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CLINICAL PRACTICE
REVIEW

The Pathophysiology of Fatigue in Parkinson's Disease and its Pragmatic Management

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Abstract: **Background:** Fatigue is 1 of the most common and most disabling symptoms among patients with Parkinson's disease (PD) and has a significant impact on their quality of life. Yet the pathophysiology of fatigue is poorly understood, while its treatment is "limited to an empirical approach based on plausible hypotheses."

Methods: PubMed was searched for articles with the key words "Parkinson's disease" or "parkinsonism" and "fatigue" that were published by or before August 2015. The analysis of articles, which were selected on subjective grounds, was used to review the current knowledge of pathophysiology and treatment outcomes in studies focused on fatigue in PD.

Conclusions: Clinical and experimental findings support the view that fatigue is a primary manifestation of PD. The main hypothesized pathophysiological mechanisms include abnormal basal ganglia (BG)-cortical mechanisms, particularly frontal loops, and an imbalance between neurotransmitters (e.g., dopamine [DA] and serotonin), along with an altered hypothalamus-pituitary-adrenal axis, neuroinflammation, cardiac sympathetic denervation, etc. Pragmatic treatment of fatigue in patients with PD includes various pharmacological (dopaminergic and psychostimulant drugs, antidepressants) and nonpharmacological strategies, although current knowledge suffers from insufficient evidence to support the use of any drug or nondrug therapy.

Fatigue is 1 of the most common, although frequently unrecognized, symptoms in Parkinson's disease (PD), with a prevalence from 33% to 81%.[1–3] It is also among the most disabling symptoms in PD (one-third of patients consider fatigue as the single most disabling symptom)[4,5] and significantly worsens the quality of life.[6] Yet fatigue is still missing a universally accepted definition and classification.[7,8] Generally, it can be defined as an overwhelming sense of tiredness, weakness, lack of energy, and exhaustion (subjective fatigue); or as a mismatch between expended effort and actual performance; or as a reduction in the capacity to either initiate or sustain voluntary activities (objective fatigue).[7–9.]

Indeed, the lack of a consistent definition (and taxonomy) for fatigue (including fatigue in PD) creates the greatest challenge to its measurements, although detailed discussion of these problems is beyond the scope of this article. Recently, several extensive reviews have addressed the problems of defining and quantifying fatigue, even in the absence of biological marker(s), and have included recommendations for the most acceptable approach to investigating fatigue in PD.[7–10.]

Fatigue may be physiologic (as a reaction to prolonged or intensive activity) or pathologic (the chronic form, induced without or with only minimal exertion, which does not recover with rest) and can be further divided into peripheral and central fatigue.[7,8] Peripheral fatigue represents loss of muscle strength caused by repeated contractions (called muscle fatigue or physical exercise fatigue). Central fatigue is a subjective perception or experience and usually is described as an abnormal degree of

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tiredness, weakness, or exhaustion that involves both mental and physical domains but in the absence of motor or physical impairment related to the central nervous system.[9,11] Mental fatigue refers to cognitive effects experienced during and after execution of attention-requiring exercises or sustained intellectual activity. Physical fatigue is caused by sustained physical activity and presents as a sense of physical exhaustion and lack of energy to perform physical tasks despite the ability and motivation to perform them.[11,12]

In preparing this report, we searched the PubMed database for articles with the key words "Parkinson's disease" or "parkinsonism" and "fatigue," that were published by or before August 2015. The authors read all articles that were published in English and selected on subjective grounds as relevant those articles that dealt with the pathophysiology and treatment of fatigue in PD (only published or in press peer-reviewed articles were included).

Pathophysiology of Fatigue in PD

Most of the evidence suggests that fatigue is an intrinsic symptom to the pathobiological substrate of PD (primary manifestation) rather than a secondary or reactive phenomenon. For instance, it may precede motor symptoms in a substantial number of patients with PD.[13] In most patients, fatigue did not correlate with PD duration or motor disability,[1,2] although some studies indicated that it worsened with underlying disease progression.[3,14,15] However, the interpretation of fatigue in PD is significantly confounded by its clustering with depression, anxiety, sleep disturbances, and apathy.[10] Although it was present in over a one-half of nondepressed patients with PD[16] and in at least one-third of drug-naive patients in the initial motor stage of the disease,[17] fatigue in PD was related to the severity of depressive symptoms.[18,19] Fatigue was 1 of the diagnostic criteria for a *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*-based diagnosis of both major depressive episode and generalized anxiety disorder. However, it is still not clear whether the observed overlaps of fatigue with affective disorders and apathy reflect a diagnostic bias or common pathophysiological mechanisms.[20] A concept of primary fatigue (fatigue in the absence of mood disorders and excessive daytime sleepiness) and secondary fatigue (the presence of mood disorders or excessive daytime sleepiness) has been proposed.[21] In general, it is distinguishable from other related symptoms, such as depression, apathy, and sleepiness,[22] suggesting that fatigue in patients with PD is largely a primary symptom and is not secondary to mood disorders, sleep alterations, or medications.

Kluger et al.[7] suggested that 1 of the critical distinctions in understanding fatigue was that, between the subjective perception of fatigue and performance fatigability (i.e., the "magnitude or rate of change in a performance criterion relative to a reference value over a given time of task performance"). These 2 aspects in PD may not be in correlation.[23] Therefore, those authors[7] proposed the following relevant factors to investigate causality of fatigue: (1) homeostatic and psychological factors (expectations, motivation, and mood, which affect both subjective and objective fatigue) based on perception of fatigue; and (2) peripheral and central factors, based on prevailing mechanisms of fatigability.

The perception of fatigue may represent a homeostatic mechanism to limit energy utilization and to prevent energy exhaustation.[7] Among various peripheral and central contributors to the sensation of muscle fatigue and the perception of fatigue, respectively, inflammatory cytokines may also play a role.[24] Patients suffering from neuroinflammatory and autoimmune diseases also frequently complain of severe, disabling fatigue.[24] An association between PD and chronic inflammation has been revealed, together with elevated levels of activated CD4 and CD8 T cells, interleukin-1β, interleukin-2, and tumor necrosis factor-α in sera and cerebrospinal fluid from patients with PD. Recently, Lindqvist et al.[25] reported that increased levels of inflammatory markers in the cerebrospinal fluid of patients with PD were significantly associated with more severe symptoms of depression, anxiety, fatigue, and cognition. After controlling for PD duration, age, gender, somatic illness, and dementia, high C-reactive protein levels were significantly associated with more severe symptoms of fatigue and depression. The hypothesized roles of cytokines and chemokines in the generation of nonmotor symptoms of PD, including fatigue, may be mediated through their ability to promote microglial activation and induction of leukocyte chemotaxis,[26] which are closely associated with chronic neuroinflammation. However, they may also have direct effects on monoaminergic neurotransmission and the hypothalamic-pituitary-adrenal axis, which have been implicated in the pathophysiology of fatigue.[24]

Hypothesized physiological mechanisms of fatigue in PD also include altered activation of the hypothalamic-pituitary-adrenal system.[9,27] Although fatigue was associated with lesions of the hypothalamus, Kluger et al.[7] suggested that this association might be indirect due to additional changes in circadian rhythms and endocrine disturbances. Critchley et al.[28] also supposed that fatigue might be influenced to some extent by circadian factors, but they failed to find any change in melatonin rhythmicity in patients with PD. Testosterone deficiency may cause symptoms resembling nonmotor symptoms of PD, including fatigue.[29] However, Kenangil et al.[29] found that mean free testosterone levels, although significantly lower in PD patients than in controls, were not correlated with Fatigue Severity Scale (FSS) scores. Finally, menstruation increased fatigue in female PD patients but also in non-PD females.[4] Therefore, despite research efforts, all these data cannot be a plausible explanation for fatigue in PD.

It is still unclear the extent to which peripheral factors (i.e., changes in muscle, the neuromuscular junction, and peripheral nerves) contribute to fatigability in PD, since objective, measurable muscle fatigue that occurs in PD is presumed to arise mainly from central causes.[22] Decrements in motor tasks are rarely due to isolated peripheral causes, because peripheral and central mechanisms (i.e., a concurrent decrement in central drive) often go "hand in hand."[8] Muscle force production is

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indeed reduced in patients who have PD compared with age-matched controls[22]; and, along with a deficit in the central activation of muscles, at least a part of muscle weakness may reflect general deconditioning or muscle hypotrophy from disuse in patients with PD who become increasingly inactive due to the functional limitations associated with the disorder[30] and mitochondrial dysfunction, which may contribute to muscle fatigability.[31] Garber and Friedman[5] studied potential physiological or psychological differences between 37 fatigued and nonfatigued patients with PD and found that fatigue was correlated with more sedentary behavior, lessened functional capacity for exercise (i.e., diastolic blood pressure and maximal oxygen uptake in an exercise test), and worse physical conditioning.

Hwang and Lin[32] used stimulated single-fiber electromyography to evaluate the neuromuscular junction in patients with PD who had disabling fatigue symptoms, but no abnormality was found in the peripheral cholinergic system. Recently, Nakamura et al.[33] reported that the pressor responses in the norepinephrine and dobutamine infusion tests were significantly greater, whereas the ^{123}I-metaiodobenzylguanidine (MIBG) heart-to-mediastinal uptake ratio was lower, in fatigued versus nonfatigued patients with PD, suggesting that autonomic dysfunction, including cardiac sympathetic denervation, was associated with fatigue in PD. Cardiac sympathetic nerves have an important role, particularly during exercise, in increasing the heart rate, cardiac contractility, and blood pressure; and, although clinical manifestations of cardiac sympathetic denervation are not obvious in patients with PD, hypothetically, it may lead to failed increases in cardiac contractility during exercise, with consequent shortness of breath or sensations of fatigue.[33] The norepinephrine infusion test detects denervation supersensitivity in peripheral vessels and is useful for detecting the presence of orthostatic hypotension (OH). Therefore, based on their results, Nakamura et al.[33] suggested that patients who have OH due to cardiovascular adrenergic dysfunction might experience fatigue.

Stevens-Lapsley et al.[34] provided evidence for lower extremity strength loss in PD and a strong negative correlation of central activation deficits with quadriceps strength, favoring the role of central factors. Interestingly enough, patients with less severe motor signs experienced some—although statistically not significant—increase in quadriceps muscle fatigability. However, in those who had more severe motor signs, no fatigability occurred, probably because they were not able to activate the quadriceps muscle fully due to insufficient central activation (i.e., they did not have sufficient muscle overload to reach a level of metabolic fatigue during repeated contractions).

Central fatigue may be defined as reduced central drive from the motor cortex due to increased inhibitory interneuron input to the cortex that is influenced by sensory input from the peripheral system.[8] Central fatigue encompasses both physical and mental components[11,12] and is highly influenced by psychological factors. Among hypothesized physiological mechanisms of fatigue in PD, 2 deserve particular attention.

First is the dysfunction of frontal striothalamocortical loops.[9] Studies using transcranial magnetic stimulation, a method that assesses the excitability of cortical motor areas, revealed higher corticomotor neuron excitability in PD compared with healthy controls during and after exercise that partially improved with levodopa (L-dopa).[23] The objective motor fatigue did not correlate with subjective perception. Data based on the same technique led to the suggestion of abnormal BG output to the cortex in PD.[35] One of the crucial features of bradykinesia in PD is the sequence effect (SE), defined as "slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive action."[3] It has been suggested that the SE may be related to fatigue, although Kang et al.[36] failed to find any relationship between the SE and the clinical measures of fatigue. Dopaminergic mechanisms do not appear to be involved in the SE.[37] The structural abnormalities associated with the SE have not yet been identified but include abnormal output of the BG to the motor cortex,[38] including the supplementary motor area, the premotor cortex, and the sensorimotor cortex,[39] that altered cortical excitability, as well as the cerebellum.[40] Recently, Lee et al. reported an association of the anterior cingulate cortex and the cerebellar inferior semilunar lobule with the severity of the SE in de novo PD patients.[41] Using technetium 99-hexamethylpropyleneamineoxime (^{99m}Tc-HMPAO) single-photon emission computed tomography, Abe et al.[42] observed that the fatigue was significantly correlated with decreased blood flow in the frontal lobe. Hypoactivation of this region fits well with the previous suggestion of Chaudhuri and Behan[9] that central fatigue may be a consequence of dysfunction in the BG loops involved in motivation of self-initiated tasks. Recently, Saez-Francas et al.[43] conceptualized performing a physical activity as a decision-making process, dealing with the choice of the optimal effort to reach the objective. The decision-making impairment in PD might be involved in fatigue perception (i.e., fatigue may partly emerge from inadequate evaluation of internal input associated with abnormal feedback of perceived exertion), implicating a role of the orbitofrontal cortex in this scenario.

Second, it has been proposed that an imbalance between different neurotransmitters may contribute to the development of fatigue in PD.[44,45] Dopaminomimetics did not consistently improve central fatigue in patients with PD. Also, L-dopa–naive patients with PD who had fatigue had similar striatal DA transporter uptake as those without fatigue.[17] These findings indicated that fatigue in PD was not simply related to striatal DA deficiency but, rather, to nondopaminergic BG pathways or, alternatively, to the dysfunction of extrastriatal dopaminergic projections. Studies of patients with chronic fatigue syndrome without parkinsonism have demonstrated that the serotonergic system may contribute to its pathophysiology.[46] Therefore, serotonergic transmission in patients with PD who had fatigue (none had a history of depression or sleep disturbance) was investigated in a combined fluorodopa F-18 (^{18}F-dopa) and 11C-labeled 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl) benzonitrile (^{11}C-DASB) (as a measure of serotonin transporter [SERT] binding) positron emission tomography study.[47] Those results demonstrated that patients who had PD with fatigue had a significant reduction of ^{11}C-DASB binding in the putamen

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(−83%), caudate nucleus (−76%), ventral striatum (−74%), and thalamus (−66%) as well as the anterior cingulate, amygdala, and insular regions compared with patients who had PD without fatigue. Striatal ^{18}F-dopa uptake was similar in the fatigued and nonfatigued groups but decreased in the caudate and insula in the group with fatigue. Therefore, the conclusion of the study was that fatigue in PD was associated with reduced serotonergic function (i.e., reduced SERT expression and consequent changes in the serotonin/DA balance) in the BG and limbic structures and possibly associated with insular dopaminergic and serotonergic dysfunction. Structural lesions and/or neurotransmitter changes within the BG (in which an integration of sensorimotor, associative, limbic, and motor information takes place[48]) and associated structures disrupt the process of integration of limbic input concerning emotional status and consequent motor output, thus resulting in a reluctance to act and a feeling of fatigue.[9,11] The insular cortex is also a part of the limbic system, with reciprocal connections with the anterior cingulate, amygdala, BG, and prefrontal cortex; and it contributes to integrating somatosensory, autonomic, and cognitive-affective information to guide behavior.[49] Selective serotonin reuptake inhibitors increase the synaptic levels of serotonin. However, a significant loss of serotonin transporter protein, as illustrated by the low ^{11}C-DASB binding in fatigued patients who have PD, makes this class of drugs less attractive for this indication and necessitates alternative strategies to increase the brain level of serotonin and serotonergic transmission.[47]

Pragmatic Management of Fatigue in PD

Treatment approaches focused on fatigue in PD are faced with 2 main limitations: (1) lack of clear insight into its pathophysiology and mechanisms, and (2) probably its multifactorial nature (biological, clinical, and psychosocial factors). Therefore, as stated by Kluger and Friedman,[22] contemporary treatment of fatigue in PD is "limited to an empirical approach based on plausible hypotheses" (Table 1).[50]

TABLE 1 Possible Algorithm for the Treatment of Fatigue in Parkinson's Disease

1. Screening and identifying fatigue
2. Is fatigue primary or secondary? Identify contributing treatable factors (depression, anxiety, apathy, sleep alterations, orthostatic hypotension, anemia…)
3. Explain nature of fatigue to a patient and caregiver
4. Nonpharmacological treatment like physical exercise*
5. Medication*
   a. Methylphenidate (level C)
   b. Dopaminergic drugs: dopaminergic agonists (pramipexole, rotigotine, rasagiline), optimization of levodopa
   c. Antidepressant drugs (nortryptyline, doxepin, SSRI…)
   d. Modafinil

*Insufficient evidence: see Morita A, Okuma Y, Kamei S, et al. Pramipexole reduces the prevalence of fatigue in patients with Parkinson's disease. Internal Med 2011;50:2163–2168.[50]
SSRI, selective serotonin reuptake inhibitors.

Before the administration of any particular pharmacological or nonpharmacological treatment, it may be useful to explain to patients and caregivers that fatigue is quite common and is "a bona fide symptom of PD."[22] Also, it is critically important to discriminate whether fatigue is primary or secondary (i.e., due to depression, apathy, drugs, altered sleep patterns, OH, other comorbid conditions, etc.) when we try to treat these causes first.[51] For instance, in 1 of the first controlled studies on the treatment of depression in PD, Andersen et al.[52] reported an additional improvement of fatigue with nortriptyline.

Recently, Franssen et al.[53] undertook a meta-analysis of all randomized controlled trials that investigated treatment effects on fatigue in patients with PD (14 studies with 1890 patients). Eleven studies investigated a pharmacological treatment (carbidopa–L-dopa,[18] pergolide,[54] pramipexole,[55] rasagiline,[56] doxepin,[57] acute tryptophan depletion,[58] modafinil,[59–61] methylphenidate,[62] and memantine.[63] Also, 1 study dealt with an online self-management intervention,[64] 2 investigated a caffeine treatment,[65] and 1 used an exercise intervention.[66] Although 4 of the 11 studies that investigated a pharmacological intervention (modafinil, bromocriptine, pramipexole, and doxepin) observed a significant treatment effect of the intervention compared with controls, the authors found insufficient evidence to support the treatment of fatigue in patients with PD using any drug or nondrug therapy.[53]

It is difficult to compare or pool studies that used dopaminergic drugs due to methodological heterogeneity (outcome measures, different drugs and dosages, duration of treatment, and control of other variables, such as depression). L-dopa may reduce both central and peripheral fatigue, although the degree of mitigation varies, depending on the severity of PD.[67] Lou et al.[23] found that L-dopa/carbidopa (100/25 mg) relieved physical fatigue in finger tapping and force generation, suggesting that physical fatigue in PD was related at least in part to DA deficiency. However, the subscores in the dimension of physical fatigue on the Multidimensional Fatigue Inventory (MFI) did not correlate with the rate changes in the finger-tapping and force-generation paradigms, probably because the MFI measured different aspects of physical fatigue compared with those measured by finger tapping and force generation. According to 1 report based on the Earlier versus Later Levodopa Therapy in Parkinson Disease (ELLDOPA) study, L-dopa reduced fatigue in patients with PD to a small degree as measured on the Fatigue Severity Scale (FSS).[17] A recent open-label, prospective, observational, 6-month, multicenter study compared 43 patients on apomorphine with 44 patients on intrajejunal L-dopa infusion. Cohen's effect sizes were "large" for both therapies with respect to total motor, nonmotor, and quality-of-life scores. The Non-Motor Symptoms Scale (NMSS) with apomorphine showed moderate improvement, whereas sleep/fatigue, gastrointestinal, urinary, and sexual dimensions of the scale showed significantly higher improvement with intrajejunal L-dopa infusion.[68]

Data on DA agonists in modulating fatigue associated with PD are not consistent. In a small group of patients, Abe et al.[54] reported that pergolide, but not bromocriptine, reduced fatigue in a 5-week study in which FSS scores decreased from 5.1 to

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4.4 with pergolide and from 4.8 to 4.7 with bromocriptine. It has been suggested that the observed dissociation was due to a possible correlation of fatigue with DA D1 receptors, because pergolide activates both DA D1 and D2 receptors, whereas bromocriptine predominantly activates DA D2 receptors. Initial reports warned that other DA agonists, such as pramipexole[69] and rotigotine,[70] may be associated with an increased incidence of fatigue compared with placebo. Shannon et al.[71] reported that fatigue occurred in 14.6% of patients who received pramipexole compared with 8.8% of placebo-treated patients, and Hauser et al.[72] reported that fatigue occurred in 6.6% and 6.8% of patients who received extended-release pramipexole and immediate-release pramipexole, respectively, compared with 2.0% of placebo-treated patients. However, in those studies, patients with fatigue were not particularly frequent. Pogarell et al.[69] observed that 10 of 34 patients who had PD with resistant tremor and received pramipexole and only 4 of 35 patients who received placebo complained of fatigue. In a study of the effect of a direct dopaminergic challenge, an acute challenge with pramipexole had a negative effect on mood and fatigue in both PD patients and controls.[55] Oved et al.[73] quantitatively measured fatigue in 15 patients with PD who were treated with DA agonists (compared with 15 healthy, age-matched controls) and underwent a continuous (30-second) motor task using 4 muscle groups before and after 3 months of treatment with DA agonists. There was no significant between-group difference after 3 months of treatment in the mean fatigue index (defined as the decay of maximal force during continuous exercise). The physiologic measures were supported by the lack of change in the patients' personal perceptions of their physical or mental fatigue before and after treatment, as measured by the MFI scores. Therefore, despite the suboptimal doses they used, the authors concluded that fatigue was not influenced by DA agonists. Quite the contrary, Morita et al.[50] reported reduced fatigue in patients with PD who received pramipexole. Of 350 nondemented patients with PD, fatigue was diagnosed in 319 (91%) based on scores ≥4 on the 16-item Parkinson Fatigue Scale (PFS), which was designed to assess fatigue exclusively associated with PD, and 24% of those patients received pramipexole. Multiple logistic regression analysis revealed that the administration of pramipexole (mean daily dose, 2.1 mg) was significantly related to low rates of fatigue in patients who had Hoehn and Yahr stage <3 PD, and this benefit was attributed to the effect on DA D3 receptors. Finally, it was recently suggested in a post-hoc analysis of the Randomized Evaluation of the 24-Hour Coverage: Efficacy of Rotigotine (RECOVER) study that rotigotine transdermal system (2–16 mg/24 hours) given at the optimal dose for 4 weeks may improve nonmotor symptoms like fatigue.[74] Of 287 randomized patients, NMSS data were available for 267 patients (178 received rotigotine, and 89 received placebo). In addition to nocturnal improvements in sleep, that post-hoc analysis of individual items from the NMSS "sleep/fatigue" domain suggested that fatigue ("fatigue [tiredness] or lack of energy") was improved significantly after treatment with rotigotine. The presence of fatigue was reduced from 77% to 60% in those who received rotigotine compared with no reduction in the placebo group. However, the rotigotine effect obtained in that post-hoc analysis may have been secondary to improved sleep. Also, it was not possible to rule out a significant motor contribution to the observed data.

In an analysis of the Attenuation of Disease Progression with Azilect Given Once Daily (ADAGIO) study, Rascol et al.[75] reported that both 1 mg and 2 mg rasagiline daily, compared with placebo, decreased PFS scores. More recently, in a substudy of ADAGIO, 1105 untreated patients with PD were randomized to receive either rasagiline 1 mg daily ($n = 270$), 2 mg daily ($n = 277$), or placebo ($n = 558$) for 36 weeks.[56] The 16-item PFS was assessed at baseline and at week 36. At 36 weeks, the patients who received placebo showed greater progression of symptoms (0.17 units) from baseline in the PFS scores compared with the 1 mg daily (0.03 units) and 2 mg daily (−0.02 units) rasagiline groups; the difference versus placebo was significant for both rasagiline groups ($P < 0.01$). These data suggested that rasagiline was associated with significantly less progression of fatigue compared with placebo over a 9-month period. However, the authors stated that it was difficult to extrapolate the observed benefits to the clinical situation, especially because the magnitude of the effect was small (i.e., the results did not imply that rasagiline was a treatment for fatigue). Smith et al.[76] evaluated the change in nonmotor symptoms in patients involved in the ADAGIO study who were taking an antidepressant and rasagiline compared with those who were taking placebo. In addition to the depression, cognition, and daytime sleepiness scores, the PFS scores also revealed significantly less worsening in the rasagiline group compared with the placebo group.

Stimulants—particularly amphetamines—were proposed to be mildly beneficial in the treatment of fatigue in PD.[4] In the Movement Disorders Society evidence-based review of treatment options for nonmotor symptoms in PD, Seppi et al.[77] reviewed 3 studies.[59,61,62] Mendonca et al.[62] examined the effects of methylphenidate (30 mg daily for 6 weeks) for the treatment of fatigue in PD in a double-blind, placebo-controlled, parallel-group, randomized clinical study in 36 patients with PD who were on stable antiparkinsonian medications and had FSS scores ≥ 27. Both FSS (mean change, 6.5 points; 95% confidence interval [CI], 0.5–12.4 points; effect size, 0.79) and MFI (mean change, 8.4 points; 95% CI, 0.7–16.0 points; effect size, 0.63) scores were reduced significantly in the treatment arm over the course of the study ($P < 0.04$), whereas the placebo group did not experience a significant decline (FSS score: mean change, 1.9 points; 95% CI, −3.4 to 7.2 points; MFI score: mean change, 48.5 points; 95% CI, −4.1 to 10.5 points) over the course of treatment. However, statistical analyses for the 2 primary outcome measures were not corrected for multiple comparisons, and no direct comparison of methylphenidate and placebo treatment was made. Therefore, although the results appeared to be positive, the quality score of the study and methodological concerns led Seppi et al.[77] to the conclusion that evidence for efficacy was insufficient. Similar conclusions were reached in 2 other randomized placebo-controlled trials in which modafinil proved inadequate for the treatment of

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fatigue in PD. Lou et al.[59] conducted a randomized, double-blind, placebo-controlled, parallel-group study to examine the efficacy of modafinil (100 mg twice daily) for 8 weeks for the treatment of fatigue in 19 patients with PD who had MFI scores ≥ 48. After 2 months, the modafinil group showed a significantly higher tapping frequency, shorter dwell time, and less fatigability in finger tapping, but without any significant difference between groups over time for any dimension on the MFI. Tyne et al.[61] conducted a 9-week, double-blind, placebo-controlled, parallel-group, randomized study of modafinil (titrated up to 400 mg daily) in 13 patients with PD for the treatment of fatigue (FSS scores > 4). No statistically significant differences were observed in the change in fatigue scores between the 2 groups. Therefore, Seppi et al.[77] concluded there was insufficient evidence for the efficacy or safety of methylphenidate or modafinil for the treatment of fatigue in patients with PD and that such an approach should be considered investigational.

Other drugs with different mechanisms were also tested. In an exploratory study evaluating memantine (20 mg daily) for several common nonmotor problems in PD, specific measures, including 1 for fatigue, did not significantly improve (mean FSS score: baseline, 37.6; final measurement; 37.4).[63] A similar conclusion was reached in a 6-weak randomized, placebo-controlled trial of caffeine (up to 200 mg twice daily), in which no significant benefit was observed on excessive daytime sleepiness or on several secondary measures, such as fatigue.[65] In a 3-arm, 6-week, randomized pilot study assessing nonpharmacologic treatment (cognitive behavioral therapy with bright-light therapy) or doxepin, a tricyclic antidepressant with selective histaminergic antagonistic action at low doses (10 mg daily), compared with an inactive placebo, in 18 patients with PD (6 in each arm) who had insomnia, fatigue was a secondary outcome.[57] Doxepin reduced the FSS, whereas nonpharmacologic treatment had no effect. Recently, Jang et al.[78] conducted an exploratory pilot study to investigate the effects of recombinant human erythropoietin (40,000 IU infused intravenously twice a week for 5 weeks) on motor and nonmotor symptoms in 26 patients with PD who were assigned randomly to recombinant human erythropoietin and placebo groups. Within the NMSS, the domains of cardiovascular autonomic function, sleep/fatigue, mood/cognition, and attention/memory showed significant benefit.

Little is known about the effects of deep brain stimulation (DBS) on nonmotor symptoms, particularly fatigue, in patients with PD. Fatigue is common after DBS surgery in PD and appears to be associated with depression, apathy, and possibly anxiety, with a negative impact on the quality of life. Funkiewiez and colleagues used the Addiction Research Center Inventory questionnaire to evaluate fatigue ON and OFF DBS in patients 3 months after surgery.[79] Despite methodological problems, they observed some improvement in momentary "fatigue" when patients were in their ON DBS state. In another study of 17 patients who underwent bilateral subthalamic nucleus (STN) DBS, there was no significant change in the mean or binary PFS score from baseline to the 6-month evaluation.[80] However, individual fatigue responses were variable and were correlated with motor and mood improvements. Therefore, these data suggested that, in the patient cohort as a whole, STN DBS did not seem to affect fatigue in PD. Previous studies of DBS have not used the Movement Disorders Society revision of the Unified Parkinson Disease Rating Scale (MDS-UPDRS), which added more nonmotor items. Chou et al.[80] found that both motor and nonmotor symptoms, as assessed by the MDS-UPDRS, improved with bilateral STN DBS 6 months after the stimulator was turned on. Individual nonmotor items in part I that improved significantly were fatigue in addition to constipation and light headedness.

The outcome of nonpharmacological treatment of fatigue in patients with PD also is not very clear. Clinical practice in various medical conditions includes a range of nonpharmacological interventions, from cooling therapy to cognitive behavioral therapy, yoga, exercise, etc., but there is limited evidence of their effectiveness. In their systematic review in PD, Franssen et al.[53] concluded that no nonpharmacological treatment showed efficacy.[57,64] Exercise is a plausible, inexpensive intervention for reducing fatigue that may extend to PD as well. However, sufficient exercise to influence fatigue may be difficult to achieve in patients with severe motor limitations,[4,14] suggesting the potential need for forced or assisted exercise to assist the individual in achieving or maintaining a given rate that exceeds their preferred voluntary intensity level. Winward et al.,[66] in a single-blinded manner, examined the effects of a 12-week prescribed exercise on physical activity levels, well-being, and fatigue (measured with the FSS) in 39 patients with PD (20 in an exercise group and 19 in a control group) but failed to find any benefit. They observed that, when the group was dichotomized into those with fatigue (FSS score ≥ 4) and those without fatigue (FSS score < 4), those who were fatigued were more likely to be less active and have a lower quality of life compared with those who were not fatigued. Adapted physical activity programs for patients with PD induced a significant improvement in motor and nonmotor symptoms, including fatigue.[81] Preliminary data suggested that aerobic walking in a community setting improved not only aerobic fitness, motor function, mood, executive control, and quality of life, but also improved fatigue in patients with mild to moderate PD.[82] Despite inconsistencies, patients with PD should be encouraged to participate in safe forms of physical activity to minimize risks (e.g., falls) associated with the disease, improve motor function, and possibly attenuate the progression of the disease.[83]

Finally, we may pessimistically conclude that, at this point in time, we have only initial insights into the pathophysiological mechanisms underlying the otherwise clinically heterogeneous phenomenon of fatigue in PD. Consequently, there are neither evidence-based guidelines nor clinically established empirical approaches to the treatment of fatigue in PD. In light of the impact that fatigue has on the quality of life of these patients, future studies should focus on nonmotor symptoms, including fatigue, hopefully bringing significant relief.

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Author Roles:

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript: A. Writing of the First Draft, B. Review and Critique.

V.S.K.: 3A,3B

A.T.: 3B

M.J.-L.: 3B

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