

MOOD SYMPTOMS IN PARKINSON'S DISEASE AND THEIR IMPACT ON A QIGONG EXERCISE'S EFFICACY FOR TREATING SLEEP QUALITY AND GAIT PERFORMANCE

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## **Abstract**

The purpose of this study was to investigate both the non-motor features associated with Parkinson's disease (PD), i.e. anxiety and depression, and these features impact the efficacy of a mild exercise intervention treating sleep dysfunction and other non-motor symptoms, as well as a gait impairment. To determine the prevalence and comorbidity of depression and anxiety symptoms and their relationship with disease progression, a retrospective database analysis was performed using data collected during the routine evaluations of 1221 patients diagnosed with PD performed during the initial visit to a PD clinic. Given the discrepancy in previous estimates of mood symptoms in PD, it was hypothesized that 50% of the population would demonstrate anxiety or depression symptoms and that severity of these symptoms would correlate with overall disease severity. Anxiety and depression symptom severity was measured with respective Beck scales, while disease duration (years since PD diagnosis), Hoehn and Yahr (HY) stage, and Unified Parkinson's Disease Rating Scale (UPDRS) scores assessed modes of disease progression. Anxiety and depression were analyzed in categories of severity, prevalence, and strength of relationship with respect to disease progression markers using correlational analysis and chi-square tests. Results of the database analysis confirm previous findings that anxiety and depression are relevant non-motor symptoms of PD as well as the hypothesis, where more nearly half the sample population was determined to have significant depression while two-thirds reported anxiety symptoms. While the severity of mood symptoms was found to be worse in patients with greater disease progression, this relationship was found to be non-linear.

A randomized controlled pilot clinical trial was then completed to assess the impact of mood disorders on the efficacy of a mild exercise intervention- Qigong meditation- on the non-motor symptoms of PD especially sleep quality, fatigue, and cognitive impairment, as well as

gait performance. Previous studies have found that mood symptoms negatively affect adherence with interventions for treating symptoms of PD. In a previous pilot study conducted in our research laboratory the practice of Qigong meditation improved sleep, fatigue, cognition, as well as gait performance in PD; however, there was no control group and the sample size was small. We hypothesized that the current pilot study would find significant improvements in the experimental group compared to the control group and in terms of non-motor symptoms, especially sleep quality, and gait performance compared to the control groups, and that mood disorders in participants might decrease efficacy of the intervention. During six weeks of intervention, both a control and experimental group performed the mild/Qigong exercise twice daily in addition to a weekly group session. While both groups performed the same body motions of the exercise, only the experimental group synchronized their breathing, sounds, and meditation with the movements. Non-motor symptoms in PD were assessed using standard evaluations. The effect of mood symptoms on efficacy of the intervention was primarily measured by the rate of compliance demonstrated by study participants reporting a history of anxiety/depression. Based on a thorough examination of potential technologies for measuring gait pattern, A Gaitmat II device was selected and used to quantify gait velocity, stride time, stride and step length. As hypothesized, participants in the experimental group reporting a history of anxiety/depression reported lower overall compliance with the exercise program than fellow participants. Further, patients in the experimental group demonstrated significant improvement in sleep quality compared to the control group while both groups improved gait performance and some autonomic symptoms including urinary and sexual functioning. Fatigue also improved in the experimental group, though not comparatively significant.

The study findings suggest the Qigong exercise may be a viable complementary therapy for treating both non-motor symptoms (NMS) and gait impairment of PD, especially sleep dysfunction. Further, mechanisms associated with the practice of Qigong may specifically slow, halt, or even reverse neurological damage associated with PD, given the neurodegenerative association with the PD symptoms improved in the study. Both the database analysis and pilot clinical trial suggest mood disorders are prevalent non-motor symptoms in PD, and that addressing these aspects is integral for providing adequate care to persons with PD and optimize the benefit of alternative therapies such as Qigong exercise in treating non-motor and motor features of the disease.

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## **Chapter 1: Introduction**

In 1817, Dr. James Parkinson first identified a disease he called the “shaky palsy,” a condition known today as the neurodegenerative disorder that bears his name, Parkinson’s disease (PD).[1] With 60,000 new cases diagnosed each year, between seven and 10 million people are affected by PD worldwide. While symptoms are both motor and non-motor, classic characteristics of the disease consist of resting tremor, rigidity, akinesia and/or bradykinesia, and postural instability.[2] A clinical diagnosis of PD is made based on the presence of bradykinesia and either distal resting tremor or rigidity, as assessed by a physician.[3] However, a completely accurate diagnosis of PD can only be made by autopsy by confirming the presence of neuronal inclusion bodies (Lewy bodies) in the basal ganglia. No means of accurately detecting Lewy bodies in patients exhibiting asymmetric cardinal symptoms of PD can lead to incorrect diagnoses of the disease.[4] In fact, PD is considered underdiagnosed in the general population due to both misdiagnosis and late diagnosis.[5] While environmental factors and family history are thought to elevate the risk for developing PD, predicting persons who are at high risk for PD remains elusive.[6]

Living with PD comes with undergoing a wide range of symptoms, which include both motor and non-motor features. While much variety exists in the experience of type, duration, and severity of these symptoms, they all impact daily functioning and overall quality of life in persons diagnosed with PD. In addition to stooped posture and reduced arm swing, other gait-related features of the disease include reduced speed and stride length. This combined gait instability predisposes persons with PD to falls, which are associated with severe injury and even mortality.[7] In addition to the motor features, non-motor symptoms of mood disorders, sleep quality, and thinking abilities are of particular concern in PD.[2]

The kind and severity of impairment resulting from these symptoms can vary significantly throughout the course of the disease. For persons in the early stages of PD, primary symptom complaints consist of slowness, tremor, stiffness, pain, and loss of smell and/or taste. Persons with advanced PD have identified the five most problematic aspects of the disease as the wearing off of medication, changes in mood, drooling, sleep disturbances, and tremor as the most problematic features of the disease.[8] Despite many therapies, PD consistently worsens with time and the mean age of death is in the mid-seventies regardless of age of onset or disease management.[2]

While non-motor symptoms (NMS) of PD impact daily living, contribute to disability, and decrease life expectancy, they are less readily recognized and too often untreated. Further, these non-motor symptoms in some cases impact quality of life more than PD motor symptoms, and may pre-date the onset of motor symptoms in PD. [9, 10] NMS include but are not limited to constipation, pain, psychosis, impaired cognition, sleep disturbances, and mood disorders.[11] Mood disorders, specifically anxiety and depression have received increased attention for their effect on quality of life in PD. [9, 10]

The standard treatment of PD symptoms include carbidopa/levodopa, dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors.[2] Anti-depressants, which include selective-serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and tricyclic anti-depressants (TCAs), are standardly prescribed as treatment for mood disorders in PD.[12]

*Neurodegeneration resulting in PD symptoms:* While a diagnosis of PD is based on the manifestation of external symptoms, a pre-clinical period of neurodegeneration is characterized by loss of dopamine neurons coupled with forebrain dopaminergic denervation. This

neurodegeneration occurs primarily in the substantia nigra pars compacta of the basal ganglia.[13] The large, neuronal cell bodies in the substantia nigra pars compacta produce and store all the components necessary for producing dopamine, the neurotransmitter necessary for regulating body movement.[4] By the time of diagnosis, a patient is estimated to have lost 30% to 50% of nigrostriatal neurons.[13, 14]

The duration of this pre-clinical period, that is, the length of time between the start of neurodegeneration and the manifestation of motor symptoms, is generally unknown in most patients. While much variability exists between persons as to the rate at which this degeneration occurs during the pre-clinical interval, [15] the range of this duration is estimated to be three to 15 years prior to observable motor symptoms.[6] The younger the age of disease onset, the longer this period is estimated to be.[13]

After disease onset, interruptions in interactions between the serotonergic, dopaminergic, and norepinephrinergic systems are thought to characterize the neuropathology of PD.[16] More specifically, evidence suggests loss of norepinephrine from the locus coeruleus, with decreases in both the number and activity of norepinephrine neurons, is integral to the pathophysiology of the disease.[17] Evidence points to damage rendered to 5-hydroxytryptamine (5-HT), which is correlated with enhanced tremor and decreased serotonergic functioning, and norepinephrine systems is associated with advancing severity of PD.[12]

## **Motor Symptoms**

*Cardinal Motor Symptoms:* The traditional markers of PD, motor symptoms present challenges to a patient's wellbeing and quality of life and their onset is typically asymmetric.[3] As previously mentioned, four primary cardinal motor symptoms are recognized as characterizing

the disease: resting tremor, rigidity, bradykinesia/akinesia (slowed/involuntary movement, respectively), and postural instability, though the latter of which is often not present in the initial stages of the disease. While these cardinal features are considered to result from dopaminergic system dysfunction, tremor may also be caused by non-dopaminergic degeneration also associated with PD pathology.[18]

Resting tremor, as assessed between 3 and 7 Hertz, is frequently the first motor symptom experienced in PD and can worsen with anxiety or tasks requiring walking. [3, 14] The rate at which severity of motor symptoms increases varies based on overall disease progression and disease duration. Typically, gait and postural instability develop later in the disease, whereas tremor remains fairly constant throughout the disease.[15]

Currently, the Unified Parkinson's Disease Rating Scale (UPDRS) is the gold standard assessment for measuring a patient's overall disease status with regard to mental, daily activities, motor, and treatment response facets of the disease.[3] Besides walking, PD motor symptoms can impair performing skilled motor tasks such as writing (micrographia) or speaking.[3, 19] Daily activities and capacity to work can be greatly inhibited by bradykinesia and affected dominant hand.[3] Motor symptoms can become unpredictable and fluctuate due to the wearing off of PD medication.[3] Not surprisingly, decreased physical activity, evident in PD patients is associated with a decline in physical functionality and is intensified by aging.[20]

*Neurodegeneration related to motor symptoms:* Loss of motor skills and involuntary movements in PD otherwise described as dopaminergic symptoms, can be primarily attributed to dysfunction in the basal ganglia.[19] More specifically, motor symptoms result from dopaminergic neuron loss in the substantia nigra pars compacta, decreasing the input of dopamine to the striatum and thereby altering the response of the globus pallidus, thalamus, sub-thalamus, and substantia nigra

pars reticularis. Lewy bodies and neurites, which consist of byproducts of the neurodegeneration, develop in the substantia nigra and are also found in the locus ceruleus, brainstem, vagus, amygdala, and hippocampus. Mutations in the alpha-synuclein gene are thought to cause autosomal dominant, PD; the presynaptic neuronal protein alpha-synuclein, is implicated in the development of neurodegeneration in PD.[21] Nevertheless, the underlying pathogenesis of gait hypokinesia, akinesia, and dyskinesia are thought to be different, given the asymmetric development of these features with respect to disease progression.[19]

*Standard treatment for motor symptoms of PD:* The dopaminergic medication levodopa combined with carbidopa is the standard treatment for motor symptoms, while dopamine agonists are also introduced early on in the disease in order to slow motor disability.[3] In earlier stages of the disease, drugs modulating catechol O-methyl transferase and MAO-B may be introduced and used throughout the course of the disease. Less commonly used are anticholinergic agents, which are primarily prescribed to younger patients with severe resting tremor and functioning cognitive faculties, can pose gastrointestinal and psychiatric side effects. [3] Imbalance in pharmacological treatment result in the slowing of and greater difficulty performing movements. [19]

The short and long-term effects of standardly prescribed medication for PD remain controversial. Several studies with varied methodology report the use of medication increases survival time and control motor symptoms, especially at the latter stages of the disease. [22] However, non-motor symptoms are typically less responsive than motor symptoms to dopaminergic therapy. [2] Furthermore, standard pharmacological care may at times fail to treat, cause, or exacerbate NMS associated with PD. [23] Given that dopaminergic drugs commonly

result in daytime sleepiness and insomnia, some studies suggest dopaminergic drugs promote sleep if they are needed to carry a patient through the night. [24]

*Gait Impairment:* Considered a motor symptom in advanced PD, gait impairment can increase the risk of falling and lead to injuries, loss of independence, and increased mortality.[7, 25, 26] Gait complications are common in PD, resulting from the progressive loss of dopamine producing cells in the basal ganglia. The absence of dopamine ultimately results in the loss of gait automaticity [27]. The characteristics of PD gait result from the combined effects of the fundamental motor symptoms discussed previously, resulting in a gait pattern with reduced arm swing and trunk rotation; forward stooped posture; reduced motion at the hips, knees, and ankles; slowness; reduced step size; and low ground clearance [28]. While persons with PD can often walk in a straight line with ease, tasks requiring turning, simultaneous mental and motor faculties, and navigating obstacles in a community setting can be remarkably difficult. Maintaining balance is another common difficulty in PD, which affects a person's safety and the ability to walk independently. Persons in the advanced stages of the disease have greater difficulty maintaining balance. The struggle to maintain balance is due to a compromised ability to maintain one's center of mass above a narrow, shifting base of support while walking, resulting in postural instability.[29]

One of the most prominent features of PD gait is a significant reduction in gait velocity. Morris, et al. [28] found that patients with PD walked with a velocity range between 0.67 – 1.0 m/s, compared to a pace of 1.25 – 1.5 m/s in healthy controls. The change in walking speed is generally considered a direct result of significant reduction in stride length, a key measure in PD progression. Stride length appears to have a significant correlation to motor UPDRS scores, where more drastic reduction in stride length indicates more severe impairment [30]. Flat-footed

walking and reduced joint range of motion in the lower limbs results in diminished vertical and frontal ground reaction forces, especially during push-off. This results in reduced movement amplitude, which occurs across all joints of the lower extremity [28].

Postural instability is another major feature of gait impairment in PD that may lead to a high incidence of falling, ranging from 38% to 62% in patients with PD over a one-year period. [28, 31] One indicator of postural instability is the increased time in double support [29]. Typically, time in double support falls in the range of 20% to 30% of the gait cycle, but may be increased to over 35% in PD patients [28]. There are other measures of gait and postural instability in patients with PD have been shown to improve as a result of interventions, including functional reach test [30], chair rise and one-leg stance [20], an variability in stride length and stride time [30, 32, 33].

The most common movement disorder in PD is hypokinesia, in which persons movements are both slower and smaller in size.[28] Patients with PD typically walk slower than non-PD persons of a similar age as measured by gait velocity. While cadence (the average step rate) may not be affected, persons with PD also take shorter steps as measured by stride length, two-thirds the length of controls on average, which can result in tripping.[7, 19] Reduced push off reaction forces, where PD patients walk with a flat-footed gait pattern and expend more energy when initiating gait, may also increase risk for tripping in PD.[19] Thus, reduced gait speed, shorter step and stride lengths along with stooped posture prominently characterize the gait impairment in persons with PD.[7, 27]

## **Non-Motor Symptoms**

While not considered cardinal features of PD, non-motor symptoms can result in disability and significantly affect overall quality of life for those with PD. [2, 8] Development of non-motor symptoms may precede the onset of traditional PD motor symptoms by years and tend to worsen with disease progression.[21, 24] Specifically, the NMS of mood disorders, constipation, and sleep problems may appear early on or even precede the development of PD motor symptoms. [8, 24] Another common NMS frequently subtle but present in the early stages of the disease is cognitive decline, which can be difficult to detect. Impaired cognition emerges as deficits in executive functioning, working memory, and visual-spatial capacity and worsens with disease progression.[21] Decreased dopaminergic innervation in nigrostriatal and mesocortical dopaminergic systems related to altered frontal cortex functioning.[21] An estimated 90% of persons diagnosed with PD suffer from NMS.[2] While NMS have received more attention in recent years, they can still negatively affect management and care of the disease.[2] The relationship between disease duration and certain NMS in PD will be examined further in this paper.

NMS characterizing the pre-motor symptom stage of PD include olfactory dysfunction, constipation, sleep fragmentation, mood disorders and Rapid Eye Movement (REM) Sleep Behavioral Disorder (RBD).[21, 24] Increasing attention given to identifying the NMS in this stage of PD has developed.[24] The role neurodegeneration plays with respect to the development of NMS during the pre-motor stages of the disease still remains unclear and continues to be a matter of study.[21] As noted, dopaminergic system dysfunction is implicated in the development of motor symptoms, yet many non-motor symptoms are attributed to deficits in non-dopaminergic mechanisms.[13] Even still, the neuroanatomical pathways responsible for

NMS remain largely unknown, making for discussion of NMS pathophysiology mostly speculative.[11]

*Autonomic symptoms:* Broadly defined as autonomic symptoms, these complications can include constipation, urgent urination, excessive salivation, and sexual dysfunction.[2, 14] The risk for developing these NMS in PD increase with respect to greater age, overall disease severity, and higher doses of dopaminergic medication.[2] The neurodegeneration of these symptoms can be attributed, in part, to Lewy bodies in the peripheral autonomic nervous system.[14]

### **Anxiety and Depression in PD**

Mood disorders, specifically anxiety and depression have long been associated with PD. Dr. Parkinson himself noted a certain melancholy in his patient who suffered from the shaking palsy.[1] With regard to anxiety, the most common forms in PD are panic disorder, generalized anxiety disorder and social phobia, with anxiety being more associated in patients with symptoms of postural instability and gait dysfunction than tremor-dominant patients.[34] Symptoms of anxiety were found to affect quality of life in non-demented PD patients, even more than depression, cognition, or motor symptoms.[9] Thought to affect motivation and cognition, anxiety in PD can exacerbate PD motor symptoms and impact overall treatment compliance.[9]

Hypotheses as to whether anxiety is a reaction to living with the disabling motor symptoms or endogenous to PD neuropathology have emerged as means of explaining anxiety in PD.[35] Social anxiety may develop in patients as a result of embarrassment caused by their motor symptoms emerging during social situations.[36] However, symptoms of anxiety may in fact predict the onset of PD, as persons pre-disposed to an anxious personality are associated

with a greater risk for developing PD.[10] Mood disorders, may then in part, prefigure the development of PD.[23] The development of anxiety symptoms several years prior to a diagnosis of PD during the pre-motor stage would suggest the neurochemical changes associated with PD are implicated in the cause of anxiety in PD.

The loss of both dopaminergic and serotonergic innervation, both associated with PD neuropathology, has been demonstrated to correlate with both anxiety and depression symptoms.[12] Further, serotonergic dysfunction has generally been implicated as the cause of most mood disorders. While patients with PD exhibit progressively diminished functioning of the serotonergic system, the rate of degeneration is non-linear and thus varies between patients. Although the exact pathophysiology remains unknown, degeneration in the locus ceruleus, as well as its dorsal ascending noradrenergic pathway may result in anxiety symptoms.[12, 37] Furthermore, anxiety may also be affected by dopamine levels, and therefore intrinsically linked to PD.[38] Reduced functioning in the limbic noradrenergic and dopaminergic systems has been shown to correlate with both anxiety and apathy in non-depressed patients. [13]

While serotonergic denervation in PD usually begins in the caudate, thalamus, hypothalamus, and anterior cingulate cortex, the denervation spreads to the basal ganglia, limbic system, and cortex as the disease progresses.[13] A study employing transcranial sonography has revealed abnormalities in the substantia nigra, as marked by hyperechogenicity, previously associated with PD, is also a common feature of depression in the general population. The findings concluded persons with depression are three more times likely to develop PD in their lifetime.[39] Further, anxiety has been postulated to even be one of earliest manifestations of PD. [40] Regardless of the exact causes, anxiety in PD is a reflection of the combined psychological and physiological conditions of the disease. [41]

While anxiety may precede a diagnosis of PD, disparate claims have been made on whether anxiety worsens along with disease progression.[40] Two studies found no significant relationship between the severity of motor symptoms and anxiety, while another found anxiety symptoms were associated with increased motor impairment.[34] Younger age of onset has been associated with higher levels of anxiety, though anxiety disturbances tend to decrease with age.[34]

Much discrepancy exists in the estimates of persons with PD who experience relevant anxiety and depression symptoms.[40] Previous studies report the prevalence of anxiety in the PD population to be as low as 5%, while others as high as 75%.[9, 16, 35, 40, 42] As the most explored mood disorder in PD, depression has been found to be the best predictor of quality of life in PD patients as measured by activities of daily living scales and is associated with greater motor disability.[9, 16, 43] While nearly 50% of persons with PD are thought to be affected by symptoms of depression, much variance exists in the estimation of this prevalence.[16, 43] Due to negative social stigma associated with mood disorders, estimates of both anxiety and depression in PD may be under-reported.[5]

*Treatment of anxiety and depression in PD:* Drugs acting on the serotonergic system, namely SSRIs and tricyclic antidepressants (TCAs) are the current standard care for managing anxiety and depression in PD. Most of these drugs elevate extracellular 5-HT levels by blocking their reuptake in their post-synaptic receptors, which are implicated in mood disorders.[44] The prevalence of use of anti-depressants and anxiolytics for the purpose of treating anxiety and depression also remains unclear. While a study found 11% of its participants reported using anti-depressants, another discovered 19% and 24% of its experimental and control groups, respectively used anti-depressants at the start of the study.[45, 46] However, by the end of the

intervention of a mind-body exercise, the experimental group's rate of use dropped to 16% while the control group increased to 33% 12 months later. [27]

While SSRIs are often employed in PD for treating mood disorders due to their relatively low side effects, a study found no significant benefit of SSRIs when tested against a placebo.[36] With the exception of older patients or those with severe depression, these medications are suggested to treat depression less effectively in persons with PD when compared to non-PD depression. However, these findings have been criticized for their small number of subjects (type II error), and there is a general lack of randomized control trials testing treatment of mood symptoms in PD.[47, 48] Although still considered by some to be an effective treatment for depression in PD patients, why SSRIs sometimes fail to curb depression symptoms in PD remains unexplained.[17] Conversely, a recent study found anti-depressants (SSRIs and TCAs), often used to treat both anxiety and depression, moderately improved mood symptoms in PD.[49] Nonetheless, well designed trials testing the efficacy of anxiolytics and anti-depressants for treating mood symptoms in PD are still lacking.[23, 36] Since mild depression is thought to account for the majority of depression in PD, non-pharmacological interventions are a preferred choice for therapy, which can include counseling, education, and cognitive behavioral therapy.[23]

Nevertheless, anxiety and depression symptoms may inhibit the efficacy of treatment interventions for both the mood symptoms themselves and PD symptoms in general in persons with PD. The presence of depression has been found to negatively correlate with adherence to antiparkinsonian therapy adherence as well as for medication in the general population.[50] Lower rates of compliance with a home-based exercise program in persons with anxiety, depression, or mental health problems were reported in a study.[50] Further, a particular form of

anxiety in PD referred to as “medication phobia” has been proposed to describe tendencies in which persons with PD avoid taking prescribed medication due to an irrational fear of it.[51] Sub-optimal compliance with anti-parkinsonian treatment has been identified as highly prevalent in the PD population, which is associated with an overall worsening of PD symptoms.[52]

## Sleep Dysfunction

Sleep dysfunction is commonly associated with PD, significantly lowering patients' overall quality of life. [2, 24, 43] Dr. James Parkinson also identified sleep disturbances as a symptom of PD in his original description of the disease.[53] More common in PD populations compared to the elderly population, sleep dysfunction in PD frequently consist of daytime sleepiness, insomnia, night-time waking, restless leg syndrome (RLS), vivid and/or violent dreams, sleep apnea, and periodic limb movements during sleep (PLMS).[14, 17, 21, 24, 43, 54] Among patients with advanced PD, sleep disorders (most commonly insomnia), daytime sleepiness, and daytime sleep attacks (though rare and often due to side-effects of medication) have been considered one of the top most prevalent symptom complaints.[8, 24] Additionally, waking during both the night and early morning are commonly caused by resting tremor, with up to 98% of patients suffering from a range of these sleep disorders.[2, 24, 53] Bradykinesia may also result in disturbed sleep, due to patients' inability to turn in bed.[17]

Perhaps the most challenging sleep disorder in PD is REM Behavior Disorder (RBD), which is characterized by a lack of normal atonia (muscle control) during REM sleep.[6] Occurring in approximately a third to a half of persons with PD, RBD will frequently enact vivid or unpleasant dreams.[24, 55] As many as 50% of persons with PD may kick or punch during REM sleep, potentially causing physical harm to both themselves and their bed partner.[56] RBD

is likely caused by neural damage in the REM sleep atonia system, resulting in a lack of muscle tone during REM sleep. [56] Further, brain imaging has revealed RBD is associated with cholinergic denervation. [13] The onset of RBD in PD is thought to occur before the onset of motor symptoms, where more than 50% of persons with RBD will develop PD an average of 13 years after having RBD.[15] Other problems related to PD such as autonomic dysfunction, cognitive impairment, longer disease duration, and RLS have also been shown to be associated with RBD in PD.[15, 56]

Sleep dysfunction is prevalent in all stages of the disease. Problems with sleep are thought to begin early in the disease, even prior to motor symptoms by several years, and intensify as the disease progresses.[2, 8, 21, 53, 55] Quality of sleep as measured by deep, REM, and sum total sleep time has been shown to decrease in patients with respect to longer disease duration.[22] Daytime sleepiness frequency positively correlates with disease severity, treatment duration, and other NMS.[24] This progression may occur at a linear rate along with other NMS such as difficulties with cognition, speech, and gait.[22] Conversely, insomnia, another common sleep problem affecting up to 50% of the PD population, does not appear to worsen with respect to overall disease progression.[22, 24] In the early stages of the disease, nocturnal cramps and nocturia (waking due to the need to urinate) are commonly experienced.[53] Age may also be a factor, as older patients complain of shortened total sleep time and unwanted awakenings.[24]

Sleep dysfunction can be difficult to distinguish from other NMS in PD due to symptom overlap. Difficulties with sleeping can be mistaken for depression or vice versa in PD, as sleep dysfunction and depression are both associated with a patient's immobility, psychomotor retardation, and apathy.[17, 23] Problems associated with sleep dysfunction such as lack of energy, insomnia, or daytime sleepiness may indicate a patient is depressed, when he or she is

fact is not.[17] However, anxiety and depression may both cause and worsen sleep disturbances in PD patients.[17, 53] Further, the worsening of depression has been associated with greater disability with respect to sleepiness.[55] Whether sleep disorders trigger anxiety and depression or if the vice versa is true remains an open question for discussion.[17] In addition to anxiety and depression, fatigue, cognitive impairment, neurodegeneration, and prescribed drugs, may all contribute to sleep disturbances in PD.[24]

While little is known regarding the pathogenesis of sleep disturbances in PD, theories have emerged speculating on the symptom's neuropathology. Sleep disturbances in PD are thought to be caused by multifactorial neuropathology specifically associated with lesions in the brainstem's central sleep regulation centers in the raphe nucleus, as well as thalamocortical pathways affecting transmission of both dopamine and serotonin.[54, 55] Other regions in the brain regulating sleep are near the substantia nigra, where PD neurodegeneration traditionally occurs may also be implicated in the development of sleep disturbances.[17] Dopamine neuron cell death itself may also negatively affect sleep quality, specifically in the midbrain's ventral tegmental area, which is also involved in the sleep-wake cycle.[24] Dysfunction of the serotonergic system, which regulates sleep cycles is also associated with the neurodegeneration of PD and may be implicated in the development of sleep disorders, as well as other NMS including depression, fatigue, and visual hallucinations.[13] Nevertheless, thus far the role dopaminergic and serotonergic neuron degeneration plays in the development of particular sleep disorders in PD remains unclear.[24, 54] Additionally, PD patients with reduced mesopontine monoaminergic capacity have been shown via neural imaging to correlate with an inability to maintain REM sleep, thus resulting in difficulties with sleep.[13]

While diagnostic tools exist to identify sleep disorders in PD, symptoms are both under-

recognized and lacking adequate treatment.[8] Despite sleep problems often predating motor symptoms in PD, the likelihood of sleepiness predicting the eventual onset of PD remains low as a predictive symptom. A study found only 9 out of 244 (less than 4%) of patients reporting sleepiness developed PD.[6] However, RBD may have greater potential as a predictive marker for PD, given that, as noted, 50% of persons affected by RBD are expected to develop PD or dementia within 10 years.[6, 24] Despite a need for more adequate care of sleep dysfunction, current care of PD may include the treatment of sleep difficulties. Nevertheless, dopaminergic treatment for motor symptoms as well as NMS medication (anti-depressants, anti-hypertensive drugs) may in fact result in further sleep difficulties.[17, 24] Further, common side effects of dopamine agonists include vivid dreaming, sleepiness, and sudden sleep attacks.[14, 54] The nonselective MAO-B inhibitor selegiline commonly prescribed to decrease the off-time of levodopa, has been implied to cause sleepiness, disruption of REM sleep, and sleep fragmentation, whereas the selective MAO-B inhibitor rasagiline has not been shown to significantly affect sleep quality.[24]

Given that standard care may exacerbate sleep dysfunction symptoms, alternative therapies may assist in treating this NMS. The practice of Qigong meditation has shown to improve sleep quality and decrease daytime sleepiness in patients with PD.[46] Tai Chi has also shown to improve both patients' sleep quality as well as overall energy.[57] Other alternatives therapies that may improve sleep quality may include better sleep habits developed by sleep hygiene education, cognitive behavioral therapy specifically for insomnia (CBTI), and relaxation training. [24]

*Fatigue:* Fatigue is another relevant NMS experienced by many persons diagnosed with PD. This NMS is perhaps the most disabling symptom of PD affecting the quality of life of up to one third

of persons with PD.[23] Often unpredictable in its onset, fatigue is characterized as the inability to initiate and sustain mental and physical activity, and is often exacerbated by physiological, psychological, and social stress.[23, 58] Patients with PD suffering from fatigue often describe the symptom as experiencing “tiredness,” “exhaustion,” and “lack of energy”. [58] Characterized by both mental and physical components, fatigue in PD affects all aspects of patients’ lives and can deter participating in and planning work, leisure, and social related activities.[58] Sometimes present before the development of motor symptoms in PD, fatigue has been shown to worsen with respect to disease progression, but is not necessarily correlated with motor dysfunction.[22, 23]

Like other aforementioned NMS in PD, fatigue is considered under-recognized and undertreated in PD. This is due in part to a wide variety of assessments and instruments used to diagnose fatigue in PD, many of which have not been validated, and perhaps also the intermittent nature of the symptom. [23, 58] Distinguishing fatigue from other NMS in PD is another challenge to recognizing and treating fatigue. Other NMS accompanying fatigue in PD include daytime sleepiness, cognition, apathy, and mood disorders.[23, 43, 54] Common characteristics of both fatigue and depression in PD include lack of energy as well as difficulties with motivation, concentration, and appetite.[23, 45, 59] Cognitive deficits are also associated with fatigue in PD; whether fatigue causes cognitive impairment or vice versa remains undetermined. [58]

While daytime sleepiness and fatigue may be considered similar in nature, studies suggest fatigue is an independent symptom of sleep disturbances in PD, though these symptoms are often co-morbid. Nevertheless, no studies have examined the sleep patterns of persons with PD in relation to fatigue. [58] Further, a relationship between motor symptoms, sleep disorders,

and fatigue remains inconsistent, nor has level of physical activity been shown to affect patients' level of fatigue in PD. [23]

Rather than being attributed to other concurrent NMS such as depression or daytime sleepiness, fatigue worsens with respect to disease progression, and is thus primarily involved in the pathological process specific to PD.[22] Conversely, dysfunction in the serotonergic system has also been suggested as a contributor to the development of fatigue as well as other accompanying NMS in PD. [13] Further, endogenous and exogenous factors are suggested to explain the co-morbidity of fatigue and other motor and NMS of PD, where the development of the disease and symptoms are inherently intertwined. [58]

### **Non-motor Symptoms May Affect Gait in PD**

Gait impairment is viewed as a motor symptom of advanced PD. [25, 26] Growing evidence suggests a significant influence on gait by non-motor symptoms especially cognitive impairment and sleep disorder. Many motor features, including bradykinesia, rigidity, gait, and postural instability show strong correlations with cognitive decline [60]. This becomes increasingly evident during cognitively challenging situations [61-64]. Simple forward walking engages a high degree of automaticity in the absence of pathology. Normally, cortical engagement is needed only when the gait pattern, direction, or speed must change in response to environmental changes [65]. However, automaticity of normal gait is compromised in PD [66, 67], often leading to increased reliance on cortical control [68, 69]. When cognitive dysfunction reaches a certain threshold, some patients may be unable to accommodate the increased cognitive demands to control walking.

Sleep disturbance in PD significantly affect clinical manifestations of the disease. PD patients with sleep disorder tend to have an increased frequency of falls and less clinical response to levodopa medication [70-72]. Rapid eye movement sleep disorder (RBD) is associated with slowness of gait [73]. Sleep disorder and abnormal gait pattern in PD may both involve the degeneration of nuclei in the rostral brainstem, primarily the pedunculopontine nucleus (PPN) [74]. The PPN plays a central role in gait and postural control as it generates the periodic locomotor activity and regulates central pattern generator in spinal cord [75, 76]. Focal lesions in the mesencephalic-pontine tegmentum, where the PPN is located, cause postural instability and loss of gait rhythmicity [77, 78]. PPN is also part of central circuitries and can modulate rapid eye movement sleep. Its dysfunction may lead to impaired maintenance of atonia and RBD [79, 80]. Improved sleep may help to alleviate dopamine sensitive symptoms [81].

Conversely, improvement in cognitive function and/or sleep may lead to improve gait performance. In a study of elderly individuals who complained sleeping disorder, Tai Chi exercise showed greater improvement in overall sleep quality as well as in gait velocity and postural stability in comparison to a low-impact exercise program [82]. However, research evidence is lacking for supporting a notion that improvement in non-motor symptoms may lead to improvement in gait performance. A previous study in our research laboratory observed an improvement in sleep quality and gait performance in a group of patients with PD after the same intervention as used in the current study.[83] Our previous study, however, did not have a control group and was limited with a small sample size. We conducted the current randomized controlled pilot trial using the same intervention to confirm whether greater improvement in sleep, cognition, and gait performance could be observed after the intervention in the experimental group in comparison to a control group.

## **Alternative Therapies**

Alternative therapies for treating symptoms of PD (those not relying on medication) include exercise, balance training, nutritional interventions, counseling, and education, which can all improve overall quality of life.[2, 3] Therapies encouraging social interaction and developing relationships tend to improve the overall wellbeing of persons with PD. However, such therapies currently lack in existing PD rehabilitation programs. [84] Exercise and physical therapy can effectively improve PD physical symptoms such as rigidity of flexed posture and develop flexibility, strength, and balance. While exercise can offer therapeutic effects for the psychopathological impact of PD, the earlier such alternative therapies are introduced, the more effective they are.[2]

*Qigong exercise:* Mild meditation exercises originating from Chinese medicine have been purported to improve quality of life in PD. The practice of one particular exercise, Qigong, which has been around for 5,000 years, is thought to activate naturally occurring physiological and psychological processes that improve one's overall health and functionality. Similar to Tai Chi, Qigong incorporates focused breathing, slow movements, and meditation to attain a relaxed state, and the exercise may improve balance and decrease risk for falls. [20] Tai Chi and Qigong are closely related Chinese medicinal exercises, with similar theoretical framework, motions, and application for improving health.[20] Tai Chi has previously shown to improve outcomes in persons with PD. Overall wellbeing and gait variability have been shown to improve with the practice of Tai Chi in PD, making it a safe intervention for persons with mild to moderate PD. [85]

Similarly, Qigong is applicable as a therapy for PD patients since it can be easily adapted for patients with special needs such as balance difficulties. [46] When compared to exercise interventions, a study showed Qigong improved quality of life in PD patients, but not significantly. [20] Qigong has also been shown to improve NMS in PD, especially sleep disturbances, but not autonomic and motor fluctuation symptoms. [46] While Qigong has been reported to improve psychological health, high blood pressure, pain, and immunity, few rigorous randomized trials have been performed to confirm the health benefits of Qigong on movement disorders such as PD.[86] Thus, the positive effects of exercise on PD symptoms remain controversial given that any treatment program may increase striatal dopamine release as part of a placebo effect.[46]

### **Aim of Study**

Thus, the characteristics of non-motor symptoms in PD remain unclear regarding not only how prevalent and severe they are, but how they change throughout the course of the disease. While many treatments exist for primarily addressing the traditional motor symptoms of the disease, potential alternative, complementary therapies may also exist for treating certain non-motor aspects of PD. Even still, how effective these therapies may be for addressing particular symptoms, and how non-motor features, specifically mood symptoms, may limit the efficacy of such interventions in PD remain unknown.

With regard to non-motor mood symptoms in PD, the question is raised: how prevalent and severe are anxiety and depression in PD with respect to stage of the disease? Considering alternative therapy possibilities, another question can be asked: is Qigong exercise a viable alternative therapy for addressing symptoms of PD, especially sleep and gait dysfunction?

Synthesizing these two questions of interest, the following primary research question can be formulated: how do mood symptoms in PD impact the efficacy of alternative therapy program Qigong exercise program for treating motor and non-motor aspects of the disease?

In order to examine the primary research question, a background research study will be conducted, which will investigate the prevalence and severity of anxiety and depression and its relation to disease severity in a general Parkinson's population, based on retrospective data analysis. A follow-up clinical trial with a between groups design will then be performed testing the effectiveness of the Qigong exercise therapy for treating non-motor and motor aspects of the disease, primarily sleep quality and gait functioning. Study participants will be recruited for trial, and their level of anxiety and depression symptoms will be assessed in relation to efficacy of the exercise.

The following hypotheses are put forth predicting the findings of the subsequent studies. It is predicted that greater disease severity will significantly correlate with increased severity of mood symptoms. Given the results of pilot study testing Qigong exercise in PD, it is hypothesized that the experimental group will see statistically comparable improvement in both sleep and gait measures and corroborate these previous findings. It would also be expected to see significant improvement in other symptoms of the disease such as cognition, fatigue, and mood. Even still, it is further postulated that the Qigong exercise program will be less adhered to less by study participants with relevant mood symptoms. Thus, it is expected that anxiety and depression will be found to be a significant non-motor symptom in PD, both regarding its prevalence and severity as well as its impact on treatments for the disease.

## **Quantitative Measurement of Gait Impairment**

Technological tools for measuring gait pattern are of particular importance for this study investigating the positive effects of Qigong therapy in PD, given that biomarkers for gait functioning are essential for determining the efficacy of new, experimental treatments for PD.[87] Investigations into gait disturbance related to PD have primarily examined the spatiotemporal, kinematic, or kinetic parameters of gait. Advantages to objectively and quantitatively analyzing gait disturbances using technical devices is the focus on the cardinal motor symptoms of the disease (bradykinesia, rigidity, tremor and postural instability) associated with PD.[88] Technologies that have been developed and tested for analyzing gait biomechanics in a laboratory setting primarily include timed tests, wearable data recorders, vision-based motion capture systems, force plates, electromagnetic systems, and pressure sensitive electronic walkways.[28, 87, 89] Thus, several alternatives exist for quantifiably assessing study participant's gait impairment and variability in a clinical setting. For this particular study's interest conducting a clinical trial for testing the effects of Qigong exercise in PD, it is of interest to examine and select a workable gait measuring system.

*Selection criteria:* An ideal technology for assessing gait disturbance in PD would be non-invasive and simple to use, provide scientifically sound data, and inexpensive. Nevertheless, many of the kinematic and spatiotemporal measuring systems available and used in a clinical setting for measuring gait in PD may be time-consuming, labor intensive in their set up, impractical, and even disrupt a person's natural gait pattern.[87, 90] Based on characteristics of the different options available, criterion was developed to determine what system measuring gait parameters should be selected for a clinical trial testing the efficacy of Qigong exercise in Parkinson's disease. Considerations for selecting a gait analysis system were categorized into

simplicity of testing, validity of relevant gait measures (scientific sound data), and practicality of system for the particular trial.

With regard to simplicity of testing, ease with which study participants interface with the system, especially given the physical impairment associated with PD systems must be considered as well as reliable acquisition and storage of data during testing procedure. Thus, duration of time and discomfort on part of the participant, and to a lower degree clinician, should be minimized. This would further include selecting a system that would most easily be accessible for study participants with respect to location of laboratory. A gait analysis system should also provide relevant, valid, and reliable gait parameters pertaining to measuring gait impairment and variability. A system should accurately measure stride length, step length, and velocity, and the most prominent signs of gait impairment, with as well as indicators of postural instability: double support time and shifts in center of mass. [7, 27, 29] Preferably, a system would allow multiple cycles for testing during each phase of testing to both strengthen reliability of data and assess for variability in the gait parameters. Finally, practicality, related to simplicity of testing, is another consideration for selection of a spatiotemporal measurement system. Cost of the system as well as ease of setup, tear down, and storage of the technology is a determining factor.[91] Further, availability of laboratory space and time is another consideration as well as the convenience and available of a system already. Further, the particular piece of technology would have been used ideally in previous studies in the laboratory measuring similar gait patterns in Parkinson's disease to verify its reliability.

*Timed Up and Go test:* The Timed Up and Go test has been used to assess motor disability in PD, where study participants are timed while doing a sequence of tasks: sit-to-stand, walking 3 meters, turning, and stand-to-sit. The longer the duration of time to complete the tasks, the

greater the gait impairment indicated.[92] This test has been used in addition to applying mobile inertial sensors and a portable data-logger (Physilog®) while performing the TUG test, dubbed the iTUG test. On its own, the TUG test is easy for a clinician to set up and for a participant to perform, primarily only requiring the materials of a chair and stopwatch. However, only one quantity is measured using this method: time. In addition to human error (starting and stopping the watch), this method does not quantitatively and sensitively assess any gait and balance. The additional sensors provided data for upper body (arm swing velocity, range of motion, and asymmetry), lower body (cadence, gait cycle time, stride velocity and length, variability of stride time and length) trunk (angular velocity and range of motion) turning (turning velocity) and sit-to-stand (velocity) parameters. While a combination of these parameters could be used to suggest generalized bradykinesia (arm swing, cadence and trunk rotation during gait, and turning velocity), a Matlab (Mathworks, Natick, MA) program separated and analyzed data from the sensors to provide the gait and postural measures. This method, however, did not sensitively assess gait variability, perhaps due to the short length of walking, but did allow for multiple cycles to be tested. While the cost of the sensors were not disclosed in study, iTUG may serve as a quick and easy way to evaluate both PD and possible therapeutic interventions.[93]

*Accelerometers:* On their own, inertial sensors in the form of wearable accelerometer-based motion detectors may also be used to measure relevant features of posture, balance, and gait.[94] By measuring acceleration and the direction, frequency, and intensity of movement, velocity, displacement, and stride length can be derived as well as when a subject walks with the device attached to their sternum, lower back, or waist. [90, 94] In addition to acceleration sensor applications on ‘smart’ devices such as phones or watches, the quarter-sized, wearable FitBit Zip (FitBit Inc., San Francisco, California) counts steps and measures stride length. [90] Wearable

accelerometers tend to be cheaper and less cumbersome than other gait measuring technology as well as more widely available. [90, 95] Kinematic data can either be logged and/or wirelessly transmitted, making recording data suitable for research purposes.[95] Given these advantages, wearable accelerometers may be applied to evaluate the change in motor symptoms of persons with PD over a longer period of time.[90] While this technology may be suited for gathering longitudinal data, it does not gather more than a few parameters (stride length and velocity) related to assessing gait impairment and variability. Given the relatively short period that the prospective trial will be run (6 weeks) with the pre-/post design, wearable accelerometers may be a useful technology, but in a future trial assessing the validity of a therapy for PD.

*Vision-based gait analysis:* Vision-based gait analysis, primarily relying on 2-D representations captured using videos have been used in previous decades to assess and describe markers of gait.[91] By recording a subject participant performing a walking task either in a single or multiple perspectives, 3-D body structures, limbs, and their kinematics can be modeled based on the 2-D projections captured in the image sequence. Body structures on consecutive frames are thus analyzed, yielding position and velocity values.[96] As opposed to “active sensing” (ie. sensory devices attached to study participant’s body), the “passive sensing” of video-based gait analysis relies on more natural signals (in this case, light wavelengths from unencumbered body) for a touch free experience. This feature is particularly advantageous compared to active sensing systems, where wearable devices may prove to be inconvenient, intrusive, or even impossible to apply for study participants. The off-line analysis of video heavily relies on making assumptions about the initial stance and physiology of the participant and as well as often probabilistic motion models (ie. the Kalman filter) offset background clutter and complex dynamics that may interfere with proper analysis.[97] The application of motion-

models and additional camera perspectives (sometimes study participants may escape view during testing) can also be used to improve the overall quality and reliability of collected data, and with algorithms, develop a 3-D limb tracking system.[97, 98] Even still, the complexity and validity of data analysis as well as the expertise required to adequately employ these methods is a drawback for this method. Light markers can be used to enhance the accuracy of this system, but occlusion (the marker signal leaving camera range) is the greatest limitation of this system.

While additional cameras can be included to offset occlusion, this adds extra costs to the system. Nevertheless, given how active markers emitting light, the light makers' strobe can be uniquely identified by the system, serving as an advantage over passive systems. Even still, light markers work wirelessly, requiring added electronics, batteries, and thus increased weight on the participant and complexity to the system.[98]

*Pilot study gait analysis:* In a pilot study examining the effects of Qigong exercise on persons with Parkinson's disease using a pre-/post-intervention, single group design, the Vicon 512 (Vicon Peak, Lake Forest, CA) video motion capture system was used (a form of vision-based gait analysis), which included 16 markers on the patient and six cameras.[83] The system was used to measure patients' gait performing both a straight-line task (walking 10 meters) turning task (walking through a doorframe) using early and late cues for a total of 12 trials, three trials for each combination. Using Matlab programming, trajectory and video data was computed to find each subject's spatiotemporal parameters of stride time, stride length, double support time, gait velocity, and gait variability.

Using this video motion capture system, multiple gait cycles were able to be tested allowing for more data collection and the assessment of gait variability in subjects. The standard markers for gait impairment in PD (stride time, stride length, double support time, gait velocity)

were able to be assessed using this system using a visual cue in multiple conditions: straight line as well as turning tasks, thus giving indication of a patient's gait pattern in multiple different scenarios.

Even still, the use of this system was not without its challenges. The collected raw trajectory data and video recordings required filtering and the development of specific Matlab programming. Further, in order to find most of the gait parameters, a foot center point was extrapolated using the foot-velocity algorithm method using other markers on the subject. For the testing, sixteen retro-reflective markers were attached to the study participant's lower body, which measured the position of their sacrum, anterior superior iliac spine, thigh, knee, tibia, ankle, heel and second metatarsal head. Both putting on this gear and performing all twelve trials is time-consuming and could prove to be difficult for persons who have pre-existing walking and balance problems, despite the Vicon system being the gold standard for gait assessment.[99] Yet in addition to measuring the kinematic parameters of stride and step length, stride time, cadence, velocity, and single/double support time, the Vicon system has also been verified to reliably assess joint angle curves, another indicator of gait impairment in PD.[100] Further, motion capture systems such as the Vicon are expensive and require complex set up and a particular lab environmental setting for use.[91]

*Force plates:* Force plates may be another technology used to assess gait variability and postural instability, also indicating for risk for falling in PD. [91] The trajectory of a study participant's center of pressure for a patient can indicate amount of sway. However, the use of force plates may be limited, especially given that not all are portable devices.[91, 101] Using the ground reaction force measured when the forefront is solely in contact with the force plate while walking across the force plate, a study participant's gait variability can be calculated using the

“ground reaction vector technique.” The portability of a system is an asset, requiring less set up time and available laboratory space. While the system may reasonably provide gait variability data and can process multiple cycles, portable force plates may not provide as accurate results as the Vicon system. Further, force plates generally do not capture other measures of gait impairment (velocity, step and stride time, etc.). Therefore, the use of force plates may best be used as supplement to other gait parameter measuring systems as well as for non-clinical application.[101]

*Electromagnetic tracking systems:* Electromagnetic systems, most notably Liberty (Polhemus, Colchester, VT), and Flock of Birds (Ascension Tech. Corp., Burlington, VT) as well as their variants rely on low-frequency electromagnetic transmitter that detect sensors that are attached to segments of participant’s body.[95, 102, 103] The electromagnetic coil transmitter determines the position and orientation of the sensors in relation to itself based on fluctuations in the magnetic field, creating changes in signal amplitude. For a trial, data is collected and transmitted to a computer while moved their hands and forearms, where it is analyzed offline using a Matlab program to assess severity and type of tremor (for PD) based on oscillations in sensor position.[103] However, the system can detect up to six degrees of motion (rotational and translational) and the displacement data can be verified easily by placing the sensor at a pre-measured distance away from the electromagnetic transmitter.[103] While nearby metallic objects may affect sensor data, this system collects and displays accurate data that is comprehensible in real-time based on wave amplitude.[95, 103] The cabling between sensors may be uncomfortable and inhibit movement of a study participant. [102] Nevertheless, the high expense, lack of availability, and available laboratory space may prohibit the use of this assessment tool for measuring kinematic and spatiotemporal parameters

in the current study.[102] Further, while the electromagnetic system may be an effective tool for assessing tremor severity, other technologies may better assess parameters more suited to gait impairment and variability in PD, which is the primary interest in this study.[95, 103]

*Electronic, pressure sensitive walkways:* Electronic walkways may also be a viable tool for measuring gait parameters in the prospective study, where the most popular systems are the GAITrite (CIR Systems Inc., Franklin, NJ) and the Gaitmat II (EQ Inc., Chalfont, PA). The GAITrite system is a 16 foot (4.9 meter) long walkway that relies on pressure sensitive pads that is analyzed by an on-board processor and transfers gait parameters (velocity, step time and stride for each foot) to a computer with application software.[99, 104] Similarly, the Gaitmat II is a four meter long walkway has been employed in previous studies, which digitally records, processes, and immediately displays a study participant's gait velocity, step length, double support time, and step variability.[105]

However a clinical walkway is limited in that it does not test gait in the complex environment in which a typical participant must function and only assesses measures pertaining to the lower body.[87, 89] While walkways may also be bulky and expensive, they do provide immediate, automatic analysis of a participant's gait pattern and can used for multiple cycles.[87] Given that the Gaitmat II has been demonstrated straightforward to use in a clinical setting and measures these parameters directly related to gait variability, including hypokinesia, this system may be a promising in terms of quantitatively assessing gait severity in PD.[28, 105]

*Selection of gait analysis technology for study:* Based on the criterion developed and an examination of possible technologies available for assessing gait pattern for the current, the electronic walkway, specifically the Gaitmat II, was selected. As a passive sensor system, the walkway is simple for study participants to use as any wearable sensors are dispensed that may

be haphazard or inconvenient; all they must do is walk a short distance of seven meters total (two meters prior to, four meters on the walkway, and two meters before stopping) for five cycles total. The system also provides immediate, displayable and storable data on the relevant gait measures after each cycle. Thus, the clinician can recognize any possible abnormalities at the time of testing, and the data can be stored for later, offline analysis.

Although the gold standard Vicon system was used in a previous study testing the same form of Qigong exercise in PD, this system may not be necessary to use in this pilot study, especially when considering the comparable simplicity of the Gaitmat system. The Gaitmat II provides sufficient baseline quantifiable gait parameters during a standard straight-line walking task that can be compared in the two group, pre-post-intervention design. The current study is small and is investigating the feasibility of the intervention in PD. If the study findings warrants further investigation of the effects of the therapy in PD on gait pattern, perhaps the Vicon system or even wearable accelerometers can be used to gather more information regarding performing more complex tasks in a future, larger, or even longer study.

Conveniently, a Gaitmat II system used in prior investigations of PD was also available for use in the laboratory near the clinician's office who will perform the UPDRS on each participant. The device can be conveniently stored in the laboratory, and requires little to no setup for each use. Given that the Gaitmat II system is borrowed, no additional cost is required of the study. Thus for the above reasons, the Gaitmat II system is the technology of choice for this particular study when assessing the effects of the Qigong exercise intervention on gait impairment.

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## **Chapter 2: A Portrait of Anxiety and Depression in the PD Population**

### **Abstract**

Parkinson's disease is a neurodegenerative condition traditionally characterized by progressively severe motor symptoms. Recently, the disease's non-motor symptoms, specifically anxiety and depression have received greater attention for contributing to impaired quality of life in PD. This study aims to elucidate the prevalence and relationship of these mood disorders as they relate to each other and other aspects of the disease. We hypothesized that relevant anxiety or depression symptoms would be reported in 50% of the PD population, and that severity of these symptoms would increase with respect to overall disease severity.

One thousand two hundred twenty one patients diagnosed with PD were systematically evaluated at a clinic for overall disease severity, anxiety and depression symptoms, and motor impairment. Twenty five percent of the sample population were receiving their first diagnosis of PD. Medical records were stored in a database and retrospectively analyzed. Sixty six percent of the sample population was found to have anxiety symptoms, while 51% was found to have mild to severe depression symptoms. These findings fall within previous estimates, though much disparity exists in these past studies. The rate of co-morbidity between these symptoms of 45% was higher than previously reported. The rate of anxiolytic use was 18% and 31% for antidepressant use, with 9% of the population prescribed both forms of medication. Of those prescribed medication for mood disorders, higher rates of anxiety and depression were reported, suggesting the efficacy of these medications may be limited.

While mood symptoms tended to worsen with overall disease severity, the study confirms previous findings suggesting the progression of serotonergic degeneration, attributed to mood disorders, is nonlinear with respect to worsening of PD. Further, findings of the study support

previous claims that a lack of consistent methods for identifying and treating mood symptoms in PD remains an issue in managing the disease. Thus, the study suggests anxiety and depression are relevant non-motor symptoms of PD, and more consistent tools are required for properly caring for mood disorders in PD.

## **Introduction**

While Parkinson's disease (PD) has been traditionally associated with cardinal motor features of bradykinesia, tremor, rigidity and postural instability, its non-motor symptoms (NMS) oftentimes affect quality of life more negatively than motor symptoms, contributing up to 60% of the decline in a patient's quality of life.<sup>[1-5]</sup> Anxiety and depression, two primary NMS in PD are associated with greater motor and cognitive impairment as well as sleep problems, social phobia, and apathy.<sup>[6, 7]</sup> Mood symptoms are often considered the result of multiple neuronal degenerations and attributed to similar noradrenergic, serotonergic and dopaminergic malfunction associated with PD.<sup>[7-9]</sup> Additionally, genetic factors have been linked to the pathogenesis of anxiety in PD.<sup>[10]</sup>

Studies examining the prevalence of anxiety and depression in patients with PD show wide disparity in diagnosis criteria, sample sizes, and estimated frequencies. <sup>[10-17]</sup> Past studies estimate 5% to 69% of the PD population suffers from anxiety. <sup>[10, 18-20]</sup> Generalized anxiety disorder, social phobia, panic disorder, and agoraphobia are the most common anxiety disorders found in PD.<sup>[20, 21]</sup> Depression in PD has been estimated to affect between 2.7% and 90% of patients depending on the study. <sup>[7, 18, 20]</sup> The frequency of major depression has been reported in 5% to 20% of the PD population while minor forms of depression affect an additional 10 to 30% of patients.<sup>[9]</sup> While variations in severity and frequency may be partially due to different diagnostic tools used in various studies, depression is considered uniformly under diagnosed.<sup>[7, 22]</sup> More studies examining the rate and severity of anxiety and depression symptoms in PD are needed.

Findings detailing the overlap between anxiety, depression, and disease progression in patients with PD remain inconclusive. The overlap rate between depression and anxiety in PD

could be quite high.[8] For example, 67% of those with depression had also an anxiety disorder while 92% of those with an anxiety disorder had co-morbid depression.[23] It has been reported that between 14% and 26% of PD patients suffer from both anxiety and depression.[23-25] Variations in past estimates of co-morbidity of these mood disorders in PD were attributed partially to the differing in diagnostic criteria.[25, 26] More severe anxiety and depression in individuals with PD often seem to accompany greater motor impairment, however, the PD stages measured by Hoehn and Yahr (HY) scale have been found not to correlate with the worsening of mood symptoms.[10, 19] Furthermore, disease duration had not been shown to correlate with anxiety symptoms, except that younger age of disease onset was associated with higher anxiety.[25] While anxiety and depression were thought to predate motor symptoms, past studies of mood disorders in the early stage of PD remain rare. [28,14] In general, there has been a lack of clarity in understanding the overlap between anxiety and depression and the relationship between disease duration/severity and mood symptoms.

A better understanding of the characteristics of mood disorders in individuals with PD may help to develop appropriate diagnosis tools and therapies for mood disorders in PD. The current study aims to examine the prevalence, severity, and relationship of anxiety and depression with PD disease progression. We expect to find a statistically significant correlation between overall disease progression and severity levels of mood symptoms.

## **Methods**

*Patient Evaluation:* A retrospective analysis of records from 1221 individuals diagnosed with idiopathic PD was performed in the current study. All patients were evaluated by the same physician specialized in patient care for PD during the patient's first visit to the Parkinson's Disease and Movement Disorder Center at the University of Kansas Medical Center. Diagnoses were made using the United Kingdom Parkinson's Disease Society Brain Bank Criteria.[\[27\]](#) Patients included in the study were determined to have PD with a confidence level of 90-100%. Any patient who did not meet the diagnostic criteria or complete requisite questionnaires and/or assessments was excluded. De-identified patient examination information was stored in a secured database.

*Prevalence of Anxiety and Depression:* Severity of anxiety and depression symptoms was evaluated using the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI). [\[28,](#) [29\]](#) BAI scores were classified by level of severity based on the scale criteria: minimal anxiety (0 - 7), mild anxiety (8 – 15), moderate anxiety (16 - 25), and severe anxiety (26 - 63). The same was done for BDI scores: minimal depression (0 - 9), mild depression (10 - 18), moderate depression (19 - 29), and severe depression (30 - 63). In the current study, mild to severe levels of anxiety and depression were considered clinically relevant. Patient scoring in mild to severe levels on both the BAI and BDI were considered to have co-morbid anxiety and depression symptoms.

*Disease duration, severity, and use of medicine for anxiety/depression:* Age and date of both initial PD symptom onset and subsequent diagnosis were recorded. Based on disease duration, subjects were divided into four categories as newly diagnosed (disease duration 0

years), early (1–5 years), established (6–10 years) and advanced (more than 10 years).[30]

Disease severity was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), which includes four sections, I-mentation, behavior and mood (MENTAL), II-activities of daily living (ADL), III-motor examination, IV- motor complications as well as Hoehn and Yahr (HY) staging of the condition and Schwab and England Activities of Daily Living Scale (SE). [31, 32]

The UPDRS score was found by totaling all five sections. The MENTAL sub-section score, which includes a question about depression was also used to measure mood.[33] HY stage was used to assess disease severity. ADL and MOTOR sub-scores were used to determine functional impairment and motor disability, respectively. Prescribed medication and dosages of anti-depressants and/or anti-anxiolytics along with Mini Mental State Exam (MMSE) scores were also gathered, (Table 2-1). [34]

*Relationship between Anxiety, Depression, and Disease Duration/Severity:* Strength of relationships between mood symptoms, disease duration, and disease severity were determined by correlating the sample's disease duration, UPDRS scores, and HY stage with BAI and BDI scores using a Pearson Correlation Coefficient (r). Strength of correlation coefficient was interpreted using Munro's descriptive range in terms of 'little, if any' (.00 - .25), 'low' (.26 - .49) 'moderate' (.50 - .69), 'high' (.70 - .89) and 'very high' (.90 – 1.00) correlation values.[35]

Furthermore, subjects were divided into sub-groups based on HY stage and range of disease duration. For each HY stage or disease duration sub-group, the number and percentage of subjects as categorized by their anxiety and depression levels were reported. Chi-squared tests were used to analyze significant difference between level of mood symptom severity with respect to disease duration or motor severity. The alpha value less than .05 was considered significant.

## Results

The data revealed that around 66% of the sample population experienced clinically relevant anxiety symptoms with 34%, 20%, and 11% experiencing mild, moderate, and severe levels of anxiety, respectfully (Table 1). About 49 percent of the sample experienced relevant depression symptoms, with 33%, 12%, and 3% experiencing mild, moderate, and severe levels of depression, respectively. Approximately 45% of the sample experienced clinically relevant symptoms of both anxiety (BAI score range of 8 – 63) and depression (BDI score range of 10 – 63). The relevant anxiety symptoms were reported in 92% of individuals who also report relevant depression symptoms. About 70% of the sample population reported either relevant anxiety, depression, or both mood symptoms.

About 18% of the sample's population were prescribed anxiolytics (diazepam, clonazepam, lorazepam, or alprazolam) and 31% prescribed antidepressants (primarily any drug classified as selective serotonin reuptake inhibitor) (Table 2). The overlap between users of the two types of medicines was 9% of the sample's population. Of persons prescribed anxiolytics, 83% still reported relevant anxiety symptoms with distribution rates of for mild, moderate, and severe anxiety, respectively. Of those prescribed antidepressants, 74% still reported relevant depression symptoms with distribution rates of for mild, moderate, and severe anxiety, respectively.

Disease duration showed little if any correlation with BAI score ( $r = .19$ ) and low correlation with BDI score ( $r = .28$ ) (Table 3). Disease severity (UPDRS score) showed significantly moderate correlation with depression ( $r = .51$ ) and low correlation with anxiety ( $r = .44$ ) scores, respectively. Similarly, HY stage showed low but significant correlation with anxiety

( $r = .40$ ) and depression ( $r = .30$ ). BAI and BDI scores were moderately correlated ( $r = .69$ ). A high correlation was found between UPDRS score and HY stage ( $r = .78$ ). Both UPDRS score and HY stage were moderately correlated with disease duration ( $r = .52$  and  $.58$ , respectively).

When grouping the sample by the level of anxiety severity, Chi-squared tests revealed that the ratio of patients with moderate ( $p=.008$ ) or severe ( $p<.001$ ) level of anxiety increased significantly as disease duration increased (Figure 1). The ratio of subjects with mild level of anxiety remained relatively constant ( $p=.880$ ), while the ratio of subjects with no obvious anxiety symptoms significantly decreased ( $p<.001$ ) across the disease duration. Similarly, the ratio of subjects with moderate levels of depression significantly increased ( $p<0.008$ ) with respect to longer range of disease duration (Figure 2). A significant decrease ( $p=.0009$ ) in the ratio of patients with no obvious depression symptoms was also found across the disease duration axis. No significant correlation was found in patients with mild or severe levels of depression with respect to disease duration.

The ratio of patients with moderate or severe level of anxiety increased significantly ( $p<0.05$ ) with increased disease severity as measured by HY stage (Figure 3). No significant change was found in the percentage of patients with mild anxiety level with respect to HY stage. However, the percentage of patients with no obvious anxiety symptoms significantly decreased across the HY stage axis. Similar findings were observed for depression levels with respect to HY stage (Figure 4).

## **Discussion**

Results of the current study regarding prevalence of mood symptoms generally agreed with past studies. We found 70% of sample population experienced relevant mood symptoms,

where the rate of anxiety symptoms was found to be 66% while the rate of depression symptoms of 49%. Both rates fall in the middle to upper end of previously estimated range of rates for anxiety (5% to 69%) and depression (2.7% to 90%).[7, 10, 18-20] The prevalence of mild depression (33%) suggest more PD patients suffer from sub-clinical forms of depression than previously estimated.[9] The prevalence of major depression in the PD population (15% at moderate and severe levels) falls within previous estimates (5% to 20%).[9] A meta-analysis of past 14 studies concluded 46% of PD patients suffer from depression, while another analysis postulated a deficit in prognostic tools that inhibited an accurate measurement of depression in PD.[15, 16] A review of 51 studies reported 17% of PD patients suffer from major depression and 22% suffer from minor depression.[17] Furthermore, we have observed a moderate level of correlation ( $r = 0.69$ ) between anxiety and depression. The overlap rate of 45% in our sample were higher than the previously estimated range of 14% to 26%. [23-25] While most of past studies used small sample sizes as well as a variety of study sites and metrics, the current study analyzed data from a specialized PD clinical center with a large sample size (n=1221). Each subject was administered using a standard examination of their motor and non-motor PD symptoms by the same neurologist, resulting in valid within-rater reliability.

Compared to a few past studies involving large samples, the current study gathered more reliable data that allowed a quantitative assessment of levels of anxiety and depression in our sample. The largest number of subjects previously reported in a study examining anxiety and depression in 1307 PD patients.[11] More than half (56%) exhibited symptoms of anxiety and more than 22% were found to suffer from depression, as assessed by the anxiety and depression section of the Non-Motor Questionnaire for PD (NMSQuest).[12] Another study used the same tool in examining 525 PD patients in the UK, USA, Germany, Israel, Japan, and Italy.[14] They

reported that 48% of PD patients experienced anxiety or depression. The NMSQuest relies on two questions about mood symptoms and does not distinguish different levels.[13] A major strength of the current study was that the same physician conducted assessments for all patients involved, while past studies relied on multiple clinics, doctors, and differing diagnostic tools for assessing mood symptoms in their sample populations. More importantly, the use of Beck criteria for mood symptom allowed us to distinguish individuals with mild, moderate, or severe mood symptoms.

The large variation reported in the literature in terms of prevalence of mood symptoms in patients with PD suggests an overall difficulty in recognizing mood symptoms in PD. Anxiety and depression in PD is thought to be atypical when compared to mood disorders in the general elderly population, reflecting both the physiological and psychological components of PD.[8, 22] However, evidence supporting a distinction between PD and non-PD depression has been inconsistent.[9] Depression in PD has been characterized as predominantly manifesting somatic features such as loss of energy or psychomotor slowing.[36] These and other common features of depression such as altered sleep and appetite, reduced memory, or weight change can overlap with PD symptoms that makes depression difficult to be diagnosed in PD populations, even for an experienced clinician.[36, 37]

Our findings of the rates of use of anxiolytics and antidepressants for treating mood symptoms in PD are consistent with previous estimates,[4, 38] however, our data further suggested that the mood symptoms in PD are generally under-treated and the effect of current pharmacological treatments is limited. First, only a portion of patients with mood symptoms take those pharmacological medicines. In the case of the current study, only 18% of the sample population took anxiolytics while 66% of the sample population were found to have anxiety

symptoms as measured by Beck Anxiety Inventory. For depression, 31% of the sample population took anti-depressants while 49% reported depression symptoms. While the current study did not account for non-pharmacological treatment, the findings, along with other reports in the literature, have suggested that anxiety and depression in PD is undertreated.[7, 22] Second, more than three-fourths of individuals prescribed a form of those medications still reported relevant mood symptoms ranging from mild to severe. Finally, it is unknown to what extent those medications have helped the individuals with mood symptoms in the current study, however, our data suggested only a limited effect. All rates of relevant anxiety or depression (mild to severe levels) were higher in the sub-group of patients prescribed medications for treating mood symptoms compared to those without such a prescription (Table 3). For instance, severe anxiety symptoms were reported in 18% of those with anxiolytics but 10% without. Therefore, the use of these medications did not treat the symptoms to a comparative level as those without subscription.

Two hypotheses have emerged regarding the cause of depression and anxiety in PD. One theory considers the altered mood as a reactive state to the perceived social and motor disabilities inherent to PD.[10, 19] The other theory suggests that the mood symptoms are intrinsic to the disease, based on the observation that the onset of mood symptoms in some PD patients occurred prior to motor symptoms.[19, 21] Further, dopamine depletion has been associated with anxiety and depression in PD, suggesting mood symptoms are either interrelated to motor dysfunction or one of the earliest signs of PD.[9, 10, 39] An anxious personality is even considered to be a risk factor for developing and progression of PD,[40] and evidence suggests mood alteration influences severity of motor symptoms.[41] Given the complexity of mood issue and limited effect of the current pharmacological treatments, future research may need to help the

development of non-pharmacological interventions that may provide a holistic benefits to patients with PD and mood symptoms.

In the current study we examined possible associations between mood symptoms and disease duration or disease stage and have some interesting findings. As expected, our data showed a high correlation between UPDRS score and HY stage, moderate correlations between BAI and BDI scores, between, and between disease duration and UPDRS score or HY stage. However, mood symptoms were only mildly correlated with disease duration or HY stage. Although dopaminergic denervation occurring may be associated with mood symptoms, disturbances in the serotonergic and noradrenergic system more closely relate to the manifestation of mood symptoms.<sup>[7]</sup> While damage to the serotonergic system is shown to increase as the disease progresses, this progression is thought to be non-linear and vary between patients with respect to disease duration.<sup>[42]</sup> The non-linear progression of serotonergic degeneration in PD may very well explain the findings of the current study.<sup>[30, 42]</sup> When grouping the sample by the severity level of anxiety or depression, we observed a clear pattern: the rate of individuals with moderate or severe mood symptoms significantly increased over disease duration, while the rate of individuals without mood symptoms significantly decreased. Similar findings were observed for HY stage too. Put together, it seemed that occurrence rate of mood symptoms in PD patients increase with either disease duration or disease stage, but may be not show a strong linear pattern.

*Limitations:* Several factors limit the implications of the study findings. The sample population may not fully represent the whole PD population given that it only consists of individuals able and willing to be examined at a clinic in an urban setting. Due to the cross-sectional design, no causal link can be established between the onset of anxiety and depression symptoms and the

development of PD symptoms. Additionally, how mood disorders develop or change as the disease progresses remains unknown. While the current study suggested mood disorders were prevalent in the PD population, little remains clear on how best to recognize and treat these symptoms in PD.

*Conclusions:* The current study examines the prevalence of anxiety and depression symptoms in a large sample group of patients diagnosed with PD. The uniform use of the Beck criteria in assessing mood symptoms allowed for direct with-in group comparison of symptoms as well as elucidating the severity level of anxiety and depression. Results of the current study confirmed previous findings that anxiety and depression are relevant non-motor symptoms, where an average of 2 out of every 3 individuals with PD are affected by anxiety and half of patients with PD suffer from depression. In general, about 70% of the sample population reported one or both mood disorders. While these symptoms may worsen as the disease progresses, findings suggest the progression is non-linear. We hypothesized that mood symptom and disease progression would be significantly correlated, and while a relationship between mood symptoms and overall disease severity was found, it was only a mild correlation. However, analyses of occurrence rates of mood symptoms by grouping the sample population by severity level revealed clear pattern of the increase in mood symptoms as either the increase in disease duration or disease stage. Such result was a unique finding of the current study. The other strength of the current study may include the use of uniform diagnostic tools which might improve the clinical assessment of mood disorders in PD. Further study is needed in discerning the relationship between disease onset and severity, and the manifestation of anxiety and depression.

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**Table 2-1 Sample Characteristics**

Mean and standard deviation characteristics of the sample population. Percentages of the total sample population are given for prevalence of subjects included in each sub-group level of the BAI and BDI scales.

Population	n=1221	BAI score	12.9 (9.6)
Gender (Male/Female)	62% 38%	BAI 0 - 7	34%
Age (years)	67.2 10.8	BAI 8 - 15	34%
Onset Age (years)	61.9 11.1	BAI 16 - 25	20%
Onset age < 61 (years)	45%	BAI 26 - 63	11%
Disease Duration (years)	5.3 (5.9)	BDI score	10.9 (7.9)
Symptom duration (years)	7.2 6.2	BDI 0 - 9	51%
Anxiolytic use rate	18%	BDI 10 - 18	33%
Antidepressant use rate	31%	BDI 19 - 29	12%
UPDRS score	40.3 (15.8)	BDI 30 - 63	3%
MENTAL sub-score	2.5 2.0	HY Stage	2.2 (1.0)
ADL sub-score	12.5 6.8	HY Stage 1	28%
Motor sub-score	25.3 9.1	HY Stage 1.5 - 2	34%
SE sub-score	80.3 12.5	HY Stage 2.5 - 3	26%
MMSE score	27.6 2.9	HY Stage 3.5 - 4	8%
Education	14.6 3.2	HY Stage 4.5 - 5	4%

**Table 3 Correlation Values**

Pearson Correlation Coefficients (r values) are given assessing the strength of relationship between subjects' assessed scores and characteristics of the sample population related to mood, disease progression, and PD disability.

R value	BDI score	BAI score	HY Stage	UPDRS score
Disease duration	0.281	0.192	0.576	0.522
UPDRS score	0.508	0.438	0.782	
HY Stage	0.301	0.396		
BAI score	0.694			

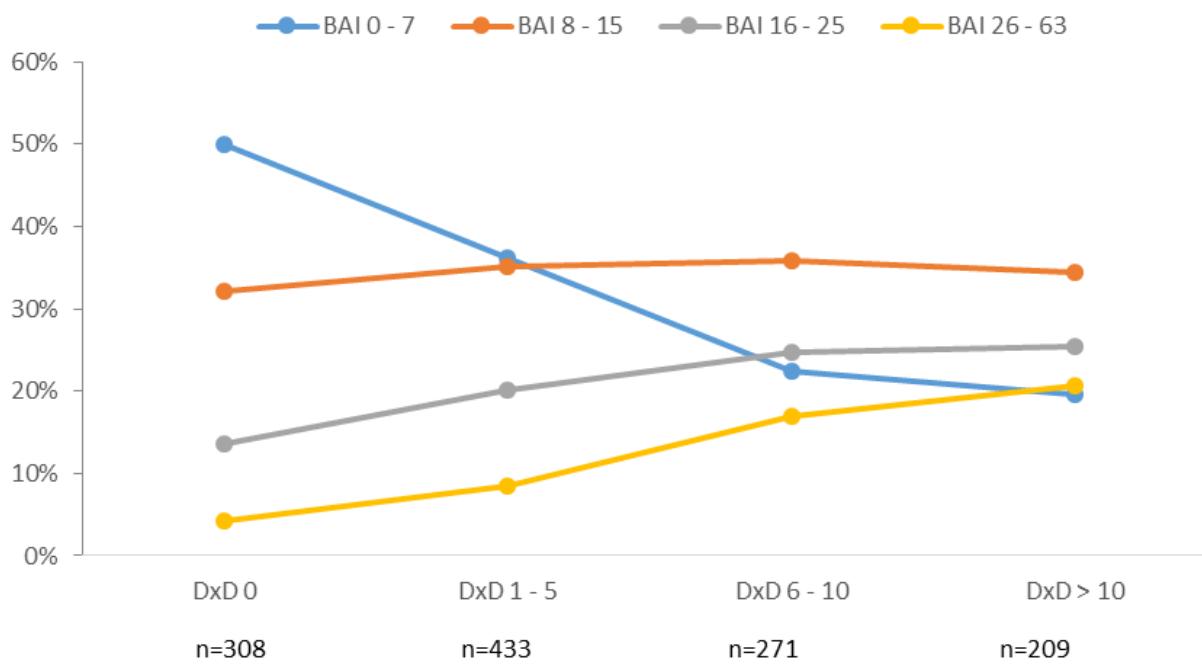
**Table 2 Anxiety level with respect to medication usage**

Subjects are classified by both their reported usage of anxiolytic and antidepressant medication usage and the average BAI score as well as prevalence of each level of anxiety are given per group.

Prescribed	Anxiolytic medication		Prescribed	Antidepressant medication	
	Yes	No		Yes	No
Prevalence	18%	82%	Prevalence	31%	69%
BAI score	17.0 (10.3)	12.1 (9.3)	BDI score	15.5 (10.0)	11.8 (9.3)
Rate (BAI 0 – 7)	17%	38%	Rate (BDI 0 – 9)	26%	47%
Rate (BAI 8 – 15)	35%	34%	Rate (BDI 10 – 18)	51%	42%
Rate (BAI 16 – 25)	30%	18%	Rate (BDI 19 – 29)	19%	10%
Rate (BAI 26 – 63)	18%	10%	Rate (BDI 30 – 63)	5%	1%

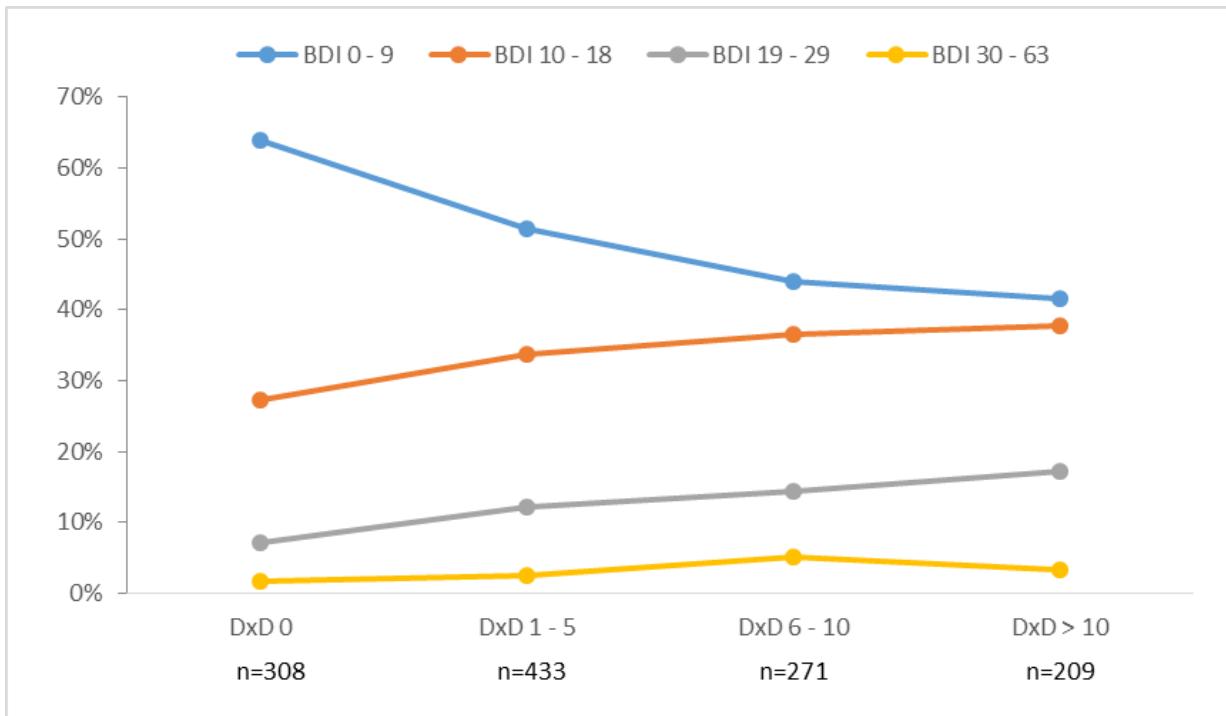
**Figure 1 Anxiety prevalence with respect to disease duration**

Categorized by ranges of disease duration (DxD, years since initial diagnosis of PD), the prevalence of subjects included in each sub-group level of the BAI scale is given. The four categories of DxD consist of newly diagnosed (disease duration 0 years), early (1–5 years), established (6–10 years) and advanced (more than 10 years), while BAI sub-group levels consist of minimal anxiety (0 - 7), mild anxiety (8 – 15), moderate anxiety (16 - 25), and severe anxiety (26 - 63). [30]



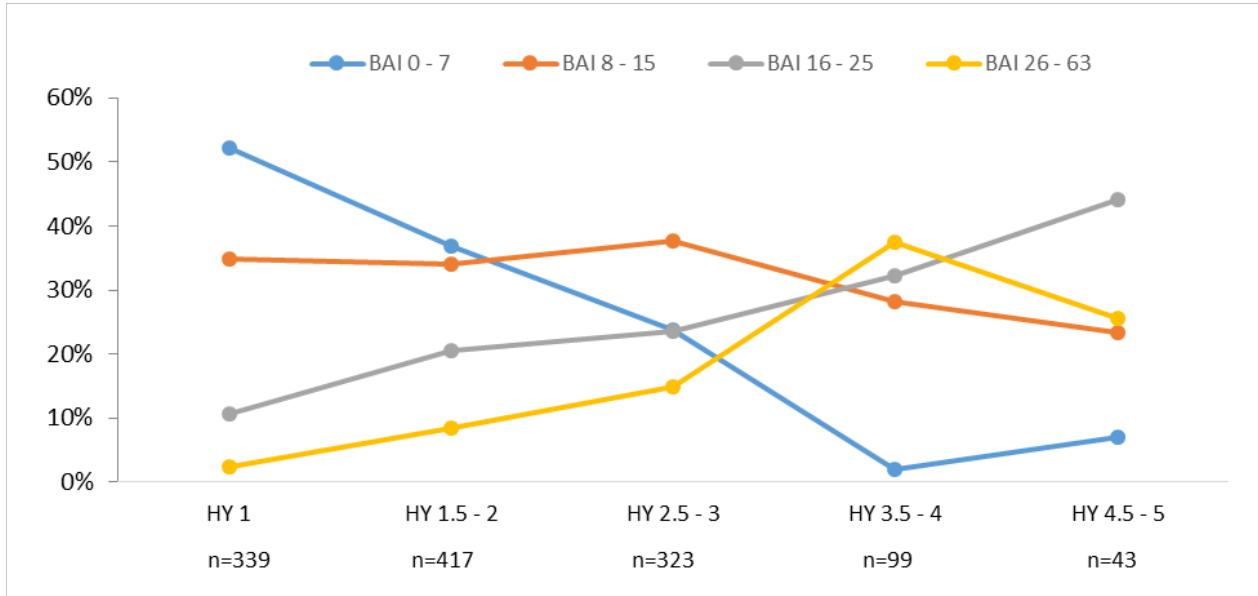
## Figure 2 Depression prevalence with respect to disease duration

Categorized by ranges of disease duration (DxD, years since initial diagnosis of PD), the prevalence of subjects included in each sub-group level of the BDI scale is given. The four categories of DxD consist of newly diagnosed (disease duration 0 years), early (1–5 years), established (6–10 years) and advanced (more than 10 years), while BDI sub-group levels consist of minimal depression (0 - 9), mild depression (10 - 18), moderate depression (19 - 29), and severe depression (30 - 63). [30]



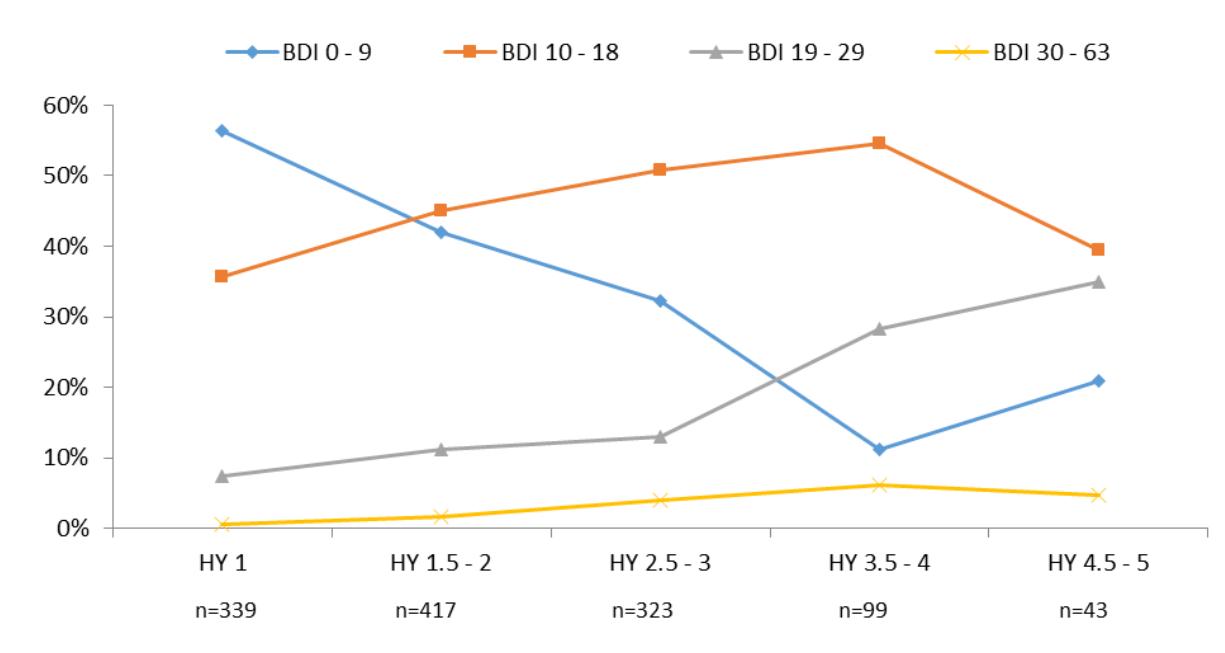
### Figure 3 HY Stage with respect to anxiety prevalence

Categorized by HY stage (disease severity), the prevalence of subjects included in each sub-group level of the BAI scale is given. HY stage range is from 1 to 5, with more advanced stage indicating more severe disease impairment and disability. BAI sub-group levels consist of minimal anxiety (0 - 7), mild anxiety (8 – 15), moderate anxiety (16 - 25), and severe anxiety (26 - 63).



#### Figure 4 HY stage with respect to depression prevalence

Categorized by HY stage (disease severity), the prevalence of subjects included in each sub-group level of the BDI scale is given. HY stage range is from 1 to 5, with more advanced stage indicating more severe disease impairment and disability. BDI sub-group levels consist of minimal depression (0 - 9), mild depression (10 - 18), moderate depression (19 - 29), and severe depression (30 - 63).



## **Chapter 3: A randomized pilot trial of Qigong exercise in PD**

### **Abstract**

While Parkinson's disease (PD) is commonly understood to consist of motor symptoms, non-motor symptom (NMS) features are receiving greater attention. Impaired sleep quality in particular affects many persons with PD, and can significantly affect quality of life. Previous findings have suggested Qigong meditation exercise may improve NMS, specifically sleep problems, as well as gait and balance issues. While standard care of PD may improve motor symptoms, alternative therapies such as Qigong meditation exercise may provide complementary benefits for treating NMS as well. This study's aim is to determine the efficacy of Qigong meditation exercise on improving sleep quality in PD as well its benefits on NMS and gait pattern. Using a randomized controlled trial, the 16 study participants with PD who completed the study were randomly assigned to either an experimental group practicing Qigong exercise or a control group practicing sham Qigong exercise. Each group consisted of 8 participants, and study participants practiced their respective exercise twice daily for a six week trial period. Pre- and post-intervention testing was performed to assess sleep quality, fatigue, thinking abilities, mood, as well as gait impairment. Standard clinical assessments specific to PD were used to assess sleep quality and disease severity, while gait impairment was assessed using a Gaitmat II system. Results suggest patients' sleep quality significantly improved in the experimental group, while improvement in fatigue approached significance. Gait performance improved in both experimental and control groups with no significant difference between the groups. Our results confirm previous findings that Qigong exercise may provide persons with PD sleep quality benefits, but that a history of mood symptoms may limit the efficacy of the exercise. Further, regular mild exercise, regardless of breathing techniques unique to Qigong, may improve gait

functioning. Additional studies with longer study duration and increased sample size are required to determine the long-term benefits of Qigong exercise for treating NMS in PD.

## **Introduction**

In recent years, non-motor symptoms (NMS) of Parkinson's disease (PD) have received increased attention.<sup>[1, 2]</sup> NMS in PD contribute to disability and shorten life expectancy, and may affect quality of life more significantly than motor symptoms.<sup>[1, 3]</sup> NMS in PD include sleep dysfunction, autonomic dysfunction, mood disorders (anxiety and depression), cognitive impairment/dementia, and sensory symptoms.<sup>[2, 4-6]</sup> Up to 88% of persons diagnosed with PD may suffer from one or more NMS.<sup>[7]</sup> Those symptoms become increasingly prevalent throughout the course of the disease and may even precede the onset of motor symptoms by a number of years.<sup>[2, 8, 9]</sup> Sleep dysfunction is a major NMS affecting up to 98% of individuals with PD and contributing significantly to decreased quality of life.<sup>[3, 8, 13]</sup> Sleep problems in PD include daytime sleepiness, insomnia, nighttime waking, restless leg syndrome (RLS), vivid and/or violent dreams, REM sleep behavior disorder, sleep apnea, and periodic limb movements during sleep (PLMS).<sup>[2-5, 8, 14]</sup> Fatigue is another prominent NMS in PD, characterized by tiredness, exhaustion, and lack of energy.<sup>[7]</sup> Up to one third of persons diagnosed with PD suffer from fatigue.<sup>[15]</sup> Cognitive impairment, ranging from mild to dementia, is the other prevalent neuropsychological symptom in PD patients. Further, anxiety and depression are also common NMS in PD and disrupt efficacy of PD treatments by significantly reducing rates of compliance for prescribed therapies. <sup>[10-12]</sup>

NMS such as sleep dysfunction, fatigue, mood disorders, and cognitive impairment are not strongly related to dopaminergic pathways <sup>[6, 8]</sup> and are thus less responsive to available PD treatments targeting the dopaminergic pathways.<sup>[1]</sup> Alternative therapies may offer potential for improving sleep quality and other NMS in PD.<sup>[8]</sup> Two forms of meditation therapy, Qigong and

Tai Chi that involve regulated breathing, slow movements, and meditation,[17] may improve sleep quality and overall energy in persons with PD.[18, 19] Qigong in particular showed promising results in improving balance, NMS especially sleep dysfunction, and quality of life in patients with PD.[17, 18, 20]

In addition to improving NMS in PD, a few pilot studies indicate the benefits of Tai Chi and Qigong on gait and balance control in persons with PD.[18, 21, 38] As a motor symptom, gait impairment in PD is common. Difficulties with gait in PD increases the risk of falling leading to injuries, loss of independence, and increased mortality.[22] Individuals with PD tend to walk with slower speed than healthy adults and take shorter but quicker strides that can result in tripping.[13, 22, 23] Decreased gait speed, step length, and stride length along with stooped posture characterize the gait impairment observed in PD.[22, 24] However, the potential benefits of Qigong remain unclear largely due to the lack of rigorous randomized trials.[20]

The presence of anxiety and depression in persons in PD may limit the effect of anti-parkinsonian therapy and other alternative therapies. Adherence to anti-parkinsonian therapy is often low in patients with PD who suffer also from anxiety or depression symptoms, which limits effects of the therapy and often associated with the overall worsening of PD symptoms.[11, 25] Individuals with PD and depression showed a lower average rate of compliance with a home-based exercise program.[10]

The current study is a randomized controlled pilot trial of a Qigong exercise in individuals with PD regarding outcomes related to sleep dysfunction, cognitive impairment, disease severity, fatigue, gait performance, anxiety and depression, and quality of life. In addition to examining outcome trends, we investigated issues related to study feasibility, especially possible influence of anxiety and depression on subjects' compliance rates to the

interventions. We hypothesize the experimental group will show significant improvement in sleep and gait measures compared to the control, and that participants with mood symptoms will comply with the exercise at a comparatively lower rate.

## Methods

Twenty-five patients with mild to moderate PD defined as Hoehn and Yahr (HY) stage between 1 and 3 were enrolled in the study. Prior to enrollment, individuals were screened for the following criteria: diagnosed with idiopathic PD; between 40 and 75 years of age, able to walk unassisted for 10 meters, no prior deep brain stimulation surgery, and no anticipated changes to PD medication within the study period. After signing an informed consent approved by the institutional review board, each participant was randomly assigned into either a control or experimental group by a computer-generated allocation number. The study participants and assessors were both blinded from the participant's group membership. Participants in the experimental group learned the Qigong exercise while the control group learned a sham Qigong exercise.

Each participant first went through the baseline assessment, which included the collection of basic medical history information, completion of subjective outcome questionnaires, and quantitative assessment of gait performance. During the evaluation, participants were asked to take their regular medication two hours prior to their evaluation in order to standardize results to a “practically defined on” state. Overall disease severity was evaluated by an experienced clinician using the Unified Parkinson's Disease Rating Scale (UPDRS) including assessment of Hoehn and Yahr (HY) stage.[26, 27] Quality of life and NMS severity were assessed using the 39-item Parkinson's Disease Questionnaire (PDQ-39) and the 30-item Non-Motor Symptoms Questionnaire (NMS-Quest).[28, 29] Anxiety and depression were assessed using the 15-item

Geriatric Anxiety Scale and the 30-item Geriatric Depression Scale, respectively, which have both been validated to assess mood disorders in PD.[30, 31] Cognitive impairment was assessed using the Mini Mental State Exam (MMSE).[32] Executive functioning and task switching was evaluated using both the Frontal Assessment Battery (FAB) and the Trail Making Test with part A (TMT-A) and B (TMT-B) assessments.[33, 34] Fatigue was measured by the 16-item Parkinson Fatigue Scale (PFS).[35] The Parkinson's Disease Sleep Scale 2 (PDSS-2) was administered to measure sleep quality, including motor symptoms at night, PD symptoms at night, and disturbed sleep. [8, 36]

Gait testing was performed using the Gaitmat II (EQ Inc, Chalfont, PA), a computerized walkway 4 meters in length used to measure gait velocity, step length, double support time, and step variability.[37] To assess gait performance, participants stood one meter in front of the track and were given instructions to walk across the walkway at a normal walking pace. The gait test was repeated five times for each participant to gather averaged walking velocity, stride length, step length, step time, swing time, stance time, and support time for both feet. Student participants were tested with these battery of baseline assessments for motor and non-motor symptoms upon completing the six-week trial period as post-intervention testing.

After the pre-intervention baseline testing, two training sessions were held in the following two weeks, in which participants in each group learned and practiced the specific Qigong exercise (intervention) or Sham Qigong (control). Participants in the intervention group received two training sessions for the “six healing sounds” Qigong exercise from an experienced instructor. This mild exercise program was selected because it is easy to learn and practice, especially for those with limited physical ability. The Qigong exercise can be performed while standing, sitting, or lying down. If practiced properly, one session takes between 15 and 20

minutes. After two training sessions, participants were instructed to perform the exercise twice daily at home; once in the morning upon waking and a second time at night just before going to bed. In addition to exercising at home, participants in this experimental group met once weekly for a group exercise session. This 45 to 60 minute session provided an opportunity for the instructor to observe and correct performance of the exercise, answer questions, and encourage group discussion of relevant issues related to both their PD symptoms or challenges related to practicing the exercise. To monitor compliance, participants maintained exercise diaries that were reviewed at weekly group sessions.

The control group followed the same procedure, but learned a sham Qigong exercise instead. The physical movements of the sham Qigong exercise were identical, but involving no deep breathing, meditation, or uttering the sounds associated with the movements. Participants in the control group likewise kept a weekly exercise diary throughout the experimental period and turned them in during group sessions. The weekly session similarly consisted of group exercise practice and discussion of relevant issues. Post-intervention assessment, which consisted of the same evaluations as in baseline assessment, was conducted on participants in both groups within two weeks after the end of the six-week intervention period.

Independent t-test was used to compare the intervention and control groups on mean values of measured variables from baseline evaluation. Changes between pre- and post-intervention scores were computed for all measured variables. Changes in overall scores of PDSS-2 and UPDRS were compared between two groups using independent t-test. Changes in their sub-scores were analyzed using MANOVA for between group significance. The MANOVA was also used to compare the two groups on NMSS, GDS, GAS, TMT-A, TMT-B, MMSE, FAB, PFS, and PDQ-39, as well as on variables from gait performance measurements. In

addition to significance of results, we were equally interested in the trends shown in our results. For this reason, we conducted post-hoc analysis using independent t-test for between group differences on all data despite the results of MANOVA analysis. Data analysis included data from only participants with rate of compliance to daily home exercise sessions greater than 50% as measured by exercise diaries. The requested home exercise sessions include two daily sessions for six weeks.

## **Results**

Baseline characteristics of age, disease duration, and symptom duration of the control and intervention groups were not significantly different (Table 3-1). Nine participants did not complete the full study due to loss of interest (n=5), physical limitations (n=2), or scheduling difficulties (n=2). Two participants, one from each group failed to meet the 50% home-exercise compliance criterion. Data from those who did not complete the study or failed the compliance criterion was excluded from analysis. No adverse effects resulted from the practice of the Qigong or sham Qigong exercise.

Averaged rate of compliance of the study participants for the two sessions (am and pm) of daily home exercise ranged from 72% to 89% (Table 3-1). The relatively lower rate of compliance in the intervention group occurred primarily during the first two weeks of the trial period, which was only 43%. Some members in the intervention group reported difficulty in memorizing all components of the Qigong exercise and uncertainty regarding their ability to perform it properly. Similar difficulty was also cited as the primary reason for withdrawing from the study in all participants who left the study early due to “loss of interest.”

Five out of 14 participants who completed the study reported a history of anxiety/depression (2 in the control group, 3 in the intervention group). The two participants with

a history of anxiety/depression in the control group reported a comparable rate of compliance (89% and 94%) to the average group rate of compliance (87%). In the experimental group, the three participants with a history of anxiety/depression reported an average rate of compliance of 64%, which was lower than the average rate of compliance (82%) of the group. Furthermore, one participant in the experimental group whose data was excluded from analysis due to low compliance reported a history of anxiety/depression.

The comparisons of baseline scores between the two groups in PDSS-2 overall score and sub-scores, and UPDRS overall score and sub-scores, found no significant differences. Averaged group means in PDSS-2 overall score and sub-scores increased in the control group, but decreased in the intervention group after the intervention (Figure 1). The primary measurement of sleep quality, PDSS-2 overall score, showed significantly ( $p<0.05$ ) greater improvement in the intervention group compared to control group (Table 3-2). Significant difference between two groups was also found in the change of a sub-score of the PDSS-2, PD symptoms at night ( $p<0.05$ ). Comparisons in other sub-scores between the two groups were found approaching significance in motor symptoms at night ( $p=0.071$ ) and disturbed sleep ( $p=0.14$ ). No significant differences were observed between two groups in changes in UPDRS overall score and sub-scores (Table 3-2). Nevertheless, while the control group's scores remained virtually unchanged between pre- and post-intervention, the mean values of the experimental group changed by 14.21% (from 51.71 to 44.36) for overall UPDRS score, and 17.46% (from 30.29 to 25.00) for its motor function sub-score, even though statistically insignificant. An examination of statistical powers for the two tests revealed only 17.4% power for UPDRS total and 11.5% power for motor function sub-score, respectively.

For secondary measurements, no significant difference in baseline values and changes between two groups were observed in scores of NMSS, GDS, GAS, TMT-A, TMT-B, MMSE, FAB, PFS, and PDQ-39 (Table 3-3). However, in a close examination of trends, some measures showed a tendency for improvement, including depression ( $p=0.144$ ), fatigue ( $p=0.179$ ), and cognitive functioning as measured by the trial-A test ( $p=0.078$ ) and frontal assessment battery ( $p=0.101$ ) (Figure 2).

No significant differences in gait performance measurements between the two groups were detected when comparing the changes in measured variables (Table 3-5). Within-group differences in pre- and post-intervention comparisons showed similar trends in the two groups. There was a same component between two groups, the smooth body movements under a structured daily exercise program. To better examine changes in gait performance after the intervention, we combined the data from both groups into one dataset and found a significant changes post intervention compared to baseline in velocity, step time, swing time, and single support time (Table 3-5). Mean velocity increased (+9.96%,  $p=.037$ ) while step time (-5.92%,  $p=.046$ ), swing time (-7.35%,  $p=.031$ ) and single support time (-7.35%,  $p=.031$ ) all decreased, indicating improvement in gait functionality. Step length (+4.12%,  $p=.070$ ), stride length (+4.16%,  $p=.068$ ), and stance time (-4.18%,  $p=.072$ ) all approached significance.

## **Discussion**

In this pilot study, we gathered information about the feasibility of a Qigong exercise program and its potential benefits in patients with PD. The compliance rates of our Qigong exercise or sham Qigong exercise programs were equal or greater than 72%, on average more than one session per day. No adverse effects resulted from the practice of either Qigong or sham Qigong exercise. As mentioned, the experimental group's lower compliance occurred during the

first two weeks after the initial training session. Some participants complained about the difficulty in memorizing the Qigong exercise, which was also cited as a primary issue in dropout cases in the intervention group. A possible solution for this issue is to slow down the pace of training activities in future trials for the specific target population.

Mood symptoms may have influenced the rate of compliance for the Qigong exercise. Past studies have reported that mood symptoms affect the compliance of a prescribed home-based exercise routine in patients with PD.[10] In the current study, participants with a history of anxiety and depression in the intervention group reported lower rates of compliance compared to the rest of the group. Rates of compliance in participants with a history of anxiety/depression in the control group, however, were not lower than that in the rest of the group. Compared to the sham Qigong, additional components and their synchronization of the Qigong exercise (regulating breath, meditation, and synchronized sounds) might make it more difficult for participants to learn and memorize, especially for those with anxiety/depression. Such difficulty was the complaint of those who dropped out of the intervention group. Given the fact that mood symptoms are quite common in patients with PD, we may increase the length of training period to slow down the pace of training activities and provide more group practice opportunities to participants in future trials.

Our results indicated that the Qigong exercise with daily home sessions may improve sleep quality. Sleep dysfunction as evaluated by PDSS-2 in the form of *motor symptoms at night*, *PD symptoms at night*, and *disturbed sleep*, are common to PD patients. [3, 8, 13, 36] In the current study, Qigong exercise improved sleep quality based on significant difference in changes in PDSS-2 total score and score of *PD symptoms at night* in comparison to the sham Qigong exercise. In addition, the scores of motor symptoms at night and disturbed sleep showed a trend

towards significant improvement in the experimental group compared to the control group. These results would suggest the combined components of deep breath, meditation, and rhythmic body movements in Qigong positively benefit sleep quality in patients with PD. In our previous study in a single group of patients with PD, we observed a significant improvement in sleep quality after Qigong exercise compared to baseline measurement.[\[38\]](#) The current randomized pilot trial used the same intervention and confirmed our previous finding through a comparison to a control group. This result agrees with a past randomized pilot trial reporting a reduction in sleep disturbance after Qigong exercise in persons with PD. [\[18\]](#) Past studies have also indicated that meditational exercise is associated with the release of neuro-hormones and other natural health recovery mechanisms.[\[17\]](#) Future studies with large sample sizes are required to further examine findings of our pilot studies.

The practice of Qigong exercise may alter the overall functionality in PD. Although not significantly significant, overall UPDRS score and motor function sub-score showed a trend towards an significant improvement in the intervention group, but not the control group. The sample size of the current pilot study may be an limiting factor. A few studies have reported mixed results on UPDRS score after Qigong exercise. A past pilot study reported that Qigong exercise did not significantly improve disease severity in PD. [\[21\]](#). A different study used an intervention of weekly Qigong session of 90 minutes for 6 months and reported significant improvement in UPDRS motor score.[\[18\]](#) The short trial period in the current study may discern potential comparative benefits of the Qigong exercise. Observable improvement of motor symptoms resulting from Qigong exercise may possibly require a longer period of time for intervention and a larger sample size in future trials.

The improvement in cognitive functioning, fatigue and depression in the Qigong exercise group approached a significant difference between two groups. Past studies have suggested that fatigue and cognitive impairment are related to each other in PD, suggesting improvement in one aspect may lead to similar improvement in its related aspect.[7, 15] A previous study testing the effects of Qigong exercise in patients with fibromyalgia suggest improvement in fatigue. [40] While Qigong exercise can offer therapeutic effects for the anxiety and depression in general population [41], some recent studies indicated such potential in patients with PD. [18, 21, 42] It has been suggested that the earlier the alternative therapies are introduced for anxiety and depression, the more effective they are. [13] The small sample size is a limiting factor in the current study. More studies with larger sample sizes are therefore needed to develop effective approaches to improve fatigue, cognitive function, and mood in PD.[7]

No group differences were observed in measured variables of gait performance, however, it was apparent in data analysis that participants in both groups showed improvement after the intervention in comparison to baseline measurement. The combined data from two groups showed statistically significant changes in velocity and step time between pre- and post-intervention measurements, and changes in step length and stride time approached significance. Both groups in the current study performed the same mild body movements on a daily basis. Slower velocity as well as shortened step length during walking have been associated with gait impairment in PD. [13, 22, 23] Sufficient evidence suggests that regular physical exercise has a positive impact on PD. [43, 44] A recent randomized controlled trial of 195 participants with mild to moderate PD found that Tai Chi training was superior to resistance training and stretching for improvement in measurements of postural stability, stride length, functional reach, and other motor function impairment. [45, 46] Further, overall well-being and gait variability

have been shown to improve with the practice of Tai Chi in PD. [47] The mild body movement involved in our interventions were similar to some body movements in Tai Chi exercise. The result of the current study suggested that the structured daily practice of the mild body movements, a component of the Qigong exercise, may lead to improvement in gait performance in patients with PD.

*Limitations:* The current study had a number of limitations. Small sample size restricted the strength of current findings, the statistical power in data analysis, and generalizability of the results. The rate of exercise compliance was also an issue, especially as it related to history of anxiety and depression. In order to deal with compliance issues, future trials should consist of slow paced training activities and increased number of Qigong sessions, and longer duration. Individualized consultation sessions focusing on anxiety/depression may be helpful too and boost participants' interest, confidence, and overall compliance.

*Conclusions:* Results of the current study suggest that Qigong exercise may be a viable alternative therapy for sleep dysfunction and other symptoms including possibly fatigue and cognitive dysfunction in PD. A history of anxiety and depression may influence the rate of compliance and therefore the efficacy of the Qigong exercise. While these aspects of our hypothesis were confirmed, the Qigong exercise was not shown to improve gait pattern compared to an exercise program with the same physical movements. However, the study findings suggest the mild smooth body movement component of Qigong may potentially improve gait performance. Qigong exercise was shown to be tolerable for long-term home-based practice without any adverse side effects. Future clinical trials with more participants and longer study duration are required to further examine the findings of the current study.

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Figure 1. Mean and standard error of the mean (SEM) of changes in the intervention and control groups in the PDSS-2 overall score and sub-scores in PD symptoms at night, motor symptoms at night, and disturbed sleep are shown. The symbol (\*) indicate statistical significance ( $p < 0.05$ ).

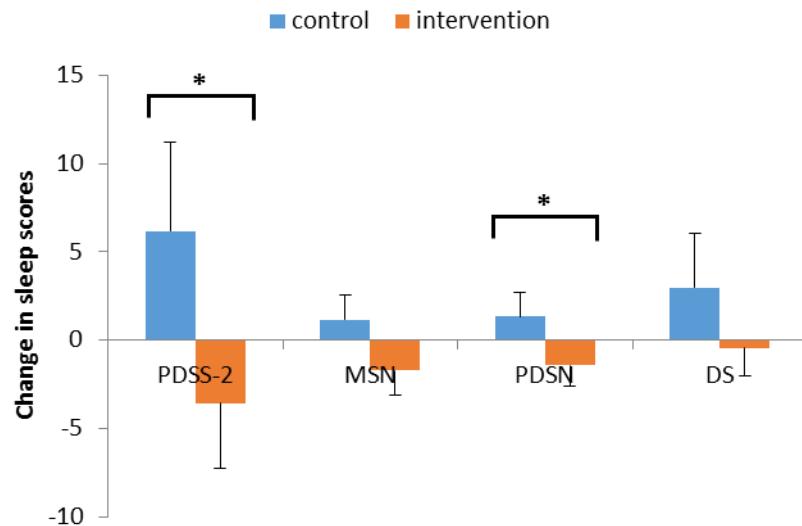
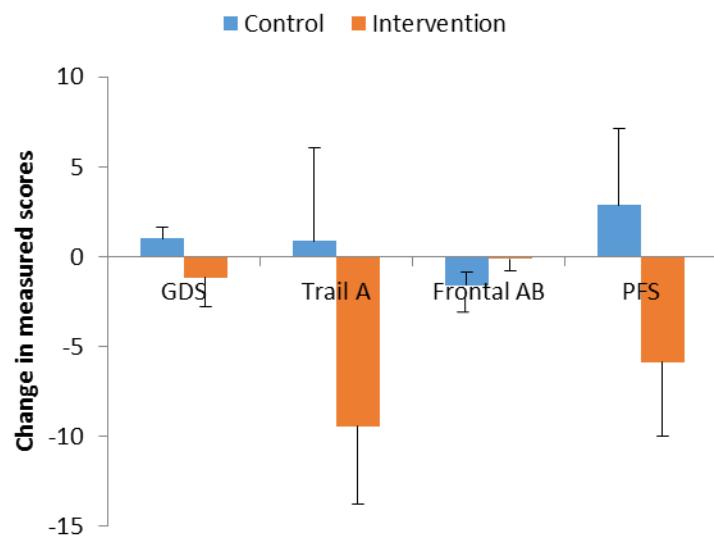


Figure 2. Mean and standard error of the mean (SEM) of changes in the intervention and control groups in the scores of GDS, Trail A, Frontal AB, and PFS are shown.



**Table 3-1 Group Characteristics and Rates of Compliance**

Mean and standard deviation characteristics of each group's participants based on self-reporting prior to the intervention. Mean and standard deviation exercise compliance is based on the percentage sessions completed out of morning, evening, and total sessions.

Group	Baseline Characteristics					Exercise Compliance	
	n	Age (yrs)	Male / Female	Disease Duration (yrs)	History of Depression / Anxiety	Morning (% Complete)	Evening (% Complete)
Control	7	67.0 ± 7.8	57%/43%	10.1 ± 3.6	29%	89% ± 11%	84% ± 14%
Experimental	7	64.5 ± 8.0	71%/29%	6.0 ± 3.6	43%	75% ± 24%	72% ± 26%

**Table 3-2 Primary Outcome Measures of Sleep Quality**

Revised Parkinson's Disease Sleep Scale (PDSS-2) scores and United Parkinson's Disease Rating Scale (UPDRS) scores for both control and experimental groups. Sub-scores for each scale are also included. Mean  $\pm$  standard deviation for pre- and post-intervention testing are given for total and sub-scores of each scale. Higher scores indicate more severe symptoms of the category. Categories in bold are those with significant difference ( $p < .05$ ) based on between groups t-test of differences between pre and post scores.

	Group				p-value	
	Control		Experimental			
	Pre	Post	Pre	Post		
<b>PDSS-2 Total</b>	<b>13.3 <math>\pm</math> 8.6</b>	<b>19.5 <math>\pm</math> 11.1</b>	<b>17.1 <math>\pm</math> 10.0</b>	<b>13.6 <math>\pm</math> 8.0</b>	<b>0.048</b>	
<i>Motor Symptoms at Night</i>	3.2 $\pm$ 2.1	4.3 $\pm$ 4.2	4.7 $\pm$ 4.6	3.0 $\pm$ 2.6	0.071	
<b>PD Symptoms at Night</b>	<b>2.8 <math>\pm</math> 1.8</b>	<b>4.2 <math>\pm</math> 3.9</b>	<b>4.4 <math>\pm</math> 3.2</b>	<b>3.0 <math>\pm</math> 2.4</b>	<b>0.038</b>	
<i>Disturbed Sleep</i>	8.0 $\pm$ 4.4	11.0 $\pm$ 5.3	8.0 $\pm$ 4.4	7.6 $\pm$ 5.1	0.141	
UPDRS Total	39.1 $\pm$ 17.2	40.0 $\pm$ 18.1	51.7 $\pm$ 32.2	44.4 $\pm$ 25.5	0.1705	
<i>Mentation, Behavior, and Mood</i>	7.3 $\pm$ 4.4	7.9 $\pm$ 3.6	8.1 $\pm$ 4.3	7.6 $\pm$ 4.3	0.2536	
<i>Activities of Daily Living</i>	10.3 $\pm$ 3.0	10.7 $\pm$ 4.9	11.3 $\pm$ 7.1	9.6 $\pm$ 4.3	0.2061	
<i>Motor</i>	19.7 $\pm$ 12.1	19.1 $\pm$ 11.0	30.3 $\pm$ 24.6	25.0 $\pm$ 23.8	0.2354	
<i>Hoehn and Yahr Stage</i>	1.9 $\pm$ 0.7	2.3 $\pm$ 0.6	2.0 $\pm$ 1.0	2.2 $\pm$ 0.9	0.3471	

**Table 3-3 Secondary Outcome Measures of Non-Motor Symptoms**

Non-Motor Symptom Geriatric Depression Scale (GDS), Geriatric Anxiety Scale (GAS), Trail Making Test parts A (TMT-A) and B (TMT-B), Mini-Mental State Exam (MMSE), Frontal Assessment Battery (FAB), Parkinson's Fatigue Scale (PFS), and Parkinson's Disease Questionnaire (PDQ-39) scores for both control and experimental groups. Mean  $\pm$  standard deviation for pre- and post-intervention testing are given. Higher GDS, GAS, TMT-A, TMT-B, and PFS scores indicate more severe symptoms while lower MMSE, and FAB scores indicate greater cognitive impairment. Higher PDQ-39 scores indicate lower quality of life in relation to PD symptoms. Scores approaching significance ( $p < .10$ ) are given in bold.

	Group				p-value	
	Control		Experimental			
	Pre	Post	Pre	Post		
GDS	$5.43 \pm 2.88^*$	$5.33 \pm 3.08$	$7.43 \pm 5.65$	$6.29 \pm 6.07$	0.2577	
GAS	$3.29 \pm 1.80$	$3.50 \pm 1.38$	$4.14 \pm 3.02$	$4.14 \pm 3.34$	0.3180	
<b>TMT-A</b>	<b><math>40.00 \pm 14.79</math></b>	<b><math>40.86 \pm 9.46</math></b>	<b><math>62.29 \pm 31.53</math></b>	<b><math>52.86 \pm 32.63</math></b>	<b>0.0776</b>	
TMT-B	$113.29 \pm 68.33$	$96.71 \pm 44.57$	$123.71 \pm 75.10$	$106.00 \pm 49.73$	0.4805	
MMSE	$28.86 \pm 1.57$	$29.07 \pm 1.02$	$29.71 \pm .49$	$29.50 \pm .76$	0.2558	
<b>FAB</b>	<b><math>16.29 \pm 1.70</math></b>	<b><math>14.71 \pm 2.81</math></b>	<b><math>17.14 \pm 1.21</math></b>	<b><math>17.00 \pm 1.00</math></b>	<b>0.0809</b>	
<b>PFS</b>	<b><math>47.14 \pm 15.13</math></b>	<b><math>50.00 \pm 9.93</math></b>	<b><math>45.86 \pm 19.43</math></b>	<b><math>40.86 \pm 23.67</math></b>	<b>0.0846</b>	
PDQ-39	$25.43 \pm 15.13$	$25.29 \pm 17.85$	$40.43 \pm 45.86$	$40.00 \pm 17.96$	0.4655	

**Table 3-4 Gait Impairment**

Gait performance for both control and experimental groups, and for combined data set. Mean ± standard deviation is given for pre and post intervention measures. P-values comparing difference in change of gait measures are given. Significant measures ( $p < .05$ ) are given in bold.

	Group comparison				p-value	
	Control		Experimental			
	Pre	Post	Pre	Post		
Velocity (m/s)	1.01 ± .13	1.14 ± .21	.96 ± .20	1.02 ± .12	0.2756	
Step Time (s)	.58 ± .02	.54 ± .07	.61 ± .08	.58 ± .03	0.3469	
Swing Time (s)	.47 ± .05	.42 ± .05	.46 ± .06	.44 ± .04	0.2144	
Step Length (m)	.58 ± .09	.61 ± .11	.58 ± .09	.59 ± .06	0.3394	
Stride Length (m)	1.17 ± .18	1.24 ± .22	1.17 ± .18	1.24 ± .22	0.3255	
Stance Time (s)	.67 ± .07	.65 ± .10	.67 ± .07	.65 ± .10	0.2515	
Combined dataset						
	pre	Post	p-value	% change		
<b>Velocity (m/s)</b>	<b>0.99 ± .16</b>	<b>1.09 ± 0.2</b>	<b>0.0369</b>	<b>9.96%</b>		
<b>Step Time (s)</b>	<b>0.59 ± .06</b>	<b>0.6 ± 0.1</b>	<b>0.0460</b>	<b>-5.92%</b>		
<b>Swing Time (s)</b>	<b>0.46 ± .05</b>	<b>0.4 ± 0.04</b>	<b>0.0305</b>	<b>-7.35%</b>		
Step Length (m)	0.58 ± 0.1	0.6 ± 0.1	0.0703	4.12%		
Stride Length (m)	1.16 ± 0.2	1.21 ± 0.2	0.0684	4.16%		
Stance Time (s)	0.71 ± 0.1	0.68 ± 0.1	0.0715	-4.18%		

## **Chapter 4: Conclusion**

### **Summary of Findings**

The database statistical analysis confirmed previous findings that anxiety and depression are indeed relevant features of PD.[1-5] Prevalence of co-existing anxiety and depression, as measured by the co-morbidity rate of both mood symptoms (45%), was found to be higher than previously estimated, while 66% and 49% of the sample population reported relevant anxiety and depression symptoms, respectively, and 70% reported one or both symptoms.[6-8] The rate of anxiolytic and anti-depressant use was 18% and 31%, respectively, while more than three fourths of persons reporting taking medication for mood disorders still reported anxiety or depression symptoms. These results both suggest the therapeutic impact of this medication may be limited. , Mild depression overall, at a rate of 33%, was also found to be higher than previously reported, and mood symptoms tended to be more prevalent in subjects with more advanced PD.[2, 9, 10] These findings support the hypothesis that serotonergic degeneration, often primarily linked to mood symptoms, may also be associated with the neuropathology of PD, but progress non-linearly with respect to disease severity. [11, 12]

The clinical trial revealed the mild exercise Qigong as a potentially beneficial complementary therapy for treating sleep dysfunction, a common complaint with persons diagnosed with PD.[13-17] However, participants with a history of anxiety/depression seemed to have greater difficulty with consistently practicing the home-based Qigong exercise, as revealed by their lower average rate of compliance.[18] After the six-week intervention period, sleep quality measures significantly improved in the intervention group who practiced Qigong compared to a control group practicing a sham form. Findings confirm the previous pilot study's results, and additionally, the experimental group's motor, cognitive functioning, fatigue, and

depression symptoms approached significance in terms of comparative improvement. [17] Both groups improved velocity, step time, stride length, and autonomic NMS related to PD, which suggests mild, regular physical exercise improves these aspects in PD.[19, 20] While aspects of the Qigong exercise may improve gait impairment in PD, such as the smooth movements or regular exercise, the hypothesis that Qigong exercise results in improved gait pattern cannot be confirmed.

Thus, a response to the original research question, "how do mood symptoms in PD impact the efficacy of alternative therapy program Qigong exercise program for treating motor and non-motor aspects of the disease?" can be put forth in light of these two studies. Taken together, the findings confirm the hypothesis put forth that mood symptoms affect a substantial number of persons with PD and may impact the efficacy of therapies for treating aspects of the disease. [1, 3-5, 18, 21, 22] Given how prevalent mood symptoms were found to be in the PD population and the limited impact of current treatment for these systems, addressing these symptoms may improve the overall effectiveness of alternative therapies such as the Qigong therapy examined in this study.[21, 23] Even still, this feasibility study has shown that Qigong exercise is a promising complementary therapy for treating sleep dysfunction and potentially other non-motor symptoms in PD.[24]

### **Clinical Implications**

Findings from the database analysis indicate motor function is still a greater indicator to overall disease severity than mood symptoms when compared to mood or quality of life. Nevertheless, study findings suggest two out of every three persons diagnosed with PD have anxiety, while 1

out of two persons have depression. The non-linear progression of mood symptoms with respect to disease severity results indicate severity of serotonergic degeneration increases asymmetrically with respect to dopaminergic degeneration most closely associated with PD.[11, 12] Regardless, developing diagnostic tools and therapies for better identifying, recognizing, and treating mood disorders in PD is essential for providing adequate care.[2, 25-27]

The influence of mood symptoms on the efficacy of Qigong exercise in PD patients can be speculated as the following. Our data showed that mood symptoms correlated with decreased compliance in Qigong exercise. This finding suggests that anxiety and depression may affect the efficacy of alternative exercise programs. Stemming from the asymmetric serotonergic degeneration associated with PD, heightened symptoms of anxiety and depression may decrease the adherence with the intervention and therefore inhibit the positive effects of the Qigong exercise.[11, 12, 18] While not specifically assessed in the database analysis, lower compliance with treatment among persons with anxiety or depression, which constitute a majority of the population of persons with PD, may partially explain why persons prescribed anxiolytics/antidepressant still reported experiencing relevant mood symptoms.[18, 28] With respect to enhancing compliance with alternative exercise programs in PD, shared decision-making coupled with a collaborative, reflective process between patients, caretakers, and physicians may improve adherence outcomes. For example, a patient and caretaker may work together to develop a daily schedule that includes time for complying with prescribed therapies for treating PD. Further, physicians can provide a list of possible alternative, complementary therapy program options that are available for the patient and discuss which therapy would be most beneficial. [29]

Based on other findings of our study, a conceptual model can be put forth explaining the relationship between dopaminergic dysfunction, cognitive dysfunction, sleep disorder, gait variability, and the implementation of the Qigong exercise in PD. Given that gait impairment correlates strongly with cognitive decline, neurodegeneration associated with PD may result in cognitive dysfunction that compromises the ability for regulating walking tasks, thereby affecting gait pattern.[30-32] Further, sleep dysfunction, specifically RBD, is associated with slowness of gait, a symptom of hypokinesia, as well as increased risks for falling and decreased clinical efficacy of dopaminergic treatments.[33-36] By releasing neuro-hormones, the practice of Qigong exercise may improve primarily sleep quality as well as potentially cognitive functioning, fatigue, and depression and thus mitigate neurodegeneration potentially caused by ROS associated with PD. [28, 37] In addition, the positive effects due to body physical movement in an exercise program may improve deficits in the automaticity of gait associated with PD.[19, 20]

## **Limitations**

The database's cross-sectional design only allowed for correlational analysis between disease severity, quality of life, and mood disorders. Thus, a causal relationship between these features of the disease and disease progression could not be established. Further, the source-analyzed data comes from complete examinations in a clinical setting, which may not adequately represent the population of persons with PD. Similarly, results from clinical trial are limited due to the study participants consisting of persons who voluntarily completed the study and were able to transport themselves to the clinic. Participants dropping out of the study early, and the initial low compliance rate of the experimental group also limit the viability of findings. However, lower compliance did shed light on the possible effects anxiety and depression have on efficacy

of the exercise. Finally, the small sample size ( $n=16$ ), removal of two subject's data due to low compliance, and loss of extraneous gait data due to equipment malfunctioning (Gaitmat data stored from one subject could not be analyzed) also limit the implications of this study.

## **Future Directions**

Given the promising results of Qigong as a viable therapy for sleep dysfunction, more trials are required to better understand and apply the potential benefits of the mind-body exercise as an alternative, complementary therapy for both motor and non-motor symptoms in PD. As noted, mood symptoms remain relevant features of PD both in their prevalence and impact on the efficacy of potential therapies for PD. Given the found limitations of the clinical trial, a future research project would further examine the potential benefits of Qigong exercise on persons with PD. Both the pre-clinical and clinical period would be extended, where participants would have a month of practice sessions before the formal clinical trial would begin. During the pre-clinical period, more time could be devoted to practicing the exercise during the weekly group sessions. Further, compliance could be enhanced by giving participants a more specific practice regimen during this time, such as only practicing part of the exercise during the first weeks of the pre-clinical trial. A future study would include targeted, patient-centered interventions that specifically address factors, specifically anxiety and depression, in order to enhance adherence with therapies treating PD.[29]

A longer study duration would also allow for a longitudinal study design, where the change in symptoms could be monitored. Such a trial with greater sample size may also shed light on how Qigong exercise may slow, halt, or even reverse the overall progression of motor and non-motor components of disease severity.[24, 38] Additionally, different tools for assessing gait variability such as using the Vicon system for examining gait pattern with respect to turning

tasks, and employing visual cues in testing may better identify and elucidate gait disturbances in PD.[39] Enhanced tools for understanding the non-motor symptoms of PD and potential alternative therapies are therefore essential for providing adequate care for persons diagnosed with Parkinson's disease.

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## Appendix: Study Evaluation Documents

NAME: \_\_\_\_\_ DATE OF BIRTH: \_\_\_\_\_  
First \_\_\_\_\_ MI \_\_\_\_\_ Last \_\_\_\_\_

ADDRESS: \_\_\_\_\_  
Street Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Zip \_\_\_\_\_

HOME #: (\_\_\_\_) - \_\_\_\_\_ CELL #: (\_\_\_\_) - \_\_\_\_\_

EMAIL: \_\_\_\_\_

1. What is your Marital Status

<input type="checkbox"/> Married	<input type="checkbox"/> Single	<input type="checkbox"/> Plan Marriage
<input type="checkbox"/> Divorced	<input type="checkbox"/> Separated	<input type="checkbox"/> Widowed

2. What is the highest level of education you have completed?

<input type="checkbox"/> High school degree	<input type="checkbox"/> Doctorate
<input type="checkbox"/> Associate degree	<input type="checkbox"/> Professional (MD, JD, DDS, etc)
<input type="checkbox"/> Bachelor's degree	<input type="checkbox"/> Other (specify) _____
<input type="checkbox"/> Master's degree	<input type="checkbox"/> None of the above (less than high school)

3. Which of the following best describes your current main daily activities and/or responsibilities?

<input type="checkbox"/> Working full time	<input type="checkbox"/> Looking for work
<input type="checkbox"/> Working part-time	<input type="checkbox"/> Keeping house or raising children full-time
<input type="checkbox"/> Unemployed or laid off	<input type="checkbox"/> Retired

4. With regard to your current or most recent job activity, in what kind of business or industry do (did) you work?

(For example: hospital, newspaper publishing, mail order house, auto engine manufacturing, breakfast cereal manufacturing, etc)

5. With regard to your current or most recent job activity, what kind of work do (did)

NAME: DATE OF BIRTH:

First MI Last

ADDRESS:

StreetAddress

City State Zip

HOME #: ( ) - CELL #: ( ) -

EMAIL

**1. What is your Marital Status**

Married Single Plan Marriage

Divorced Separated Widowed

**2. What is the highest level of education you have completed?**

High school degree Doctorate

Associate degree Professional (MD, JD, DDS, etc) Bachelor's degree - Other (specify)

Master's degree None of the above (less than high school)

**3. Which of the following best describes your current main daily activities and/or responsibilities?**

Working full time \_ Looking for work \_ Working part-time \_ Keeping house or raising children full-time

Unemployed or laid off Retired

**4. With regard to your current or most recent job activity, in what kind of business or industry do (did) you work?**

(For example: hospital, newspaper publishing, mail order house, auto engine manufacturing, breakfast cereal manufacturing, etc)

**5. With regard to your current or most recent job activity, what kind of work do (did)**

---

you do? (Job Title)

(For example: registered nurse, personnel manager, supervisor of order department, gasoline engine assembler, grinder operator, etc.)

6. Do you smoke cigarettes?

YES  NO

If yes, how many packs per day? \_\_\_\_\_

7. Do you drink alcohol?

YES  NO

If yes, how many drinks? \_\_\_\_\_ /day \_\_\_\_\_ /week \_\_\_\_\_ /month

8. How much caffeine do you consume in an average day?

Coffee, # ounces \_\_\_\_\_

Tea, # ounces \_\_\_\_\_

Caffeinated soda, # ounces \_\_\_\_\_

9. Do you exercise regularly?

YES  NO

How often (1x/day; 3x/week, etc) \_\_\_\_\_

What type of exercise? \_\_\_\_\_

10. Outside of exercise, how would you rate your daily activity level?

High activity  Low activity

Moderate activity  Little or no activity

11. How long have you had Parkinson's disease?

Time since onset of symptoms \_\_\_\_\_

Time since diagnosis \_\_\_\_\_

12. Do you have any other chronic health conditions? (check all that apply)

11.

12.

you do? (Job Title)

How often (1x/day, 3x/week, etc)

(For example: registered nurse, personnel manager, supervisor of order department, gasoline engine assembler, grinder operator, etc.)

Do you smoke cigarettes?

YES NO

If yes, how many packs per day?

**Do you drink alcohol?**

YES NO

If yes, how many drinks? /day /week /month

How much caffeine do you consume in an average day?

Coffee, # ounces

Tea, # ounces

Caffeinated soda, # ounces

Do you exercise regularly?

YES NO

What type of exercise?

Outside of exercise, how would you rate your daily activity level?

High activity Low activity

Moderate activity Little or no activity

How long have you had Parkinson's disease?

Time since onset of symptoms

Time since diagnosis

Do you have any other chronic health conditions? (check all that apply)

---

If yes, give details

Heart Disease	<input type="checkbox"/> NO	<input type="checkbox"/> YES	_____
Diabetes	<input type="checkbox"/> NO	<input type="checkbox"/> YES	_____
Depression/Anxiety	<input type="checkbox"/> NO	<input type="checkbox"/> YES	_____
Cancer (list type)	<input type="checkbox"/> NO	<input type="checkbox"/> YES	_____
Alcohol/Drug Abuse	<input type="checkbox"/> NO	<input type="checkbox"/> YES	_____
	<input type="checkbox"/> NO	<input type="checkbox"/> YES	_____
	<input type="checkbox"/> NO	<input type="checkbox"/> YES	_____
	<input type="checkbox"/> NO	<input type="checkbox"/> YES	_____
	<input type="checkbox"/> NO	<input type="checkbox"/> YES	_____

13. Current medication list

Heart Disease

Diabetes

Depression/Anxiety

Cancer (list type)

Alcohol/Drug Abuse

Current medication list

NO YES

NO YES NO YES

NO YES

   NO YES

NO YES

NO YES

NO YES

NO YES.

If yes, give details



## PDQ-39 QUESTIONNAIRE

Please complete the following

*Please tick one box for each question*

*Due to having Parkinson's disease,  
how often during the last month  
have you....*

	Never	Occasionally	Sometimes	Often	Always or cannot do at all
1 Had difficulty doing the leisure activities which you would like to do?	<input type="checkbox"/>				
2 Had difficulty looking after your home, e.g. DIY, housework, cooking?	<input type="checkbox"/>				
3 Had difficulty carrying bags of shopping?	<input type="checkbox"/>				
4 Had problems walking half a mile?	<input type="checkbox"/>				
5 Had problems walking 100 yards?	<input type="checkbox"/>				
6 Had problems getting around the house as easily as you would like?	<input type="checkbox"/>				
7 Had difficulty getting around in public?	<input type="checkbox"/>				
8 Needed someone else to accompany you when you went out?	<input type="checkbox"/>				
9 Felt frightened or worried about falling over in public?	<input type="checkbox"/>				
10 Been confined to the house more than you would like?	<input type="checkbox"/>				
11 Had difficulty washing yourself?	<input type="checkbox"/>				
12 Had difficulty dressing yourself?	<input type="checkbox"/>				
13 Had problems doing up your shoe laces?	<input type="checkbox"/>				

*Please check that you have ticked one box for each question before going on to the next page*

## PDQ-39 QUESTIONNAIRE

Please complete the following

*Please tick one box for each question*

*Due to having Parkinson's disease, how often during the last month*

have you.... Never Occasionally Sometimes Often Always

or cannot do 1 Had

difficulty doing ! at all

the leisure activities which you would like to do?

2 Had difficulty looking after

your home, e.g., DIY, housework, cooking?

3 Had difficulty carrying bags

of shopping? :

4. Had problems walking half | a mile? -

5 Had problems walking 100 -

yards?

6 Had problems getting

around the house as easily as you would like?

7 Had difficulty getting

around in public?

8 Needed Someone else to

accompany you when you went out?

9 Felt frightened or worried

about falling over in public?

10 Been confined to the house more than you would like?

11 Had difficulty washing

yourself?

12 Had difficulty dressing - yourself?

13 Had problems doing up

your shoe laces?

*Please check that you have ticked one box for each question before going on to the next page*

Page 3 of 12 Questionnaires for patient completion

*Due to having Parkinson's disease,  
how often during the last month  
have you....*

*Please tick one box for each question*

	Never	Occasionally	Sometimes	Often	Always or cannot do at all
14 Had problems writing clearly?	<input type="checkbox"/>				
15 Had difficulty cutting up your food?	<input type="checkbox"/>				
16 Had difficulty holding a drink without spilling it?	<input type="checkbox"/>				
17 Felt depressed?	<input type="checkbox"/>				
18 Felt isolated and lonely?	<input type="checkbox"/>				
19 Felt weepy or tearful?	<input type="checkbox"/>				
20 Felt angry or bitter?	<input type="checkbox"/>				
21 Felt anxious?	<input type="checkbox"/>				
22 Felt worried about your future?	<input type="checkbox"/>				
23 Felt you had to conceal your Parkinson's from people?	<input type="checkbox"/>				
24 Avoided situations which involve eating or drinking in public?	<input type="checkbox"/>				
25 Felt embarrassed in public due to having Parkinson's disease?	<input type="checkbox"/>				
26 Felt worried by other people's reaction to you?	<input type="checkbox"/>				
27 Had problems with your close personal relationships?	<input type="checkbox"/>				
28 Lacked support in the ways you need from your spouse or partner? <i>If you do not have a spouse or partner tick here</i>	<input type="checkbox"/>				
29 Lacked support in the ways you need from your family or close friends?	<input type="checkbox"/>				

*Please check that you have ticked one box for each question before going on to the next page*

*how often during the last month*

*have you.... Never*

14 Had problems writing |  
clearly?

15 Had difficulty cutting up  
your food?

16 Had difficulty holding a  
drink without spilling it?

17 Felt depressed?

18 Felt isolated and lonely?

T

19 Felt weepy or tearful?

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20 Felt angry or bitter?

21 Felt anxious?

22 Felt worried about your  
future?

23 Felt you had to conceal  
your Parkinson's from people?

24 Avoided situations which  
involve eating or drinking in public?

25 Felt embarrassed in public  
due to having Parkinson's disease?

26 Felt worried by other  
people's reaction to you?

27 Had problems with your  
close personal relationships?

28 Lacked support in the  
ways you need from your spouse or partner?

*if you do not have a spouse or  
partner tick here*

29 Lacked support in the  
ways you need from your family or close friends?

*Please tick one box for each question*

Occasionally Sometimes

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Often Always

or cannot do at all

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*Please check that you have ticked one box for each question before going on to the next page*

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age 4 of 12

Questionnaires for patient completion

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<i>Due to having Parkinson's disease, how often during the last month have you....</i>		<i>Please tick one box for each question</i>				
		Never	Occasionally	Sometimes	Often	Always
30	Unexpectedly fallen asleep during the day?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31	Had problems with your concentration, e.g. when reading or watching TV?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
32	Felt your memory was bad?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
33	Had distressing dreams or hallucinations?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
34	Had difficulty with your speech?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
35	Felt unable to communicate with people properly?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
36	Felt ignored by people?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
37	Had painful muscle cramps or spasms?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
38	Had aches and pains in your joints or body?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
39	Felt unpleasantly hot or cold?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

*Please check that you have ticked one box for each question before going on to the next page*

*Thank you for completing the PDQ 39 questionnaire*

**how often during the last month have you.... Never Occasionally Sometimes Often Always**

Never	Occasionally	Sometimes	Often	Always
<input type="checkbox"/>				

30 Unexpectedly fallen asleep

during the day?

31 Had problems with your  
concentration, e.g. when reading or watching TV?

Never	Occasionally	Sometimes	Often	Always
<input type="checkbox"/>				

-

32 Felt your memory was t

bad?

33 Had distressing dreams or  
hallucinations?

34 Had difficulty with your  
speech?

35 Felt unable to  
communicate with people properly?

36 Felt ignored by people?

37 Had painful muscle  
cramps or spasms? |

38 Had aches and pains in  
your joints or body?

39 Felt unpleasantly hot or  
Cold?

*Please check that you have ticked one box for each question before going on to the next page*

*Thank you for completing the PDQ 39 questionnaire*

Page 5 of 12 Questionnaires for patient completion

# PD NMS QUESTIONNAIRE

Name: ..... Date: ..... Age: .....

Centre ID: ..... Male  Female

## NON-MOVEMENT PROBLEMS IN PARKINSON'S

The movement symptoms of Parkinson's are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems is listed below. Please tick the box 'Yes' if you have experienced it during the past month. The doctor or nurse may ask you some questions to help decide. If you have not experienced the problem in the past month tick the 'No' box. You should answer 'No' even if you have had the problem in the past but not in the past month.

### Have you experienced any of the following in the last month?

	Yes	No		Yes	No
1. Dribbling of saliva during the daytime .....	<input type="checkbox"/>	<input type="checkbox"/>	16. Feeling sad, 'low' or 'blue' .....	<input type="checkbox"/>	<input type="checkbox"/>
2. Loss or change in your ability to taste or smell .....	<input type="checkbox"/>	<input type="checkbox"/>	17. Feeling anxious, frightened or panicky .....	<input type="checkbox"/>	<input type="checkbox"/>
3. Difficulty swallowing food or drink or problems with choking .....	<input type="checkbox"/>	<input type="checkbox"/>	18. Feeling less interested in sex or more interested in sex .....	<input type="checkbox"/>	<input type="checkbox"/>
4. Vomiting or feelings of sickness (nausea) .....	<input type="checkbox"/>	<input type="checkbox"/>	19. Finding it difficult to have sex when you try .....	<input type="checkbox"/>	<input type="checkbox"/>
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces) .....	<input type="checkbox"/>	<input type="checkbox"/>	20. Feeling light headed, dizzy or weak standing from sitting or lying .....	<input type="checkbox"/>	<input type="checkbox"/>
6. Bowel (fecal) incontinence .....	<input type="checkbox"/>	<input type="checkbox"/>	21. Falling .....	<input type="checkbox"/>	<input type="checkbox"/>
7. Feeling that your bowel emptying is incomplete after having been to the toilet .....	<input type="checkbox"/>	<input type="checkbox"/>	22. Finding it difficult to stay awake during activities such as working, driving or eating .....	<input type="checkbox"/>	<input type="checkbox"/>
8. A sense of urgency to pass urine makes you rush to the toilet .....	<input type="checkbox"/>	<input type="checkbox"/>	23. Difficulty getting to sleep at night or staying asleep at night .....	<input type="checkbox"/>	<input type="checkbox"/>
9. Getting up regularly at night to pass urine .....	<input type="checkbox"/>	<input type="checkbox"/>	24. Intense, vivid dreams or frightening dreams .....	<input type="checkbox"/>	<input type="checkbox"/>
10. Unexplained pains (not due to known conditions such as arthritis) .....	<input type="checkbox"/>	<input type="checkbox"/>	25. Talking or moving about in your sleep as if you are 'acting' out a dream .....	<input type="checkbox"/>	<input type="checkbox"/>
11. Unexplained change in weight (not due to change in diet) .....	<input type="checkbox"/>	<input type="checkbox"/>	26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move .....	<input type="checkbox"/>	<input type="checkbox"/>
12. Problems remembering things that have happened recently or forgetting to do things .....	<input type="checkbox"/>	<input type="checkbox"/>	27. Swelling of your legs .....	<input type="checkbox"/>	<input type="checkbox"/>
13. Loss of interest in what is happening around you or doing things .....	<input type="checkbox"/>	<input type="checkbox"/>	28. Excessive sweating .....	<input type="checkbox"/>	<input type="checkbox"/>
14. Seeing or hearing things that you know or are told are not there .....	<input type="checkbox"/>	<input type="checkbox"/>	29. Double vision .....	<input type="checkbox"/>	<input type="checkbox"/>
15. Difficulty concentrating or staying focussed .....	<input type="checkbox"/>	<input type="checkbox"/>	30. Believing things are happening to you that other people say are not true .....	<input type="checkbox"/>	<input type="checkbox"/>

All the information you supply through this form will be treated with confidence and will only be used for the purpose for which it has been collected. Information supplied will be used for monitoring purposes. Your personal data will be processed and held in accordance with the Data Protection Act 1998.

Developed and validated by the International PD Non Motor Group  
For information contact: susanne.tluk@uhl.nhs.uk or alison.forbes@uhl.nhs.uk

# PD NMS QUESTIONNAIRE

Name: ..... \* \* \* \* \* \* \* \* \* \* \* r n n w = a m + - - - m a Date ..... A9e:  
.....

Centre D: Male  Female

**NON-MOVEMENT PROBLEMS IN PARKINSON'S** The movement symptoms of Parkinson's are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems is listed below. Please tick the box 'Yes' if you have experienced it during the past month. The doctor or nurse may ask you some questions to help decide. If you have not experienced the problem in the past month tick the 'No' box. You should answer 'No' even if you have had the problem in the past but not in the past month.

**Have you experienced any of the following in the last month?**

- | Yes                            | No                             | 1. Dribbling of Saliva during the daytime  |
|--------------------------------|--------------------------------|--|
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 16. Feeling sad, low' or 'blue' .....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 2. Loss or change in your ability to taste or smell .....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 17. Feeling anxious, frightened or panicky .....   |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 3. Difficulty swallowing food or drink or problems   |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 18. Feeling less interested in sex or more<br>with choking .....                                       |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | D. 19. interested in sex .....   |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 4. Vomiting or feelings of sickness (nausea).....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 19. Finding it difficult to have sex when you try .....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)..... |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | D D from sitting or lying .....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 6. Bowel (fecal) incontinence .....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | [T] 21. Falling .....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 7. Feeling that your bowel emptying is incomplete .....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 22. Finding it difficult to stay awake during activities<br>after having been to the toilet .....      |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | [ ] Such as working, driving or eating .....   |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | DI DI  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 8. A sense of urgency to pass urine makes you .....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 23. Difficulty getting to sleep at night or staying<br>rush to the toilet .....                        |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | [ ] asleep at night .....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 9. Getting up regularly at night to pass urine .....   |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | [ ] 24. Intense, vivid dreams or frightening dreams .....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | D D  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 10. Unexplained pains (not due to known conditions .....   |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 25. Talking or moving about in your sleep as if you<br>such as arthritis) .....                        |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | [ ] are 'acting' out a dream .....   |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | [ ]  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 11. Unexplained change in weight (not due to .....   |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 26. Unpleasant sensations in your legs at night or<br>Change in diet) .....                            |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | [ ] while resting, and a feeling that you need to move ....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 12. Problems remembering things that have .....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 27. Swelling of your legs .....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | happened recently or forgetting to do things .....   |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 13. Loss of interest in what is happening around<br>you or doing things .....                          |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | [ ] 29. Doublevision ..., D D  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 14. Seeing or hearing things that you know or are .....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 30. Believing things are happening to you that other<br>told are not there .....                       |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | [ ] people Say are not true .....  |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 15. Difficulty concentrating or staying focussed .....   |
| ..... <input type="checkbox"/> | ..... <input type="checkbox"/> | 28. Excessive sweating   |

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in accordance with the Data Protection Act 1998.

Developed and validated by the International PD Non Motor Group For information contact: Susanne.tlukQuhl.nhs.uk or  
aiison.forbesouhl.nhs.uk

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## Non-Motor Symptom assessment scale for Parkinson's disease

Name Initial: \_\_\_\_\_

Date: \_\_\_\_\_

Symptoms assessed over the **last month**. Each symptom scored with respect to:

Severity: 0 = None;

1 = Mild: symptoms present but causes little distress or disturbance to patient;

2 = Moderate: some distress or disturbance to patient;

3 = Severe: major source of distress or disturbance to patient.

Frequency: 1 = Rarely (<1/wk);

2 = Often (1/wk);

3 = Frequent (several times per week);

4 = Very Frequent (daily or all the time).

(Bracketed text in questions within the scale is included as an explanatory aid).

	<b>Severity</b>	<b>Frequency</b>
<b>Domain 1: Cardiovascular including falls</b>		
1. Did you experience light-headedness, dizziness, weakness on standing from sitting or lying position?	[ ]	[ ]
2. Did you fall because of fainting or blacking out?	[ ]	[ ]
<b>Domain 2: Sleep/fatigue</b>		
3. Did you doze off or fall asleep unintentionally during daytime activities? (For example, during conversation, during mealtimes, or while watching television or reading).	[ ]	[ ]
4. Did fatigue (tiredness) or lack of energy (not slowness) limit your daytime activities?	[ ]	[ ]
5. Did you have difficulties falling or staying asleep?	[ ]	[ ]
6. Did you experience an urge to move the legs or Restlessness in legs that improves with movement when he/she is sitting or lying down inactive?	[ ]	[ ]
<b>Domain 3: Mood/cognition</b>		
7. Has you lost interest in his/her surroundings?	[ ]	[ ]
8. Has you lost interest in doing things or lack motivation to start new activities?	[ ]	[ ]
9. Did you feel nervous, worried or frightened for no apparent reason?	[ ]	[ ]
10. Did you seem sad or depressed or has he/she reported such feelings?	[ ]	[ ]
11. Did you have flat moods without the normal "highs" and "lows"?	[ ]	[ ]
12. Did you have difficulty in experiencing pleasure from their usual activities or report that they lack pleasure?	[ ]	[ ]
<b>Domain 4: Perceptual problems/hallucinations</b>		
13. Did you indicate that he/she sees things that are not there?	[ ]	[ ]

## Non-Motor Symptom assessment scale for Parkinson's disease

Name Initial: Date:

Symptoms assessed over the last month. Each symptom scored with respect to: Severity: 0 = None;

1 = Mild: symptoms present but causes little distress or disturbance to patient; 2 = Moderate: some distress or disturbance to patient; 3 = Severe: major source of distress or disturbance to patient.

Frequency: 1 = Rarely (<1/wk),

2 = Often (1/wk), 3 = Frequent (several times per week); 4 = Very Frequent (daily or all the time). (Bracketed text in questions within the scale is included as an explanatory aid).

Severity

Frequency Domain 1: Cardiovascular including falls 1. Did you experience light-headedness, dizziness, weakness

on standing from sitting or lying position? [ ] [

|

2. Did you fall because of fainting or blacking out? [ ] [ ]

Domain 2: Sleep/fatigue 3. Did you doze off or fall asleep unintentionally during daytime activities? (For example, during conversation, during mealtimes, or [ ] [ ] while watching television or reading).

4. Did fatigue (tiredness) or lack of energy (not slowness) limit your daytime activities? [ ] [ ]

5. Did you have difficulties falling or staying asleep? - [ ] [ ]

6. Did you experience an urge to move the legs or Restlessness in legs that improves with movement when he/she is sitting or lying down inactive? [ ] [ ]

Domain 3: Mood/cognition

7. Has you lost interest in his/her surroundings? [ ] [ ] 8. Has you lost interest in doing things or lack motivation to

start new activities? [ ] [ ] 9. Did you feel nervous, worried or frightened for no apparent reason? [ ] [ ] 10. Did you seem sad or depressed or has he/she reported such feelings? [ ] [ ] 11. Did you have flat moods without the normal "highs" and "lows"? - [ ] [ ] 12. Did you have difficulty in experiencing pleasure from their usual activities or report that they lack pleasure? [ ] [ ]

Domain 4: Perceptual problems/hallucinations 13. Did you indicate that he/she sees things that are not there? [ ] [ ]

---

	Severity	Frequency
14. Did you have beliefs that you know are not true? (For example, about being harmed, being robbed or being unfaithful)	<input type="checkbox"/>	<input type="checkbox"/>
15. Did you experience double vision? (2 separate real objects and not blurred vision)	<input type="checkbox"/>	<input type="checkbox"/>
<b>Domain 5: Attention/memory</b>		
16. Did you have problems sustaining concentration during activities? (For example, reading or having a conversation)	<input type="checkbox"/>	<input type="checkbox"/>
17. Did you forget things that he/she has been told a short time ago or events that happened in the last few days?	<input type="checkbox"/>	<input type="checkbox"/>
18. Did you forget to do things? (For example, take tablets or turn off domestic appliances?)	<input type="checkbox"/>	<input type="checkbox"/>
<b>Domain 6: Gastrointestinal tract</b>		
19. Did you dribble saliva during the day?	<input type="checkbox"/>	<input type="checkbox"/>
20. Did you have difficulty swallowing?	<input type="checkbox"/>	<input type="checkbox"/>
21. Did you suffer from constipation? (Bowel action less than three times weekly)	<input type="checkbox"/>	<input type="checkbox"/>
<b>Domain 7: Urinary</b>		
22. Did you have difficulty holding urine? (Urgency)	<input type="checkbox"/>	<input type="checkbox"/>
23. Did you have to void within 2 hours of last voiding? (Frequency)	<input type="checkbox"/>	<input type="checkbox"/>
24. Did you have to get up regularly at night to pass urine? (Nocturia)	<input type="checkbox"/>	<input type="checkbox"/>
<b>Domain 8: Sexual function</b>		
25. Did you have altered interest in sex? (Very much increased or decreased, please underline)	<input type="checkbox"/>	<input type="checkbox"/>
26. Did you have problems having sex?	<input type="checkbox"/>	<input type="checkbox"/>
<b>Domain 9: Miscellaneous</b>		
27. Did you suffer from pain not explained by other known conditions? (Is it related to intake of drugs and is it relieved by antiparkinson drugs?)	<input type="checkbox"/>	<input type="checkbox"/>
28. Did you have a change in ability to taste or smell?	<input type="checkbox"/>	<input type="checkbox"/>
29. Did you have a recent change in weight (not related to dieting)?	<input type="checkbox"/>	<input type="checkbox"/>
30. Did you experience excessive sweating (not related to hot weather)?	<input type="checkbox"/>	<input type="checkbox"/>

**TOTAL SCORE:**

Developed by the International Parkinson's Disease Non-Motor Group.  
Contacts: ray.chaudhuri@uhl.nhs.uk or alison.forbes@uhl.nhs.uk

14. Did you have beliefs that you know are not true?

(For example, about being harmed, being robbed or being unfaithful)

15. Did you experience double vision?

(2 separate real objects and not blurred vision)

Domain 5: Attention/memory 16. Did you have problems sustaining concentration during activities?

(For example, reading or having a conversation)

17. Did you forget things that he/she has been told a short time ago or events that happened in the last few days?

18. Did you forget to do things?

(For example, take tablets or turn off domestic appliances?)

Domain 6: Gastrointestinal tract 19. Did you dribble saliva during the day?

20. Did you have difficulty swallowing?

21. Did you suffer from constipation?

(Bowel action less than three times weekly)

Domain 7: Urinary 22. Did you have difficulty holding urine? (Urgency)

23. Did you have to void within 2 hours of last voiding? (Frequency) 24. Did you have to get up regularly at night to pass urine? (Nocturia)

Domain 8: Sexual function

25. Did you have altered interest in sex?

(Very much increased or decreased, please underline)

26. Did you have problems having sex?

Domain 9: Miscellaneous

27. Did you suffer from pain not explained by other known conditions?

(Is it related to intake of drugs and is it relieved by antiparkinson drugs?)

28. Did you have a change in ability to taste or smell?

29. Did you have a recent change in weight (not related to dieting)?

30. Did you experience excessive sweating (not related to hot weather)?

TOTAL SCORE: Developed by the International Parkinson's Disease Non-Motor Group.

Contacts: ray.chaudhuri(G)uhl.nhs.uk or alison.forbes(6)uhl.nhs.uk

Severity

[ ]

[ ]

Frequency

[ ]

[ ]

## Parkinson's Disease Sleep Scale (PDSS-2)

Name Initial: \_\_\_\_\_

Date: \_\_\_\_\_

Please rate the severity of the following based on your experiences during the past week (7 days). Please make a cross in the answer box.

	Very often (6 to 7 days a week)	Often (4 to 5 days a week)	Sometimes (2 to 3 days a week)	Occasionally (1 day a week)	Never
1. Overall, did you sleep well during the last week?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
2. Did you have difficulty falling asleep each night?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
3. Did you have difficulty staying asleep?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
4. Did you have restlessness of legs or arms at night causing disruption of sleep?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
5. Was your sleep disturbed due to an urge to move your legs or arms?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
6. Did you suffer from distressing dreams at night?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
7. Did you suffer from distressing hallucinations at night (seeing or hearing things that you are told do not exist)?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
8. Did you get up at night to pass urine?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
9. Did you feel uncomfortable at night because you were unable to turn around in bed or move due to immobility?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
10. Did you feel pain in your arms or legs which woke you up from sleep at night?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
11. Did you have muscle cramps in your arms or legs which woke you up whilst sleep at night?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
12. Did you wake early in the morning with painful posturing of arms or legs?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
13. On waking, did you experience tremor?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
14. Did you feel tired and sleepy after waking in the morning?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
15. Did you wake up at night due to snoring or difficulties with breathing?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0

## Parkinson's Disease Sleep Scale (PDSS-2)

Name Initial: Date:

Please rate the severity of the following based on your experiences during the past week (7 days). Please make a cross in the answer box.

Very often Often Sometimes Occasionally Never (6 to 7 days (4 to 5 days (2 to 3 days (1 day a week) a week) a week) a Week)

1. Overall, did you sleep well during the last week? Do [ ] 2 D3 D4 2. Did you have difficulty falling asleep each night? PI4 [ ] 3 [12 DA □ 0 3. Did you have difficulty staying asleep? D4 D3 [12 [14 PI 4. Did you have restlessness of legs or arms at night D4 D3 PI2 D4 Clo

causing disruption of sleep?

5. Was your sleep disturbed due to an urge to move D4 CI3 D2 D4 PI  
your legs or arms?

6. Did you suffer from distressing dreams at night? D4 D3 D2 [ ] Do 7. Did you suffer from distressing hallucinations at night D4 D3 D2 D4 PI

(seeing or hearing things that you are told do not exist)? 8. Did you get up at night to pass urine? D4 [13 D2 D4  
Do 9. Did you feel uncomfortable at night because you PI4 PI3 D2 D4 Do  
were unable to turn around in bed or move due to immobility?

10. Did you feel pain in your arms or legs which woke D4 D3 □ 2 [14 00  
you up from sleep at night?

11. Did you have muscle Cramps in your arms or legs PI4 D3 D2 □ 1 00  
which woke you up whilst sleep at night?

12. Did you wake early in the morning with painful D4 D3 D2 [14 Do  
posturing of arms or legs?

13. On waking, did you experience tremor? PI4 TI2 D2 PI PI

14. Did you feel tired and sleepy after Waking in D4 D3 [12 D4 □ 0  
the morning?

15. Did you Wake up at night due to Snoring or D4 [ ] 3 D2 D1 PI  
difficulties with breathing?