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The Effects of Yoga Versus Mindfulness on Anxiety in Individuals with Parkinson's Disease

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THE EFFECTS OF YOGA VERSUS MINDFULNESS ON ANXIETY IN INDIVIDUALS WITH PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease is a progressive neurodegenerative disease that causes debilitating motor deficits in addition to many non-motor symptoms. Tremors, stiffness, and abnormal gait changes are easily recognized as disabling; however, effects from anxiety are more insidious to disease burden which negatively affect both motor and psychological capabilities. Anxiolytics or antidepressants are often prescribed but can cause adverse side effects, prompting the need for alternative treatments. Yoga and mindfulness therapies are favorable alternative treatments known to reduce anxiety. This two-arm, single-blinded randomized controlled trial compares effects of yoga and mindfulness therapies in the reduction of anxiety for patients with Parkinson's disease. Yoga is hypothesized to have greater statistically significant effect in reducing anxiety compared to mindfulness due to its combined mental and physical benefits. However, if both interventions demonstrate positive outcomes, both may prove to be beneficial adjunctive treatments for patients with anxiety in Parkinson's disease or other neurodegenerative movement disorders.

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

1.1.1 Overview of Parkinson's Disease and Related Anxiety

Parkinson's disease (PD) is a progressive neurodegenerative disease that results in debilitating motor and cognitive deficits that drastically decrease quality of life and health status. There is a direct association between the incidence of PD with aging; as such, prolonged life expectancies in recent decades contribute significantly to the increase in diagnoses and subsequent healthcare expenditures.[1] In 2020, one million US citizens were estimated to be living with PD; and the prevalence has been projected to increase by at least 60,000 patients per year.[1] The annual healthcare expenditures were estimated to be $12,350 - $17,136 per patient in 2020.[2]

Although the inciting factor triggering idiopathic Parkinson's disease has not been identified, the underlying neuropathology and symptomology of Parkinson's disease have been well-established. Abnormal α-synuclein accumulations in various cells including Lewy bodies result in the degeneration of dopaminergic neurons in the substantia nigra.[3] The resultant loss of dopamine supply for this area of the brain disrupts the coordination of movements which results in tremors, bradykinesia, and rigidity. [4,5] Although the development of motor symptoms is often gradual, actual rates of progression may differ among each patient. Unfortunately, PD is neither reversible nor curable.

In addition to the more classic motor symptoms of PD, there are psychological symptoms that accompany the disease. The underlying pathophysiology of the psychological changes is also not fully understood, but most research in this area has implicated alterations in dopaminergic system and transporter availability, structural amygdala changes, and loss of noradrenaline neurons in the locus coeruleus as potential

etiologies.[6] Other neurobiological explanations include disruptions of frontal-striatal circuits that regulate stress, cognition, affect, motivation, and behavior.[7]

The diminished abilities to regulate new physical and emotional stressors from PD often result in secondary diagnoses of anxiety disorders at a later age. Anxiety disorders as determined by DSM-V have been diagnosed in patients with Parkinson's disease and include generalized anxiety disorder (14%), social anxiety disorder (13.8%), anxiety not otherwise specified (NOS) (13.3%), specific phobia (13%), and panic disorder (6.8%).[5]

1.1.2 Treatments of Parkinson-Related Anxiety

A study conducted by Broen et al. in 2016 revealed that 31.1% of patients with Parkinson's disease (PwP) had anxiety disorders or clinically relevant anxiety symptoms.[8] Despite being a fairly prevalent symptom experienced by PwP, there are no formal guidelines for treatment of anxiety in this population.[8,9] Several agents including Bromazepam, selective serotonin reuptake inhibitors (SSRI), and cognitive behavioral therapies (with or without pharmacotherapy) have been trialed to varying efficacies.[10] Many of these therapies also have the potential to lead to adverse drug interactions and debilitating side effects, sometimes resulting in higher healthcare expenditures.[11]

In the search for cost-effective therapies, researchers have turned towards investigating psychological treatments that aim to reduce negativity in internal responses to emotional or physical situations that may trigger anxiety.[12]

A precedent has been set for the use of alternative therapies such as mindfulness or yoga in progressive neurological disorders such as multiple sclerosis (MS) and Huntington's disease (HD). These disorders closely resemble PD in their multisystemic disease course, neurodegeneration, and incurability.[7] In a systematic literature review,

mindfulness based therapies were found to have a greater positive effect in patients with MS-related anxiety than antidepressants in patients with PD-related anxiety.[7] Although mindfulness was not studied for PD-related anxiety, the authors suggested that mindfulness had high potential in reducing PD-related psychological distress.

Mindfulness has been shown to effectively increase self-awareness while preventing habitual and negative responses to emotions or physical impairments.[13] This is accomplished through increased attention and self-awareness of emotions, sensory perceptions, and thinking patterns in a non-judgmental manner.[10] The response to difficult situations then becomes slowed and methodical—leading to less anxiety and an enhanced repertoire of coping skills over time.[14] The medial cortex, amygdala, lateral frontal regions, hippocampus, and basal ganglia have all been studied to be affected by mindfulness.[15] Specifically, it has been demonstrated that mindfulness down-modulates outputs from the amygdala, which has been associated with reductions in anxiety and fear-related behaviors.[16,17] While there is ongoing investigation on the effect of mindfulness on other cortical structures, impact studies have demonstrated that mindfulness has shown positive effects on quality of life based on both mental health and well-being questionnaires.[16]

With yoga, the psychological benefits have been associated with relaxation of the physical body. Research findings indicate that yoga decreases emotional stress and reduces the autonomic sympathetic, fight-or-flight heightened responses.[18] Yoga has also been shown to directly reduce the oxidative stress that results in dopaminergic neurodegeneration in the substantia nigra. The oxidative stress involving reactive oxygen and nitrogen species along with diminished antioxidant protection cause improper

skeletal muscle contraction and muscle fatigue.[19,20] The physical practice of yoga exercises and poses are known to reduce oxidative stress by increasing both endogenous enzymatic and nonenzymatic antioxidants.[20] The result contributes to a slowing of the loss of dopaminergic neurons, which in turn reduces the disruption to the previously described frontal-striatal circuits that control mood and behavior.

Other theorized effects of yoga includes a downregulation of the hypothalamic-pituitary-adrenal axis as a means of reducing anxiety.[21] Studies in this area have shown that deep breathing, meditation, and active exercises in yoga correlate with reduced levels of cortisol and catecholamines, and increased levels of serotonin, melatonin, and GABA. These changes in neurotransmitter activity have all been implicated in promoting positive mental health benefits.[22] The increase in GABA neurotransmitters in yoga is a mechanism of action that many anxiolytics, like benzodiazepines, attempt to mimic exogenously.[23] Breath control in yoga has been studied and found to benefit anxiety and panic disorder by activating the parasympathetic nervous system via vagal stimulation and reducing the activity of the sympathetic nervous system.[23]

To date, there have been no head-to-head studies comparing the efficacy of yoga and mindfulness in decreasing anxiety. It is suspected that yoga may demonstrate a more significant reduction in anxiety over mindfulness due to combined physical and neurochemical responses like increased endogenous opioids, which improve moods and decrease pain.[23]

1.2 STATEMENT OF THE PROBLEM

Studies have shown that high levels of anxiety lead to accelerated motor dysfunction, poor treatment compliance, and rejection of leisure and social activities.[11] These changes all drastically decrease quality of life.[24,25] Many pharmacological agents

with anxiolytic properties like SSRI, buspirone, and benzodiazepines have been tried in Parkinson populations. But, many of these agents block dopamine or increase risk for falls and confusion, making them especially dangerous in patients with primary physical and/or cognitive impairments.[11] The dopaminergic therapies that are used to alleviate motor symptoms in Parkinson's are minimally efficacious toward the psychological symptoms that patients experience. In some instances, dopaminergic treatments may worsen such symptoms. Treatment of non-motor symptoms typically subjects patients to polypharmacy, unwanted side effects, and higher medical expenditures. Despite the relatively high prevalence of anxiety in patients with Parkinson's disease, there are very few studies that address anxiety as primary outcomes;[11] or, evaluate non-pharmacological options for treatments of Parkinson's-related anxiety.[24]

1.3 GOALS AND OBJECTIVES

Patients with Parkinson's disease would benefit from low-cost, low-risk nonpharmacological therapies designed to improve functional abilities across multiple domains (physical, cognitive, and mood/affect). Research-based outcomes indicated that both mindfulness therapy and yoga therapy improve psychological symptoms.[26] Our objective is to determine which therapy has greater impact in reducing anxiety in patients with Parkinson's Disease. This study will be designed and powered to examine reduction of anxiety as the primary outcome. The study will also utilize inventories and indexes tailored specifically for Parkinson's anxiety.

1.4 HYPOTHESIS

Patients with Parkinson's disease who practice yoga weekly for 8 weeks will have statistically significant mean differences in anxiety scores on the Parkinson Anxiety Scale (PAS) and Beck Anxiety Inventory (BAI) as compared to patients who practice

mindfulness-based therapies for the same number of sessions. We expect to see decreases in anxiety-related symptoms as our primary outcome. The secondary outcomes will be improvements in health status, motor symptoms, and changes in anxiety medication usage. We also hypothesize that the benefits of both therapies will be maintained at 3-months and 6-months post-intervention.

1.5 DEFINITIONS

Mindfulness Therapy – conscious awareness, openness, and non-judgment of present moment

Yoga Therapy – Specific application of yoga activities (postures, breathing, meditation) used to aid recovery or rehabilitation from illness, injury, or disability[22]

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CHAPTER 2: REVIEW OF THE LITERATURE

2.1 INTRODUCTION

From August 2020 to May 2021, a systematic literature search was carried out on PubMed, Cochrane, and Scopus with different combinations of the key terms: “Parkinson* anxiety”, “Parkinson*” “antidepressants”, “Parkinson* AND tricyclic antidepressants”, “Beck anxiety Parkinson”, “Parkinson Anxiety Scale”, “CBT”, “yoga”, “yoga therapies”, “mindfulness”, and “mindful meditation”. The following MeSH phrases were also used on PubMed: “Parkinson* anxiety”, “yoga”, and “mindfulness”. Results were narrowed with filters for publication dates in the last decade and the following article types: randomized controlled trial, meta-analysis, and systematic literature review. On CINAHL, the following were searched: (MH "Parkinson Disease") AND (MH "Anxiety+") “yoga therapy” “mindfulness” and “anxiety disorders”. Several articles were also extracted from the reference lists of other articles.

2.2 REVIEW OF EMPIRICAL STUDIES

2.2.1 Overview of Pharmacological Therapies in Parkinson-Related Anxiety

Systematic literature reviews performed by Broen et al. on Parkinson-related anxiety revealed that an average of 31% of patients with Parkinson’s disease met criteria for DSM-V anxiety disorders and another 25.7% for clinically significant anxiety symptoms.[1] Despite the importance of anxiety and psychological disability in PD, there were limited numbers of well-designed controlled studies regarding prescribing practices in this population.[2] A cross-sectional study by Pontone et al. demonstrated that among 38 patients with Parkinson-related anxiety, only 53% were actively receiving pharmacological treatment.[3] Of those receiving treatment, the most commonly used anxiolytics were selective serotonin reuptake inhibitors (SSRI), with 30.1% and 38.9%

prescribed in patients with and without depression, respectively.[3] This was in contrast to benzodiazepines, which were the medication of choice for non-PD populations.[3] The avoidance of benzodiazepines in patients with Parkinson's (PwP) was based on the known side effects such as increased fall risks, cognitive impairment, and medication dependency.[3]

Although the study by Pontone et al. provided useful documentation of the prescription patterns in Parkinson-related anxiety, it lacked the details of treatment schedules and efficacies.[4] The study also did not account for the use of alternate, non-pharmacological therapies in Parkinson-related anxiety. Additional studies are necessary to determine the efficacy of pharmacological treatments as well as the reasons for low prescription rates.

2.2.2 The Effects of Mindfulness on Anxiety

In recent years, the use of mindfulness-based interventions has become more prevalent due to its low-cost and convenience as a psychological treatment. Research pursuits have focused on assessing its efficacy in anxiety syndromes both as an independent treatment option and as an adjunct to other treatment modalities.[5,6]

Boettcher and Kladnitski et al. each performed randomized controlled trials and separately found online mindfulness programs to be effective for primary anxiety disorders (social anxiety disorder, panic disorder, general anxiety disorder, and anxiety not-otherwise-specified). In the Boettcher et al. study, 91 patients were assigned to either an online mindfulness treatment group or an online discussion forum control group.[7] Participants showed decreases in symptoms of anxiety, depression, and insomnia with more notable reductions from pre- to post- assessment (Cohen's d=1.58) in the mindfulness group as compared to the control group (d=0.49).[7] The primary outcomes

measured on the Beck Anxiety Inventory (BAI) also showed large group differences (d=0.99) post-treatment between the two treatment groups.[7,8] Clinically, 16 participants (40%) of the mindfulness group achieved the criteria of improvement and recovery compared to 4 participants (9%) in the control group. These differences in response rate were deemed significant ($\chi^2 = 11.04$, $p = 0.002$).[7] However, the anxiety scores between post-intervention to 6-month follow up were not determined to be significant (t = -0.95, p=0.347).[7]

Kladnitski et al. took a similar approach and delivered mindfulness sessions online over a 14-week period for patients with primary DSM-V based diagnoses of primary anxiety and major depressive disorders.[8] Within the mindfulness group, a reduction of 1.08 (95% CI of 0.55 to 1.60) was found between baseline and post-treatment, and 1.14 (95% CI of 0.60 to 1.69) from baseline to 3-month follow-up.[8] This was in contrast to the treatment-as-usual (TAU) response of 0.34 (95% CI of -0.14 to 0.82) from baseline to post-treatment. The response from baseline to follow-up was not reported in the TAU group.[8] The comparison of reduction in anxiety between the mindfulness and TAU interventions was significant at 1.00 (95% CI of 0.46 to 1.54) post-intervention. These results were unexpectedly greater than the moderate differences found in other studies.[8] Clinically, 73.1% of the 40 participants in the mindfulness group no longer met the DSM-V criteria for anxiety or depressive disorders at 3-months follow-up; however, an attrition rate (23-35%) suggested that these improvements may not be sustainable.[8]

The Kladnitski et al. study was sufficiently powered to detect statistically significant differences between interventions and treatment as usual care, but revealed

that the benefits of mindfulness may not necessarily be maintained beyond treatment completion without continued observance of mindfulness practices.[8] The authors surmised that future trials would likely require at least 200 participants in each group to achieve statistical significance between mindfulness and TAU.[8] Based on these findings, it was also suggested that mindfulness training was a viable stand-alone therapy option for individuals with anxiety, and that daily use of mindfulness therapy will support long-term benefits.[8] Since both Boettcher and Kladnitski et al. concluded that three months was an insufficient duration to conduct post-treatment follow-up, future studies should have longer monitoring periods in order to more accurately comment on the long term efficacy of mindfulness treatments.[7,8]

Sundquist et al. conducted a head to head comparison study on mindfulness-based interventions (MBI) against cognitive behavioral therapy (CBT) and pharmacological treatments.[6] Their qualifying inclusion criteria covered a broad range of anxiety disorders that included all the diagnoses similarly observed in patients with Parkinson's (panic disorder, GAD, mixed anxiety and depressive disorder, other mixed anxiety disorders, and anxiety NOS).[6] This study did not target patients with Parkinson's disease. The MBIs group had drastically decreased the median scores on the anxiety subscale of the Hospital Anxiety and Depression Scales (HADS) from baseline to post-intervention assessment ($p < 0.001$).[6] Primary outcomes of HADS also revealed that MBIs were not inferior to CBT or pharmacological treatment controls (97.5% one-sided CI with an upper limit 3.16).[6] Unfortunately, the study population was restricted to participants 20-64 years old,[6] and as such, results could not be generalized to older populations or Parkinson's patients, who are generally >60 years old.[9]

Dissanayaka utilized a specific mindfulness training, called Mindfulness-Based Stress Reduction (MBSR), which facilitates adaptation to the stress and management of medical illnesses.[10] This study was designed specifically to determine efficacy of the mindfulness training for reduction of motor and neuropsychiatric deficits in PwP.[10] Dissanayaka believed that mindfulness practices would improve selective and sustained attention, working memory, executive functioning, and motor ability, which would prove especially beneficial for PwP.[10] Anxiety-related symptoms were assessed using the Geriatric Anxiety Inventory (GAI). Outcomes demonstrated that the postintervention mean GAI scores were significantly reduced from baseline ($Z = -2.20$, $p = 0.03$), and that 21% of the 14 participants experienced clinically significant reductions in their anxiety-related symptoms.[10]

Limitations to this study were that the sample size was small. Outcomes indicated no significant differences between the mean GAI scores from baseline to 6-months follow-up ($Z = -1.29$, $p = 0.20$).[10] This finding, along with the findings from Kladnitski et al. study, suggested that the benefits of mindfulness may be nullified if consistent practice is not maintained post-intervention.[10] As for motor symptoms, the scores from the Movement Disorder Society-United PD Rating Scale did not show improvements in follow-up and post-intervention from baseline.[10]

2.2.3 The Effects of Yoga on Anxiety

Yoga promotes both physical and psychological well-being[11] through various techniques that include physical postures (asanas), breath regulation (pranayama), meditation/mindfulness, and relaxation.[12] Over the past two decades, yoga has been revitalized in mainstream culture, but internationally it has already been accepted as a form of complementary medicine for both physical and mental health.[13-15]

Cramer et al. conducted a systematic meta-analysis to assess the efficacy and safety of yoga in patients with a wide scope of anxiety disorders.[13] The research included adults with mean ages 30-38.5 years old, who met DSM-IV criteria for primary anxiety disorders or who scored moderate or higher for anxiety according to clinical anxiety rating scales and questionnaires.[13] Primary anxiety outcomes included improvements in the severity of anxiety or complete remission of anxiety based on objective clinician-rated or subjective self-rated scales.[13]

The meta-analysis revealed that yoga had positive, short-term effects (12 weeks from randomization) on anxiety compared to no treatment based on standardized mean differences (SMD) = -0.43; 95% CI = -0.74 to -0.11; P=0.008.[13] When compared to other relaxation techniques such as meditation, yoga showed an even greater reduction of anxiety (SMD = -0.86; 95% CI = -1.56 to -0.15; P=0.02). The results of this meta-analysis were not without limitations. Beyond the 12 weeks of study, there were no changes in the remission of anxiety between intervention and control groups.[13] Cramer et al. also found that a statistical significance was not achieved in subjects with DSM-IV diagnosed anxiety disorders, but was achieved on questionnaires in individuals with self-reported clinical symptoms.[13]

De Manincor conducted a single-arm crossover RCT to evaluate the effects of individualized yoga therapies on depression and anxiety.[10] 101 subjects were enrolled based on scores obtained from completion of the Depression Anxiety Stress Scale (DASS-21). The participants were divided up into either the yoga intervention or the non-intervention control group. The control group had a 6-week delay in interventions during which they maintained regular activities.[15] The intervention group participated in six

weeks of yoga treatment with certified yoga instructors. A total of four group sessions were held. In each session, the instructors worked with each participant to create individualized routines that were adapted to the participant's specific physical and mental symptoms.[15] Individuals were then encouraged to practice these routines at home in between sessions. Compliance with the home regimen was recorded. These individualized routines had a mixture of physical postures and movements, breathing exercises, relaxation, mindfulness, and meditation techniques.[15] At 6 weeks, the control group was started on the same individualized yoga training and treatment schedule.[10]

On the anxiety subscale of DASS-21, there were no significant reductions of anxiety between treatment and control groups (AMD -1.91; 95% CI = -4.58 to 0.76; P=.16, effect size = -0.35).[15] The researchers determined some data points to be outliers due to their Cook's distance values > 0.04. When these suspected outliers were trimmed, the pre- and post-anxiety scores became statistically significant in the treatment group (AMD -2.58; CI: -4.71 to -0.35; P=0.02; effect size -0.40).[15] Significant reductions in scores were also observed in the overall mean composite anxiety, depression, and stress scores (AMD -8.77; 95% CI = -16.58 to -0.97; P=.03, effect size = -0.50) between the intervention and control groups at 6 weeks post-intervention (P<0.01).[15]

The ability to adapt yoga techniques to fit various physical capabilities within the home environment and without explicit guidance were some of the benefits observed from these individualized, at-home treatments.[15] Overall, psychological benefits were positive with the yoga interventions, but were not specific to target the anxiety symptoms. Despite attempts to minimize selection and performance biases, the study

design introduced heterogeneity within the individualized yoga interventions, making it difficult to generalize the outcomes to broader groups.

Boulgarides investigated the potential psychological and physical benefits of yoga specifically for patients with PD. Prior to the initial assessment, a medical history, Unified PD Rating Scale (UPDRS), and Hospital Anxiety and Depression Scales (HADS) were performed. The following physical assessments were also performed: Berg Balance Scale (BBS), Modified Dynamic Gait Index (mDGI), 30-second chair stand (TSCS), Sit-and-Reach tests (SRT), Apley's Scratch test (AST), Functional Reach Test (FRT), and timed Single-Leg Balance (SLB) test.[16]

Outcomes from the Boulgarides et al. study were determined through minimal detectable changes (MDC), which are the amount of measurable changes in test scores that allow the study to confidently state that the change was not the result of measurement errors.[16] 20% of participants achieved MDC for the HADS anxiety subscale.[16] Post-ANOVA analysis revealed statistically significant mean differences in the 30-second chair stand (TSCS) and bilateral sit-and-reach tests (SRT) at $\alpha = 0.10$.[16] Outcome measures demonstrated significant improvement post-intervention for TCSC ($p = 0.03$) but a lack of significant changes in the controls ($p = 0.39$).[16] The majority of participants (60%) met the MDC of > 1.64 for TSCS with the yoga intervention.[16] SRT on the right and left side demonstrated significance at $p = 0.02$ and 0.03 respectively with 70% of participants achieving an MDC of >3 inches between fingertips and toes on the right and 40% achieving 3.5 inches on the left.[16] The study concluded that a sample of 10 participants was sufficient to observe significant differences in the HADS subscales between control and intervention periods at an $\alpha = 0.01$. For TSCS, a sample size of 33

was needed to satisfy an $\alpha = 0.01$; and for SRT, a sample size of 153 was needed to detect significant differences at 80% power and 0.01 level of significance.[16]

Despite a small sample size and low statistical power, Boulgarides et al. found adequate measures to assess flexibility, strength, motor control, balance, anxiety, and depression. The study also showed positive effects of yoga on anxiety and certain physical parameters. Boulgarides et al. also minimized confounders by utilizing the same cohort for both the control and intervention groups through a waitlist design.

2.3 REVIEW OF POSSIBLE CONFOUNDING VARIABLES

Despite the standardization of the mindfulness or yoga group therapies, the relationship between participants and instructors occasionally became potential confounders. Several studies observed variability among the amount of time instructors spent on each individual, either to encourage adherence or to monitor risk.[8] However, the increased attention from instructors were often found to influence treatment adherence and thus primary outcomes.[8]

Among group members, participants showed benefits from positive group interactions that resulted in greater accountability, increased feedback, and overall social support and encouragements.[17] The social networking and group interactions could also confound results, especially when they were compared to controls or other interventions that did not utilize group formats, such as the waitlist controls.[8,15]

Aside from group therapies, many studies employed home regimens to be practiced between group sessions. De Manincor et al. customized home routines for each participant in addition to group yoga lessons. They found that these personalized routines confounded effects on anxiety and health status depending on compliance with home

practice times and regimen variabilities.[15] The heterogeneity of these routines made it difficult to determine the efficacy of treatment on the group and also difficult to differentiate between the efficacy of one personalized routine over another.[15]

As for participant-dependent confounders, compliance to research protocol to attend group lessons and to practice home regimens were confounding factors.[15] The effect of participant adherence as a confounding factor was verified when Kladnitski et al. assessed participants' expectancy of treatment efficacy in each participant at the beginning of the study.[8] It was determined that adherence was a better predictor of outcome than treatment expectancy.[8] However, the perceived efficacy of treatment was also a reportable factor in determining the participants' adherence to protocol.[8]

Additionally, subjects who have experience with yoga or mindfulness-based therapies could also affect the association between interventions and anxiety symptom outcomes.[18] Hofmann's study tried to account for this confounding variable by setting an ineligibility standard that anyone who had experiences of five or more yoga/mindfulness sessions would not be enrolled in the study. [11] Because of this enrollment criteria, challenges were reported regarding enrollment of subjects who were treatment naïve to both mindfulness and yoga.

2.4 REVIEW OF RELEVANT METHODOLOGY

2.4.1 Study Setting and Design

A literature review was conducted to assess study designs used for yoga and mindfulness therapies. There was a clear preference to utilize two-arm randomized control efficacy trials with intervention groups receiving standardized yoga or mindfulness therapies and control groups receiving a variety of care interventions. These interventions ranged from standardized CBT, stress education, and stretch resistant

training,[11,19] while other control groups took the form of delayed intervention.[16,20] The interventional groups received weekly, hour-long yoga or mindfulness sessions for 8-12 weeks in groups of 4-6 participants with 1-2 instructors.[11,16,18-20] The addition of home independent regimens varied among the studies. Since yoga and mindfulness have the greatest impact with consistent practice, the implementation of standardized home exercises was ideal for maximizing benefits without confounding the effects of the group sessions. Kwok et al. standardized the home workouts to 20-minute practices twice weekly with booklets outlining instructions for each exercise.[19] Boulgarides et al. encouraged home practice but required documentation of time spent on each activity (breathing, meditation, and posing exercises).[16] Cheung et al. thought home exercises would confound results so they refrained from prescribing any independent treatments.[20]

Randomization and blinding techniques included randomized computer-generated groups blinded to research assistants collecting the data and the statisticians performing the data analyses.[20] Block permutation stratified by site was utilized in one study to ensure equal allocation of participants from each recruitment site to either the control or treatment group.[11,21] Both methods were able to minimize selection and evaluator biases. Other confounders were minimized by matching variables for group formats, frequency, duration, venue, and number of participants per group.[19]

2.4.2 Selection Criteria

Participants included in the studies were over 18 years old with moderate PD (as determined by Hoehn and Yahr scores of 2-3) and formal DSM-V diagnoses including GAD, social anxiety disorder, panic disorder, or agoraphobia.[8,11] The H&Y criteria excluded participants with either mild PD who were high functioning or those with severe PD who had no ability to ambulate unassisted.[16]

Comorbid depressive disorders were allowed in these studies, but other psychiatric disorders including PTSD, substance use, eating disorders, organic mental disorders, psychosis, bipolar disorders, developmental disorders, or significant suicidal ideation were excluded.[8,11,22] Pontone et al. justified the inclusion of concurrent depressive disorders by their findings where they found no differences in the class or dosing of psychiatric medications for anxiety in patients with or without depressive comorbidities.[4] Therefore, depression was deemed an unlikely confounding factor in the treatment of anxiety.[3] However, the other psychiatric disorders were likely to affect the psychiatric regimen of anxiety or increase the participants' risk for hospitalization while in the study.

2.4.3 Patient Recruitment and Screening

Patient recruitment occurred both locally and regionally through convenience sampling.[19] Most local recruitment came from outpatient neurology and movement disorder clinics while broader populations were reached through Parkinson's disease associations, community-based research registries (region dependent), and support groups. [10,16,20] Many studies tried to reduce selection biases by widening their search to regional databases like PD associations, support groups, and national research registries. But there was no evidence to suggest that the socioeconomical or cultural characteristics of the local populations were not diverse.[10] The results from the local populations were therefore deemed generalizable to a larger population. Another issue with recruiting over a wide geographic area was the increased travel time for participants and caregivers to study sites, which risked attrition and noncompliance to group interventions and follow-ups.

A series of motor and non-motor screening assessments were performed post-recruitment. Motor assessments included: the Movement Disorder Society - United PD Rating Scale (MDS-UPDRS) and an assortment of physical assessments: Berg Balance Scale (BBS), Modified Dynamic Gait Index (mDGI), 30-Second Chair Stand (TSCS), Sit-and-Reach Test (FRT), and timed Single-Leg Balance (SLB) test.[16] Non-motor tests included several anxiety and mood assessments: Hospital Anxiety and Depression Scale,[16] Geriatric Anxiety Inventory,[10] Beck Anxiety and Depression inventory[20], and Hamilton Anxiety Rating Scale[11]. Having both motor and non-motor assessments as part of the screening process ensured that participants could physically execute yoga poses and the clinical assessments.

Hofmann et al. found that despite an overall agreement that anxiety symptoms were captured on various anxiety scales, there was no consensus among authors on the best cut-off values to determine if symptoms were clinically significant.[11] Therefore, authors set different threshold levels of anxiety based on their own prior experiences or those found in other studies.[1]

2.4.4 Data Collection

Most studies performed evaluator-blinded assessments at baseline (week 0), post-intervention (week 8 or 12), and at 6 months follow-up.[11,16,20] Fewer studies included mid-intervention assessments.[11]

The assessments at baseline included informed consent, motor, and non-motor assessments.[16] The same motor and non-motor tests were repeated post-intervention and at subsequent follow-ups. Assessing outcomes immediately following the intervention period provided data on the short-term efficacy of yoga and mindfulness. The 6 months follow-up provided data on the long-term efficacy of these interventions.

Most studies intended for participants to maintain consistent practice post-intervention until the follow-up assessments. However, since there were no organized sessions post-intervention, it was difficult to encourage and remind patients to practice at home. Dissanayaka et al. incorporated a "telephone mindfulness booster session" to refresh knowledge and skills learned from the interventions but also to encourage continued practice.[10] Based on the above, instead of a telephone session, participants may benefit from a 3-months follow-up to ensure continued practice of home regimens. Additional data obtained may find correlations between compliance with anxiety and motor symptoms.

2.4.5 Outcome Measures

For primary outcomes, there were several studies that used either the Beck Anxiety Inventory (BAI), Hospital Anxiety and Depression Score (HADS), and Hamilton Anxiety Rating Scales (HARS). Leentjens et al. sought to validate the clinimetric properties of HARS, BAI, and HADS.[22] The study found that all scales (BAI, HADS, and HARS) had low positive predictive value and moderate negative predictive value at the optimal cut-off scores. This resulted in an underestimation of the severity and prevalence of anxiety in PwP.[22]

Leentjens et al. then developed a novel scale with improved validity and clinimetric properties called the Parkinson Anxiety Scale (PAS).[23] The scale was intended to be an assessment of anxiety severity rather than a screening or diagnostic tool. [23] To create PAS, canonical correlation analysis of questions from HARS, BAI, and a Rasch analysis were performed and incorporated to fully capture the spectrum of anxiety symptoms. The outcome resulted in a patient- and observer-rated scale comprised of 12 items: five items assessing persistent anxiety, four items for episodic anxiety, and

three items for avoidance behavior.[23] Each item scored on a 5-point Likert scale (0=not or never and 4=severe or almost always).[23]

Both patient- and observer-rated scales had high AUC (85.1% and 85.9 respectively), sensitivity, and specificity for any anxiety disorder at the optimal cut-off scores, which was set as the threshold for whether a patient had an anxiety disorder or not.[23] The patient-rated version had better sensitivity (0.81 vs 0.71) but worse specificity (0.74 vs 0.91) than observer-rated versions.[23]

Face validity was found higher in PAS than existing scales because PAS was able to separate clinically evident and relevant domains into separate subscales. PAS was also more effective in capturing symptoms of anxiety not otherwise specified (NOS) compared to other anxiety scales, since the symptoms of NOS were specific to Parkinson's disease.[1,23] The scale eliminated biases towards persistent symptoms that were observed in HARS or episodic symptoms, as seen with BAI. Group validity in PAS was good, the AUC and Youden index of PAS was higher than in HARS, BAI, or HADS.

The PAS was validated based on a three-month study period. To date, no longitudinal studies have been published regarding the sensitivity of the PAS for anxiety symptom changes beyond a year. In addition, anxiety has not been adequately assessed in other PD studies. The adjunctive use of the BAI will document the subtleties of episodic anxiety. This is more reliable to capture the more mild or transient cases of anxiety given an estimated >50% of patients who have some degree of PD related anxiety.[11,24] BAI also has high internal consistency and test-retest probabilities when assessing the severity of anxiety symptoms within the mental health populations.[11]

For secondary outcomes, most studies had a combination of quality of life, health status, adherence rates, and motor symptoms.[8,13] Health status was an important therapeutic outcome in many studies as it often determined the subject's ability to perform physical, emotional, and social activities.[4] Many studies found anxiety was associated with an additional 17% of variance in health status after controlling for depression.[4] And anxiety was directly associated with poor health status even after factoring out motor disabilities. Many studies utilized either the Parkinson's Disease Questionnaire version-39 or version-8 questionnaires. PDQ-8 is a shortened form of PDQ-39, which is the most frequently used questionnaire that explores patient-reported measures of health status. Both assess the impact of Parkinson's disease on functioning and well-being across eight different dimensions including relationships, social situations and communication.[25] If PDQ-8 is used in place of PDQ-39, there is no concern that PDQ-8 will be less sensitive or specific as it has summary indices similar to those of PDQ-39, with good validity, test-retest reliability, and internal consistency (ICC=0.96).[26]

As for motor measurements, Dissanayaka used the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS) to assess motor disability. Both MDS-UPDRS and the original UPDRS assess motor function by measuring motor performance, activities of daily living, mobility, quality of life, and psychological status.[16] The primary difference is the addition of more detailed instructions and descriptions of methods for data acquisition in MDS-UPDRS, which allows participant to complete the assessment without provider input or the need for further clarification.[27] MDS-UPDRS was also found to better differentiate between the nuances of symptom severity.[27]

The physical assessments in PwP commonly include: the Berg Balance scale, modified Gait Index, Functional Reach Test, Sit-and-Reach Test Apley's Scratch Test, the 30-second chair stand, and the single leg balance test. In review of these assessments, Boulgarides found that only the single leg balance test (SLB), sit-and-reach test (SRT), and the 30-second chair stand (TSCS) demonstrated changes in scores post-yoga interventions, and thus recommended only using these outcome measures for future studies.[16] Although there are few studies using the SLB, SRT, and TSCS that support the findings of Boulgarides, for the purposes of this study, these three assessments will suffice in assessing participants' function, balance, and strength.[16]

2.4.6 Sample Size and Statistical Analysis

The meta-analysis performed by Cramer et al. demonstrated that yoga's effect size on depression when compared to aerobic exercises was moderate at 0.59.[28] When Kwok et al. conducted their study on the effect of yoga on anxiety, their aim was to replicate the outcomes. 60-90 participants per arm were calculated to be necessary for 80% power at a 5% level of significance, with an attrition rate of 20-25%.[15,19]

For statistical analyses, Kladnitski et al. compared baseline group characteristics and discrepancies among clinical settings using between-subject ANOVAs and chi-square analyses.[8] Both normally-distributed dependent and independent baseline variables between the intervention and control groups were analyzed with *t*-tests.[16] For variables that were not normally distributed, the Wilcoxon rank sum test and Spearman's rank correlation coefficients were used.[16] For within-group comparisons, paired *t*-tests were used and Fisher's exact test for categorical variables.[20]

To identify the differences of mean outcome scores between pre-treatment, post-treatment, and at follow-up, Analysis of Variance (ANOVA) was used given continuous

outcome variables compared in ≥ 3 groups.[16] When comparing treatment effects between groups, a linear regression was applied after adjusting for the baseline scores and levodopa levels.[20] For studies with wait-list control groups, a linear mixed model was applied, also after adjusting for baseline scores and levodopa levels.[11,20] Primary and secondary analyses utilized mixed-effects regression models (MRMs) with intention-to-treat analysis, minimizing any potential attrition.[11]

2.5 CONCLUSION

Both mindfulness and yoga have been shown to be as effective and not inferior to current first-line treatments for anxiety disorders[29], such as cognitive behavioral therapy and pharmacological agents.[6] Dissanayaka et al. targeted the use of mindfulness and yoga to Parkinson-related primary anxiety disorders and found similar positive outcomes.[30] Although mindfulness and yoga show efficacy and credibility as stand-alone therapies for anxiety,[8] the long-term effects are not well-established in the PD population. Therefore, both are better suited as adjunctive treatments rather than primary mainstay treatments of Parkinson-related anxiety.[30] The preferred role as adjunctive therapies was further examined by Saeed et al. in a systematic literature review, which found a small response outcome favoring yoga as a stand-alone therapy. It did not determine any benefit from mindfulness as an effective monotherapy for anxiety.[5] Interestingly, all of the mentioned studies reported no safety risks for either yoga or mindfulness as adjunctive therapies when used in conjunction with SSRI, anxiolytics, and CBT.[5]

For study designs, yoga and mindfulness demonstrated reductions in symptoms when practiced 60-minutes per week for 3-24 weeks.[5] Most studies conducted their interventions in small group sessions of 4-6 participants and 1-2 instructors. In addition to group sessions, the majority of the studies incorporated additional independent at-home

exercise routines. The greatest yield was observed when yoga or mindfulness practices were standardized to reduce potential confounding effects of the group therapies.[19]

Most studies recruited from local neurology offices but often sampled from regional sources such as PD associations and support groups. It was noted that when recruiting from a large geographic area, there was a higher attrition rate due to the inconvenience of increased travel time.

Participants with moderate Parkinson severity without cognitive impairments or comorbid mental health disorders were recruited and referred to these studies. Though most mental health disorders like PTSD, eating disorders, or psychosis were excluded, comorbid depressive disorders were permissible after Pontone et al. found that it would not change the treatments for anxiety disorders.[3]

The spectrum of anxiety disorders including persistent or episodic anxiety phenomenas[31] are now more broadly and accurately captured by the Parkinson Anxiety Scale.[23] However, its novelty and lack of longitudinal studies warrant supplementation with the Beck Anxiety Inventory or the Hospital Anxiety and Depression Scales to better capture symptomatic changes over time.[32] Secondary outcomes included physical abilities, quality of life assessments, medication regimens, and other mood symptoms.[11,19,20,30] These outcomes have all been studied with positive outcomes in studies on yoga and mindfulness therapies. It is likely that this study will not only affirm these positive outcomes, but also decipher if one practice may be preferred over another.

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CHAPTER 3: STUDY METHODOLOGY

3.1 STUDY DESIGN

The proposed study will utilize a two-arm, single-blinded randomized controlled trial to examine the efficacy of yoga and mindfulness therapies in patients with Parkinson-related anxiety. Both treatments will be administered in eight weekly sessions by two certified instructors using groups of 4-6 patients. The Parkinson Anxiety Scale (PAS) and Beck Anxiety Inventory (BAI) will be assessed at the following time points: pre-intervention, post-intervention, 3 months, and 6 months follow-up by research assistants blinded to the intervention assignments.

3.2 STUDY POPULATION

Patients who received DSM-V based anxiety diagnoses after being diagnosed with Parkinson's disease will be eligible for the study. We will be recruiting patients with moderate Parkinson's disease as determined by a score of 2-3 on the Hoehn & Yahr Scale. Patients may be taking pharmacological agents for anxiety, but their dosing must remain stable for at least 6 weeks prior to enrollment and throughout the study (barring emergency discontinuation). Participants must be fluent in English and have scored >24 on the Folstein Mini-Mental State Exam (MMSE) to minimize any confounding factors associated with cognitive impairments.

Patients may have comorbid diagnoses of depression but not PTSD, substance use, eating disorders, or organic mental disorders. To further minimize confounders, patients may not have extensive experiences with yoga or mindfulness therapies (no more than 5 lessons taken in their lifetime). More detailed inclusion and exclusion criteria can be found in Table 1 below.

Table 1. Study Eligibility

Inclusion criteria	Exclusion Criteria
• Ability to give informed consent • Age > 18 • Ability to speak, read, and write English • New anxiety disorders diagnosed after Parkinson's Disease onset • Stable on current medication regimen for minimum of 6 weeks with intention of continuing during their active participation • Folstein Mini Mental State Exam (MMSE) score >24 • Scores 2-3 on Hoehn & Yahr scale • Parkinson Anxiety Scale score ≥ 12 • Willingness and ability to perform yoga and mindfulness interventions and comply with requirements of study protocol	• Inability to understand study protocol and informed consent process • Serious medical illness or potential need for hospitalization that will interfere with participation in study • Significant suicidal ideation or behaviors within the past year • Cognitive impairments with score ≤23 on MMSE • Comorbidity of dementia, PTSD, personality disorder, eating disorder, psychosis, or bipolar disorder • Prior experiences of more than 5 yoga or mindfulness sessions • Any concomitant psychotherapy • Any physical conditions that preclude participant from performing yoga exercises • Frequent alcohol, marijuana/CBD, or recreational drug use

3.3 STUDY RECRUITMENT AND SAMPLING

The proposed study will recruit all its patients from movement disorder, general neurology, primary care, and internal medicine clinics within the Yale New Haven Hospital system and the greater New Haven area. Patients with idiopathic PD who meet eligibility criteria will be invited to participate in the study.

The screening visit will include the Folstein Mini Mental State Exam (MMSE) Hoehn and Yahr Rating Scale (H&Y), Parkinson Anxiety Scale (PAS), and Beck Anxiety Inventory (BAI). The H&Y scale will be rated by the principal investigator, Dr. Richardson, to determine the severity and progression of the patients' Parkinson's

disease. Patient will need to have an H&Y score of 2-3 and PAS score ≥ 12 for enrollment. This means that the participants will have moderate Parkinson's disease severity and at least mild clinical anxiety symptoms. Formal consent will be obtained from the participants who meet these screening criteria to be enrolled into the study.

3.4 SUBJECT PROTECTION AND CONFIDENTIALITY

The study will be reviewed by the Human Investigation Committee of Yale University School of Medicine and the Yale New Haven Health System. All study personnel and staff will be required to complete the Health Insurance Portability and Accountability Act (HIPAA) training and the Yale Human Subjects Protection training. Any extraction of patient information in electronic medical records will be carried out on university or hospital-approved, encrypted, and secured devices. Protected health information (PHI) that are non-electronic will be secured in a locked cabinet in the locked office of the principal investigator, Dr. Diana Richardson where only she and the co-investigator will have access. Any PHI will be disposed of in a secure manner after completion of study.

Consent will be provided in written and verbal form by the participant. Explanation of consent forms will be provided by trained co-investigator or clinical research assistants and participants will be encouraged to voice any questions or concerns at the time. The participant will also be allowed to withdraw from the study at any time. The consent form will include a detailed study description that will outline the duration of participation as well as the potential risks and benefits of the study. English versions will be available to the participants, please refer to Appendix A for an example of the informed consent.

3.5 STUDY VARIABLES AND MEASURES

3.5.1 Treatment Interventions

Two active groups will participate in eight weeks of interventions. Each session will consist of an hour-long yoga or mindfulness therapy with two certified instructors in groups of 4-6. Each yoga and mindfulness session will be matched for group format, venue, time, and attention during these sessions.

The first session will consist of an overview of the intervention and will set group and home exercise expectations. For the rest of the mindfulness sessions, participants will practice a modified Mindfulness-Based Cognitive Therapy (MBCT) routine for Parkinson's disease. These are listed in Table 2 and will include formal sitting meditation exercises, diaphragmatic breathing, and body scanning.

Yoga sessions will be structured to start with warm-up activities (gentle general movements, poses, breathing, and facial/vocal poses and sounds), then transition to standing, seated, and lying poses listed in Table 3. Each session will conclude with meditation and deep relaxation.

All participants will be required to practice 20 minutes of their particular intervention (yoga or mindfulness) twice a week. The home regimen will be detailed in a booklet and will reflect the lessons from that prior week.

Table 2. Mindfulness Treatment Schedule

Session	Key topics
Week 1	Introduction to mindfulness The mental states of "autopilot" and "mindfulness" First-hand experience of mindfulness: the raisin exercise Mindfulness practice: body scan
Week 2	Relationships between thoughts and emotions Awareness of pleasant events Mindfulness practice: sitting meditation

Week 3	Mindfulness practice: 3-minute breathing space Mindfulness practice: mindful stretching and walking Awareness of unpleasant events
Week 4	Automatic thoughts (autopilot) can lead to emotional distress Practice of meditation techniques learned previously
Week 5	Sitting meditation focusing on a difficult of stressful situation
Week 6	Thoughts are not facts Using the 3-minute breathing space in stressful situations
Week 7	Relationships between daily activities and depression Generate list of pleasure/mastery activities Identifying relapse triggers
Week 8	Course review Keeping a long-term meditation practice going

Table 3. Yoga Treatment Schedule

Session	Key topics
Week 1	Introduction to yoga **Yoga pose practice:** *Tadasana* **(**basic standing pose), *Hasta Chakrasana* (standing backward bend), and *Supta Padangusthasana* (knee straight, belt over one foot, leg drawn toward head)
Week 2	**Yoga pose practice:** *Tadasana Urdhva Baddha Hastasana* (Standing pose, arms outstretched, fingers intertwined. Palms face forward, then arms are lifted so palms face the ceiling), *Paschimotanasana* (knees apart, forward bend putting hands on chair in front)

Week 3	**Yoga pose practice:** *Modified Vrksasana* (Balanced on one foot, heel of opposite foot placed on ankle of standing foot. Hand on chair if needed), *Apasana* (one knee drawn to chest, then other knee, then both)
Week 4	**Yoga pose practice:** *Virabhadrasana 2* (One leg forward, back foot slightly turned in. Arms out to sides and head turned in same direction as front leg), *Marichiyasana* (Spinal rotation)
Week 5	**Yoga pose practice:** *Modified Trikonasana* (one leg forward with toes forward. Back foot slightly turned in. Arms out at shoulder level), *Spinal rolls* (knees bent and foot on floor, knees allowed to fall one direction, head turned in opposite side)
Week 6	**Yoga pose practice:** *Virabhadrasana 3* (One leg forward with knee slightly bent. Palms together at chest or raised slightly overhead), *Jathara parivartasana* (one leg straight, opposite knee drawn out to the side)
Week 7	**Yoga pose practice:** *Ardha Chadrasana* (Legs together, arms overhead, thumbs intertwined. Stretch done on one side then the other), *Setu Bandhasana* (Bridge, with arms at sides, hips lifted off floor
Week 8	Course review Keeping a long-term yoga practice going

3.5.2 Primary Outcome Measures

The primary outcome measures will demonstrate improvements and remissions of anxiety symptoms according to the Parkinson Anxiety Scales (PAS) and Beck Anxiety Inventories (BAI). For PAS, both a patient-rated and an observer-rated scale will be completed to accurately assess the severity of anxiety symptoms. Both scales will be comprised of 12 items: five items assessing for persistent anxiety, four items for episodic anxiety, and three items for avoidance behavior.[1] Each item will then be scored on a 5-point Likert scale (0=not or never and 4=severe or almost always).[1]

To further capture the full spectrum and progression of a patient's anxiety symptoms, self-reported BAI will supplement the PAS. BAI is a 21-item self-reported inventory that assesses episodic symptoms that have bothered participants in the recent month, for example, inability to relax, dizziness, or racing heart. Decreases in PAS and BAI scores over time will signify clinical improvements in anxiety symptoms. For the schedule of assessments, refer to Table 4.

3.5.3 Secondary Outcome Measures

Secondary outcomes will include any changes in health status scores (PDQ-8) and motor symptoms as measured by MDS-UPDRS and physical tests. Additionally, any changes in the patient's medications for anxiety will be assessed by the PI, Dr. Richardson at baseline, post-treatment, and subsequent follow-ups.

PDQ-8 will be used to determine any reductions in self-reported health status outcomes, an important therapeutic outcome in the treatment of Parkinson's disease. Low PDQ-8 scores demonstrate strong abilities to perform physical, emotional, and social activities.[2]

The patient's motor symptoms will be evaluated by Dr. Richardson on the Movement Disorder Society – Unified PD Rating Scale (MDS-UPDRS). MDS-UPDRS is a clinimetric assessment that rates 65 items that include the non-motor experiences of daily living, motor experiences of daily living, motor examination, and motor complications. There will be 20 questions completed by the patient and a fourth section that will be completed by the medical provider to assess motor fluctuation and dyskinesias. The minimum detectable change (MDC), which is the amount of change in test scores needed to ascertain a true measurable change, has not been studied in MDS-UPDRS but is 13 points in the original UPDRS.

The physical tests will include the 30-second chair stand, single-leg balance test, and sit-and-reach tests. The 30-second chair stand demonstrates function, balance, and leg strength by counting the number of times the patient can alternate between sitting and standing without the use of their arms in 30 seconds. The minimum detectable change (MDC) for this study will be 1.64 repetitions.[3] The single-leg balance test measures the duration a patient can stand on one leg, which is a proxy test for fall risks in older adults.[3] Lastly, the sit-and-reach test measures the distance from fingertips to toes when the patient reaches their hands toward an extended leg while seated on the edge of the chair. The other side is then repeated in the same way. There is no recorded MDC in PwP but the MDC is 3 inches on the right and 3.5 on the left in patients with type 2 diabetes.[3]

3.6 METHODOLOGY

The PAS, BAI, PDQ-8, MDS-UPDRS, and physical assessments will be administered prior to randomization of participants. In an effort to minimize selection bias, the study will utilize non-clinical personnel or a third-party statistician to randomize groups using a computerized random number generator. Participants will either be placed into (1) yoga and treatment-as-usual group or (2) mindfulness and treatment-as-usual group. To further minimize selection bias, each participant will be de-identified and assigned an arbitrary study-related number. The treatment assignments will also be concealed from the clinical research assistant and medical provider who will be administering the PAS, BAI, PDQ-8, MDS-UPDRS, and physical exam assessments.[4]

The two treatment groups will be matched closely on group formats, frequency (8 weeks), duration (60 minutes), number of participants per group (4-6), and venue. Each of the mindfulness and yoga group sessions will undergo monitoring to ensure adherence to treatment protocols. Each session will be audio-recorded and 20% of each recording

will be graded to ensure that the participants receive appropriate forms of treatment, comparable instructions, and similar amount of attention from instructors. The mindfulness and yoga instructors will collect the home regimen diary, documenting adherence to the assigned therapy (20 minutes of daily practice, twice a week). These records will then be given to the research assistants.

The MBCT and yoga therapies have all been adapted to fit the physical capabilities of PwP, and previous studies have reported no specific safety concerns. However, adverse events will be monitored directly by the two instructors during the group sessions as participants will be exposed to new techniques of mindfulness or yoga during that time.

3.7 DATA COLLECTION

The timing of each assessment is listed in Table 4. Once consent has been received from each participant, they will undergo assessment and interviews with the clinical research assistant (CRA) to gather baseline demographics (age, sex, years of education, family history of Parkinson's or psychiatric disorders). Therapeutic and histories will be obtained to determine anxiolytic regimen and for other medical histories that may affect study.

At baseline, both the evaluator- and self-rated Parkinson Anxiety Scale (PAS) and Beck Anxiety Inventory (BAI) will be administered, which will continue post-intervention, at the 3 months, and 6 months follow-up. For secondary measures, the PI, Dr. Richardson, will assess for any changes in physical abilities using MDS-UPDRS and other required physical assessments (30-second chair stand, single-leg balance test, and sit-and-reach tests). The PDQ-8 will also be administered, and the clinical research assistant will interview the patient to elucidate pharmacologic adherence and any changes

in anxiolytic regimen. Follow-up appointments will be in-person and scheduled at the post-intervention visit with email and phone reminders sent out the day before to prevent attrition.

Table 4. Timeline of Assessments

	Informed Consent	Demographics	Medical Review	H&Y Scale	MMSE	PAS, BAI	Anxiolytics	PDQ-8	MDS-UPDRS and Physical Tests
Screening	X	X	X	X	X	X			
Baseline						X	X	X	X
Post-Tx						X	X	X	X
3 mo f/u						X	X	X	X
6 mo f/u						X	X	X	X

Note: f/u = follow-up

3.8 SAMPLE SIZE CALCULATION

For a clinically significant effect size of 0.6 to be detected, a 2.1 and 3.4 points difference on PAS and BAI respectively would need to be measured between baseline and post-intervention. The study will utilize Cohen's categories in determining magnitude of overall effect with a small differential ranging from SMD = 0.2-0.5; medium from SMD = 0.5-0.8, and large SMD>0.8.[5] This study will aim for a moderate effect size of SMD ≈ 0.6 given the time and resource constraints of the study while maintaining a power of 80% and an alpha of 0.05. The sample size will include 69 participants per group, assuming from previous studies that a maximum of 20% of participants may withdraw.

3.9 ANALYSIS

The intention-to-treat principle will be applied to all statistical tests to reduce attrition. Demographic and Parkinson diagnostics features between both groups will be analyzed using Welch's *t*-test or chi-square tests. For within-group comparisons, paired *t*-tests will be used and Fisher's exact test for categorical variables.

Short-term, medium-term, and long-term outcomes will be analyzed separately with short-term outcomes defined as post-intervention (week 8), medium-term as 3 months follow-up, and long-term as 6 months follow-up.

Standardized mean differences (SMD) with 95% confidence intervals will be calculated from mean differences divided by pooled standard deviation for primary and secondary outcomes.[5] Negative SMD will indicate beneficial effects of yoga or mindfulness at post-intervention or follow-ups compared to baseline. Repeated measures of Analysis of Variance (ANOVA) will be used when assessing for change in more than two time points, such as when assessing for the changes in anxiety scores, PDQ-8, and MDS-UPDRS. For all procedures, the statistical tests will be 2-tailed with an alpha set at 0.05.

Table 5. Demographics and Analysis

	Yoga and TAU (N = 69)	Mindfulness and TAU (N = 69)	Test for Significance
Demographic Features			
Age (y), mean (SD)			Paired t-test
Sex (male/female)			χ^2
Years of education, mean (SD)			Paired t-test
MMSE, mean (SD)			Paired t-test
Health Status (PDQ-8), mean (SD)			Paired t-test
Family history of PD, % (N)			χ^2

Family psychiatric history, % (N)			χ^2
PD Features			
Age symptom onset (y), mean (SD)			Paired t-test
Symptom duration mean, (SD)			Paired t-test
Hoehn & Yahr stage			χ^2
Presence of unpredictable off periods, % (N)			χ^2
Total levodopa equivalents, mean (SD)			Paired t-test
Psychiatric Features and Comorbidities			
Presence of comorbid depressive disorder, % (N)			χ^2
Presence of multiple anxiety disorders, % (N)			χ^2
Current Anxiolytic regimen (% Daily/PRN)			χ^2
Compliance of Study Interventions			
Mean sessions attended (Total = #)			Paired t-test
Mean home practice minutes/week (range)			Paired t-test

3.10 TIMELINE AND RESOURCES

Once the study application is submitted and IRB approval is obtained, recruitment in movement disorder, general neurology, and primary care clinics within the Yale New Haven Hospital System and greater New Haven area will commence. Site recruitment and participants referrals will be ongoing for 12 months or until the enrollment goal has been achieved.

During the recruitment period, those who meet eligibility criteria will be invited to the study. Once screening and enrollment are completed, the participants will be randomized to an intervention group where they will complete an eight-week course of

either yoga or mindfulness interventions with 6 months of follow-up. The entire study will be expected to finish under two years.

A binder will include all consent forms and the number/letter assignments of the participants. There will be separate participant folders for all the surveys and questionnaires. All binders and folders will be placed in a locked cabinet in Dr. Richardson's office where only the investigators and clinical research assistants will have access.

Study personnel will include:

- Principal investigator and co-investigator: *Dr. Diana Richardson and Winifred Tung, PA-SII*
- Clinical research assistants (1 per 12 patients)
- 2 yoga instructors and 2 mindfulness instructors
- Third-party statistician/data analyst

3.11 REFERENCES

1. Leentjens AF, Dujardin K, Pontone GM, Starkstein SE, Weintraub D, Martinez-Martin P. The Parkinson Anxiety Scale (PAS): development and validation of a new anxiety scale. Mov Disord. 2014;29(8):1035-1043.
2. Pontone GM, Williams Jr Fau - Anderson KE, Anderson Ke Fau - Chase G, et al. Anxiety and self-perceived health status in Parkinson's disease. (1873-5126 (Electronic)).
3. Boulgarides LK, Barakatt E, Coleman-Salgado B. Measuring the effect of an eight-week adaptive yoga program on the physical and psychological status of individuals with Parkinson's disease. A pilot study. Int J Yoga Therap. 2014;24:31-41.
4. de Manincor M, Bensoussan A, Smith CA, et al. INDIVIDUALIZED YOGA FOR REDUCING DEPRESSION AND ANXIETY, AND IMPROVING WELL-BEING: A RANDOMIZED CONTROLLED TRIAL. Depress Anxiety. 2016;33(9):816-828.
5. Cramer H, Lauche R, Anheyer D, et al. Yoga for anxiety: A systematic review and meta-analysis of randomized controlled trials. Depress Anxiety. 2018;35(9):830-843.

CHAPTER 4: CONCLUSION

4.1 ADVANTAGES AND DISADVANTAGES

In the recent decade, validation studies have been conducted on the safety of yoga and mindfulness for patients with Parkinson's disease (PwP). However, none of these studies assessed their effects on anxiety specifically in this population. There are a limited number of clinical measures available to track the severity of anxiety associated with Parkinson's disease. The scales that are available are often too specific and do not capture the full spectrum of anxiety disorders. This study addresses gaps in both the measurement and management of Parkinson-related anxiety by 1) using adaptive yoga and mindfulness regimens to reduce anxiety symptoms in patients with moderate PD, and 2) by using an assessment appropriate for measuring anxiety in Parkinson's disease.

The Parkinson Anxiety Scale (PAS) has high sensitivities and specificities for a wide range of DSM-V based anxiety disorders. Although the PAS has been validated in this study population for the assessment of anxiety disorders, it requires supplementation with additional rating scales due to the need for a more longitudinal assessment tool.[1] Researchers have suggested the use of BAI to supplement PAS when assessing longitudinal changes of anxiety in this population. Although there is a 6-month follow-up in this study, it is insufficient to determine any long-term benefits of yoga or mindfulness. Future studies may benefit from including a longer monitoring period.

There may have been confounding effects of sample bias if participants enrolled into the study with preconceived expectations of the benefits of yoga or mindfulness therapies. In this case, they may have been more motivated to practice at home or minimize their anxiety when completing questionnaires.[2] One way to combat the placebo effect in future studies is to screen participants for preconceptions or assumptions they may have for the efficacy of yoga. Another potential confounder is that the group

sessions share features of a support group atmosphere, fostering placebo effects. This effect may not occur at the follow-up visits, where the participants are solely completing home individualized exercises. These potential confounders will all need to be further explored in future studies with longer periods of follow-up.

As yoga and mindfulness practices become more mainstream in the community, there is greater feasibility of using these interventions as therapies. There likely will be few barriers to hiring certified instructors to lead modified mindfulness and yoga treatment sessions. Additional studies would be appropriate to determine efficacy across the spectrum of the PD population. The mindfulness and yoga programs used in the study were scripted, so we cannot assume that other programs in the community would be tailored to the PD population. Instead, comparisons of various modified yoga or mindfulness programs will be useful to determine the most suitable regimen for PD-related anxiety disorders.

4.2 CLINICAL AND/OR PUBLIC HEALTH SIGNIFICANCE

The advantages of yoga and mindfulness as adjunctive therapies are two-fold: addressing anxiety at a low-cost and minimizing polypharmacy. Since Parkinson's disease (PD) is a chronic neurological condition, rehabilitation is usually limited to periods of exacerbation or functional decline due to cost.[2] Unlike the accepted referrals to rehabilitation for motor deficits, symptoms of anxiety are often inadequately addressed by clinicians. Since yoga and mindfulness regimens can be adapted and practiced at home for management of anxiety, the cost of therapy is minimal in comparison to potential hospitalizations or medications. The benefits of the yoga or mindfulness regimens will also have cumulative and lasting positive effects.

Polypharmacy in patients with Parkinson's disease (PwP) is common where four or five classes of dopaminergic medications may be prescribed. This is then often combined with anxiolytics and other medications for non-neurological conditions. Many of these medications may have side effects such as nausea, vomiting, and drowsiness. The advantages of modified yoga and mindfulness are avoidance of pharmacological side effects in addition to minimal safety risk for falls or injury.

The prevalence rates of anxiety among PwP vary widely (6-55%) and lifetime prevalence rates far exceeds that of the general population.[3] Since anxiety significantly affects quality of life, sleep, concentration, and energy levels[2], patients suffering from PD-related anxiety need therapies that will directly address the psychological and physical consequences of their symptoms. Both yoga and mindfulness have been found to improve health status while decreasing stress and clinical symptoms of anxiety. Additional studies are warranted to fully explore the benefits of these therapies in Parkinson's disease and similar neurodegenerative illnesses.

4.3 REFERENCES

1. Leentjens AF, Dujardin K, Pontone GM, Starkstein SE, Weintraub D, Martinez-Martin P. The Parkinson Anxiety Scale (PAS): development and validation of a new anxiety scale. Mov Disord. 2014;29(8):1035-1043.
2. Boulgarides LK, Barakatt E, Coleman-Salgado B. Measuring the effect of an eight-week adaptive yoga program on the physical and psychological status of individuals with Parkinson's disease. A pilot study. Int J Yoga Therap. 2014;24:31-41.
3. Broen MPG, Narayen NE, Kuijf ML, Dissanayaka NNW, Leentjens AFG. Prevalence of anxiety in Parkinson's disease: A systematic review and meta-analysis. Movement Disorders. 2016;31(8):1125-1133.

Appendix A: Consent and Privacy Rule Authorization Form

CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

Adapted from 200 PR.1 Informed Consent for Research Participation: Competent Adult Participants

Title of Study: The Effects of Yoga Versus Mindfulness on Anxiety in Individuals with Parkinson's Disease
Principal Investigator: Diana Richardson, M.D.
Co-Investigator: Winifred Tung, PA-SII
Affiliation: Yale New Haven Hospital and Yale School of Medicine

Invitation to Participate and Study Purpose:

We would like to extend an invitation to participate in our study of yoga and mindfulness therapies for Parkinson-related anxiety. You have been referred because you have been previously diagnosed with Parkinson's disease as well as with an anxiety disorder. The current study will enroll 120 total participants from primary care, internal medicine, general neurology, and neurology movement disorder clinics in the YNHH system and within the greater New Haven area. Active participation in the study will require a total of 10 months from enrollment and baseline assessments to the last follow-up.

To decide your willingness to participate, please continue to read the following details about the study. A research staff member will then review the purpose, procedures, risks, and benefits of the study and to make sure that all questions or concerns are addressed.

Description of Study and Procedures:

- Enrollment in this study requires that you meet set inclusion and exclusion criteria. These criteria are as follows:

Inclusion criteria	Exclusion Criteria
• Ability to give informed consent • Age > 18 • Ability to speak, read, and write English • New anxiety disorders diagnosed after Parkinson's Disease onset • Stable on current medication for minimum of 6 weeks with intention of continuing stable dose • Folstein Mini Mental State Exam (MMSE) score >24	• Inability to understand study protocol and informed consent process • Serious medical illness or potential need for hospitalization that will interfere with participation in study • Significant suicidal ideation or behaviors within the past year • Cognitive impairments with score ≤23 on MMSE • Comorbidity of dementia, PTSD, personality disorder, eating disorder, psychosis, or bipolar disorder

• Willingness and ability to perform yoga and mindfulness interventions and comply with requirements of study protocol • Assessment on Hoehn & Yahr scale is stage 2-3 • Parkinson Anxiety Scale score ≥ 12 for enrollment	• Prior experiences of more than 5 yoga or mindfulness sessions • Any concomitant psychotherapy • Any physical conditions that preclude participant from performing yoga exercises • Frequent alcohol, marijuana/CBD, or recreational drug use

- A written informed consent form (this document) is to be signed by both you, the participant, and the Primary Investigator (Dr. Diana Richardson) or Co-Investigator (Winifred Tung, PA-SII). The purpose of this informed consent is to outline the study purpose and study designs so that you will understand your responsibilities as a participant in the study. Enrollment in this study is optional. Once enrolled, you may discontinue your enrollments at any time with notification to the PI.
- Following enrollment in the study, additional demographic and pertinent medical history will be obtained regarding your diagnosis of Parkinson's disease and of your diagnosis of anxiety. We will also require a detailed list of your current medications and may request additional information of relevant family medical history. If needed, we may request that you provide medical records from doctors who manage your Parkinson's Disease and your anxiety. This study is HIPAA compliant so that no personal identification information will be associated with the study documents completed as a result of your participation.
- During your participation in this study, you will complete various written and physical evaluations. These assessments will be performed on five different visits throughout the 10-month period. The written assessments will be questionnaires regarding your anxiety symptoms, thinking ability, and physical abilities. There will also be three physical tests to determine strength, ability to maintain balance, and fall risks.
- Below is a chart indicating the activities that will occur at each rating visit:

	Informed Consent	Demographics	Medical Review	H&Y Scale	MMSE	PAS, BAI	Anxiolytics	PDQ-8	MDS-UPDRS and Physical Tests
Screening	X	X	X	X	X	X			
Baseline						X	X	X	X
Post-Tx						X	X	X	X

3 mo f/u						X	X	X	X
6 mo f/u						X	X	X	X

- You will be assigned to one of two treatment groups by a random process such that each group will have an equal number of participants with similar degrees of Parkinson's and anxiety. One treatment group will receive yoga therapy and the other group will receive the mindfulness therapy. Each group will meet once a week for 60 minutes for 8 consecutive weeks. Each group will have 3-5 other participants, including yourself, and 1-2 instructors. Details of these therapies will be explained in full prior to and at the treatment sessions. You will be required to attend each treatment session, and the need to make-up sessions will be evaluated on a case-by-case basis.
- In the case that you miss more than 2 treatment sessions or rating sessions, you will be automatically un-enrolled from the study.
- In addition to group sessions, there will be detailed yoga or mindfulness home exercises to complete. You will be required to complete these twice per week and record the times in a diary. The exercises will reflect what is learned in the preceding group sessions that week.

Risks or Inconveniences:

This study is deemed low to no risk. There are no specific physical risks associated with participation in this study. Due to the nature of Parkinson's disease, baseline physical symptoms may increase risks for falls. The yoga and mindfulness interventions have been adapted for Parkinson's disease and tested in previous studies with no adverse consequences. As for anxiety symptoms, yoga and mindfulness are not expected to worsen any symptoms.

Expected Benefits:

The mindfulness or yoga therapies may improve anxiety symptoms and reduce the need for anxiety medications. They may also benefit physical abilities, mood, and thinking abilities.

Economic Considerations:

There will be no costs for participation in the study; however, there will also be no paid reward for enrollment in the study.

Confidentiality of Information:

Any identified information obtained or reviewed in this study will remain confidential and only disclosed as require by the United States or Connecticut law. Only the parties listed in the research authorization form attached will be granted access to identifiable information we collect. When the study is published, there will be no information that

will link your identity to the study unless you give specific permission to disclose personal information.

If needed, your information in electronic medical records will only be accessed through university approved, encrypted, and secure electronic devices. All healthcare providers will be subject to the Health Insurance Portability and Accountability act (HIPAA). Any data on paper will be kept in binders in a locked cabinet in the locked office of the principal investigator.

Research Subject's Rights

You are able to decline enrollment into the study and may discontinue participation at any point throughout the study. However, any data gathered prior to withdrawing participation may still be used in the study analyses to ensure study integrity and study oversight. There will be no penalty or loss of benefits associated with withdrawal of participation. Please notify the Primary Investigator, Dr. Diana Richardson or Co-Investigator, Winifred Tung, PA-II, with a written notice if you choose to withdraw.

Authorization:

I have read (or have ben read) this form and have decided to participate in the project described. The general purpose, risks, and benefits are clear and acceptable to me.

By signing this form, I give permission to researchers to use information about myself and my child for the purposes described in this form. By declining participation, I understand that I will not receive the therapies in this study.

Name of Participant (Print): _____

Signature of Participant: _____ Date: _____

Name of Person Obtaining Consent (Print): _____

Signature of Person Obtaining Consent: _____Date: _____

Any further questions or concerns about this research project may be directed to the Principal Investigator at her office: Dr. Diana Richardson 203-932-5711 x 4724

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919.

If you have questions about your rights as a research participant, or you have complaints about this research, you can contact the Yale Institutional Review Boards at 203-785-4688 or email hrpp@yale.edu.

YALE UNIVERSITY

RESEARCH AUTHORIZATION

Subject Name:			
		Medical Record #:	
Principal Investigator:		**IRB #:**	
Principal Investigator's Contact Information:			

To the Subject:

The health-related information that we gather about you in this study is personal. The Yale School of Medicine and the Yale New Haven Hospital researchers are required by law to protect the privacy of the information known as protected health information or PHI. All reasonable efforts will be made to protect the confidentiality of your PHI, which may be shared with others to support this research, to conduct public health reporting, and to comply with the law as required. Despite these protections, there is a possibility that information about you could be used or disclosed in a way that it will no longer be protected by federal law. For example, some of the individuals listed on page 2 of this form may not be required by law to meet HIPAA standards for privacy of health information. These individuals or companies are nonetheless required through other agreements with Yale to keep your information confidential.

In this form, we describe who will be working with this information and ask for your permission to use the information in the research study.

Please read this form carefully. If you have any questions, please ask the Principal Investigator listed above before signing this form.

By signing this form, you give permission for the researchers to use and/or disclosure the information as described below, for this research study. The reason for the uses and disclosures is to assess yoga and mindfulness effects on anxiety symptoms related to Parkinson's disease.

You have a right to refuse to sign this form. Your health care outside the study, the payment for your health care, and your health care benefits will not be affected if you do not sign this form.

If you do not sign this form, you will not be able to enter this research study and will not receive treatment as a study participant.

If you sign this form, you may change your mind at any time, but the researchers may still use the information collected before you changed your mind in order to complete the research.

This form will never expire unless and until you change your mind and retract it. To retract the permission to use your information, please tell the study staff or write to Dr. Diana Richardson or Winifred Tung, PA-SII.

You will not be allowed to see or copy the part of your medical records that describe a research treatment until the research is completed, but you may see and copy the research treatment information at the end of the research in agreement with institutional medical record policies.

You have a right to receive a copy of this form after you have signed it. If after you have signed this form you have any questions about your rights, please contact the Yale Privacy Officer at 203/436-3650.

Use and Disclosure Covered by this Authorization

(1) Who will disclose, receive, and/or use the information?

The following person(s), class(es) of persons, and/or organization(s) may share, use, and receive the information listed below in connection with this Study. These persons are authorized to use and disclose the information to the other parties on this list, to you or your personal representative, or as permitted by law.

- ❑ The following health care facilities or research site(s) and research staff involved in this study:

  YNHH, Yale School of Medicine, Research Investigators, Clinical Research Assistants

- ❑ Health care providers at **your PCP, neurology, or movement disorder clinic** who referred and connected you to this study

- ❑ Laboratories and other individuals and organizations that analyze your health information in connection with this study, in accordance with the study's protocol

- ❑ The members and staff of the Human Investigation Committee that approved this study

- ❑ Those individuals at Yale who are responsible for the financial oversight of research including billings and payments

- ❑ Principal Investigator: Dr. Diana Richardson

- ❑ Additional members of the Research Team

- ❑ Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

- ❑ Others (as described below)

(2) What personal health information will be used or disclosed?

The following information about you may be used and disclosed:

- ❑ Research study records.

- ❑ Medical and laboratory records of only those services provided in connection with this Study.

- ❑ The entire research record and any medical records held by Yale New Haven Hospital created from: _Parkinson's disease diagnosis_____ to: ___present_____

- ❑ The following information:

Signature

I have read this form and all of my questions about this form have been answered. By signing below, I authorize the described uses and disclosures of information.

_____
Signature of Subject or Personal Representative

_____
Print Name of Subject or Personal Representative

_____
Date

_____
Description of Personal Representative's Authority

THE SUBJECT OR HIS OR HER PERSONAL REPRESENTATIVE MUST BE PROVIDED WITH A COPY OF THIS FORM AFTER IT HAS BEEN SIGNED

Reviewed and Acknowledged

_____

Human Investigation Committee
Yale University

Appendix B: Hoehn & Yahr Rating Scale*

- Stage 0 indicates no sign of disease
- Stage 1 indicates unilateral disease
- Stage 2 indicates bilateral disease without impairment of balance
- Stage 3 indicates mild to moderate bilateral disease with some postural instability, but physically independent
- Stage 4 indicates severe disability, but able to walk or stand unassisted
- Stage 5 indicates confinement to bed or wheelchair unless aided by someone else

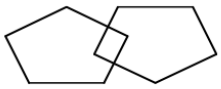
* Interpretation of rating scale results: Hoehn & Yahr Stage 0 & 1 (mild), Hoehn & Yahr Stage 2 & 3 (moderate), Hoehn & Yahr Stage 4 & 5 (advanced)

Appendix C: Folstein Mini-Mental State Examination (MMSE).

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

*Used to assess cognitive and mental faculties; scores 24-30 indicates normal cognition.

Appendix D: Parkinson Anxiety Scale

The Parkinson Anxiety Scale (PAS); English version

A. Persistent anxiety

Please mark one circle for each item below

In the past four weeks, to what extent did you experience the following symptoms?

A.1. Feeling anxious or nervous
- o Not at all, or never
- o Very mild, or rarely
- o Mild, or sometimes
- o Moderate, or often
- o Severe, or (nearly) always

A.2. Feeling tense or stressed
- o Not at all, or never
- o Very mild, or rarely
- o Mild, or sometimes
- o Moderate, or often
- o Severe, or (nearly) always

A.3. Being unable to relax
- o Not at all, or never
- o Very mild, or rarely
- o Mild, or sometimes

- o Moderate, or often
- o Severe, or (nearly) always

A.4. Excessive worrying about everyday matters

- o Not at all, or never
- o Very mild, or rarely
- o Mild, or sometimes
- o Moderate, or often
- o Severe, or (nearly) always

A.5. Fear of something bad, or even the worst, happening

- o Not at all, or never
- o Very mild, or rarely
- o Mild, or sometimes
- o Moderate, or often
- o Severe, or (nearly) always

B. Episodic anxiety

Please mark one circle for each item below

In the past four weeks, did you experience episodes of the following symptoms?

B.1. Panic or intense fear

- o Never
- o Rarely
- o Sometimes
- o Often
- o Nearly always

B.2. Shortness of breath

- o Never
- o Rarely
- o Sometimes
- o Often
- o Nearly always

B.3. Heart palpitations or heart beating fast (not related to physical effort or activity)

- o Never
- o Rarely
- o Sometimes
- o Often
- o Nearly always

B.4. Fear of losing control

- o Never
- o Rarely
- o Sometimes
- o Often
- o Nearly always

C. Avoidance behavior

Please mark one circle for each item below

In the past four weeks, to what extent did you fear or avoid the following situations?

C.1. Social situations (where one may be observed, or evaluated by others, such as speaking in public, or talking to unknown people)

- o Never
- o Rarely
- o Sometimes
- o Often
- o Nearly always

C.2. Public settings (situations from which it may be difficult or embarrassing to escape, such as queues or lines, crowds, bridges, or public transportation)

- o Never
- o Rarely
- o Sometimes
- o Often
- o Nearly always

C.3. Specific objects or situations (such as flying, heights, spiders or other animals, needles, or blood)

- o Never
- o Rarely
- o Sometimes
- o Often
- o Nearly always

Appendix E: Beck Anxiety Inventory

Beck Anxiety Inventory (BAI)

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not at all	Mildly, but it didn't bother me much	Moderately – it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding / racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky / unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint / lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot / cold sweats	0	1	2	3

Beck Anxiety Inventory (BAI)

About: This scale is a self-report measure of anxiety.

Items: 21

Reliability:
Internal consistency for the BAI = (Cronbach's a=0.92)
Test-retest reliability (1 week) for the BAI = 0.75 (Beck, Epstein, Brown, & Steer, 1988)

Validity:
The BAI was moderately correlated with the revised Hamilton Anxiety Rating Scale (.51), and mildly correlated with the Hamilton Depression Rating Scale (.25) (Beck et al., 1988).

Scoring:

	Not at all	Mildly, but it didn't bother me much	Moderately – it wasn't pleasant at times	Severely – it bothered me a lot
All questions	0	1	2	3

The total score is calculated by finding the sum of the 21 items.
Score of 0-21 = low anxiety
Score of 22-35 = moderate anxiety
Score of 36 and above = potentially concerning levels of anxiety

References: Beck, A.T., Epstein, N., Brown, G., & Steer, R.A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*, 56, 893-897.

Appendix F: Parkinson's Disease Questionnaire (PDQ-8)

Many people with Parkinson's Disease report problems from time to time. We are interested in how you have been in your general health over the last four weeks.

Please complete this form by placing a tick or check mark in one box on each line.

Over the past four weeks have you, because of your Parkinson's Disease...	Never	Occasionally	Sometimes	Often	Always or cannot do at al
(7)...had difficulty getting around in public places?	☐	☐	☐	☐	☐
(12)...had difficulty dressing yourself?	☐	☐	☐	☐	☐
(17)...felt depressed?	☐	☐	☐	☐	☐
(27)...had problems with close relationships?	☐	☐	☐	☐	☐
(31)...had problems with concentration?	☐	☐	☐	☐	☐
(35)...felt unable to communicate properly?	☐	☐	☐	☐	☐
(37)...had painful muscle cramps and pains?	☐	☐	☐	☐	☐
(25) Over the **past four weeks** have you felt embarrassed by having Parkinson's Disease?	☐	☐	☐	☐	☐

PDQ-8 will assess health status across eight different dimensions including relationships, social situations and communication.

Appendix G: Movement Disorder Society – United Parkinson's Disease Rating Scale

Patient Questionnaire:

Instructions:

This questionnaire will ask you about your experiences of daily living.

There are 20 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever. If you do not have the problem, simply mark 0 for NO.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in your average or usual function over the past week including today. Some patients can do things better at one time of the day than at others. However, only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

You may have other medical conditions besides Parkinson's disease. Do not worry about separating Parkinson's disease from other conditions. Just answer the question with your best response.

Use only 0, 1, 2, 3, 4 for answers, nothing else. Do not leave any blanks.

Your doctor or nurse can review the questions with you, but this questionnaire is for patients to complete, either alone or with their caregivers.

Who is filling out this questionnaire (check the best answer):

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)	
1.7 SLEEP PROBLEMS Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning. 0: Normal: No problems. 1: Slight: Sleep problems are present but usually do not cause trouble getting a full night of sleep. 2: Mild: Sleep problems usually cause some difficulties getting a full night of sleep. 3: Moderate: Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night. 4: Severe: I usually do not sleep for most of the night.	**SCORE** ☐
1.8 DAYTIME SLEEPINESS Over the past week, have you had trouble staying awake during the daytime? 0: Normal: No daytime sleepiness. 1: Slight: Daytime sleepiness occurs, but I can resist and I stay awake. 2: Mild: Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV. 3: Moderate: I sometimes fall asleep when I should not. For example, while eating or talking with other people. 4: Severe: I often fall asleep when I should not. For example, while eating or talking with other people.	☐

	SCORE
1.9 PAIN AND OTHER SENSATIONS Over the past week, have you had uncomfortable feelings in your body like pain, aches, tingling, or cramps? 0: Normal: No uncomfortable feelings. 1: Slight: I have these feelings. However, I can do things and be with other people without difficulty. 2: Mild: These feelings cause some problems when I do things or am with other people. 3: Moderate: These feelings cause a lot of problems, but they do not stop me from doing things or being with other people. 4: Severe: These feelings stop me from doing things or being with other people.	☐
1.10 URINARY PROBLEMS Over the past week, have you had trouble with urine control? For example, an urgent need to urinate, a need to urinate too often, or urine accidents? 0: Normal: No urine control problems. 1: Slight: I need to urinate often or urgently. However, these problems do not cause difficulties with my daily activities. 2: Mild: Urine problems cause some difficulties with my daily activities. However, I do not have urine accidents. 3: Moderate: Urine problems cause a lot of difficulties with my daily activities, including urine accidents. 4: Severe: I cannot control my urine and use a protective garment or have a bladder tube.	☐

	SCORE
1.11 CONSTIPATION PROBLEMS Over the past week have you had constipation troubles that cause you difficulty moving your bowels? 0: Normal: No constipation. 1: Slight: I have been constipated. I use extra effort to move my bowels. However, this problem does not disturb my activities or my being comfortable. 2: Mild: Constipation causes me to have some troubles doing things or being comfortable. 3: Moderate: Constipation causes me to have a lot of trouble doing things or being comfortable. However, it does not stop me from doing anything. 4: Severe: I usually need physical help from someone else to empty my bowels.	☐
1.12 LIGHT HEADEDNESS ON STANDING Over the past week, have you felt faint, dizzy, or foggy when you stand up after sitting or lying down? 0: Normal: No dizzy or foggy feelings. 1: Slight: Dizzy or foggy feelings occur. However, they do not cause me troubles doing things. 2: Mild: Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down. 3: Moderate: Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling. 4: Severe: Dizzy or foggy feelings cause me to fall or faint.	☐

	SCORE
1.13 FATIGUE Over the past week, have you usually felt fatigued? This feeling is <u>not</u> part of being sleepy or sad. 0: Normal: No fatigue. 1: Slight: Fatigue occurs. However it does not cause me troubles doing things or being with people. 2: Mild: Fatigue causes me some troubles doing things or being with people. 3: Moderate: Fatigue causes me a lot of troubles doing things or being with people. However, it does not stop me from doing anything. 4: Severe: Fatigue stops me from doing things or being with people.	☐
Part II: Motor Aspects of Experiences of Daily Living (M-EDL)	
2.1 SPEECH Over the past week, have you had problems with your speech? 0: Normal: Not at all (no problems). 1: Slight: My speech is soft, slurred or uneven, but it does not cause others to ask me to repeat myself. 2: Mild: My speech causes people to ask me to occasionally repeat myself, but not every day. 3: Moderate: My speech is unclear enough that others ask me to repeat myself every day even though most of my speech is understood. 4: Severe: Most or all of my speech cannot be understood.	☐

	SCORE
2.2 SALIVA AND DROOLING Over the past week, have you usually had too much saliva during when you are awake or when you sleep? 0: Normal: Not at all (no problems). 1: Slight: I have too much saliva, but do not drool. 2: Mild: I have some drooling during sleep, but none when I am awake. 3: Moderate: I have some drooling when I am awake, but I usually do not need tissues or a handkerchief. 4: Severe: I have so much drooling that I regularly need to use tissues or a handkerchief to protect my clothes.	☐
2.3 CHEWING AND SWALLOWING Over the past week, have you usually had problems swallowing pills or eating meals? Do you need your pills cut or crushed or your meals to be made soft, chopped, or blended to avoid choking? 0: Normal: No problems. 1: Slight: I am aware of slowness in my chewing or increased effort at swallowing, but I do not choke or need to have my food specially prepared. 2: Mild: I need to have my pills cut or my food specially prepared because of chewing or swallowing problems, but I have not choked over the past week. 3: Moderate. I choked at least once in the past week. 4: Severe: Because of chewing and swallowing problems, I need a feeding tube.	☐

	SCORE
2.4 EATING TASKS Over the past week, have you usually had troubles handling your food and using eating utensils? For example, do you have trouble handling finger foods or using forks, knives, spoons, chopsticks? 0: Normal: Not at all (no problems). 1: Slight: I am slow, but I do not need any help handling my food and have not had food spills while eating. 2: Mild: I am slow with my eating and have occasional food spills. I may need help with a few tasks such as cutting meat. 3: Moderate: I need help with many eating tasks but can manage some alone. 4: Severe: I need help for most or all eating tasks.	☐
2.5 DRESSING Over the past week, have you usually had problems dressing? For example, are you slow or do you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry? 0: Normal: Not at all (no problems). 1: Slight: I am slow, but I do not need help. 2: Mild: I am slow and need help for a few dressing tasks (buttons, bracelets). 3: Moderate: I need help for many dressing tasks. 4: Severe: I need help for most or all dressing tasks.	☐

	SCORE
2.6 HYGIENE Over the past week, have you usually been slow or do you need help with washing, bathing, shaving, brushing teeth, combing your hair, or with other personal hygiene? 0: Normal: Not at all (no problems). 1: Slight: I am slow, but I do not need any help. 2: Mild: I need someone else to help me with some hygiene tasks. 3: Moderate: I need help for many hygiene tasks. 4: Severe: I need help for most or all of my hygiene tasks.	☐
2.7 HANDWRITING Over the past week, have people usually had trouble reading your handwriting? 0: Normal: Not at all (no problems). 1: Slight: My writing is slow, clumsy or uneven, but all words are clear. 2: Mild: Some words are unclear and difficult to read. 3: Moderate: Many words are unclear and difficult to read. 4: Severe: Most or all words cannot be read.	☐
2.8 DOING HOBBIES AND OTHER ACTIVITIES Over the past week, have you usually had trouble doing your hobbies or other things that you like to do? 0: Normal: Not at all (no problems). 1: Slight: I am a bit slow but do these activities easily. 2: Mild: I have some difficulty doing these activities. 3: Moderate: I have major problems doing these activities, but still do most. 4: Severe: I am unable to do most or all of these activities.	☐

	SCORE
2.9 TURNING IN BED Over the past week, do you usually have trouble turning over in bed? 0: Normal: Not at all (no problems). 1: Slight: I have a bit of trouble turning, but I do not need any help. 2: Mild I have a lot of trouble turning and need occasional help from someone else. 3: Moderate: To turn over I often need help from someone else. 4: Severe: I am unable to turn over without help from someone else.	☐
2.10 TREMOR Over the past week, have you usually had shaking or tremor? 0: Normal: Not at all. I have no shaking or tremor. 1: Slight: Shaking or tremor occurs but does not cause problems with any activities. 2: Mild: Shaking or tremor causes problems with only a few activities. 3: Moderate: Shaking or tremor causes problems with many of my daily activities. 4: Severe: Shaking or tremor causes problems with most or all activities.	☐
2.11 GETTING OUT OF BED, A CAR, OR A DEEP CHAIR Over the past week, have you usually had trouble getting out of bed, a car seat, or a deep chair? 0: Normal: Not at all (no problems). 1: Slight: I am slow or awkward, but I usually can do it on my first try. 2: Mild: I need more than one try to get up or need occasional help. 3: Moderate: I sometimes need help to get up, but most times I can still do it on my own. 4: Severe: I need help most or all of the time.	☐

	SCORE
2.12 WALKING AND BALANCE Over the past week, have you usually had problems with balance and walking? 0: Normal: Not at all (no problems). 1: Slight: I am slightly slow or may drag a leg. I never use a walking aid. 2: Mild: I occasionally use a walking aid, but I do not need any help from another person. 3: Moderate: I usually use a walking aid (cane, walker) to walk safely without falling. However, I do not usually need the support of another person. 4: Severe: I usually use the support of another person to walk safely without falling.	☐
2.13 FREEZING Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor? 0: Normal: Not at all (no problems). 1: Slight: I briefly freeze, but I can easily start walking again. I do not need help from someone else or a walking aid (cane or walker) because of freezing. 2: Mild: I freeze and have trouble starting to walk again, but I do not need someone's help or a walking aid (cane or walker) because of freezing. 3: Moderate: When I freeze I have a lot of trouble starting to walk again and, because of freezing, I sometimes need to use a walking aid or need someone else's help. 4: Severe: Because of freezing, most or all of the time, I need to use a walking aid or someone's help.	☐

This completes the questionnaire. We may have asked about problems you do not even have, and may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this questionnaire.

Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's disease, mark the patient's clinical state using the following definitions:

ON is the typical functional state when patients are receiving medication and have a good response.
OFF is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see." Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "**UR**" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a Is the patient on medication for treating the symptoms of Parkinson's disease? ☐ No ☐ Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's disease, mark the patient's clinical state using the following definitions:

☐ ON: On is the typical functional state when patients are receiving medication and have a good response.

☐ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on levodopa ? ☐ No ☐ Yes

3.C1 If yes, minutes since last levodopa dose: _____

	SCORE
3.1 SPEECH Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables), and tachyphemia (rapid speech, running syllables together). 0: Normal: No speech problems. 1: Slight: Loss of modulation, diction, or volume, but still all words easy to understand. 2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow. 3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood. 4: Severe: Most speech is difficult to understand or unintelligible.	☐
3.2 FACIAL EXPRESSION Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling, and parting of lips. 0: Normal: Normal facial expression. 1: Slight: Minimal masked facies manifested only by decreased frequency of blinking. 2: Mild: In addition to decreased eye-blink frequency, masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted. 3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest. 4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.	☐

3.3 RIGIDITY

Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity.

0: Normal: No rigidity.

1: Slight: Rigidity only detected with activation maneuver.

2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved.

3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort.

4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.

SCORE

☐ Neck

☐ RUE

☐ LUE

☐ RLE

☐ LLE

3.4 FINGER TAPPING

Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.

2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.

3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.

☐ R

☐ L

	SCORE
3.5 HAND MOVEMENTS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.	☐ R ☐ L
3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down, and then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st supination-pronation sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.	☐ R ☐ L

	SCORE
3.7 TOE TAPPING Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the 1st tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.8 LEG AGILITY Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the 1st tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.	☐ R ☐ L

	SCORE
3.9 ARISING FROM CHAIR Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt up to a maximum of two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13. 0: Normal: No problems. Able to arise quickly without hesitation. 1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair. 2: Mild: Pushes self up from the arms of the chair without difficulty. 3: Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using the arms of the chair, but can get up without help. 4: Severe: Unable to arise without help.	☐
3.10 GAIT Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13. 0: Normal: No problems. 1: Slight: Independent walking with minor gait impairment. 2: Mild: Independent walking but with substantial gait impairment. 3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person. 4: Severe: Cannot walk at all or only with another person's assistance.	☐

	SCORE
3.11 FREEZING OF GAIT Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment. 0: Normal: No freezing. 1: Slight: Freezes on starting, turning, or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking. 2: Mild: Freezes on starting, turning, or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking. 3: Moderate: Freezes once during straight walking. 4: Severe: Freezes multiple times during straight walking.	☐
3.12 POSTURAL STABILITY Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13. 0: Normal: No problems. Recovers with one or two steps. 1: Slight: 3-5 steps, but subject recovers unaided. 2: Mild: More than 5 steps, but subject recovers unaided. 3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner. 4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.	☐

	SCORE
3.13 POSTURE Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair, during walking, and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning. 0: Normal: No problems. 1: Slight: Not quite erect, but posture could be normal for older person. 2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so. 3: Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient. 4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.	☐
3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA) Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking. 0: Normal: No problems. 1: Slight: Slight global slowness and poverty of spontaneous movements. 2: Mild: Mild global slowness and poverty of spontaneous movements. 3: Moderate: Moderate global slowness and poverty of spontaneous movements. 4: Severe: Severe global slowness and poverty of spontaneous movements.	☐
3.15 POSTURAL TREMOR OF THE HANDS Instructions to examiner: All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L

	SCORE
3.16 KINETIC TREMOR OF THE HANDS Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L
3.17 REST TREMOR AMPLITUDE Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking, and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor. As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating. Extremity ratings 0: Normal: No tremor. 1: Slight: < 1 cm in maximal amplitude. 2: Mild: ≥ 1 cm but < 3 cm in maximal amplitude. 3: Moderate: ≥ 3 cm but < 10 cm in maximal amplitude. 4: Severe: ≥ 10 cm in maximal amplitude. Lip/Jaw ratings 0: Normal: No tremor. 1: Slight: < 1 cm in maximal amplitude. 2: Mild: ≥ 1 cm but < 2 cm in maximal amplitude. 3: Moderate: ≥ 2 cm but < 3 cm in maximal amplitude. 4: Severe: ≥ 3 cm in maximal amplitude.	☐ RUE ☐ LUE ☐ RLE ☐ LLE ☐ Lip/Jaw

3.18 CONSTANCY OF REST TREMOR | **SCORE**

Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating.

0:	Normal:	No tremor.
1:	Slight:	Tremor at rest is present ≤ 25% of the entire examination period.
2:	Mild:	Tremor at rest is present 26-50% of the entire examination period.
3:	Moderate:	Tremor at rest is present 51-75% of the entire examination period.
4:	Severe:	Tremor at rest is present > 75% of the entire examination period.

☐

DYSKINESIA IMPACT ON PART III RATINGS

A. Were dyskinesias (chorea or dystonia) present during examination? ☐ No ☐ Yes

B. If yes, did these movements interfere with your ratings? ☐ No ☐ Yes

HOEHN AND YAHR STAGE

0: Asymptomatic.

1: Unilateral involvement only.

2: Bilateral involvement without impairment of balance.

3: Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.

4: Severe disability; still able to walk or stand unassisted.

5: Wheelchair bound or bedridden unless aided.

☐

Patient Name or Subject ID	Site ID	Assessment Date (mm-dd-yyyy)	Investigator's Initials
_____	___ ___ ___	____ - ____ - ____	___ ___ ___

MDS UPDRS Score Sheet

1.A	Source of information	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.3b	Rigidity– RUE	
			3.3c	Rigidity– LUE	
Part I			3.3d	Rigidity– RLE	
1.1	Cognitive impairment		3.3e	Rigidity– LLE	
1.2	Hallucinations and psychosis		3.4a	Finger tapping– Right hand	
1.3	Depressed mood		3.4b	Finger tapping– Left hand	
1.4	Anxious mood		3.5a	Hand movements– Right hand	
1.5	Apathy		3.5b	Hand movements– Left hand	
1.6	Features of DDS		3.6a	Pronation- supination movements– Right hand	
1.6a	Who is filling out questionnaire	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.6b	Pronation- supination movements– Left hand	
			3.7a	Toe tapping– Right foot	
1.7	Sleep problems		3.7b	Toe tapping– Left foot	
1.8	Daytime sleepiness		3.8a	Leg agility– Right leg	
1.9	Pain and other sensations		3.8b	Leg agility– Left leg	
1.10	Urinary problems		3.9	Arising from chair	
1.11	Constipation problems		3.10	Gait	
1.12	Light headedness on standing		3.11	Freezing of gait	
1.13	Fatigue		3.12	Postural stability	
Part II			3.13	Posture	
2.1	Speech		3.14	Global spontaneity of movement	
2.2	Saliva and drooling		3.15a	Postural tremor– Right hand	
2.3	Chewing and swallowing		3.15b	Postural tremor– Left hand	
2.4	Eating tasks		3.16a	Kinetic tremor– Right hand	
2.5	Dressing		3.16b	Kinetic tremor– Left hand	
2.6	Hygiene		3.17a	Rest tremor amplitude– RUE	
2.7	Handwriting		3.17b	Rest tremor amplitude– LUE	
2.8	Doing hobbies and other activities		3.17c	Rest tremor amplitude– RLE	
2.9	Turning in bed		3.17d	Rest tremor amplitude– LLE	
2.10	Tremor		3.17e	Rest tremor amplitude– Lip/jaw	
2.11	Getting out of bed		3.18	Constancy of rest tremor	
2.12	Walking and balance			Were dyskinesias present?	☐ No ☐ Yes
2.13	Freezing			Did these movements interfere with ratings?	☐ No ☐ Yes
3a	Is the patient on medication?	☐ No ☐ Yes		Hoehn and Yahr Stage	
3b	Patient's clinical state	☐ Off ☐ On	**Part IV**		
3c	Is the patient on levodopa?	☐ No ☐ Yes	4.1	Time spent with dyskinesias	
3.C1	If yes, minutes since last dose:		4.2	Functional impact of dyskinesias	
Part III			4.3	Time spent in the OFF state	
3.1	Speech		4.4	Functional impact of fluctuations	
3.2	Facial expression		4.5	Complexity of motor fluctuations	
3.3a	Rigidity– Neck		4.6	Painful OFF-state dystonia	

Appendix H: Adaptive Yoga Poses and Descriptions.

Standing Poses		
Pose	**Description**	**Incorporates**
Tadasana	Basic standing pose.	Balance, posture, diaphragmatic breathing
Tadasana Urdhva Baddha Hastasana	Standing pose, arms outstretched, fingers intertwined. Palms face forward, then arms are lifted so palms face the ceiling.	Balance, stretch of hands/wrists, arms, shoulders, and upper back, breath control
Hasta Chakrasana	Standing backward bend.	Stretch and strengthen hips, abdominals, and shoulders, open chest, breath control
Modified Vrksasana	Balanced on one foot, heel of opposite foot placed on ankle of standing foot. Hand on chair if needed.	Balance, leg strength, focus, coordination, breath control
Modified Trikonasana	One leg forward with toes forward, back foot slightly turned in. Arms out to side at shoulder level. Chair held for balance if needed.	Balance, leg strength, hip flexibility, open chest, breath control
Virabhadrasana 3	One leg forward with knee slightly bent. Palms together at chest or raised slightly overhead. Chair held for extra balance.	Balance, leg strength, hip flexibility, open chest, breath control
Virabhadrasana 2	One leg forward with toes forward, back foot slightly turned in. Arms out to sides. Head turned in same direction as front leg.	Balance, leg strength, hip flexibility, open chest, breath control
Ardha Chadrasana	Legs together, arms overhead, thumbs intertwined. Stretch done one side then the other.	Balance, flexibility of trunk and shoulders, strength of trunk, breath control
Adho Mukha Svanasana	Knees straight or slightly bent, hands on wall, chair back, or chair seat. Rocking backwards, and legs and back straighten.	Flexibility for hamstrings, trunk extension, shoulder, strength, breath control
Prasarita Padottanasana	Legs apart, forward bend with hands on chair.	Flexibility for hamstrings, trunk extension, shoulder strength, breath control

Poses done seated on a chair		
Pose	**Description**	**Incorporates**
Upavasta Konasana	One leg on another chair with slight forward bend	Hamstring flexibility, breath control
Paschimotanasana	Knees apart, forward bend putting hands on chair in front	Hip flexibility, breath control
Marichiyasana	Spinal rotation	Trunk flexibility, breath control
Poses done lying down		
Pose	**Description**	**Incorporates**
Supta Padangusthasana	Knee straight, belt over one foot, leg drawn toward head	Hamstring flexibility, breath control
Apasana	One knee drawn to chest, then other knee, then both knees	Hip and spine flexibility, breath control
Spinal Rolls	Knees bent and foot on floor, knees allowed to fall one direction, head turned in opposite direction	Spine, hip, neck flexibility, breath control
Jathara parivartasana	One leg straight, opposite knee drawn out to the side	Hip flexibility, breath control
Setu Bandhasana	Bridge, with arms at sides, hips lifted off floor	Trunk, hip and leg strength, breath control
Savasana	Supine with legs straight or supported on chair seat with focused breathing and deep relaxation	Breath control, relaxation, and meditation. Addresses focus, depression, and anxiety.

Appendix I: Adaptive Mindfulness Descriptions

Mindfully Eating A Raisin

Mindfully eating a raisin. At the beginning of most mindfulness-based stress reduction classes, we introduce this formal practice, which involves eating a raisin mindfully, to demystify the concept of meditation. (If you don't have a raisin, any small nut or berry will do.)

As you do this practice, put aside all distractions, turn off the phone, and focus direct, clear awareness (interest) on each aspect and each moment of the experience.

If you are reading this meditation, take five minutes or so to do this practice.

Loving Kindness

Loving-kindness meditation, is the repetition of phrases of intention that express our caring and well-wishes. Loving-kindness meditation can be done either lying down or sitting up. In the loving-kindness guided meditation below, are phrases that work well for most people, but if these words don't resonate with you, feel free to make up your own. Gently allow the words to change on their own and to change from one practice to the next.

MBSR Body Scan

Techniques

Lie on your back — ideally on top of a yoga or exercise mat for comfort — with your legs spread out in front of you and your arms to the side, palms up in a receiving fashion. Cover yourself with a blanket if you tend to get cold so you are not distracted midway through the body scan. First, simply lie there and notice what it feels like to be connected to the ground.

Start with your left toes. Don't visualize them, just check in and see how they feel. Are they cold? Are they holding tension? Focus your exhales on the point of your attention, directing your breath deep into your toes. Let your awareness of your toes go and move your attention to your heel, focusing your breath to your left heel.

Move upward to your arch, your ankle, your calf, your knee, your thigh and then duplicate the process with your right leg, starting with your right toes.

Once you have scanned your legs, concentrate your awareness and breath on your pelvis, traveling to your lower back, abdomen, chest, shoulders, arms, hands, neck and head.

Once you have scanned the individual body parts, unite them, focusing on how the fingers connect to the hands, which connect to the arms and so on and so forth. Be aware of sensations — the feel of the blanket or the chill of the air on your skin. *The objective of the body scan is to see the body as a perfect whole, united by the breath flowing in and out of the body.*

Guided Meditation

The sensations of the in-breath are always happening in the present moment. When we pay attention to the sensations of the body breathing in and out, it allows us to receive feedback from our physical and emotional states. In this way the breath acts as a two way street and supports the healing of the body and deeper emotional states.

How To Work With Physical Pain

We all experience physical pain from time to time. The first step in working with pain is to assess whether it's acute or chronic.

Acute Pain, usually has a physical cause and is often associated with a recent injury or physical problem. It may require immediate medical attention.

Chronic Pain, may also have a physical cause, *it's likely to be associated with cognitive and emotional components,* as well, such as despair, anger, fear, or confusion.

Mindfulness meditation has been shown to be helpful with chronic pain. There are three important steps in applying mindfulness to chronic pain.

1. Recognizing – dropping into the body; feeling the tension and pain.
2. Accepting- without judgment any emotional reactions to the pain and tension.
3. Understanding- learning how to live with pain and emotions one moment at a time.

How To Work With Emotional Pain

The body scan can help you get in touch with difficult, daunting, and even overwhelming emotions. The first step is to learn to identify these feelings more readily so that you can work with them more creatively.

Take anxiety, for example. If you're unaware of anxiety in the moment, it could be influencing your behavior in ways that actually increase anxiety instead of relieving it. The body scan can also help you tune in to physical sensations that can serve as a signpost as to whether certain emotions are present. With anxiety, you may notice tightness in the chest, tension in the shoulders or back, or cramping in the stomach. You can use awareness of these sensations to alert you that you might be anxious, allowing you to work with that emotion before it snowballs.

Opening meditation:
Becoming aware of body sensations, emotions and thoughts in this present moment.

Guidelines for participation:
self-care
confidentiality
communication with instructor

Guided internal reflection:
What are you here for?
What is your intention?
What do you really want?
What has brought you here?
What are your expectations for the program?

Raisin-eating exercise:
Reflecting (not taking a personal position) on the experience.
Focusing on direct sensory observation -what can be seen, felt, smelled, tasted, heard.
Noticing if your observations of the immediate experience of mindfully eating, are becoming personal opinions and theories.

Abdominal breathing:
Notice the moment-to-moment awareness of the eating awareness and to experience (beginners mind & non-judgment) of the breath in the same way.
Introduction various comfortable postures for lying down: corpse pose and sitting in a chair.
Focusing on the feeling of the abdomen rising and falling with the in-breath and the out-breath, mindfully "tasting" the breath in the same way open minded way as tasting the raisin.
Non-judgmentally observing one's own breathing from moment to moment; and gently bringing one's attention back to the breath and the present moment when it wanders.
From mindfulness of breathing, we move into the guided body scan where we lie on floor or sit in comfortable position.

Practice: Walking Meditation.

Practice: Mindful yoga, slowly going through the sequence of postures on the Lying-down Yoga recording, with comments interspersed as required. Emphasis is on mindfulness and approaching one's current limits with gentleness. We are encouraged to avoid any postures we feel would cause injury or a setback, or to experiment with caution and care when in doubt. Particular attention is paid to chronic problems with the lower back, neck, and chronic pain in general.

Reflecting on the experience of practicing the yoga postures.

Pleasant Events Calendar consider leading a short guided reflection that asks us to select one pleasant event, focusing on physical sensations, emotions and thoughts as they arise as memory and then as they arise in the present moment.

Review the Pleasant Events Calendar, being particularly attentive to exploring the ordinariness of experiencing a moment as pleasant. With an emphasis on mind/body connections, patterns, what we observed/learned about ourselves.

Adapted from Kabat-Zinn's Mindfulness Based Stress Reduction

Appendix J: Participant Diary of Home Regimen

Subject #

	Date	**Amount of Time**
Week 1		
Week 1		
Week 2		
Week 2		

Appendix K: Sample Size Calculation

Results | Matrices | Design

Power	Total Sample Size	Target Power	Means Scale Factor	Variability Scale Factor	Test	Power Method	Type I Error Rate
0.805	55	0.8	0.1	0.6	Hotelling Lawley Trace	conditional	0.05

Sample size calculations were performed with Glimmpse. Power calculations indicated a sample size of at least 55 participants were needed to detect a 1 SD difference between groups in the primary outcome anxiety measures. This means 2.1 and 3.4 points differences on PAS and BAI respectively. An attrition rate of 20% was accounted for, which brings the total of participants per group to 55/0.8 = 68.75 persons, rounded to 69 persons.

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Cognitive Behavioral Therapy, Mindfulness-Based Cognitive Therapy and Acceptance Commitment Therapy for Anxiety Disorders: Integrating Traditional with Digital Treatment Approaches
The effects of cognitive behavioral and mindfulness-based therapies on psychological distress in patients with multiple sclerosis, Parkinson's disease and Huntington's disease: Two meta-analyses
Mindfulness group therapy in primary care patients with depression, anxiety and stress and adjustment disorders: randomised controlled trial
A randomized controlled trial to improve psychological detachment from work and well-being among employees: a study protocol comparing online CBT-based and mindfulness interventions
Which treatment worked better for whom? Moderators of group cognitive behavioral therapy versus adapted mindfulness based stress reduction for anxiety disorders
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