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Research Article

The Effects of Whole Body Periodic Acceleration on Non-Motor Symptoms in Persons with Parkinson's disease: A Pilot Study

Abstract

Background and Purpose: In Parkinson's disease (PD), some common non-motor symptoms include depression, anxiety, sleep disturbances. Non-motor symptoms affect quality of life. In PD, Nitric Oxide (NO) production is reduced, which inhibits sleep. Whole body periodic acceleration (WBPA) has been found to increase secretion of NO. In persons with PD, the effects of WBPA on sleep regulation and activity levels have yet to be evaluated. This study assessed whether WBPA would improve non-motor symptoms in persons with Parkinson's disease when compared to gender matched controls.

Methods: There were 10 participants. Five participants had PD and 5 healthy older adults (8 men; 2 women), mean age 74.1 (SD 9.2 years) participated. Activity trackers were employed to monitor sleep, awakenings, and step counts 24 hours per day over 6 weeks. Sleep was also assessed using Sleep Quality Index, (PSQI); depressive symptoms, with the Patient Health Questionnaire (PDQ-9), and the (PDQ-8), a Parkinson's disease Quality of Life report. WBPA interventions were for 45 minutes, 3 times per week for 4 weeks. Participants wore the activity trackers for 7 days before and after the intervention. Blood pressure (BP) was monitored before and after each session.

Results: Repeated measures and paired t tests were used to assess data. Significantly decreased BP pre vs. post p .017 was found when groups were combined, also the controls only BP pretest to posttest t test was significant p.004; other significant findings were PD group PDQ-9 also had improved depressive symptoms p .025. Minimally Clinically Significant Differences (MCID) were also found in the PD participants, in the PSQI (4.25) points. PDQ-8 was trending toward improvement with 4.4 points improvement.

Conclusion: This was the first study to assess the WBPA on non-motor symptoms of PD patients. Self-reports confirmed improvements in depression symptoms and sleep. Even with a mean increase of 600 steps daily, decreased physical activity in those with mild to moderate PD was evidenced compared to controls. Interventions such as this may have a significant role in PD management non-motor symptoms. Further study with larger groups is warranted using WBPA.

Introduction

Parkinson disease (PD) is a progressive neurological disorder that affects 1 percent of individuals over 60 years of age [1]. Individuals with PD present with at least one of four cardinal clinical symptoms, which include bradykinesia, tremor, rigidity, and postural instability [2]. In addition, there are non-motor signs which include depression, anxiety, sleep disturbances, and social changes which may include isolation and need for a caregiver. Non-motor symptoms affect quality of life, institutionalization, and health costs [3]. Presently, other non-pharmacological treatments including complementary and alternative approaches for non-motor symptoms lack convincing evidence [4].

Sleep disturbances are associated with complaints of increased daytime sleepiness, cognitive decline, and depression [5]. Sleep has an important role in motor learning and memory in people with neurological impairments. Sleep disturbances can manifest in several ways in PD: they can be described as insomnia, sleep fragmentation, and rapid eye movement behavior disorder. Sleep fragmentation is

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defined as interruption of sleep, leading to a lighter sleep that interferes or disrupts a normal sleep pattern [6]. Over 80% of individuals with PD suffer from sleep fragmentation [7]. The reasons behind these disturbances are still controversial, however, certain PD medications can contribute to sleep disturbances. Amantadine, selegeline, and serotonin reuptake inhibitors which are common anti-PD medications can alter sleep patterns in PD [8]. The most common sleep disturbances are obstructive sleep apnea (OSA), restless leg syndrome (RLS), and rapid eye movement (REM) sleep behavior disorder [8].

REM sleep consists of a dreaming state in which there is activation of the cortex and hippocampus on electroencephalogram (EEG), rapid eye movements, and loss of muscle tone [9]. REM sleep is important because it plays a role in maintaining proper noradrenaline tone and when lacking, alters brainstem noradrenergic cell firing, which prevents accurate registration and discrimination of emotional salience and changes the responsivity of the amygdala. Nitric oxide (NO) in neurons facilitates sleep, particularly REM sleep [9,10]. In patients with PD, NO production is reduced, which selectively inhibits REM sleep secondary to decreased acetylcholine release [10,11]. In addition to improving sleep quality, NO also improves memory, assists the immune system, regulates blood pressure (BP) by dilating arteries, decreases inflammation, increases smell recognition, increases endurance/strength, and assists gastric motility [12,13].

Whole Body Periodic Acceleration (WBPA) is a recently recognized, non-invasive, and promising therapy for a diverse and growing list of disorders. Studies have shown that WBPA replicates the effects of exercise by increasing pulsatile shear stress to the vascular endothelium which increases the secretion of NO and induces vasodilation [14,15]. According to Sackner, WBPA increases the amount of brain derived neurotropic factor (BDNF) protein and glial derived neurotropic factor (GDNF) protein in animals. BDNF is a growth factor that supports the differentiation of neurons. GDNF aides in survival of dopaminergic neurons and motor neurons, which die in patients with PD. Therefore, by increasing BNDF and GDNF, WBPA has the potential to maintain the levels dopamine in patients with PD [16].

The effects of WBPA in both healthy participants and patients with PD on sleep regulation and daily activity levels have yet to be evaluated. Understanding the physiological effects of WBPA on these populations will provide a greater understanding of how WBPA might be used as a treatment technique for those with PD. We hypothesized that WBPA would improve non motor symptoms (sleep and depression) and therefore enhance activity levels (steps) in patients with Parkinson's disease when compared to gender matched controls.

Methods

This pilot study was approved by the New York Institute of Technology IRB board and registered on ClinicalTrials.gov Identifier: NCT02874261. The source of participants recruited was from the Academic Health Care Center at NYIT. Thirteen participants participated in the study. Ten participants completed the protocol (8 male and 2 female) with a mean age of 74.10 +/- 9.25 years. (Table 1) The mean BMI was 26.1 for both groups. The median score on the UPDRS was 32.5. One of the participants UPDRS could not be completed because of scheduling issues. Participants with and without PD, meeting the inclusion criteria, were invited to participate on a rolling basis. An a priori decision was made to include 5 PD and 5 control participants in this pilot study. All PD participants were currently taking levodopa/carbidopa therapy for symptoms. Persons undergoing medication changes were not included. We required subjects to maintain their current medication regime.

The inclusion criteria included participants with Hoehn and Yahr 1-3 (participants with PD) sleep disturbances (participants with PD) and in possession of a smart phone Apple® or Android, or willingness to use an iPad 2® that was provided by the researchers. Exclusion criteria included persons that did not have sleep disturbances, inability to commit to time requirements for WBPA, those currently undergoing medication modifications, difficulty tolerating the supine position, and other factors such as pain of orthopedic origin that interfered with sleep.

After the subject consented, demographic data was recorded including: age, sex, height, weight, BP and UPDRS (participants with PD). Participants were then loaned the Jawbone UP3® (Figure 1) and were synced to the UP app on either a smart phone or an iPad2. Participants completed the Pittsburg Sleep Quality Index (PSQI), Patient Health Questionnaire (PHQ-9), Parkinson's disease Quality of Life (PDQ-8), (participants with PD only). Participants were instructed on the use and care of the JawboneUP3®. In addition, the participants were instructed to wear the JawboneUP3® all the time except when swimming, showering or charging.

All participants wore the JawboneUP3® for 1 week prior to WBPA to collect baseline data which included: total sleep time, the number of awakenings per night, and activity (daily step count). This was followed by an intervention of three, 45-minute sessions per week on the WBPA bed for 4 weeks using the following parameters: 120 Hz frequency, 16 mm

Table 1: Demographics.

Variable	N	Minimum	Maximum	Mean	SD
Age	10	61	89.00	74.10	9.25
BMI	10	21.46	33.50	26.28	4.17

Figure 1: Jawbone UP3.

oscillation.[16] The range in frequency for WBPA for humans is between 100-150 Hz, with a 30-45 minute duration [16].

With Rokutunda et al., found a benefit was evidenced for persons with peripheral arterial disease when administered for a single session and a second group for seven sessions [17]. With the greater frequency they found less variability in responses and more subjects improved. We elected to proceed for 4 weeks with the rationale that a time frame longer in duration would demonstrate greater improvements. Blood pressure was taken before and after each session. Participants continued to wear the JawboneUP3® for one-week post intervention in order to get post WBPA data and the self-report questionnaires.

With their feet stabilized on the bed footplate and a pillow beneath their knees and head, participants were instructed to lie quietly while the bed was in motion. (Figure 2) While on the bed, the researchers synced the JawboneUP3® to the UP app and recorded data since the previous session on a monthly calendar.

Three self-report questionnaires were self-administered by all participants at the start and end of the study. The PSQI was used to measure recall of sleep quality over a 1 month time interval and consisted of 19 questions. A score greater than 5 has a sensitivity of 89.6% and a specificity of 86.5% for sleep quality disturbances [18]. The minimal clinically important difference (MCID) is a change of 3 points [17-19]. Secondly, the PHQ-9 self-report is a subset of the MD PRIME. This tool consisted of 9 subjective questions was used to screen, diagnose, monitor and measure severity of depressive symptoms. Scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe and severe depressive symptoms respectively. A score greater than or equal to 10, has a sensitivity and specificity of 88% for major depression [20]. The MCID for the PHQ-9 is 5 points [20]. Lastly, the PDQ-8 is a Parkinson's disease specific questionnaire which contains 8 questions from the original PDQ-39 that measure specific aspects of functioning and well-being that are adversely impacted by Parkinson's disease. The questionnaire has both a high sensitivity: 98.7% and high specificity: 88.4%. The MCID is a change in score of > 5.78 points. The ICC is 0.75 with a CI of 95 [21]. The JawboneUP3® tracked sleep time, sleep awakenings, and activity levels, for each day the entire study period. In addition, tracking data

Figure 2: Whole Body Periodic Acceleration Unit.

were synced to the UP app on the smart phone and recorded by the researchers. Sleep time was the number of hours spent asleep per night. Sleep awakenings was defined as the number of times one woke up during the night. Activity levels were the number of daily steps. When using the JawboneUP3®, studies have shown a high sensitivity and poor specificity for sleep tracking and generally high validity for step count. However, as with many of the newest activity trackers, little or no research has been done on the reliability specifically of the Jawbone UP3® [22].

Data was analyzed using SPSS 23. The independent variable was WBPA. The dependent variables were sleep disturbances (JawboneUP3® and Pittsburg Sleep Quality Index), depression (PHQ-9 Questionnaire), quality of life (PDQ-8), daily activity (JawboneUP3®), and BP measurements taken before and after intervention. The JawboneUP3® data was taken from the app as the total number of steps for each day, the total amount of sleep in hours and minutes and the number of times the subject woke up each night. We studied these variables preintervention WBPA, total 4 weeks of intervention WBPA, and 7 days post intervention. Systolic BP was used during statistical analysis. To test our hypothesis, we assessed for main effects and interactions in the dependent variables data assessed using the JawboneUP3® and a repeated measures design. We also assessed for differences between pre and post WBPA administration using the 3 self-report questionnaires and systolic BP using a paired t-test ($p < 0.05$).

Results

A repeated measures ANOVA revealed no significant main effect within or interactions between the groups of dependent variables for the sleep, awakening, activity, with p values of 0.73, 0.91, 0.58, table 2.

Self-Administered questionnaires

PHQ-9 results demonstrated significant change in the PD group, table 2, indicating that depressive symptoms were measurably less. The PD group pre PHQ-9 scores indicated mild depressive symptoms.

PSQI showed a mean improvement of 4.25 points for the PD group which meets the minimal detectable change for this outcome [18]. PSQI and PDQ-8 assessments indicated no significant differences found pre and post interventions for these 2 self-reported questionnaires. Although trending improvements were demonstrated as noted on the previous table, the level of improvements for these self-reports were below significance (Table 2).

Blood pressure a difference was noted between the combined groups pre and post intervention SBP (p =0.017). There was a within group change in the control participants (p=0.004) and there was no within group change in the PD group in SBP (p= 0.474).

In terms of activity results, a significant difference between the experimental and control group in activity levels at the start of the study ($p = 0.01$) was noted. However, there was no

significant difference in recorded sleep patterns or awakenings between groups (Table 3).

Discussion

This study is the first to observe WBPA as a possible non pharmacologic complementary treatment to help improve depression, sleep dysfunctions, quality of life and physical activity in PD. Sleep disturbances and reduced levels of physical activity are 2 factors associated with a poor quality of life in individuals with mild to moderate PD [6]. Fatigue is one of the most common complaints in PD and can be associated with other side effects such as anxiety, depression, reduced cognition, and difficulty functioning with everyday activities [6].

We believe that small group size was a factor in achieving significance in this study. This is evidenced by trending improvements in the dependent variables; PSQI, PDQ-8, BP, and sleep. We observed reductions in PDQ-9 that were statistically significant, which indicated that depressive symptoms were measurably less after WBPA. The improvements noted in the PSQI and PDQ-8 were below the level of significance, but may still have clinical relevance. Furthermore, the improvements on the PSQI met the MCID for that assessment.

Table 2: Means and SD of Jawbone UP3 Variables by group.

Variables	PD Pre	PD Post	Control Pre	Control Post	Combined	Significance*
Sleep (hours)	7.74 ±1.52	7.24 ±.76	6.40 ±1.31	6.52 ±1.01	6.89±.93	.73
Awakenings (#)	3.91 ±4.70	1.72± .77	1.58± .33	1.68±.63	1.68± 5.2	.91
Activity(steps)	3770 .46	4306.52	7264.20	6876.20	5591.36 ± 2738.92	.59

Table 3: Dependent variable descriptives by group.

Variable	PD	SD	Control	SD	Combined Groups	SD
PSQI						
Pre	9.80	3.89	2.50	1.90	6.12	4.52
Post	5.60	2.30	2.75	2.60	4.12	2.54
Significance	.07		.78		.61	
PDQ-8						
Pre	20.20	10.80	NA	NA	NA	NA
Post	15.80	15.20	NA	NA	NA	NA
Significance	.51					
PHQ-9						
Pre	5.60	.54	.25	.54	3.0	
Post	4.20	1.09	.50	.89	2.5	
Significance	*.02		.789		.223	
**BP						
Pre (mmHg)	136	14.40	128	20.40	135	
Post(mmHg)	134	17.60	122	19.38	125	
Significance	.47		*.004		*.017	

*<P.05
**BP pre-post times indicate means before and after 45 minute WBPA intervention over the course of the study

It is important in this study of the effects of WBPA, to recognize that in all groups, the mean systolic BP values were lower at post intervention when compared to pre intervention. Non-significant values could be attributed to type 2 error. A larger group size may change that result. We are confident that there was a significant effect of WBPA on blood pressure because of clinically observed signs of vasodilation (flushing of the head and neck) across the groups. This is an indicator of vasodilation. This agrees with other studies. WBPA has been shown to cause vasodilation in animals and humans [16,23].

One of the pathophysiological reasons for autonomic abnormalities is denervation of the sympathetic nervous system (SNS) and reduced levels of the neurotransmitter catecholamine norepinephrine (NE) [7-9]. Levodopa and dopamine agonists that are commonly used to treat PD cause further inhibition of the SNS which reduces NE levels and BP further [6]. This inhibition of the SNS not only impacts on positional BP responses, but also affects acute responses to external stress. For example, NE typically increases during exercise, which increases heart rate (HR) and BP to meet the demands of the body [10]. Parkinson's disease suppresses NE, BP and HR responses during exercise stress [8]. Although the PD group was maintained on their stable medication regime, we noted a trend toward an appropriate exercise response.

Unlike sleep and awakening, at the baseline, there was a significant difference between the groups regarding daily activity (steps). The findings in this study agree with Canning et al. [24], in that individuals with PD are significantly less active than age controlled non-PD. The reduced level of activity can be explained by increased limitations in activity and participation caused by PD. The validity of the Fitbit and Jawbone UP (older generation of the tracker used) on the step count was generally high. However, it has been shown that at slower gait speeds, the trackers tend to under estimate steps [24]. When one considers that all the participants were free living community dwellers, underreporting of steps due to slow gait speed, may help account for the large discrepancy between the two groups regarding daily activity. Lastly, there has not been any research specifically performed on the reliability of JawboneUP3® trackers.

Although our pilot study sample size is too small to make a general assumption that WBPA makes no statistical meaningful change in PD participants' activity or sleep, statistical significance only focuses on the null value of the effect. Clinical significance is primarily based on the practical value, or relevance of a particular treatment, and this may or may not involve statistical significance as an initial criterion [25]. Most important, clinical significance may be defined by the smallest clinically beneficial effects and safety. This study showed an increase of 600 steps per day in our PD group over 4 weeks of WBPA therapy. Rehabilitation professionals realize, that this can mean a significant improvement in every day daily activities for persons with PD.

BP clinically decreases after the use of WBPA across both groups. We believe that group size was a factor in masking other possible significance during this study. This is evidenced by trending improvements in PSQI, PDQ-8, BP, and sleep.

There were no randomized controlled clinical trials to guiding this research. The selection of parameters was based on the work of Sachner [16] and Rokutanda et al. [17], Optimal dosing of WBPA has yet to be determined. Future efforts should endeavor to achieve this important goal.

Interestingly, the PD participants were sleeping the same amount of time as non-PD, and the number of awakenings was similar in both PD and non-PD. Surprisingly, the controls slept less (6.24 hours) than the PD participants (7.20 hours) as recorded by the JawboneUP3® at the post intervention measure. Participants with PD reported having difficulty with sleep, according to their own reports however, most had greater than 7 hours of sleep per night.

Participants with PD continued to report fatigue and decreased sleep quality but to a lesser degree on post assessments. So, although our findings were not significant, our findings may have clinical relevance. Furthermore, the JawboneUP3® was showing comparable results from the control group, who reported sleeping well. This finding supports the work of Evenson [23], who found activity trackers tend to overestimate total sleep and under estimate wake after sleep onset, resulting in high sensitivity and poor specificity. In addition, all of the participants reported getting up at night to urinate. This would account for > 50% of the awakenings we had that were identified by the JawboneUP3®. Future studies should consider having participants keep a record of the number of times they woke up during each night.

One major limitation of this study was the sample size. There were only 10 participants included, making it difficult to find a true significance. The sample size was kept at 10 because of the required time commitment on the part of the participants. Reduced number of visits per week would assist recruitment in future studies. The accuracy of the JawboneUP3® in sleep and activity may be questionable. Participants reported sleep and awakening times that differed from the values recorded on the UP app. Other issues with data collection stemmed from the intermittent difficulties pairing or syncing to device, occasional non-compliance with wearing and charging the JawboneUP3®. When those events occurred, it was fortunate that the app stored data for up to 30 days. On three occasions, a participant found the tracker had fallen off during the night. Another time a participant was unable to remember to charge the JawboneUP3® so the researchers took that task over. Fortunately, the battery life on each JawboneUP3® was 7 days. The JawboneUP3® was used with the default factory settings. We had a few instances where the sleep data did not record. We averaged the sleep time over each of the four weeks instead of analyzing one day at a time for the four weeks on the WBPA. In addition, the UP app was updated mid study which changed the presentation of the data but did not affect collection. A limitation of the JawboneUP3® was its wrist size was too tight for people of size who found it too tight or it didn't fit at all.

Future Studies should determine JawboneUP3® reliability with the PD population. Additional studies on the topic are needed to further understand the effects of WBPA on the sleep and activity levels of persons with mild to moderate PD and a

therapeutic dosage and intensity. A larger sample size should be utilized to increase power of findings and reduce error. In addition to the JawboneUP3® sleep data, participants could keep sleep diaries to compare and validate findings from the JawboneUP3. It would also be beneficial for a study to be done with the similar parameters and outcome measures, that includes the measurement of NO pre and post WBPA in order to help determine the specific levels of NO and changes in dependent variables. Lastly, a PD medication wash out might be another future study consideration.

Conclusion

To our knowledge, this was the first study that analyzed the non-motor effects of Parkinson's disease regarding treatment with WBPA, using fitness trackers to monitor motor and non-motor behaviors. PD participants demonstrated improvements in depression after WBPA. There was a 600 step increase in the PD group post intervention. Overall, WBPA was well tolerated and safe for individuals with mild to moderate PD. More study to assess this intervention's efficacy in older adults with PD would be beneficial

References

1. Gazewood JD, Richards DR, Clebak K (2013) Parkinson disease: An update. Am Fam Physician 87: 267-273. **Link:** https://goo.gl/deCnsH

2. Schenkman M, Hall DA, Baron AE, Schwartz RS, Mettler P, et al. (2012) Exercise for people in early- or mid-stage parkinson disease: A 16-month randomized controlled trial. Phys Ther 92: 1395-1410. **Link:** https://goo.gl/Z8GEYp

3. Bhimani R (2014) Understanding the burden on caregivers of people with parkinson's: A scoping review of the literature. Rehabil Res Pract. Link: https://goo.gl/LqBVqR

4. Bega D, Zadikoff C (2014) Complementary & Alternative Management of Parkinson's disease: An Evidence-Based Review of Eastern Influenced Practices. Journal of Movement Disorders 7: 57-66. **Link:** https://goo.gl/xeCbNv

5. Neikrug AB, Avanzino JA, Liu L, Jeanne EM, Loki N, et al. (2014) Parkinson's disease and REM sleep behavior disorder result in increased non-motor symptoms. Sleep Med 15: 959-966. **Link:** https://goo.gl/z3RTyE

6. Claassen DO, Kutscher SJ (2011) Sleep disturbances in parkinson's disease patients and management options. Nat Sci Sleep 3: 125-133. **Link:** https://goo.gl/bHa9tA

7. Askenasy JJ (2001) Approaching disturbed sleep in late parkinson's disease: First step toward a proposal for a revised UPDRS. Parkinsonism Relat Disord 8: 123-131. **Link:** https://goo.gl/oAJJM3

8. Barone P, Amboni M, Vitale C, Bonavita V (2006) Treatment of nocturnal disturbances and excessive daytime sleepiness in parkinson's disease. Neurology 63: 35-38. **Link:** https://goo.gl/NFgYCp

9. Lu J, Sherman D, Devor M, Saper CB (2006) A putative flip-flop switch for control of REM sleep. Nature 441: 589-594. **Link:** https://goo.gl/JFFrHx

10. Goldstein AN, Walker MP (2014) The role of sleep in emotional brain function. Annu Rev Clin Psychol 10: 679-708. **Link:** https://goo.gl/zqJodW

11. Gautier-Sauvigne S, Colas D, Parmantier P, Pierre C, Abdallah G, et al. (2005) Nitric oxide and sleep. Sleep Med Rev 9:101-113. **Link:** https://goo.gl/v3qHV4

12. Picchioni D, Reith RM, Nadel JL, Smith CB Sleep (2014) plasticity and the pathophysiology of neurodevelopmental disorders: The potential roles of protein synthesis and other cellular processes. Brain Sci 4: 150-201. **Link:** https://goo.gl/1hpzDg

13. Shinde UA, Mehta AA, Goyal RK (2000) Nitric oxide: A molecule of the millennium. Indian J Exp Biol 38: 201-210. **Link:** https://goo.gl/y79m4u

14. Derentowicz P, Markiewicz K, Wawrzyniak M, Czerwinska-Kartowicz I, Bulawa E, et al. (2000) Nitric oxide (NO)--nobel prize in medicine and physiology for 1998. Med Wieku Rozwoj 4: 209-217. **Link:** https://goo.gl/HJKTxM

15. Takase B, Hattori H, Tanaka Y, Akimi U, Masayoshi N, et al. (2013) Acute effect of whole-body periodic acceleration on brachial flow-mediated vasodilatation assessed by a novel semi-automatic vessel chasing UNEXEF18G system. J Cardiovasc Ultrasound 21: 130-136. **Link:** https://goo.gl/xKZNn5

16. Sackner M (2012) Whole Body Periodic Acceleration: "Passive Exercise" for Parkinson's disease. J Parkin dis Rest Legs Syn 2: 1-5.

17. Rokutanda T, Izumiya Y, Miura M, Shota F, Kenei S, et al. (2011) Passive exercise using whole-body periodic acceleration enhances blood supply to ischemic hindlimb. Arterioscler Thromb Vasc Biol 31: 2872-2880. **Link:** https://goo.gl/ziL3sP

18. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ (1989) The pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Res 28: 193-213. **Link:** https://goo.gl/R5V8xt

19. Sackner MA, Gummels E, Adams JA (2005) Nitric oxide is released into circulation with whole-body, periodic acceleration. Chest 127: 30-39.

20. Lowe B, Unutzer J, Callahan CM, Perkins AJ, Kroenke K (2004) Monitoring depression treatment outcomes with the patient health questionnaire-9. Med Care 42: 1194-1201. **Link:** https://goo.gl/exJGwm

21. Kroenke K, Spitzer RL, Williams JB (2001) The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med 16: 606-613.

22. Tan LC, Luo N, Nazri M, Li SC, Thumboo J (2004) Validity and reliability of the PDQ-39 and the PDQ-8 in english-speaking parkinson's disease patients in singapore. Parkinsonism Relat Disord 10: 493-499. **Link:** https://goo.gl/m6saHD

23. Evenson KR, Goto MM, Furberg RD (2015) Systematic review of the validity and reliability of consumer-wearable activity trackers. Int J Behav Nutr Phys Act. **Link:** https://goo.gl/kRLDjz

24. Canning CG, Ada L, Johnson JJ, McWhirter S (2006) Walking capacity in mild to moderate Parkinson's disease. Arch Phys Med Rehabil 87: 371-375. **Link:** https://goo.gl/b5fqC6

25. Fethney J (2010) Statistical and clinical significance, and how to use confidence intervals to help interpret both. Aust Crit Care 23: 93-97. **Link:** https://goo.gl/Q5NuVs