14 per 100,000 person years in developed countries. When restricted to ages 65 and above, the incidence increases dramatically to 160 per 100,000 person-years. Based on American and European data, the prevalence of PD among people 65 years or older has been estimated at 950 per 100,000 (Hirtz et al., 2007).

Patients classically present with a resting tremor, rigidity, bradykinesia, gait impairment and postural instability, which are known as the "cardinal features" of PD. It is a progressive illness and motor symptoms usually present unilaterally with gradual progression to involve the other side of the body. Also present are any number of non-motor symptoms (NMS) including postural instability, autonomic dysfunction (i.e. orthostatic hypotension, gastrointestinal (GI) disturbances), mood disorders, sleep disturbances, speech difficulties and dementia. These NMS are also referred to as non-dopaminergic symptoms as most are refractory to dopamine replacement therapy (DRT) (Olanow & Schapira, 2012). As gait dysfunction and postural instability are important in the consideration of falls in PD, they are discussed in greater detail below.

Falls

Prospective studies have estimated that around two-thirds of patients with PD will experience at least one fall per year (Wood, Bilclough, Bowron, & Walker, 2002). Indeed, a recent systematic review found that an average of 60.5% of PD patients have fallen at least once and that 29% of falls are recurrent (Allen, Schwarzel, & Canning,

2013). Fall-risk is a complex matter which is individual to each patient and their circumstances, making prediction of falls a difficult task. Proposed risk factors for falls include freezing of gait, "stooped" posture, cognitive dysfunction, balance control problems and muscle weakness in the legs (Latt, Lord, Morris, & Fung, 2009). The National Parkinson Foundation's Falls Task Force has recently developed a summary of generic and PD-specific fall risk factors, with the single most important risk factor being a personal history of previous falls (van der Marck et al., 2014). A summary of these risk factors as described by Fasano and colleagues (Fasano, Canning, Hausdorff, Lord, & Rochester, 2017) can be found in Table 1 below.

Table 1: Generic (age-related) and PD-specific fall risk factors identified by the Falls Task Force promoted by the National Parkinson Foundation

Generic	**Specific (PD-related)**
Anxiety	Axial rigidity
Arthrosis	Cognitive (frontal) impairment
Cardiac arrhythmia	Disease severity
Daily use of alcohol	Dual tasking
Depression	Dyskinesias
Environmental hazards	Fall history
Female gender	Freezing of gait and festination
Old age	Functional neurosurgery (particularly STN DBS)
Orthostatic hypotension	Higher total doses of levodopa
Osteoporosis	Use of dopamine agonists, anticholinergic
Other comorbidities (vertigo, peripheral neuropathy)	Postural abnormalities

Polypharmacy (use of > 3 drugs other than anti-PD) Sedative drugs, particular (multiple) benzodiazepines Use of an assistive device Visual and ocular motor impairment Weakness due to inactivity	Postural instability Shuffling and small scaled gait Slow mobility Transfers Urinary incontinence

Note. Reprinted from "Falls in Parkinson's Disease: A Complex and Evolving Picture" by Fasano, A. et al., 2017, *Movement Disorders*, *32(11),* p.1525.

A prospective investigation of the direct causes of falls in PD determined that 31% of falls were sudden falls, 20% were due to freezing and festination, 12% each were due to neurologic and sensory disruptions or environmental factors, respectively, 11% were contributed to postural instability, 4% were secondary to orthostatic hypotension and 3.6% were a result of severe dyskinesia (Rudzińska et al., 2013). As intrinsic causative factors were dominant in this study, there exists a basis for pharmacologic intervention especially considering that 23% of falls were contributed to neurologic deficits and postural instability – two factors that may be ameliorated with cholinergic therapy. This will be discussed in further detail in the section entitled "*Drugs Affecting Cholinergic Neurotransmission."*

Gait Dysfunction

Common gait abnormalities in PD include a slowed gait velocity, a decreased stride length manifesting as a shuffling gait, festination and a freezing of gait where the patient experiences a momentarily block and is unable to initiate or continue forward gait. Freezing of gait is a phenomenon where patients seem unable to lift their feet from the ground and typically occurs upon initiation of gait, when a patient attempts to initiate a

turn or when adjusting their step. This freezing may occur spontaneously as the disease progresses and often leads to falls (Giladi et al., 2001).

Freezing of gait and falls are closely linked in PD, perhaps because both are relatively common in later stages of the illness and less common in *de novo* Parkinson's. Both conditions are also unresponsive to DRT and may even exhibit a paradoxical worsening with therapy. Therefore, it is hypothesized that the two may be interrelated and share a non-dopaminergic origin (Bloem, Hausdorff, Visser, & Giladi, 2004).

Another observation is that PD patients may exhibit a decreased braking capacity. In normal subjects, the CoM tends to fall during the swing limb period; however, the subject is able to brake and reverse the fall before foot contact. In PD patients, both step length and velocity are reduced which may result in a marked reduction in braking capacity and an increase in postural instability during gait. This is thought to be a result of both dopaminergic and non-dopaminergic lesions. The above was demonstrated in a study conducted by Chastan and colleagues that compared 32 normal controls to 32 patients with PD. In the PD group, dopamine replacement therapy improved gait in all and braking capacity in 7 of 32 patients, however, those with impaired braking capacity also had a small N-mesencephalon surface area compared to PD patients with normal braking capacity (Chastan et al., 2009). The PPN is a cholinergic structure of the mesencephalon and as mentioned previously, it is hypothesized to play a crucial role in gait initiation and postural control. The role of the PPN in PD will be discussed further in the following section.

Postural Instability

Postural instability is considered one of the cardinal features of PD, presenting 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, patients tend to fall more frequently and also display a debilitating fear of falling, contributing significantly to disease morbidity (Adkin, Frank, & Jog, 2003).

Postural instability manifests as a progressive loss of postural reflexes, however the underlying pathophysiologic mechanisms are complex, involving both the underlying disease process and compensatory mechanisms, and are poorly understood (Benatru et al., 2008). Patients with PD also have a "stooped" posture, essentially pushing the foot CoP forward, and is an independent risk factor for falls (Latt et al., 2009). However, it is unknown whether this posture is compensatory or causal (Kim et al., 2013).

Postural instability is often measured either through clinical balance tests or using static or dynamic computerized posturography. Computerized posturography measures the foot CoP and other sway paramaters including its mean velocity and area of displacement. The mean velocities of CoP displacement and the total area of CoP displacement are validated measures of fall risk (J. E. Visser et al., 2008). However, the measurement of balance using static computerized posturography in PD has yielded conflicting results, with some showing increased or normal (Schieppati & Nardone, 1991) and even reduced postural sway (F. Horak, Nutt, & Nashner, 1992). It is likely that the heterogeneity of PD and its treatment as well as the variations in study design are contributing to the variation in these observations.

Alterations in Postural Reflexes

Patients with PD display abnormal APAs and APRs and the type of abnormality may depend on the stage of illness. In early PD, patients exhibit exaggerated APAs as shown by Inkster and colleagues. In their study, patients with PD tended to overuse hip strategies to place the CoM excessively forward in preparing to stand from a chair. Conversely, patients in the more advanced stages tend to have diminished APAs (Bleuse et al., 2008). Bleuse and colleagues demonstrated that PD patients in the "OFF" phase displayed reduced APA magnitude compared to normal controls. Patients were required to stand on a force platform and perform a right shoulder flexion movement to grasp a handle in front of them under various conditions. Patients with PD showed a reduced magnitude of their APAs as the maximal velocity peak of the CoP appeared later and the amplitude of the CoP backward displacement was lower.

With respect to APRs, PD patients exhibit decreased trunk rotation and ankle torque changes in response to support surface rotations, which suggests a stiffening response to postural perturbations (Carpenter, Allum, Honegger, Adkin, & Bloem, 2004). Postural reflexes also show a disordered activation in PD as destabilizing (medium-latency stretch responses) stretch reflexes are increased, while stabilizing (long-latency stretch responses) stretch reflexes are unaffected or lessened (Carpenter et al., 2004; Kim et al., 2013). The distal-proximal activation sequence of long-latency reflexes was also reversed following toes-up platform rotations in patients with advanced disease reflecting an inappropriate selection of motor programs and modulation of postural reflexes (Beckley, Bloem, Van Dijk, Roos, & Remler, 1991).

Patients also show a disability in adjusting to changes in postural demands such as the inability to suppress an initial postural response and adjust for a rapid change. PD patients have shown a reduced ability to suppress ankle muscle responses following rapidly changing translations in support surface. PD patients also display reduced suppression of both medium and long-latency postural reflexes when converting from a freestanding position to holding onto an object for support (F. Horak et al., 1992).

Pathophysiology of Abnormal Postural Reflexes

Dysfunction in the basal ganglia likely contributes, in part, to the disordered postural reflexes in PD. As the inhibitory capacity of the substantia nigra reticulata is reduced secondary to dopaminergic deficit, medium-latency reflex amplitudes are increased (Scholz et al., 1987), whereas the reversal in the sequence of long-latency reflexes represents disordered selection and initiation of motor programs (Beckley et al., 1991).

The supplementary motor area connects indirectly with the basal ganglia (described below) and studies have shown altered function of this area in PD (Cunnington et al., 1996). As this area is thought to be involved with the preparation of voluntary movement and more specifically APAs, this may provide a partial explanation for the aberrant

APAs, as described in the previous section, that are observed throughout the course of PD (Massion, 1992).

Pathophysiology of Parkinson's Disease

Pathologically, PD is characterized by hypofunction and loss of dopaminergic neurons in the substantia nigra pars compacta, reductions in striatal dopamine and Lewy body deposition (Olanow & Schapira, 2012). The substantia nigra pars compacta is one of two components of the substantia nigra. The substantia nigra forms part of the basal ganglia along with the striatum, globus pallidus and the subthalamic nucleus. The basal ganglia are a group of subcortical nuclei that play a critical role in regulating motor function (Olanow & Schapira, 2012).

The basal ganglia receive input from the cerebral cortex via the striatium, while the globus pallidus and substantia nigra pars reticulata (the other division of the substantia nigra) provide output to thalamocortical and brainstem motor regions. This output provides inhibition to thalamic and brainstem neurons that connect to motor areas of the cerebral cortex and spinal cord. The main role of the dopaminergic projections from the substantia nigra pars compacta is to modulate neuronal firing in the basal ganglia (Olanow & Schapira, 2012). Therefore, it can be seen how dysregulation (or denervation) in the substantia nigra pars compacta may result in decreased modulation or increased firing of output neurons in the basal ganglia. This results in increased inhibition of thalamic and brainstem neurons and subsequent reductions in the activation of cortical motor systems. This is what leads to the development of clinical parkinsonian symptoms (Olanow & Schapira, 2012).

While dopaminergic loss may explain the majority of motor symptoms in PD, neurologic dysfunction in PD is widespread involving many brain structures and neurotransmitter systems, including serotonergic and cholinergic systems (Olanow & Schapira, 2012). While dopaminergic dysfunction is an important consideration in PD and represents the major target of pharmacotherapy, the remaining discussion will focus mostly on non-

dopaminergic pathways and in particular, cholinergic dysfunction and its role in postural control.

Cholinergic Pathophysiology in Postural Instability

Studies have shown that projections from the parabrachial and raphe nuclei as well as the locus coeruleus innervate the vestibular network and support hypothesis of serotonergic and noradrenergic involvement, respectively (Balaban, 2002; Grimbergen, Langston, Roos, & Bloem, 2009). However, the role of ACh has been an area of intense study in PD and fall-risk.

As mentioned previously, the PPN is a major source of ACh in the central nervous system and cholinergic neurons of the PPN are hypothesized to play a crucial role in gait initiation and postural control (Karachi et al., 2010). Studies show significant degeneration of this region in PD as well as in the nBM, which provides cholinergic stimulation to the cerebral cortex. Deep brain stimulation to the PPN has also shown some promise in decreasing falls in PD (Moro et al., 2010) as well as improving daytime sleepiness and executive function (Fasano, Daniele, & Albanese, 2012), both of which may indirectly contribute to fall risk.

As well, PET imaging of AChE activity has shown that cortical cholinergic hypoactivity is greater in PD patients who have fallen versus those who have not (N. Bohnen et al., 2009). This same study also showed that reduced AChE activity in the thalamus is also associated with falls in PD even after controlling for motor symptoms. However, it may also be useful to compare PD to progressive supranuclear palsy, where falls are an early presenting feature. Again, PET imaging of AChE activity has shown widespread reductions in cholinergic activity across the cerebral cortex in PD and PSP as well as more severe hypoactivity in subcortical areas in PSP than in PD (Gilman et al., 2010). This suggests a subcortical contribution to falling. The severity of gait and balance disorders in the study by Gilman and colleagues was correlated with cholinergic deficits in the midbrain and cerebellum. As the PPN has significant connections with both of

these structures as well as the thalamus, these studies lend support to the critical role of the PPN in postural control.

Parkinson's Disease Dementia (PDD)

Epidemiology and Clinical Characteristics

Dementia is exponentially more common among sufferers of PD than it is amongst the general population with one prospective, population-based study estimating a six-fold greater risk (Aarsland et al., 2001). A meta-analysis of 27 studies estimated the mean prevalence of dementia in PD at 39.9% (Cummings, 1988), with more recent estimates hovering around 30% (Aarsland & Kurz, 2010). Various risk factors for dementia in PD have been identified including age, older age at onset of PD, as well as duration and severity of PD (Aarsland et al., 2001).

Clinically, patients with PDD display hallmark deficits in executive function, characterized by major deficiencies in attention and planning. Patients also experience significant visuospatial impairments and difficulties with verbal memory. However, an important distinction in PDD is that patients experience less memory decline than those with AD, but the above deficits are usually more profound. Another distinguishing feature is that cognitive symptoms typically fluctuate in PDD, whereas AD patients experience a slow but progressive decline (Bronnick, Emre, Lane, Tekin, & Aarsland, 2007).

Pathophysiology of PDD

Cognitive dysfunction in PD is likely multifactorial and related to a variety of factors including lesions in the subcortical nuclei and degeneration of subcortico-cortical pathways. Lewy body inclusions are found in both cortical and limbic structures. Patients with PD also frequently display AD tau pathologies in combination with these features, however Lewy body disease is more closely correlated with cognitive function than AD

pathology (Emre, 2003; Jellinger, 2006; Kövari et al., 2003). As mentioned previously, significant degeneration of the nBM occurs in PD, with autopsy studies showing more progressive loss in the presence of cognitive impairment (Jellinger, 2006). In fact, PET studies comparing PDD to AD have shown that cortical AChE activity (serving as a marker for cholinergic activity) is even more reduced in PDD than in AD even when controlling for dementia severity (N. I. Bohnen et al., 2003). Degeneration of the PPN may also play a role as it may be involved in the sleep-wake cycle, consciousness and arousal (Perry et al., 1999). Decreased cholinergic output from the PPN may cause attentional dysfunction and fluctuations in consciousness and alertness, hallmark features of PDD (Yarnall et al., 2011).

A PET study conducted by Hilker and colleagues compared the uptake of cholinergic and dopaminergic markers (N-[^{11}C]-methyl-4-piperidyl acetate (MP4A) and ^{18}F-fluorodopa (FDOPA), respectively) in PD patients with and without dementia to age-matched controls (Hilker et al., 2005). Striatal dopaminergic marker uptake was not different between PD and PDD. However, PDD patients showed more severe cholinergic deficits in several regions. The reduction in global cortical MP4A binding was quite severe in PDD (29.7%, $p < 0.001$ vs. controls), but less so in PD (10.7%, $p < 0.01$ vs. controls). Interestingly, the PDD group also showed lower parietal, frontal and temporo-parietal MP4A uptake rates.

Although important, ACh is unlikely to be the sole culprit in PDD. It must be mentioned that dopaminergic and noradrenergic pathways are likely involved, particularly in the case of executive dysfunction and attention (Emre, 2003). Serotonin may also play a role in visual hallucinations (Ballanger et al., 2010), underlining the widespread neurologic dysfunction observed in PD and PDD.

PDD and Postural Control

Fall-risk is increased in patients with dementia (Nutt, Marsden, & Thompson, 1993). As postural control is simultaneously a reflexive and cognitive process, patients with PDD

represent a special case in that they display both aberrant anticipatory and reactive postural adjustments as well as cognitive dysfunction (Kim et al., 2013). The integration and re-weighting of visual, vestibular and proprioceptive information required to maintain posture and balance may be significantly impaired in the presence of cognitive dysfunction (F. B. Horak, 2006).

The most important aspect of this cognitive dysfunction is likely attention deficits, as this increases postural instability, as discussed previously, and as evidenced by the use of dual-task paradigms in both the elderly (Teasdale & Simoneau, 2001) and PD populations (Marchese, Bove, & Abbruzzese, 2003). As well, visuospatial deficits and decreased planning ability may respectively alter sensory perception and voluntary reactive strategies to maintain postural control.

CHAPTER 3: PHARMACOLOGY OF CENTRAL NERVOUS SYSTEM DRUGS AND CONSIDERATIONS IN POSTURAL CONTROL

Drugs Affecting Dopaminergic Neurotransmission

Pharmacology

As this discussion focuses on cholinergic contributions to PD, the pharmacology of dopaminergic drugs will be discussed only in brief. Levodopa is the "gold standard" treatment for motor symptoms of PD. Levodopa is a pro-drug that is capable of crossing the blood-brain barrier (BBB). Levodopa is decarboxylated to dopamine once it has entered the CNS via DOPA-decarboxylase. Because DOPA-decarboxylase is also present in the periphery, levodopa is commercially supplied in combination with carbidopa, which inhibits the peripheral conversion of levodopa to dopamine. Dopamine itself is unable to cross the BBB. Administration of levodopa thereby increases the amount of dopamine available for binding to dopamine receptors in the striatum. Levodopa and carbidopa are also available in combination with entacapone, an inhibitor of catechol-O-methyl transferase. This enzyme is also responsible for the peripheral and central breakdown of levodopa and monoamines such as dopamine. Other DRTs consist of dopamine agonists such as pramipexole and ropinirole that bind to and activate dopamine receptors in the striatum. Levels of dopamine may also be increased by inhibitors of monoamine oxidase, such as selegiline. Monoamine oxidases are a group of enzymes responsible for inactivating dopamine and other neurotransmitters in the CNS (Micromedex® Product Monographs for Sinemet®, Comtan®, Mirapex®, Requip®, Eldepryl®).

Efficacy

The introduction of DRT has drastically improved motor symptom control in PD. Postural and gait-related symptoms also tend to improve with DRT, however this is often limited to the early stages of the disease and these symptoms are significantly less

responsive to DRT than motor symptoms (Vu, Nutt, & Holford, 2012). These symptoms usually become refractory to DRT in later stages where it is likely that the disease has spread to involve non-dopaminergic pathways (Kim et al., 2013).

The study by Vu and colleagues (Vu et al., 2012) was a relatively large modeling study comprising a cohort of 795 initially untreated patients with PD. These patients were followed for nearly 8 years for the cardinal features of tremor, rigidity, bradykinesia, and postural instability and gait disorder (PIGD) derived from the total unified Parkinson's disease rating scale (total UPDRS), cognitive status as per the mini-mental status exam (MMSE) and depression from the Hamilton depression scale (HAM-D). The PIGD subscale was the sum of falling, freezing, walking, gait and postural stability. Using a quantitative prediction model, the authors found that levodopa had a relatively low potency for effect on PIGD (ED_{50} of 1237 mg/day compared to 7–24 mg/day for other motor and non-motor symptoms).

Clinical Trials

Bloem and colleagues (Bloem et al., 1996) conducted a study that compared 23 patients with idiopathic PD and 24 healthy controls. Patients stood on a forceplate and received 20 sequential 4-degree toes-up rotations. Patients with PD were tested in the OFF (i.e. no DRT for at least 12 hours) and ON state (i.e. 1 hour after DRT) and controls tested and re-tested after 1 hour. Destabilizing medium latency responses in the gastrocnemius muscles and long latency responses in the tibialis anterior muscles were recorded via EMG. Changes in CoP (foot) and CoG were also assessed. In the OFF state, increased ML amplitudes and decreased long latency amplitudes were observed in PD patients compared to controls (both ps <0.05). An increased posterior CoG displacement was observed and the initial forward (i.e. destabilizing) movement of the CoP increased, with a delayed posterior movement of the CoP (i.e. corrective action of long latency responses). In the ON state, medium latency amplitudes reduced, however they were still elevated compared to controls. The displacement of the CoP was only marginally improved in the ON state and no improvements were observed in the later postural

responses. Therefore, the increased posterior CoG displacement was also unimproved in the ON state. Because these postural responses appear to be relatively non-responsive to DRT. These observations provide evidence of non-dopaminergic pathways in postural instability.

In a similar study, Horak and colleagues (F. Horak, Frank, & Nutt, 1996) showed that the main postural deficit in PD was a reduced capacity to rapidly generate EMG bursts and subsequent force against the support surface following external perturbations, which may be explained by bradykinesia and rigidity. Surprisingly, patients in the OFF state were able to scale postural responses to changes in displacement velocity and amplitude, however, they showed decreased torque responses overall. As above, these patients showed abnormally small agonist and excessive antagonist activity. Muscle EMG tone was also higher in the OFF state compared to controls. Little changed in the ON state except that levodopa decreased background EMG tone and passive stiffness following perturbations. In fact, worsened scaling abilities were observed in the ON state. DRT did not affect the latencies or order of postural responses to external perturbations. These observations led the authors to conclude that the role of dopamine may be relegated to the control of background muscular tone and the production of adequate EMG responses and their related forces for postural responses.

Drugs Affecting Noradrenergic Neurotransmission

Pharmacology

As this discussion focuses on cholinergic contributions to PD, the pharmacology of noradrenergic drugs will be discussed only in brief. Because of the observation that methylphenidate (MPH) is a central nervous system stimulant traditionally used for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adults, it has gained attention in PD and PDD as a potential pharmacologic treatment for the cognitive and attention deficits characteristic of the disease. MPH inhibits the reuptake of dopamine and norepinephrine from the synapse via blockade of presynaptic

norepinephrine and dopamine transporters, thereby increasing post-synaptic receptor activation in the striatum and prefrontal cortex (Kimko, Cross, & Abernethy, 1999). Other drugs such as idazoxan and select stereoisomers of dihydroxyphenylserine have been studied in PD, however these drugs are considered experimental (Grimbergen et al., 2009).

Clinical Trials

It appears as if MPH may have some benefit in ameliorating freezing of gait in PD. A small double-blind crossover study has shown that single doses of MPH 20 mg may improve gait speed, timed-up-and-go test and stride-time variability in older adults (Ben‐Itzhak, Giladi, Gruendlinger, & Hausdorff, 2008). Similarly, freezing of gait improved in an open-label pilot study of 5 PD patients treated with single doses of MPH 10 mg (Auriel, Hausdorff, Herman, Simon, & Giladi, 2006).

MPH may represent a therapeutic option for freezing of gait in advanced PD refractory to DRT and DBS. In their randomized, placebo-controlled, double blind, multi-centre trial, Moreau and colleagues (Moreau et al., 2012) compared 90 days of MPH at a dose of 1mg/kg/day to placebo in PD patients younger than 80 years old with severe gait abnormalities and freezing of gait despite DRT and subthalamic DBS. The primary outcome of the number of steps taken in the stand-walk-sit test was measured under an acute levodopa challenge to control for the confounding effects of levodopa. In the 65 patients completing the study (n=69 randomized), patients in the methylphenidate group made fewer steps at 90 days compared to patients in the placebo group (median of 31 versus 33 steps; p=0·017). Adverse effects were more common in the MPH group with more patients experiencing heart rate elevations and weight loss.

The results of the above trial contradict an earlier double blind, placebo-controlled crossover trial showing no benefit of MPH at doses of up to 80 mg per day on gait as measured by stride length and velocity (Espay et al., 2011). However, this was a smaller trial with only 17 patients completing the study and a different outcome was assessed.

Therefore, the risks and benefits must be considered in each individual patient before treatment with MPH can be recommended. According to the literature, the study of MPH for postural instability has not been formally reported.

Drugs Affecting Cholinergic Neurotransmission

Pharmacology

The major target of drug therapy in AD and PDD is AChE, an enzyme responsible for the breakdown of ACh in the central nervous system via hydrolysis. Inhibitors of this enzyme serve to decrease the breakdown of ACh in the synaptic cleft, thereby increasing the levels of ACh available for binding to post-synaptic receptors (Pope, Karanth, & Liu, 2005). Currently available AChEIs include donepezil, galantamine and rivastigmine, with each having slightly different pharmacokinetic and pharmacologic properties. Of the three, rivastigmine is the only AChEI approved for the treatment of PDD in Canada.

Rivastigmine is reversible inhibitor of the AChE and the butyrylcholinesterase enzyme. Inhibition of AChE results in the central effects of increased ACH, however the additional activity of rivastigmine at butyrylcholinesterase is responsible for its increased peripheral effects compared to donepezil, which is specific for the AChE enzyme (Weinstock, 1999). Like ACh, rivastigmine binds to the active site of AChE and undergoes hydrolysis. This hydrolysis reaction produces a phenolic compound and a carbamyl moiety that remains bound in the enzyme active site (Anand & Gharabawi, 1996). This benefit of rivastigmine lies in the fact that this carbamyl moiety remains bound, and thus inactivates the enzyme, for a relatively long period of time compared to the acetyl moiety produced by hydrolysis of ACh. The acetyl derivative of ACh dissociates within microseconds from the enzyme active site, allowing the enzyme to continue degrading ACh (Polinsky, 1998). Alternatively, a single-dose study has shown that 3 mg of rivastigmine induces inhibition of AChE in the cerebrospinal fluid for at least 10 hours (Enz, Meier, & Spiegel, 1994).

A more recent, yet small, PET study comparing AD patients on donepezil (n=6) to patients on rivastigmine (n=5) shows that rivastigmine reduced AChE activity by 37% in the frontal (p=0.003, Bonferroni corrected), 28% in the temporal (p = 0.03, uncorrected) and 28% in the parietal cortex (p = 0.05, corrected) (Kaasinen et al., 2002). The results were similar for donepezil. The authors attribute the observation that these agents were more active in the frontal cortex to that fact that temporoparietal AChE is diminished in AD.

Cholinesterase Inhibitors and Fall Risk

The observation that anticholinergic medications tend to increase the risk of falling has served as a springboard for the generation of cholinergic hypotheses in postural control. However, others argue that cholinesterase inhibitors may actually increase fall risk via their adverse cardiovascular effects. Because of their cholinergic effects, AChEIs may alter cardiovascular autonomic tone and indeed, heart rate variability, a measure reflecting cardiac autonomic function, is impaired in patients with dementia taking donepezil (McLaren, Allen, Murray, Ballard, & Kenny, 2003). In their population-based cohort study, Gill and colleagues reported that patients using AChEIs for dementia experience more hospital visits for symptomatic bradycardia, syncope, permanent pacemaker insertion and hip fractures than matched controls (Gill et al., 2009). These observations are important to consider, especially in a PD population where up to half of patients may experience orthostatic hypotension (Ziemssen & Reichmann, 2010).

Clinical Trials

Systematic review has confirmed that cholinesterase inhibitors are effective in improving cognitive function, behavioural disturbances and activities of daily living in patients with PDD (Rolinski, Fox, Maidment, & McShane, 2012). In particular, Wesnes and colleagues demonstrated that rivastigmine improves attention compared to placebo in their randomized, 24-week, double blind, multi-centre trial in 487 patients with PDD (Wesnes, McKeith, Edgar, Emre, & Lane, 2005).

With regards to executive dysfunction, Schmitt and colleagues analyzed the secondary outcomes of the landmark EXPRESS trial (Emre et al., 2004), which initially established the efficacy of rivastigmine for PDD (Schmitt, Farlow, Meng, Tekin, & Olin, 2010). Of the 541patients in the EXPRESS trial, only a portion had data for Letter Fluency (n=402), Card Sorting (n=71) and Color-Word Interference subtests (n=97), and the Symbol Digit Modalities Test (n=65). These are all components included in the Delis-Kaplan Executive Function System (D-KEFS) measures of executive function. For Letter Fluency, rivastigmine improved the number of correct responses, set loss errors, and responses made (all $p < 0.05$), but not repetition errors. Improvements in Card Sorting ($p= 0.03$), and more correct substitutions on the Symbol Digit Modalities Test ($p= 0.02$) were also observed. Therefore, along with improving cognitive and behavioural function, rivastigmine also appears to improve attention, executive functions, problem solving and planning, which may have implications for postural control and balance.

With regards to gait velocity and variability, both are hypothesized to be measures of fall-risk (Montero-Odasso et al., 2005; Sheridan, Solomont, Kowall, & Hausdorff, 2003). In this instance, donepezil has been studied in a small open-label trial comparing donepezil (5 mg/day for one month then 10 mg/day) treated AD patients (n=6) with untreated elderly patients with mild cognitive impairment (n=8) (Montero-Odasso, Wells, & Borrie, 2009). After both 1 and 4 months of treatment, patients on donepezil showed significant improvements in gait velocity (under both single and dual-task conditions) from baseline. When compared to controls, donepezil-treated patients also exhibited less gait variability. Building on this study, the authors completed a phase II trial of donepezil in 43 patients with mild AD (Montero-Odasso et al., 2015). After 4 months of treatment, both normal and dual-task gait velocity were improved (108.4 ± 18.6 to 113.3 ± 19.5 cm/s, $p = 0.010$; and 80.6 ± 23.0 to 85.3 ± 22.3 cm/s, $p = 0.028$, respectively). Step time variability did not change significantly.

However, there are marked differences between PDD and AD as previously mentioned. Particular to falls in PD, Chung and colleagues have embarked on a study of

cholinesterase inhibitor for falls in PD (Chung et al., 2010). As outlined in previous sections, the authors also rationalize the use of donepezil for falls based on the observation that (1) anticholinergic medications increase falls in the elderly, (2) there is evidence of cholinergic cell loss in the PPN in patients with PD and (3) that ACh plays a critical role in cognition and dementia is associated with an increased risk of falls. In their randomized, placebo-controlled crossover trial of 23 patients with PD without dementia and frequent falls, patients were given donepezil 5-10 mg daily or placebo for 6 weeks, with a 3-week washout between treatments. Daily fall frequency was significantly decreased with donepezil versus placebo (0.13 ±0.03 versus 0.25 ± 0.08; $p<0.05$). Those with the highest initial fall frequency benefited the most. While promising, this data must be replicated in larger trials and in patients with PDD.

In the most significant trial to date, Henderson and colleagues (E. J. Henderson et al., 2016) examined the effect of oral rivastigmine on step time variability in PD patients without dementia. In their randomized, double-blind, placebo-controlled study, patients were randomized in a 1:1 ratio to either oral rivastigmine (3-12 mg daily) or placebo for 32 weeks. Patients must have fallen at least once within the previous year, been able to walk 18 m without assistance and had no prior use of an AchEI. A total of 130 patients were enrolled; 59 were assessed in the placebo group and 55 in the rivastigmine group. At 32 weeks, patients assigned to rivastigmine had improved step-time variability for both normal walking (ratio of geometric means 0·72, 95% CI 0·58–0·88; p=0·002) and under a dual-task condition (0·79; 0·62–0·99; p=0·045). As a secondary outcome, the authors analyzed the number of falls per month; patients on rivastigmine experienced a significant reduction in monthly falls. Gastrointestinal side-effects were more common in the treatment group.

Consequently, the available literature suggests a cholinergic etiology for postural instability in PD and subsequently, PDD. Notably, patients with PDD experience attention deficits as well as visuospatial and executive dysfunction, which has been related to cholinergic degeneration in the nBM and PPN and to an increased risk of falling (Yarnall et al., 2011). Treatment with AChEIs in PD populations has shown

promise in reducing fall-risk (Chung et al., 2010) and surrogate measures of fall-risk (E. J. Henderson et al., 2016). Therefore, it is not unreasonable to believe that these agents may have benefit in PDD where the cholinergic deficit may be even greater. Owing to the lack of published data characterizing the neuropathology, clinical presentation and treatment of postural instability specific to PDD, the studies found in the succeeding chapters are an attempt to fill this gap in the literature.

The case study presented in Chapter 4 outlines a case of PSP, a rare Parkinsonian illness characterized by frequent falls. There is little to no literature to guide pharmacologic treatment of the disease and there exists no established standard of care. Patients are usually managed on a case-by-case basis and for this reason a case report of successful medication therapy contributes a great deal to the body of literature. As the PPN, among other structures, is thought to be heavily involved in the pathogenesis of PSP, the objective of treatment was to increase central cholinergic tone, as well as dopamine and noradrenaline, in a "multiple neurotransmitter" strategy using donepezil and selegiline, a monoamine oxidase inhibitor (MAOI). It was hypothesized that balance control, quantified using the CoP and measured using dynamic posturography, would improve with donepezil and even more so with the addition of selegiline.

In Chapter 5, the main article of this thesis is presented. The objective of this study was to compare the efficacy and safety of oral and transdermal rivastigmine for postural instability in patients with PDD who were candidates for an AChEI. The primary outcome was the change in mean velocity of the centre of pressure (CoP) after 6 months. 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.

CHAPTER 4: DONEPEZIL AND SELEGILINE TO IMPROVE BALANCE CONTROL IN EARLY PROGRESSIVE SUPRANUCLEAR PALSY

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Résumé

Contexte: Aucune thérapie pharmaceutique efficace a été identifiée pour le traitement de la paralysie supranucléaire progressive (PSP). **Méthodes:** Nous décrivons un patient avec PSP du sous-type Parkinson et instabilité posturale avec des chutes. Le patient a commencé le donépézil 10 mg par jour pendant 3 mois suivi par 6 mois de la sélégiline en combinaison. La fréquence des chutes, le test de traction clinique et la posturographie dynamique informatisée étaient employés pour l'analyse. **Résultats:** Après 3 mois de donépézil, la fréquence des chutes a diminué de 5 à 1 par semaine et un test de traction initialement pathologique est devenu normal. Des améliorations posturographiques ont eu lieu avec le donépézil et après 3 et 6 mois avec la sélégiline. Des bienfaits cliniques ont

été observés au cours d'un an et plus. **Conclusions:** Des améliorations ont été observées avec le donépézil et, dans une moindre mesure, la sélégiline.

Abstract

Background: No single pharmacologic treatment has proven effective for the symptomatic management of progressive supranuclear palsy. **Methods:** We report a case of postural instability and falls secondary to PSP of the Parkinson's subtype and initial monotherapy with donepezil 10 mg daily for 3 months followed by a novel investigation of selegiline in combination for 6 additional months. Fall frequency, clinical pull testing and computerized dynamic posturography were used to assess response. **Results:** After 3 months of donepezil, fall frequency decreased from approximately 5 to 1 per week and an initially pathologic pull-test had normalized. Posturographic improvements occurred with donepezil monotherapy and after 3 and 6 months of combination therapy with selegiline. Clinical improvements were observed over the course of more than one year. **Conclusions:** Improvements in clinical and posturographic measures of balance control were observed with donepezil monotherapy and, to a minimal extent, with the addition of selegeline.

Introduction

Progressive Supranuclear Palsy (PSP) is an atypical parkinsonian syndrome characterized by early falls and non-responsiveness to levodopa (Golbe, 2001). In PSP, neuronal degeneration involves not only the prefrontal cortex and striatonigral structures, but also the thalamus and mesencephalic locomotor area, namely the pedunculopontine-cuneiform complex (PPN) (J. Henderson, Carpenter, Cartwright, & Halliday, 2000; Hirsch, Graybiel, Duyckaerts, & Javoy-Agid, 1987). This region, known as the major source of cholinergic afferents to the thalamus, has been recently implicated in the control of gait and posture in Parkinson's disease (N. Bohnen et al., 2009; Karachi et al., 2010). Recent positron emission tomography (PET) studies by Zwergal et al. confirm the functional disturbance of the PPN in PSP and establish a correlation between postural

imbalance and falls and the functional pathology of the thalamus (A Zwergal et al., 2011; Andreas Zwergal et al., 2013).

There is no standard of care for management of PSP. Reported pharmacological trials have been negative or disappointing, including two trials of donepezil designed to study cognitive endpoints (Fabbrini et al., 2001; Litvan et al., 2001; Nieforth & Golbe, 1993).

We report a case of postural instability secondary to PSP of parkinsonian subtype (PSP P), which exhibited improvements early in the disease course in response to initial monotherapy with donepezil, and further by combined treatment with selegiline. This combination aimed to increase central cholinergic tone, as well as dopamine and noradrenaline, in a "multiple neurotransmitter" strategy. Experimental data showing a significant decrease in frontal acetylcholine binding in the presence of low noradrenergic tone added support for the combination (Acquas, Wilson, & Fibiger, 1998).

Materials and Methods

Donepezil 10mg once daily for three months was followed by the addition of selegiline 5mg twice daily. Computerized dynamic posturography (Pro Balance Master ®, NeuroCom ® International Inc., Clackamas, Oregon, USA) was performed prior to medication, after 3 months of donepezil and after 3 and 6 months of the combination (i.e. at 6 and 9 months). More specifically, to test adaptation of postural responses to repeated support surface displacements, five sets each of toes-up and toes-down platform rotations (8° amplitude, 400 milliseconds) were delivered. Pull test and fall frequency were assessed after 3 months of donepezil, with further evaluation at 9 months (6 months of combination) and again at 18 months as logistical barriers precluded any intermediate evaluation.

Balance recovery was quantified using response latencies and the magnitude and velocity of centre of foot pressure (CoP) displacements. The onset latency represents the time interval between the onset of platform movement and the onset of CoP displacement in the direction of the loss of balance. The early component of this latency represents the time between the onset of the perturbation- evoked balance recovery response until the

maximal velocity reached by the CoP. The late component of this latency is defined as the time between the onset of maximal velocity and when CoP velocity returns to zero. A custom-written software program (Matlab 2007b, Mathworks Inc., Natick, MA, USA) was used to compute CoP variables.

A formal review by an institutional ethics committee was not sought as the decision to publish the current case was made retrospectively and both patient and caregiver provided consent for publication of any finding of medication trials.

Case Report, Results and Discussion

Presented is a 58-year old male with a 9-month history of motor complaints. Over the preceding year, the family noted a progressive psychomotor slowing with frequent falls as well as a mildly slowed, dysarthric speech and occasional dysphagia. Brain computed tomography was unremarkable and brain magnetic resonance imaging did not reveal sufficient vascular damage to suspect small vessel disease as an etiology. The patient had mild left deafness and complained of dizziness while walking and losing balance when changing position abruptly without support. Otherwise, the patient maintained an active lifestyle. Falls were mostly backward and according to patient and caregiver, averaged at approximately 5 per week in the months leading to diagnosis.

Initial neurological exam was notable for slowness of vertical saccades and square wave jerks on fixation. There was evidence of mild facial, lingual and pharyngeal motor slowness, with bradylalia, aprosody, mild difficulties in coughing maneuvers, as well as mild extra pyramidal rigidity and bradykinesia, without decrement on the left side, without tremor. The patient exhibited abnormal glabellar and snout reflexes, an unsteady tandem walk without lateralization and a pathological pull-test with significant retropulsion and risk of falling backward if unprotected by the examiner. The diagnosis of PSP was confirmed at 18-month follow-up with the appearance of specific supra-nuclear vertical gaze abnormalities.

Clinical improvement was reported by the patient and confirmed by the caregiver:

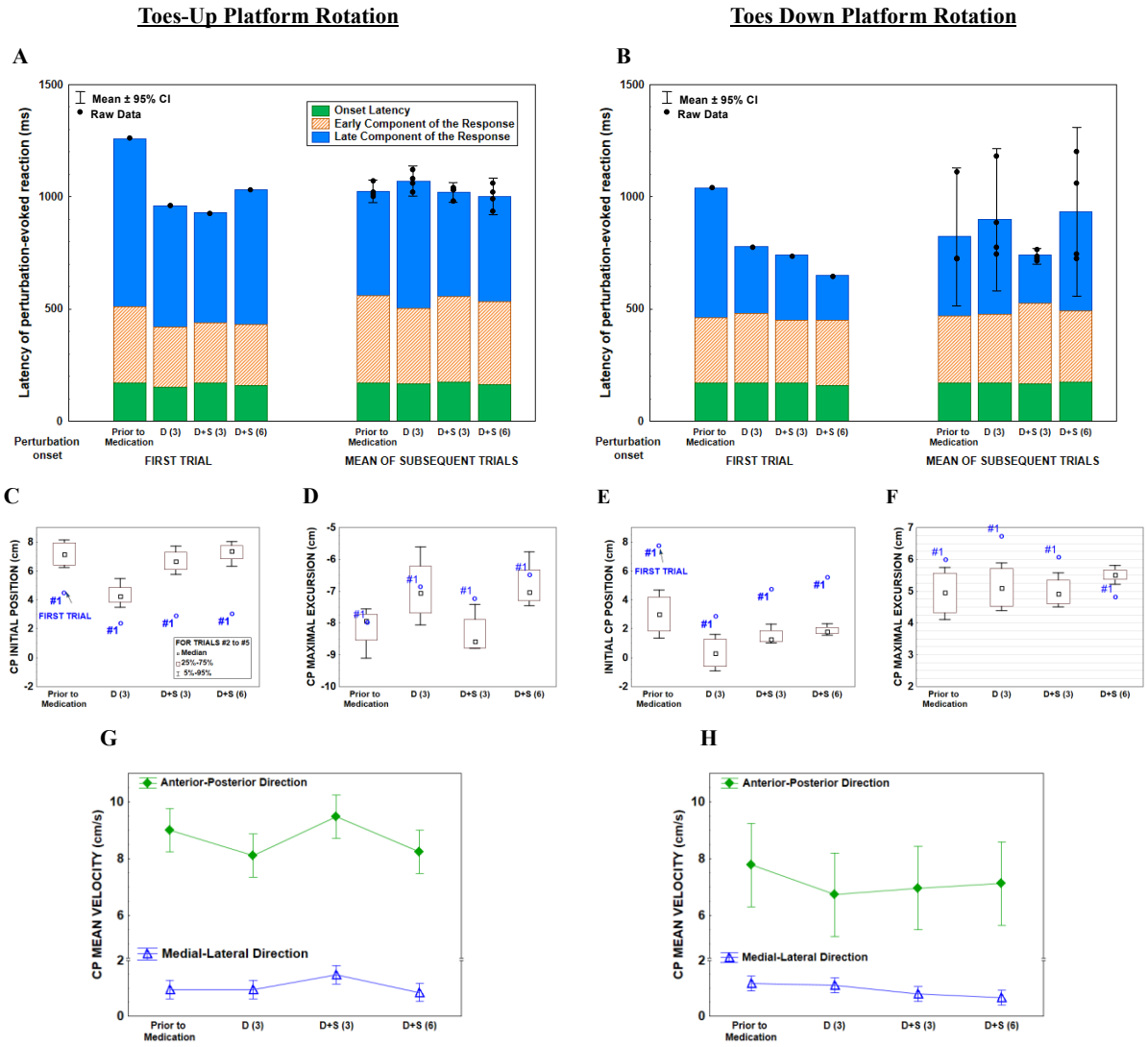
After 3 months of donepezil, both patient and caregiver reported a marked decrease in

fall frequency to approximately 1 per week. The patient noted transient mild urinary incontinence; no other adverse events were reported. The pull test normalized at 3 months and remained normal at 9 months. With the addition of selegiline, patient and caregiver reported no additional benefit, deterioration or adverse events. At the 18-month evaluation, the pull-test returned to baseline. Clinical deterioration of balance occurred between 15 and 18 months following drug initiation.

Postural improvements were observed at each posturometric evaluation:

Figure 1 illustrates balance recovery during computerized dynamic posturography for both toes-up (panels A,C,D,G) and toes-down (panels B,E,F,H) platform rotations at baseline and for each treatment. The initial CoP position taken prior to the onset of platform rotation, as well as the maximal CoP displacement during the perturbation-evoked CoP displacements are illustrated in panels C-F. The mean CoP, which is an indicator of overall postural stability during recovery, is described in panels G-H.

Figure 1: Balance recovery during computerized dynamic posturography



D (3): after 3 months of donepezil; D+S (3) and D+S (6): after 3 and 6 months, respectively, of the combination of donepezil and selegiline.

As seen in Figure 1, for toes-up rotations only (panel D), the maximum displacement of the CoP after 3 months of donepezil and after 6 months of combination therapy was reduced compared to baseline. This may be important as toes-up platform rotations perturb the centre of mass posteriorly, corresponding to the directional preponderance for falls observed in this case. As per panel G, CoP mean velocity improved in both directions following donepezil and after 6 months of the combination, but not after 3 months. For toes- down, results were more consistent across time. Interestingly, CoP

velocity in the medial-lateral direction decreased in the toes-down direction, indicative of improved medial-lateral balance control during recovery.

Improvement was perceived by the patient and observed by the caregiver, mainly in response to donepezil, with a clinically significant, progressive reduction in backward falls. This observation supports the role of a cholinergic intervention in postural sensory integration by the thalamus or in attentional cortical mechanisms, under the control of the PPN and the nucleus basalis of Meynert, respectively. Contributions of PPN-thalamic cholinergic projections in postural sensory integration in Parkinson's disease has been recently observed through a correlation between increased postural sway, established as a risk of falling, and reduced thalamic acetylcholinesterase activity (Müller et al., 2013).

Improvement in prefrontal anticipatory mechanisms is also possible as posturometric improvements occurred mostly in the latter trials at each evaluation; adjustments of preparatory leaning stance are shown in the apparent alteration of the initial position of the CoP across trials. Evidence that effective strategies to minimize perturbation were learned may have implications for physical and rehabilitation therapy.

Improvement of medial lateral balance control during recovery was unexpected; a cholinergic modulation of the cerebellum, which is involved in the refinement of lateral stability, is also possible as it displays connections with the PPN (Gilman et al., 2010).

Our observations, while notable, are difficult to interpret. It is unclear if these improvements represent a true pharmacotherapeutic effect, a placebo response, or a learning effect. The clinician, however, is not accustomed to improvement in dynamic balance in PSP in the first year following diagnosis. The aforementioned negative trial of donepezil reported by Litvan et al. (Litvan et al., 2001), was conducted in a later stage of PSP (an average of 46 months after diagnosis) and assessed mainly cognitive parameters as opposed to postural outcomes.

The importance of providing beneficial results of individual medication trials, particularly if objective data is available, cannot be overlooked in the absence of an evidence-based approach to PSP treatment. Further investigation into the combined use

of acetylcholine, dopamine and noradrenaline modulators to reduce falls in early PSP is warranted.

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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.

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

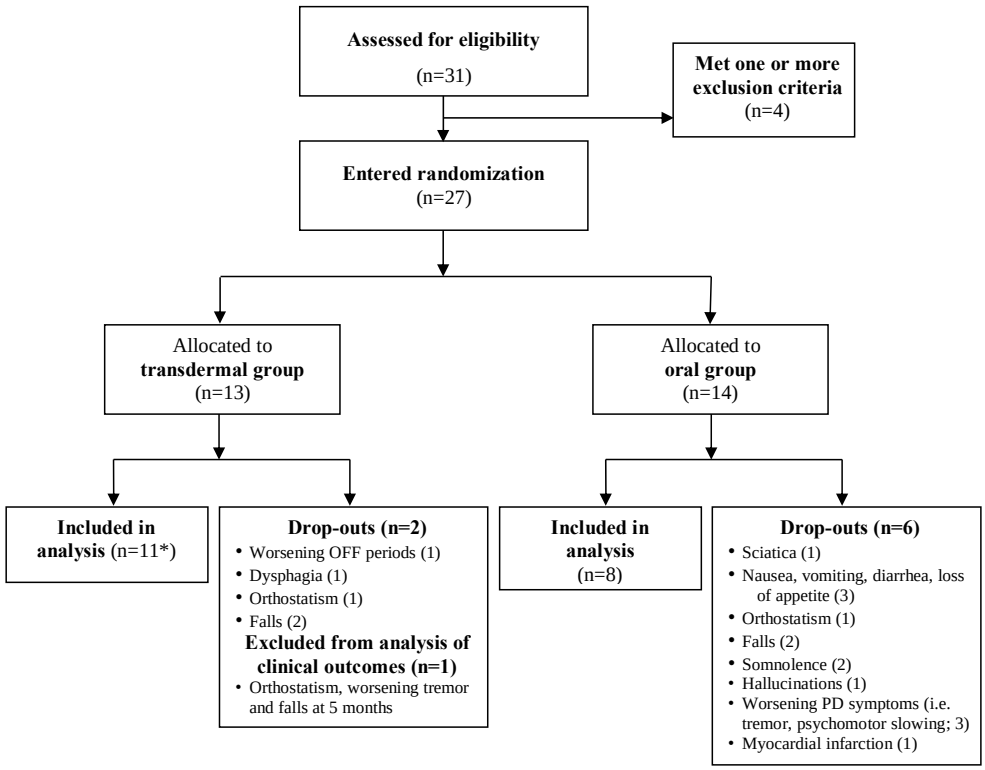
All analyses were carried out using Statistical Package for the Social Sciences (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) with $\alpha = 0.05$. To test for normality and equivalence of variances, the Shapiro-Wilk test and the Levene test were used,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

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 ≥ 0.33; between ps ≥ 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.

GENERAL CONCLUSIONS

Because of the complex nature of postural control in humans, combined with the effects of aging and disease, our understanding of its underlying processes is still developing. Aging, PD and PDD all have detrimental, yet differential, effects on various aspects of postural control and it is often difficult to separate one from the other in the etiology of a particular balance problem. However, advances in medical imaging and assessment methods have allowed us to further our understanding of these underlying mechanisms so that we may eventually focus on treatment strategies to overcome these deficits. While the contribution of various neurotransmitter systems cannot be overlooked, the role of cholinergic pathways, particularly the PPN, in postural instability secondary to PD is biologically plausible and has been supported by neuroimaging studies. Both Henderson et al. (E. J. Henderson et al., 2016) and Chung et al. (Chung et al., 2010) have demonstrated in well-designed, prospective, randomized, placebo-controlled trials that acetylcholinesterase inhibitors can improve step time variability and falls in PD patients with a history of falling, respectively. Expanding on this preliminary evidence to include patients with PDD should be considered an area for future research.

The study presented in Chapter 6 attempts to address this deficiency in the literature. Based on the obtained results, rivastigmine may improve certain elements of postural control, notably the mean velocity of the CoP. 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, patients presented in Chapter 6 who were at the highest risk of postural instability, such as women and benzodiazepine users, may benefit the most. At the very least, these results suggest that balance is not adversely affected with rivastigmine, as is a risk with any medication affecting the central nervous system. In addition to being the first study to investigate the effects of rivastigmine on postural control in the PDD subset, this is the first study to use rivastigmine patches. As this route was generally better tolerated, while maintaining a

comparable degree of effectiveness, this allows some flexibility when developing a personalized treatment approach for an individual patient.

It is clear that more research is needed into potential pharmacotherapeutic strategies to reduce fall-risk in patients with PDD. In particular, large, prospective, multi-centre, randomized, controlled trials are needed to clarify the work that has already been reported cholinesterase inhibitors. While posturographic studies such as ours offer the benefit of objective and quantitative data, clinical endpoints such as fall frequency and quality of life are also important outcomes to consider in future studies. With appropriate treatment for postural instability and a reduction in fall-risk, it is reasonable to hope that patients and caregivers may experience an improved quality of life, which should be the ultimate goal in both research and patient care.

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