

Fatigue in Parkinson Disease: An Integrative Review

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ABSTRACT

Fatigue, one of the most prevalent and underassessed nonmotor symptoms in patients with Parkinson disease (PD), is reported to be a major cause of disability and reduced quality of life. The purpose of this review was to systematically examine the scientific literature and report how fatigue is defined and measured and what interventions are used to treat it. A synthesis of the current literature will expose the current state of the science of fatigue in PD, propose areas for future research, and offer practice implications. An integrative review of the literature was conducted. The electronic databases CINAHL, Psychinfo, and PUBMED were searched using the keywords "Parkinson's disease," "fatigue," "definition," "mental fatigue," "physical fatigue," "measurement," "interventions," "treatment," and "methylphenidate." One hundred fourteen articles were found. Nineteen studies met review criteria. No universal definition of fatigue in PD was found, making it difficult to measure. However, central, physical, mental, and peripheral fatigues were described. Six scales were found that measure fatigue in PD; only one specific to PD, the Parkinson Fatigue Scale, measured physical fatigue. Seven studies reported interventions to treat fatigue and were categorized as medication, exercise, and alternative interventions. None of these interventions had a significant effect on fatigue. Findings showed that (a) there is a lack of a universally accepted definition of fatigue because of its subjective nature, (b) existing fatigue measurement tools do not measure all types of fatigue in PD, and (c) no intervention had a significant effect on fatigue. There is a need to define and explore fatigue further using qualitative methods. Further development of instruments to measure fatigue in women, younger onset, and older adults with PD is needed. A focus on person-centered interventions to reduce fatigue in patients with PD is a research priority.

Keywords: definition, fatigue, interventions, measurement, nonmotor Parkinson symptoms, Parkinson disease

Parkinson disease (PD) is a neurodegenerative condition that affects more than one million people in the United States (Abrantes et al., 2012). PD typically affects adults older than 60 years, and its incidence is projected to double by the year 2030 because of the growing aging population in the United States (Dorsey et al., 2007; O'Brien, Ward, Michels, Tziveleakis, & Brandt, 2009). The symptoms of PD include both motor and nonmotor symptoms (NMSs). Motor symptoms including tremor, bradykinesia, rigidity, and postural instability have been the focus of numerous medical studies. NMSs including sleep disturbance, pain, fatigue, behavioral and mood changes, and autonomic symptoms are less well studied (Vernon, 2009). As a result, the focus of this article is on the NMS of fatigue.

Fatigue, one of the most prevalent NMS, is estimated to affect approximately 58% of individuals with PD and is reported to be a major cause of disability and reduced quality of life (Friedman et al., 2010). It typically presents earlier in the course of the disease, and the incidence tends to increase as the illness advances (Friedman, Abrantes, & Sweet, 2011). A study of patients with PD applying for Social Security Disability Insurance revealed that the primary incapacitating symptom that contributed to work disability was fatigue (Zesiewicz, Patel-Larson, Hauser, & Sullivan, 2007). Despite this, fatigue is often not assessed in office visits, even by trained specialists, and is often underrecognized as a symptom of PD by patients themselves (Bonnet, Jutras, Czernecki, Corvol, & Vidailhet, 2012). Typically, patients have difficulty describing fatigue and often attribute it to other conditions such as depression (Brown, Dittner, Findley, & Wessely, 2005).

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The authors declare no conflicts of interest.

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DOI: 10.1097/JNN.0000000000000131

Purpose

The purpose of this integrative review is to systematically examine the scientific literature, report how fatigue is defined and measured in people with idiopathic PD, and describe existing interventions to treat fatigue in PD. A synthesis of the current literature will expose the current state of the science of fatigue in

PD, propose areas for future research, and offer practice implications.

Organizing Framework and Method

We used the integrative review methodology described by Whittemore and Knafl (2005). Articles published between 1993 and 2013 were reviewed. The following databases were searched utilizing the keywords indicated in Table 1: CINAHL, Cochrane Central Register for Control Trials, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, MEDLINE, PubMed, and Psych Info. Reference lists of studies were also hand searched for inclusion of other relevant sources. The search was restricted to English-language, peer-reviewed publications that included human adult subjects over 18 years old with a diagnosis of PD. Intervention studies that included fatigue as a measurable outcome variable were included. Case reports, abstracts, editorials, dissertations, and unpublished manuscripts were excluded. Nineteen studies met the inclusion criteria and were reviewed using Whittemore and Knafl's methodology.

Definition of Fatigue in PD

Five studies were reviewed that defined different types of fatigue recognized in PD. The major types of fatigue described include central, physical, mental, and peripheral. There have been no formal qualitative studies to date that describe the actual experience of fatigue by patients with PD. However, Friedman (2009) offers anecdotal descriptions of fatigue provided by patients during office visits. Terms such as "tiredness, exhaustion, debilitating, and lack of energy" were used to define fatigue (Friedman, 2009, p. 187). Others state that fatigue is akin to "waking up from anesthesia, or walking through a viscous medium" (Friedman, 2009, p. 187).

No studies were found that specifically defined the fatigue that occurs in PD. The literature reviewed largely discussed epidemiology, pathophysiology,

Although fatigue in Parkinson disease (PD) has been described anecdotally by patients with PD and includes several core features, no specific, universally-accepted definition was evident.

measurement, and medical treatment of fatigue. Each article reviewed the types of fatigue typically seen in patients with PD, but no literature was identified that strictly defined fatigue in this population. All articles report the lack of a universally accepted definition of fatigue that makes fatigue research challenging and further complicates the understanding of this NMS in PD.

Fatigue in PD has several core features identified anecdotally in clinical practice by Friedman (2009; Friedman et al., 2011). Patients report that fatigue is an unpleasant sensation associated with decreased quality of life, unrelated to physical activity but limits activities, and is worsened by emotional stress. Many patients also report that fatigue decreases after exercise (Friedman, 2009). Current definitions of components of fatigue with associated definitions are described below.

Central Fatigue

Central fatigue, prevalent in PD, is also found in many neurological disorders and is attributed to subcortical dysfunction (Smith & Hale, 2007). Friedman (2009) describes central fatigue as the "failure of physical and mental tasks that require self-motivation and internal cues in the absence of demonstrable cognitive failure or motor weakness" (p. 187). Central fatigue is thought to be subjective in nature and is further divided into two types: physical and mental fatigue.

Physical Fatigue

Physical fatigue occurs by generating force through motor tasks (Friedman, 2009; Friedman et al., 2011; Lou, 2009). It encompasses a feeling of physical exhaustion and decreased energy to perform physical tasks or activities. However, the person experiencing physical fatigue may still have the capability and drive to perform desired tasks (Friedman et al., 2011). This is felt to be a subjective type of fatigue common in people diagnosed with PD.

TABLE 1. Integrative Review Search Terms

Search Terms	Number of Citations
Parkinson disease + fatigue + definition	5
Parkinson disease + mental fatigue	23
Parkinson disease + physical fatigue	50
Parkinson disease + fatigue + measurement	44
Parkinson disease + fatigue + interventions	34
Parkinson disease + fatigue + treatments	58
Parkinson disease + fatigue + methylphenidate	15

Mental Fatigue

This type of central fatigue is described as the “effort one must put forth to pay attention to tasks” (Lou, 2009, p. 197). Friedman (2009) elaborates on this definition by explaining that mental fatigue is the struggle one experiences in starting and sustaining mental tasks. This is also felt to be a subjective phenomenon. Falup-Pecurariu (2013) also used the same definition of mental fatigue in a clinical article describing the assessment of fatigue in patients with PD.

Peripheral Fatigue

Peripheral fatigue is defined as a physiological process in which a “muscle loses strength with repeated contractions” (Friedman et al., 2011, p. 2000). Other terms such as “muscle fatigue” and “physical fatigability” have been used interchangeably to describe peripheral fatigue (Friedman, 2009; Lou, 2009). The presence of bradykinesia and tremors may cause power loss in muscles because of repeated contractions and lead to peripheral fatigue (Friedman et al., 2011). This type of fatigue, in contrast to central fatigue, is objective and can be quantitatively measured using a motor task or force generation, such as finger tapping. In the clinical environment, patients are asked to tap the index finger to the thumb, and the speed is used as a measure of bradykinesia. In research trials, this is typically measured using an electronic keyboard that assesses change in tapping speed over time (Lou, 2009).

Challenges of Defining Fatigue in PD

Fatigue is largely a subjective concept, which makes it difficult to have a universally accepted definition. There is currently no qualitative data available that include narrative patient accounts describing fatigue in PD (Smith & Hale, 2007). Furthermore, the literature reviewed primarily reports epidemiology, pathophysiology, measurement, and treatment of this NMS. Although the articles include brief sections defining fatigue in PD, no research studies currently exist where patients are asked about how they define fatigue. All authors state that the lack of a clear definition of fatigue and its associated characteristics complicates future research in this area. Without an adequate definition, it is difficult to measure and assess fatigue in the clinical setting.

Scales Measuring Fatigue in PD

Seven studies were evaluated that measured fatigue in patients with PD. Six scales that report valid and reliable measures of fatigue in PD were found (see Table 2). However, many of the instruments did not measure the different components of fatigue described earlier. Most authors also point out that the lack of

TABLE 2. Scales Measuring Fatigue in Parkinson Disease

Instrument	Fatigue Severity Scale	Functional Assessment of Chronic Illness Therapy-Fatigue	Multidimensional Fatigue Inventory	Parkinson Fatigue Scale	Fatigue Impact Scale for Daily Use	Modified Fatigue Impact Scale
Type/component of fatigue measured	Functional impact of fatigue; physical and mental fatigue	Experience and impact of fatigue	1. General fatigue 2. Physical fatigue 3. Mental fatigue 4. Reduced motivation 5. Reduced activity	Physical fatigue; impact of fatigue on daily function; fatigue severity	Severity of fatigue in daily life	Impact of fatigue on physical, cognitive, and psychosocial functions

a clear definition of fatigue further complicates the development of an instrument specific to this population. Sample sizes in the studies using these instruments ranged from 50 to 495 participants with mean age of 67 (range = 42–90) years. The samples were largely male (range = 54%–67.7%) with subjects in earlier stages of illness with average Hoehn and Yahr stage between 2 and 3. The following section describes six instruments used to measure fatigue in studies of patients with PD.

Parkinson Fatigue Scale (PFS)

The PFS is the only fatigue scale specifically developed for patients with Parkinsonism. It was designed to measure one construct, physical fatigue, and its impact on daily functioning. It is a 16-item self-report measure of fatigue severity developed in focus groups of people with Parkinsonism. The instrument shows high internal consistency reliability with a Cronbach's alpha of .98 (Brown et al., 2005). Construct validity was established by correlating it with the Fatigue Severity Scale (FSS; $r = .84$) and the Rhoten Fatigue Scale ($r = .68$ –.78; Friedman et al., 2010).

FSS

The FSS was originally developed to assess fatigue in persons with multiple sclerosis and systemic lupus erythematosus. It is a self-administered nine-item rating scale that examines severity and impact of fatigue, including physical and mental aspects, on function (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). It has been tested in the PD population, and psychometric properties have resembled those found in non-PD populations (Friedman et al., 2010; Hagell et al., 2006). The FSS has a Cronbach's alpha of .94 (Friedman et al., 2010, p. 810). Construct validity of the FSS has also been supported because the scale has moderate-to-strong correlations with other fatigue scales including the PFS ($r = .84$, $p < .001$) and the Functional Assessment of Chronic Illness Therapy-Fatigue ($r = .71$, $p < .0001$; Grace, Mendelsohn, & Friedman, 2007; Hagell et al., 2006).

Functional Assessment of Chronic Illness Therapy-Fatigue

The Functional Assessment of Chronic Illness Therapy-Fatigue is a 13-item self-report scale developed in the oncology population to assess the experience and impact of fatigue (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997). Hagell et al. (2006) tested the scale in patients with PD and found the tool to be a reliable measure of fatigue with Cronbach's alphas between .90 and .92 and test-retest reliability of .85 over a 2-week period. Construct validity of this tool has been supported with strong correlations to scores on the

Nottingham Health Profile-energy scale ($r = -.70$; Hagell et al., 2006).

Fatigue Impact Scale for Daily Use (D-FIS)

The D-FIS was adapted from the Fatigue Impact Scale and was designed to evaluate the daily impact of fatigue on a person with a symptomatic chronic medical illness. This scale was initially tested in subjects with a flu-like illness (Fisk & Doble, 2002). It is an eight-item self-administered scale with three subscales: cognitive, physical, and psychosocial. Fatigue is defined as "...a feeling of physical tiredness and lack of energy that many people experience from time to time" (Fisk & Doble, 2002, p. 271). In a sample ($n = 142$) of patients with PD, it has shown adequate internal consistency reliability with a Cronbach's alpha of .93 and content validity when compared with the Multidimensional Fatigue Inventory (MFI) General Fatigue measure ($r = .55$ –.69, $p < .05$; Martinez-Martin et al., 2006).

Modified Fatigue Impact Scale

Schiehser et al. (2013) examined the validity of the Modified Fatigue Impact Scale, a 21-item self-report measure of the impact of fatigue in patients with PD on three components: physical, cognitive, and psychosocial (subscales). This scale was initially developed to assess fatigue in the multiple sclerosis population. The Modified Fatigue Impact Scale was found in this small sample ($n = 100$) to have good internal consistency reliability with Cronbach's alphas between .95 and .96 and convergent validity when correlated with the Positive and Negative Affect Schedule fatigue subscale ($r = .585$, $p < .001$).

MFI

The MFI is a 20-item self-report measure of five dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, motivation, and activity. The MFI does not provide a definition of fatigue, and its psychometric properties were initially tested in patients with cancer receiving radiotherapy and those diagnosed with chronic fatigue syndrome (Smets, Garssen, Bonke, & De Haes, 1995). In the PD population, the MFI has been shown to be valid in several studies because there have consistently been higher fatigue scores among patients with PD versus healthy control groups (Friedman et al., 2010). Elbers, van Wegen, Verhoef, and Kwakkel (2012) investigated the reliability of the MFI and reported internal consistency of the five subscales with Cronbach's alphas ranging from .74 to .92 and test-retest reliabilities ranging from .65 to .80 at 1 week and 3 weeks.

Challenges of Measuring Fatigue in PD

The six fatigue scales reviewed had adequate reliability in patients with PD. There has only been one fatigue scale specifically designed for patients with Parkinsonism, the PFS, but this was not considered to be superior to the other scales by the Movement Disorder Society Task Force (Friedman et al., 2010). One limitation of the PFS is that it was tested in a population with Parkinsonism rather than idiopathic PD; therefore, fatigue in patients with PD may be experienced differently. The PFS also does not assess for the cognitive and emotional aspects relating to fatigue (Friedman et al., 2010).

Only one scale, the D-FIS, defined fatigue. This definition was consistent with anecdotal descriptions by patients in clinical practice (Friedman, 2009). However, none of the scales measured the types of fatigue described in the definition section. The lack of a universal definition of fatigue in PD continues to present a challenge when measuring this largely subjective construct.

The sample characteristics themselves also pose several limitations. Most of the studies utilized smaller, nonrepresentative samples including mostly male participants in earlier stages of illness (Hoehn and Yahr stages 2–3) and did not include younger or advanced-aged persons with PD. Patients with comorbidities such as depression, dementia, and other psychiatric diseases were excluded from these studies. Before interventions can be developed that reduce fatigue in PD, further refinement and psychometric evaluation of these scales is necessary in populations of people with PD that have not been included in current studies. Interventions and treatment for fatigue in PD will be reviewed in the next section.

Interventions to Minimize Fatigue in Patients With PD

Seven studies met the inclusion criteria and were included in this review. Interventions to minimize fatigue in patients with PD were grouped into three categories: medications ($n = 4$), exercise ($n = 2$), and alternative interventions ($n = 1$). Sample sizes in the studies ranged from 10 to 1108 participants with age ranges from 31 to 87 years. In all studies, there were more male than female participants, with an average of 60% male participants. The length of intervention and follow-up ranged from 6 weeks to 36 months. The stage of Parkinson varied among studies with few including patients in the later stages of illness. One study included patients with early-stage PD (Stocchi, 2013), whereas the others contained participants with stage 3–4 disease per Hoehn and Yahr rating.

Medication Interventions

One study examined the effect of methylphenidate (Ritalin, Concerta) on fatigue in PD. Two studies

reviewed modafinil (Provigil) as a pharmacological intervention, and one study utilized rasagiline (Azilect) as an intervention.

Methylphenidate (Ritalin, Concerta)

Methylphenidate is a central nervous system stimulant and dopamine antagonist, typically used to treat attention deficit or attention hyperactivity disorder. In a double-blind placebo-controlled trial, Mendonca, Menezes, and Jog (2007) evaluated the effect of 10 mg of methylphenidate three times a day on fatigue measured with the FSS and the MFI in 36 patients with PD in the United Kingdom. Among the groups, there was a significant reduction in mean fatigue scores at 6 weeks when compared with baseline using paired Student's t test on both the FSS (6.5 points) and MFI (8.4 points; $p < .04$).

Modafinil (Provigil)

Modafinil is a central nervous stimulant medication that is an effective treatment for narcolepsy and hypersomnia. Its mechanism of action is largely unknown. Lou et al. (2009) conducted a randomized, double-blinded, placebo-controlled study over three visits: baseline, month 1, and month 2. The aim of this study was to determine if 200 mg/day of modafinil improved subjective and physical fatigability (peripheral fatigue) in PD. The MFI was used to measure subjective fatigue. There was no significant change in MFI scores at 1 month and 2 months when compared with baseline.

Tyne, Taylor, Baker, and Steiger (2010) also explored the effect modafinil had on fatigue by performing a randomized, double-blinded control study in the United Kingdom utilizing a total daily dose of 400 mg/day. The FSS was utilized to collect data, and findings indicated no significant reduction in fatigue at baseline (mean = 6.1, $p = .312$) and at week 9 (mean = 5.7, $p = .312$).

Rasagiline (Azilect)

Rasagiline is an inhibitor of monoamine oxidase type B that is approved as an adjunct agent and monotherapy to treat motor symptoms of PD. Stocchi (2013) assessed the benefits of rasagiline on fatigue in patients with early PD at baseline and 36 weeks after initiating either 1 or 2 mg/day of the medication. The placebo-controlled, double-blind, delayed-start sub-study used the PFS to measure fatigue. Findings at 36 weeks revealed that the rasagiline group experienced significantly less fatigue than the placebo group. The adjusted mean of PFS scores from baseline to 36 weeks in the placebo group showed the greater reduction in fatigue in the 2-mg group.

Alternative Interventions and Physical Activity

Alternative Interventions

In a small case series study of 10 patients with PD, Donoyama and Ohkoshi (2012) observed that fatigue scores on the Visual Analogue Scale (0–100) decreased from 52 to 27 after a one-time 30-minute Japanese massage intervention.

Physical Activity

Two studies evaluated the effect of physical activity on fatigue in patients with PD. Abrantes et al. (2012) described the level of fatigue and exercise habits in 45 participants with PD. Fatigue was reported by 45.38% of the sample, and those who reported higher levels of physical activity had significantly less fatigue ($r = -.35, p < .05$).

Winward et al. (2012) examined the effects of a prescribed exercise regimen on fatigue in patients with PD. Thirty-nine participants were randomized into an exercise group or a wait-list control group. Participants in the intervention group were involved in an exercise program at a community gym and were required to complete five 30-minute aerobic sessions and two strength sessions per week for 12 weeks. Sixty-five percent of the sample reported a high level of fatigue that was measured by the FSS. Findings indicated that there was no difference between the exercise and control groups in fatigue ($F = 0.095, p = .76$).

Summary

With the exception of the study utilizing methylphenidate to treat PD-related fatigue, none of the interventions had a significant impact on fatigue. Across studies, sample sizes were small, primarily male, and largely in the mid-late 60s. None of the studies included participants with a co-diagnosis of dementia, depression, or other psychiatric comorbidities, which may have an independent influence on fatigue. For the medication and physical activity studies, no objective measures of compliance with the prescribed interventions were described.

The rasagiline study was the only one that included participants in the earlier stages of PD. This study used the PFS that measures physical fatigue, so it is unknown whether rasagiline has an effect on mental or peripheral fatigue based on this study's findings.

Discussion

Analysis of the literature revealed that there is no clear definition of fatigue in PD. Central, physical, mental, and peripheral fatigues have all been recognized as occurring in PD, but there is no universally accepted definition of fatigue specific to PD. Patients with PD experience fatigue that is objective, peripheral fatigue,

but this symptom is difficult to measure, and no studies reviewed explored this specific type of fatigue. Definitions varied; therefore, measurement is difficult.

Fatigue scales used to measure this symptom in PD have shown adequate reliability and validity, but there is no specific scale that measures both physical and mental fatigue that has been widely tested in this population. The scales are not based on definitions described in the PD literature, and the studies included mostly small, largely male samples in the earlier stages of illness. Furthermore, only one scale, the D-FIS, provides a definition of fatigue that is consistent with anecdotal descriptions provided by patients with PD in clinical practice (Friedman, 2009). None of the studies included participants with a co-diagnosis of dementia, depression, or other major psychiatric comorbidity that could have an influence on the type and degree of fatigue experienced in this population.

Examining the existing interventions to treat fatigue, there is little evidence that physical activity has been effective. One exercise study was found and indicated a negative correlation between exercise and fatigue; however, this was not an intervention study, and causality cannot be inferred. The PFS was also utilized here, and again, this tool is primarily focused on physical fatigue.

Only one medication study using methylphenidate had a statistically significant effect on fatigue (Mendonca et al., 2007). The rest of the medication studies did not reach statistical significance perhaps because of small sample sizes, low dose of intervention, and limitations with measurement tools.

Although the massage intervention showed an improvement in fatigue, the sample size was small, and a Visual Analogue Scale was used versus one of the reviewed instruments that has some established reliability and validity in the PD population. However, this small study does help to highlight that, perhaps, alternative and complementary interventions may improve fatigue in PD.

Similar to the fatigue measurement studies described earlier, women, minorities, younger onset, and people over 70 old are largely underrepresented in the fatigue literature in PD. Persons with coexisting psychiatric diagnoses and dementia were also excluded, thus limiting the generalizability of the findings.

Implications for Research

There are several research and practice implications based on this review. First, there is a need for a clear definition of fatigue and its characteristics. There is a need for rich, descriptive, qualitative studies about the experience of fatigue in PD. Data from patient accounts need to be obtained and analyzed to better understand this concept and move toward a more universal understanding of this phenomenon. Second, limitations

in the measurement of fatigue exist because of lack of clear defining characteristics noted above and also limited psychometric evaluation of existing instruments in the PD population. Larger studies with representative samples are needed to refine existing instruments. Descriptions of the experience are needed to validate the constructs included in the instruments. In addition, no studies were identified that evaluated for the utility of these instruments in clinical practice. Further studies are needed to determine if these tools are helpful in the office setting and, if so, how often should they be used to assess for fatigue in patients with PD.

Third, most of the tested interventions include medication treatments. In many of these studies, there was no measurable effect of the medications mostly because of small sample sizes and lack of validation that the patient actually took the medication as prescribed. Nursing science needs to advance the study of fatigue in PD and develop effective nonpharmacological interventions. Finally, further intervention studies are needed to develop treatments that have a statistically and clinically significant effect on fatigue in PD.

For the studies reviewed, the participants were mostly men and over the age of 60 years. Future fatigue research should examine if fatigue is experienced differently among men and women. In addition, is the experience of fatigue different in young-onset or significantly older aged patients with PD?

Implications for Practice

Fatigue has been shown to negatively affect quality of life and increase disability in patients with PD. It is a prevalent NMS and is often not assessed during office visits. Practicing nurses should be aware of its significance and assess for fatigue during office appointments and patient encounters. Nurses can also use the described measurement tools to evaluate for the presence of fatigue and its impact on one's daily functioning. Advanced practice nurses can discuss possible pharmacologic and alternative therapies to treat fatigue in appropriately identified patients. Although no successful physical activity intervention studies have been identified to date, there is anecdotal evidence that suggests exercise may improve the subjective experience of fatigue and improve quality of life.

Conclusions

The purpose of this integrative review was to systematically review the scientific literature, report how fatigue is defined and measured in people with idiopathic PD, and describe existing interventions to treat fatigue in PD. The synthesis of the literature revealed that there is a lack of a clear universal definition of fatigue in PD. Although various measurement tools to assess

fatigue exist, further psychometric testing is needed in the PD populations. Finally, there are few successful interventions that have had a significant impact on reducing fatigue.

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The authors and planners have disclosed that they have no financial relationships related to this article.

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