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REVIEW

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Identifying and responding to fatigue and apathy in Parkinson's disease: a review of current practice

Claudia Lazcano-Ocampo [a,b,c#], Yi Min Wan [a,b,d#], Daniel J van Wamelen [a,b,e], Lucia Batzu [a,b], Iro Boura [a,b], Nataliya Titova [f], Valentina Leta [a,b], Mubasher Qamar [a,b,g], Pablo Martinez-Martin [h] and K Ray Chaudhuri [a,b]

[a]King's College London, Department of Neurosciences, Institute of Psychiatry, Psychology & Neuroscience, De Crespigny Park, London, UK; [b]Parkinson's Foundation Centre of Excellence, King's College Hospital, Denmark Hill, London, UK; [c]Department of Neurology, Hospital Sotero Del Rio, Santiago, Chile; [d]Department of Psychiatry, Ng Teng Fong General Hospital, Singapore;; [e]Cognition and Behaviour; Department of Neurology; Nijmegen, Radboud University Medical Centre; Donders Institute for Brain, The Netherlands; [f]Department of Neurology, Neurosurgery and Medical Genetics, Federal State Budgetary Educational Institution of Higher Education «N.I. Pirogov Russian National Research Medical University» of the Ministry of Healthcare of the Russian Federation, Moscow, Russia; [g]Queen Elizabeth the Queen Mother Hospital, East Kent Hospitals University NHS Foundation Trust, Margate, UK; [h]Center for Networked Biomedical Research in Neurodegenerative Diseases (CIBERNED), Carlos III Institute of Health. Madrid, Spain

ABSTRACT

Introduction: Fatigue and apathy are two key non-motor symptoms in Parkinson's disease (PD), with documented negative impact on Quality of life (QoL) and a frequent burden for caregivers.

Areas covered: In this review, the authors comment on the latest pathophysiology, clinical phenomenology, the most frequently used scales for fatigue and apathy in PD with a focus on available therapeutic strategies.

Expert opinion:The identification of fatigue and apathy in PD is mainly hampered by the lack of a clear consensus on these subjective symptoms. The pathophysiological processes remain unclear, and the large variation in prevalence is likely due to the heterogeneous PD populations and the lack of an enriched cohort of people with fatigue and/or apathy as main symptoms. Treatment strategies, and especially level 1 evidence for specific treatments for fatigue and apathy in PD, remain scarce. The best evidence to date is doxepin, rasagiline and levodopa infusion therapy (for fatigue), and rivastigmine (for apathy). Further efforts should be made to properly identify these two major symptoms in PD, to correctly detect those who may benefit most from tailored personalized interventions.

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Fatigue; apathy; Parkinson's disease; scales; treatment

1. Introduction

Parkinson's disease (PD) is a neurodegenerative syndromic condition involving both motor and non-motor symptoms (NMS). Virtually omnipresent, NMS of PD often start a decade or more before motor symptoms manifest [1]. Among the known NMS, fatigue and apathy are two of the more troublesome ones reported [2].

1.1. Fatigue

Fatigue, from the Latin *fatigare*, is defined as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion, which is unrelated to physical activity [3]. Two main forms of fatigue exist: 1) *physiological fatigue*, which constitutes a reaction to intense and prolonged activity and, as such, is predictable and transient, and 2) *pathological fatigue*, which involves feelings of tiredness at rest and a disproportionate lack of energy that compromise daily activities and quality of life (QoL) for a prolonged period of time, usually more than 3 months [4,5]. A further distinction can be made between subjective fatigue and objective fatigue (fatigability); as these conditions do not necessarily correlate [6]. *Subjective fatigue* is a feeling of finding it tiring or troublesome to initiate a mental or physical activity for days to weeks, whereas *fatigability* refers to problems maintaining physical and mental effort at a certain level during a short period of time [6]. Subjective fatigue can be further categorized in physical and mental fatigue, where *physical fatigue* is described as a sense of disproportionate physical exhaustion despite the incentive to perform a task, whilst *mental fatigue* is the experience during and after prolonged activity involving cognitive tasks that require sustained attention and mental effort [7]. However, the severity of mental fatigue does not correlate well with physical fatigue in PD, suggesting a separate subjacent mechanism [8].

1.2. Apathy

The term 'apathy', introduced by the Stoics (Greek: *apatheia* (ἀπάθεια) meaning 'without feeling or suffering'), refers to the loss of motivation and lack of concern toward the external world. It was initially conceptualized by Marin et al. [9] but was

CONTACT Claudia Lazcano-Ocampo c.lazcano.ocampo@gmail.com Institute of Psychiatry, Psychology & Neuroscience, Department of Basic and Clinical Neuroscience, De Crespigny Park, London SE5 8AF, United Kingdom. Tel. +44 2032997189
[#]Authors are to be considered as joint first authors.

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Article highlights

- Fatigue and apathy are key, yet often undetected, non-motor symptoms in Parkinson's disease.
- Both symptoms have a tangible impact on quality of life in people with PD.
- The pathophysiology underlying these symptoms remains largely unclear and evidence supports both dopaminergic and non-dopaminergic pathways.
- The scale with best psychometric properties for fatigue so far is the Parkinson's Fatigue Scale, and for apathy is the Starkstein Apathy Scale.
- Treatment strategies for both symptoms lack level 1 evidence base.
- The best evidence for fatigue treatment is for doxepin, rasagiline, and levodopa infusion therapy.
- The best evidence for apathy treatment is for rivastigmine.
- Further efforts towards individualized strategy-driven research and treatment are needed.

later revised and adapted for PD by Starkstein et al. [10,11]. Absence of motivation is usually the cornerstone in defining apathy, which additionally includes a decrease in goal-oriented behavior and cognition, and a reduction in emotional expression [12].

Conventionally considered a unitary construct, apathy is currently represented by three key aspects with different clinical manifestations [13–15]:

a. *Affective-emotional apathy* – the impairment of linking affective and emotional signals with manifest behavior, expressed by emotional blunting and modified social interaction.
b. *Cognitive apathy or 'cognitive inertia'* – the impairment of conceiving and achieving goal-directed behavior, expressed by executive functioning.
c. *Behavioral apathy or 'auto-activation'* – the inability to activate and maintain spontaneous patterns of action and thought in the presence of spared ability to generate externally driven behavior, which affects both emotional and cognitive responses.

In this narrative review, we aim to summarize updated evidence-based recommendations on how to identify and respond to fatigue and apathy in PD.

2. Methods

A computerized search of PubMed, PsycINFO, EMBASE, CINAHL, the WHO International Clinical Trials Registry and the Cochrane Library of literature published up until December 2019 to identify all potentially eligible studies was conducted. For PubMed, we used the Medical Subject Heading (MeSH) term 'fatigue', or 'apathy', combined with the MeSH term 'Parkinson' or 'Parkinson's'. All MeSH terms were expanded to include all subheadings to identify all relevant articles. All potentially eligible studies were considered regardless of publication type. The Cochrane Database of Systematic Reviews and the reference lists of each article were also manually checked to identify additional studies. No language, publication date, or publication status restrictions were imposed. Selection and independent assessment of the abstracts were done by the research team from the Parkinson Foundation Centre of Excellence in non-motor research at King's College Hospital and King's College London. Disagreements were resolved by a consensus-based discussion.

3. Epidemiology

3.1. Fatigue

Fatigue in PD is more prevalent than in age-matched controls, even in early disease stages, with a clear negative impact on QoL, being described as one of the most three disabling symptoms by more than 50% of the people with PD (PwP) [16–18]. Its prevalence in PD ranges from 33% to 81% averaging to about 50%; these fluctuations in the estimated figures possibly attributed to differences in measurement methods and sampled populations [16]. To date, it seems to be that there is no correlation between fatigue and disease duration and motor symptoms, and could be associated to other non-motor symptoms such as anxiety, apathy, and sleep disturbances, as described in a recent meta-analysis [19]. Once fatigue is present, it is likely to persist or aggravate over time [16,20].

3.2. Apathy

Apathy has been reported in *de novo* PD, early in the disease preceding motor symptoms, and in advanced disease stages [21–24], being noted to progress parallel to the evolution of PD [25–27]. Due to its nature, occurrence of apathy in PD is likely underestimated. Reported prevalence ranges between 13.5% and 70% [28], with a recent meta-analysis reporting a pooled prevalence of 39.8% [12], although, similar to fatigue, these figures could be confounded by other comorbid NMS and the heterogeneity of the sampled populations and the measurement methods. The prevalence of apathy in PD excluding depression was about 42.8%, whilst its prevalence excluding cognitive impairment was reportedly in the range of 28%-39%, depending on methods of diagnosis [12]. The prevalence of pure apathy, after excluding both depression and cognitive impairment, is reported to be about 22.6% [12].

4. Pathophysiology

4.1. Fatigue

The understanding of fatigue pathophysiology has been a challenging concept, partly due to inconsistencies in fatigue definition and use of different methods of assessment across studies [29]. To date, and in spite of several efforts, it remains elusive to segregate the pathophysiology and understanding of fatigue from other NMS in PD, since it is not clear whether the occasional co-occurrence of these symptoms could be attributed to a common mechanism, like the degeneration of serotonergic pathways and abnormal activity and connectivity of limbic-cortical circuits [19], or to diagnostic bias [30].

No association was found between dopaminergic nigrostriatal degeneration, one of the hallmarks of PD pathology, and fatigue through neuroimaging studies [8,31], except for one study where nigrostriatal dopaminergic denervation assessed with [^{11} C] DTBZ PET was a significant predictor of fatigue in participants with mild PD [32] (Figure 1). Lack of association between fatigue and motor symptoms of PD could be another indirect indication that non-nigrostriatal dopaminergic dysfunction produces fatigue in PD [19], while the finding of reduced F-dopa uptake in the insular cortex of PD participants with fatigue might suggest a dysfunction of extrastriatal dopaminergic projections [8]. Interestingly, a link was reported between serotonergic denervation in the basal ganglia and associated limbic circuits using [^{11} C] DASB PET scan [8] (Figure 1). Modifications in serotonergic signaling could potentially affect the frontal-basal ganglia circuitry and integration of limbic input and motor functions and might represent a possible mechanism underlying fatigue in PD [19].

Dysfunction of circuits connecting the basal ganglia and medial frontal areas (frontal striato-thalamo-cortical loops) has also been suggested to be involved in fatigue pathophysiology [33]. In one study, fatigue perception was associated with decreased blood perfusion in the frontal lobes, suggesting that dysfunction in the frontal cortex might be a cardinal contributor to fatigue [34]. In an fMRI study conducted on a cohort of 'drug-naïve' patients with PD, fatigue was associated with decreased connectivity in the supplementary motor area and increased connectivity in the prefrontal and posterior cingulate cortices within the default mode network (DMN) [35].

Neuroinflammation may also be assumed to account for different levels of fatigue and disability seen in many patients with neurological and autoimmune diseases [36]. In a study with PD patients, fatigued subjects had elevated interleukin (IL)-6 serum levels compared to non-fatigued patients [37], while in another study, after controlling for possible confounders, high CRP levels in the CSF were significantly associated with more severe symptoms of fatigue and depression [38].

Finally, animal models have shown that the overexpression of alpha-synuclein in mice could diminish their performance over wheel-running compared with wildtype control, probably related to reduction of the daytime electrical activity of the suprachiasmatic nucleus neurons (SCN) and motor centers who are targets of the SCN [39,40]. Rat models have also supported the influence of neuroinflammation with a higher production of IL-1β which is not only related to central fatigue but other neurological conditions such as stroke, brain trauma, multiple sclerosis, Alzheimer's disease, PD, and chronic diseases like depression [41].

4.2. Apathy

The neural networks underlying apathy in PD provide a conjectural foundation to spearhead an exploration of cognitive, behavioral, and emotional domains of apathy [13], as well as investigate possible neuropsychological correlates of each domain.

Pre-clinical studies in rodents have proposed that apathy may stem from dysfunction of the dopaminergic mesocorticolimbic system, and additionally recommended that D3 R be targeted in the reversal of motivational deficits in PD [42]. Furthermore, it has been suggested that apathy represents the opposing end of a behavioral dopamine-dependent continuum from impulse control disorders (ICDs) in PD [43]. In support of the hypodopaminergic etiology, several studies suggested that apathy is mainly associated with deficits in the dopaminergic networks (Figure 2), as it is closely related to the brain reward system [44–46]. For instance, Thobois et al. compared the PET scans of 12 people with PD who suffered from post-DBS apathy with those who did not and demonstrated that the grow up with apathy had lower endogenous dopamine [47]. A recent study also revealed that apathy was inversely correlated to a marker of both dopamine and noradrenaline transporters ([11 C]RTI-32) in the ventral striatum [48]. The emergence of apathy after rapid reduction of anti-

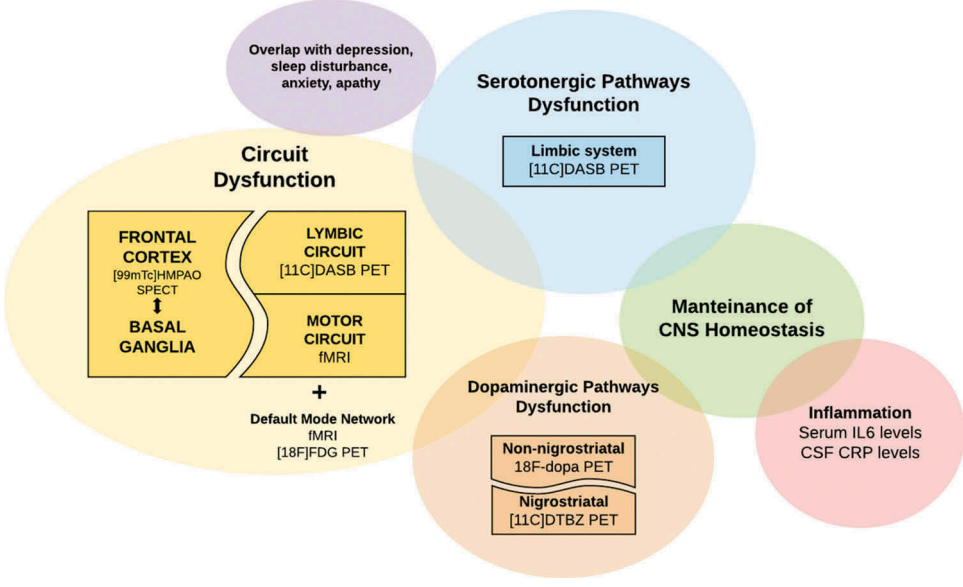

Figure 1. Different brain networks and neurotransmitter systems involved in Parkinson's disease fatigue.

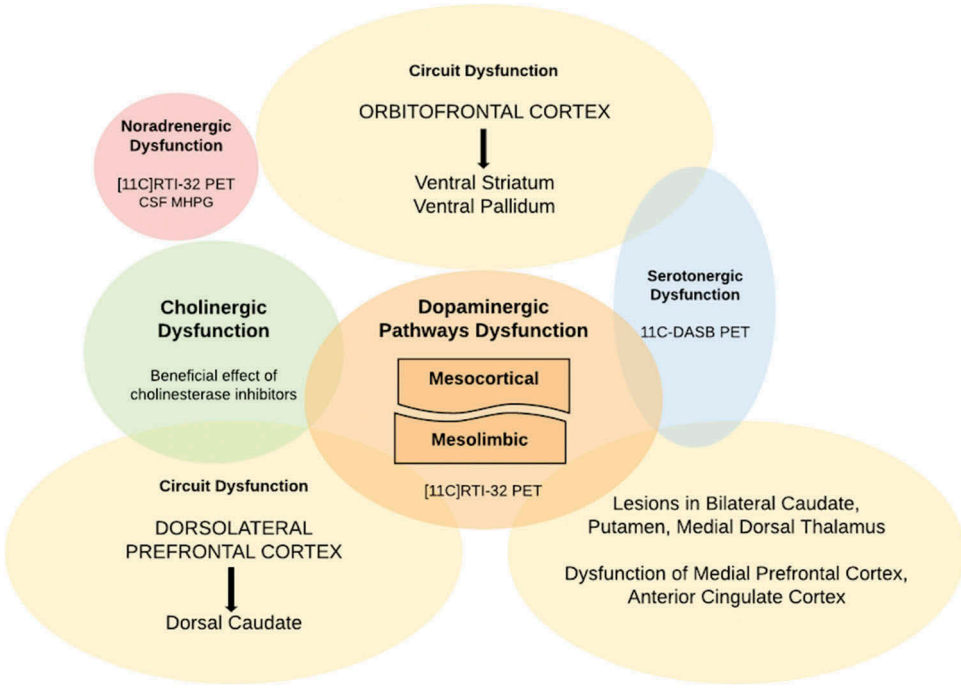

Figure 2. Circuit dysfunctions and different neurotransmitter systems involved in the pathophysiology of apathy.

parkinsonian drugs post-deep brain stimulation (DBS) [46] and the description of the positive influence of levodopa treatment on self-reported motivation in PD patients [45] also endorsed that apathy in PD is, at least in part, a dopamine-dependent syndrome.

On the other hand, the relationship between apathy and executive function [22], depression [21,22], and sleep disturbances [22] implicates additional non-dopaminergic origins. Mayeux et al. found a correlation between the CSF concentration of 3-methoxy-4-hydroxyphenylglycol (MHPG), the major metabolite of noradrenaline, and cognitive measures of bradyphrenia [49], which advocates that bradyphrenia (which is similar to the concept of apathy) in PD may be related to dysfunction of catecholaminergic pathways and the locus coeruleus. Evidence of a disruption in the serotonergic systems is also revealed by the 2016 study in *de novo* PD, when 15 patients with apathy primarily demonstrated greater serotonergic alteration in the ventral striatum, the dorsal, and the subgenual parts of the bilateral anterior cingulate cortices, as well as in the right-sided caudate nucleus and the right-sided orbitofrontal cortex, as compared to those without apathy [50]. Finally, the cholinergic systems may also play a vital modifying role on motivation in PD, given the robust link between PD apathy and cognitive impairment which is elaborated later in this text, and also based on the therapeutic benefit of cholinesterase inhibitors for treating apathetic behavior in some without depression and dementia [51].

In structural and functional imaging studies, apathy has been associated with the frontal cortex, basal ganglia, substantia nigra, anterior cingulate cortex, and orbitofrontal cortex in PD [52,53]. A 2010 study of apathy in PD revealed an association between apathy and decreased gray matter density in the anterior and posterior cingulate and bilateral inferior frontal gyri, as well as associated structures such as right precuneus, insula and bilateral precentral, inferior parietal, and inferior frontal cortex [53,54]. In addition, Skidmore and colleagues [54] reported a correlation of apathy with abnormal patterns of activation in the left supplementary motor cortex, the right orbitofrontal cortex, and the right middle frontal cortex, supporting the assumption that apathy in PD is related to orbitofrontal lobe dysfunction.

Studies of apathy in different neurodegenerative disorders have revealed that it may be a consequence of severe neuronal loss in the basal ganglia despite a lesser degree of prefrontal pathology, implying that apathy could be addressed as a 'prefrontal-like' syndrome due to lesions mainly affecting the basal ganglia. The failure to generate basal ganglia output to the frontal lobes and to select, extract, and augment the relevant incoming signal from background noise makes the transmission of the extracted signal to the prefrontal cortex (in order to maintain ongoing and generate new behavior) impossible [14,55].

In general, apathy is complex and multidimensional in etiology, with divergent mechanisms across different neurodegenerative disorders and across different stages of PD.

5. Description of symptoms

5.1. Clinical features of fatigue

Fatigue can go unrecognized by physicians, but given the significant impact on QoL in PD, and repercussions on public health care it is important not to miss this symptom [56,57].

Furthermore, it can significantly affect the caregiver's QoL when fatigue is associated with dementia [58], which could potentially increase the need of institutionalization. When addressing fatigue, it is important to ask the patients to describe their complaints, as fatigue is often referred to as

an unbearable tiredness, utter exhaustion, and a feeling of severe illness, which could be helpful to distinguish (a) from daytime sleepiness, as fatigue does not improve after sleeping, (b) from apathy as patients usually want to do activities but are limited due to lack of energy and (c) from depression, as it is not related to mood [18]. However, as fatigue overlaps frequently with these NMS, the approach to manage these patients in a holistic manner becomes a challenge, emphasizing on the need to take a comprehensive non-motor history aided by validated tools such as the NMS questionnaire. Time of onset can be used to rule out secondary causes of fatigue, such as other health issues (stroke, chronic diseases) or the concomitant use of medication that can worsen it, e.g. beta-blockers [59]. In addition, Kluger recommended considering the diurnal pattern of fatigue in PD, with it worsening during the afternoon. Fatigue can be a feature of non-motor fluctuation and is often associated with an off state [60], thus suggesting a dopaminergic basis in this scenario.

5.2. Clinical features of apathy

As a neuropsychiatric symptom, apathy in PD is often found to intersect with other neuropsychiatric syndromes such as depression, anhedonia, and anxiety. A study in 2017 assessed 40 Pw Pwith dementia and revealed that apathy was associated with advanced dementia, and could exist independent of depression [61]. The main differentiating clinical parameter between depression and apathy (once considered part of the depression symptomatology) is the mood, as it remains 'neutral' in the latter and negatively affected in the former [62]. While depression incorporates guilt and suicidal intentions, apathy does not often show such symptoms; rather, it identifies with emotional indifference or lack of emotional response to positive or negative events [63,64]. Apathy can indeed occur separately from depression in PD [65,66], and both independently exert a negative impact on QoL [66–68].

Symptoms exclusive to apathy are summarized in Table 1.

Studies examining apathy in neurodegenerative conditions have found that those with apathy have lower Mini-Mental State Examination (MMSE) scores than those without, and this have demonstrated impairment in impulse control, attention, visual and verbal memory, and verbal fluency [69]. Associated not only with PD dementia (PD-D) [61,70], apathy has also been found in PD patients with mild cognitive impairment (PD-MCI) and is postulated to be the key neuropsychiatric herald for the conversion to dementia [71]. Indeed, a very recent study [72] demonstrated apathy to be the staunchest behavioral predictor of early cognitive decline in PD.

Table 1. Exclusive symptoms of apathy.

Apathy symptoms
Reduced initiative
Reduced participation in external activity
Loss of interest in daily or social activities
Reduced interest in starting new activities
Reduced interest in the happenings of the external environment
Emotional indifference
Reduced emotional reactivity
Lack of concern about other people's feelings, or interests

For PwP, apathy exerts a negative impact on QoL [73] and poses significantly greater burden on the caregiver, which has negative implications on the caregiver's physical, emotional, and psychosocial well-being [74]. Increased caregiver distress, in turn, contributes to the QoL decline in PD, leading to an increased risk of premature institutionalization [75].

On the whole, apathetic Pw Pwere found to be more likely to have greater motor deficiency, major executive dysfunction, and a greater risk of developing dementia than those who were non-apathetic [26]. They are also more likely to have greater olfactory deficits, possibly due to overlapping dysfunction in associated brain regions [76]. The dimension of emotional blunting serves as a modifier for PD with apathy, leading to worse QoL and greater caregiver burden, even in the absence of dementia [77].

6. Measuring fatigue and apathy in PD

6.1. Sign-posting and screening with the non-motor symptoms scale

The NMS Scale (NMSS) [78] is a multidimensional tool, used to quantify a wide range of non-motor symptoms occurring in PD, each one scored for severity and frequency by the physician and evaluating a time frame of 1 month. The NMSS is composed of 30 items grouped into 9 domains, the collective sum of which comprises the total score. Fatigue, together with sleep disturbances, is a key component of domain 2 of the NMSS (sleep/fatigue domain) as well apathy in domain 3, and both can be scored based on the multiplication of its severity and its frequency [79]. The development of an updated version of the NMSS was launched in 2015 with the support of the International Parkinson and Movement Disorder Society (MDS) and the final version of the MDS-NMS is now published [80]. In this new scale, physical and mental fatigue is specifically addressed under the 'Others' domain and fatigue has also been included in an optional section targeting non-motor fluctuations (NMF) [80,81]. Furthermore, apathy is a specific domain in it (domain C) showing good domain-based clinimetric attributes in the first international validation study. In the context of a holistic NMS evaluation, the MDS-NMS provides a one-stop assessment of apathy as well as the ability to measure other possible comorbid NMS in an individual with PD.

6.2. Specific fatigue scales

Most subjective fatigue rating scales are self-reported questionnaires aiming to give a measure of individual perceptions of fatigue, nevertheless clinician-rated scales have also been probed to be useful (Table 2) In 2010, an MDS Task Force published a critical review on rating scales and provided recommendations on their endorsement for screening fatigue in PD and assessing its severity [82].

6.2.1. The fatigue severity scale (FSS)

The FSS [83] is the only 'recommended' fatigue scale for both screening and quantifying severity of PD subjective fatigue by the MDS Task Force. The FSS is brief and easy to administer.

Table 2. Rating scales for fatigue in Parkinson's disease.

Rating Scales to evaluate fatigue in Parkinson's disease				
Scale	Time to complete	Number of items	Rater	Advantages
MDS – Non-motor Rating Scale (MDS-NMS)	15 – 40 minutes	52	Self-rated	• Holistic tool to assess fatigue and fatigue fluctuations in the context of all nonmotor symptoms
Fatigue Severity Scale (FSS)	5 min	9	Self-Rated	• Brevity and ease of administration • Applicable to PD patients in all ages, genders, and severity stage • Good discrimination of PD patients from healthy controls
Fatigue Assessment Instrument (FAI)	10 – 30 min	29	Self-rated	• Assessment of multidimensionality of fatigue • Definition of fatigue provided
Multidimensional Fatigue Inventory (MFI)	5 – 10 min	20	Self-Rated	• Brevity • Assessment of multidimensionality of fatigue
Parkinson's Fatigue Scale (PFS-16)	15 min	16	Self-rated	• Brevity and ease of administration • Good discrimination of PD patients from healthy controls • Good discrimination between fatigued and non-fatigued patients
Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F)	5 min	13	Self-rated	• Brevity • Available in more than 50 languages
Modified Fatigue Impact Scale (MFIS)	5 – 10 min (2 – 3 min for short version)	21 (5 for short version)	Self-rated	• Brevity • Assessment of multidimensionality of fatigue • Abbreviated version easy to use in clinical settings. • Definition of fatigue provided
Fatigue Impact Scale for Daily Use (D-FIS)	8 min	5	Self-rated	• Brevity • Designed for daily administration • Definition of fatigue provided
Clinical Global Impression Scale (CGIS)	1 min	1	Clinician-rated	• Brevity and ease of administration
Visual Analog Fatigue Scale (VAFS)	1 min	1	Self-rated	• Brevity and ease of administration • Assessment of patient's overall status of well-being.
Non-Motor Symptoms Scale (NMSS)	5 – 10 min (whole scale)	4 (30 for whole scale)	Clinician-rated	• Brief and ease of administration

However, it lacks a clear definition of fatigue, potentially reducing its ability to independently discriminate fatigue related to PD pathophysiology from other PD-related conditions. An extended 29-item multidimensional version of the FSS, the *Fatigue Assessment Inventory* (FAI) [84], has been developed. However, despite providing a definition of fatigue and giving information on different dimensions, its clinimetric properties need to be further studied.

6.2.2. The multidimensional fatigue inventory (MFI)

The MFI [85] provides information about five dimensions of fatigue: general, physical, mental fatigue reduced motivation and reduced activity. The strengths of the MFI are its multidimensionality and its good psychometric properties. It has shown to be sensitive to change in one study in PD patients [86]. Weaknesses are the lack of definition of subjective fatigue and insufficient data on its reliability in PD, as well as the need of confirmatory studies regarding its underlying dimensions.

6.2.3. The Parkinson's fatigue scale (PFS 16)

The PFS [87] is the only rating instrument specifically designed for PD. It is a 16-item self-rated scale, aiming to assess a single construct reflecting the physical aspects of fatigue in PD and its impact on daily function. The PFS seems also to be responsive to changes due to treatments [88,89]. It has also been validated for use in advanced PD and its responsiveness has been recently reaffirmed [90]. The PFS is short and easy to complete, although it does not define fatigue and its focus on the physical dimensions might preclude the detection of meaningful nonphysical aspects of fatigue in PD.

6.2.4. The functional assessment of chronic illness therapy-fatigue scale (FACIT-F)

The FACIT-F is a self-reported scale developed to assess fatigue and anemia-related concerns experienced in people with cancer and has been validated in PD [91]. The strengths of the FACIT-F lie in its briefness and availability, in robust psychometric properties and in a good correlation with other fatigue scales in PD. However, the FACIT-F lacks a definition of fatigue and it showed low sensitivity to change in PD.

6.2.5. Other scales for fatigue

Several other rating scales for subjective fatigue have been developed and some of them have been previously used in PD studies. However, they were not included by the MDS Task Force because of insufficient psychometric data [82]. These scales include the Fatigue Impact Scale for Daily Use (D-FIS) [92], a brief and

comprehensive 8-item scale with satisfactory psychometric attributes designed for daily administration, and the Clinical Global Impression Scale (CGIS) [93], a rating instrument which can investigate all aspects of a chosen condition with a numerical measure (usually 5 or 7-point rating) for symptom severity. Interestingly, a recent study aiming to investigate the dimensionality of the constructs of fatigue identified the single-item Visual Analog Fatigue Scale (VAFS) as a potential reliable estimate for the overall sensation of excessive fatigue experienced by individuals with PD [94].

6.3. Scales for apathy

An arsenal of instruments is currently used to measure apathy (Table 3), which a few of the more important ones are described more extensively below, with most being self-reported subjective questionnaires. The Movement Disorder Society (MDS) Task Force to Assess the Clinimetric Properties of Apathy and Anhedonia Scales in PD [95] identified four apathy rating scales: the Apathy Evaluation Scale (AES); the abbreviated version of the AES, known as the Apathy Scale (AS); the Apathy Inventory (AI); and the Lille Apathy Rating Scale (LARS). The AS, AI, and LARS were specifically developed for PwP, but only the AS meeting criteria to be 'recommended' [95].

6.3.1. Apathy evaluation scale (AES)

The AES is a generic scale which has been specifically validated in PD population, including *de novo* PD [96], PD with comorbid dementia and depression [97,98], PD-MCI [99], as well as PD with STN-DBS [100]. There are three versions of this scale available: Patient (AES-S), Caregiver (AES-I), and Clinician (AES-C). The AES-C was one of the first instruments created to assess apathy in neurologic populations, and one of the first to quantify apathy based on a psychological definition. The AES-C has good internal consistency; however, those who are more cognitively impaired tend to score higher [101]. It has good interrater and test–retest reliability, and moderate item-total correlations. The informant- and patient-based versions have a good convergent validity, but concurrent validity with the NPIa is weak [97,101]. It reportedly has the highest sensitivity and specificity with both being 90% [96].

6.3.2. Starkstein apathy scale (AS)

The AS is a condensed and modified version of the AES developed by Marin et al., in 1991 [11]. It was specifically developed as a less demanding scale for people with PD, as compared to the AES. The reliability and validity of the original, patient-based, version of AS has been established [10], with excellent inter-rater reliability, test–retest reliability, and questionable-to-excellent internal

Table 3. Rating scales for apathy in Parkinson's disease.

Rating Scales to evaluate apathy in Parkinson's disease				
Scale	Time to complete	Number of items	Rater	Advantages
MDS – Non-motor Rating Scale (MDS-NMS)	15 – 40 minutes	52	Self-rated	• Holistic tool to assess apathy in the context of all nonmotor symptoms
Apathy Evaluation Scale (AES)	20 min	18	Self-report (AES-S) Informant (AES-I) Clinician (AES-C)	• Original quantitative scale assessing apathy • Has been extensively used in PD research • Suitable for all PD stages • Highest sensitivity and specificity of all apathy scales
Starkstein Apathy Scale (AS)	10–12 min	14	Self-Rated	• Informant version available • Brief and easy to complete • Suitable for all PD stages • Good sensitivity to change • Good balance of sensitivity and specificity • Recommended for screening and assessing severity by the MDS-Task Force
Lille Apathy Rating Scale (LARS)	20–25 min	33	Informant or self-rated	• Four composite subscales including intellectual curiosity, self-awareness, emotion, and action initiation • Sensitivity to change showed • Comprehensive and easy to use
Neuropsychiatry Inventory Apathy (NPIa) subscale	5 min	Screening question + 8 sub-questions	Informant-based interview	• NPI (complete scale) has been validated and extensively used in PD populations both with and without dementia
Ardouin Scale of Behavior in Parkinson's Disease (ASBPD) – Part II	NA (1 hour for the whole scale)	21 (whole scale)	Clinician-rated	• Evaluation of activity level, cognitive level, and emotional level
Apathy Inventory (AI)	NA	3	Self-rated	• Brief and easy to use • Informant version available • Assessment of frequency and severity of three domains: emotional blunting, lack of initiative and lack of interest
Frontal Symptoms Behavioral Scale (FrSBe) - Apathy Subscale	10 min	12	Informant, self-rated (2 versions)	• Brief and sensitive to change
MDS-UPDRS* (Part I)	30 min (whole scale)	13 (one for apathy)	Self-rated	• Extensively used in PD
Non-Motor Symptoms Scale (NMSS) – Mood/Apathy Domain	5 – 10 min (whole scale)	6 (30 for the whole scale)	Clinician-rated	• Brief and easy to administer

consistency [102,103]. As the instrument is based on a self-reporting system, those whose spontaneity is excessively low or have advanced dementia likely cannot answer the questions, which may limit the use of AS, but may be used in those with mild cognitive impairment [95]. The advantages of the AS are its brevity, its ease of administration, and its extensive worldwide use. It has been shown to be sensitive to change as well, especially in pharmacological treatment [104,105], as well as in treatment by DBS [106].

6.3.3. Lille apathy rating scale (LARS)

The LARS is a structured clinician-administered scale specially designed for PD and validated in a group of PD patients with and without dementia [107]. To date, it had shown sensitivity to change in two treatment studies and could discriminate apathy in PD from healthy controls [108]. It can be used in people with mild-to-moderate PD. However, it did not quite meet the MDS criteria for 'recommended' [95].

6.3.4. Neuropsychiatry inventory (NPI)- apathy (NPIa) subscale

The Neuropsychiatry Inventory (NPI) was developed to assess and measure neuropsychiatric disturbances in dementia [109]. The NPIa subscale (Item G) assesses apathy change over the past month or since the last evaluation. There is a lack of studies assessing the psychometric properties of the NPIa in PD. Despite this and it being a generic instrument, the NPI has been used extensively in the PD population [110–112] and it has been shown to be valid in PD populations both with and without dementia [110,113].

6.3.5. Ardouin scale of behavior in Parkinson's disease (ASBPD)

The ASBPD was a semi-structured clinician-conducted interview developed to evaluate several neuropsychiatric symptoms (NPS) and non-motor fluctuations, as existing scales do not identify all NPS present in those with PD [114]. Although considered to be overall reliable in detecting apathy, with acceptable internal consistency and test–retest reliability, studies of its convergent validity showed significant association with standardized rating scales measuring depression and anxiety, rather than with pure symptoms of apathy [114].

6.3.6. Apathy inventory (AI)

The AI is a three-item scale to assess global and subdomain apathy (emotional blunting, lack of initiative and lack of interest); one item for each domain [115]. This is a self-reported generic scale in which the user assesses his own behavior for each item (Yes/No), and then bisects a line reflecting severity of behavior on a 12-point scale ranging from mild to severe). Its brevity and ease of use made it attractive for use. However, although AI was disease-specific for evaluation of apathy in PD, no studies other than the original have used it in the PD population. Furthermore, it is copyrighted by CoBTeK – Association Innovation Alzheimer, and permission is needed before it can be used.

6.3.7. Frontal symptoms behavioral scale (FrSBe)

FrSBe [116] is a brief, reliable, and valid measure of three frontal behavioral syndromes: apathy, disinhibition, and executive dysfunction. It is sensitive to changes over time since it includes both baseline and current assessments of behavior. However, it needs to be purchased and is not freely available.

6.3.8. Movement disorder society–unified Parkinson's disease rating scale (MDS-UPRDS) Part I

The MDS-UPDRS [117] is a patient-rated scale, which retains the UPDRS structure of four parts with a total summed score, but the parts have been modified to provide a section that integrates non-motor elements of PD. It is a PD-specific scale and is available online although permission from the MDS is needed to use it. It has been translated into multiple languages and has been used in mild-to-moderate PD.

6.3.9. The MDS non-motor rating scale (MDS-NMS)

Apathy is a specific domain in the newly validated MDS-NMS (domain C) [81] and it shows good domain-based clinimetric attributes in the first international validation study. In the context of a holistic NMS assessment, the MDS-NMS provides assessment of apathy as well as the ability to measure other possible comorbid NMS in a patient using one tool.

7. Current therapy for fatigue and apathy

Although approximately one-third of PwP consider fatigue as the single most disabling symptom of their disease [118,119], treatment options are still very limited. In 2019, the MDS Evidence-Based Medicine (EBM) Committee published recommendations on treating PD-NMS [120] from which we based our recommendations for fatigue and apathy treatment, with the addition of recent evidence from both pharmacological and non-pharmacological perspectives (Table 4; Table 5).

7.1. Pharmacological treatment

7.1.1. Dopaminergic therapy

7.1.1.1. Levodopa. In the clinical trial, ELLDOPA (early PD enrolled in the Earlier vs. Later Levodopa), a total of 361 PD patients were enrolled and divided in four groups: carbidopa/levodopa 37.5/150 mg, 75/300 mg, and 150/600 mg per day vs. placebo [31]. After 40 weeks receiving medication and 2 weeks of washout period, increases in fatigue score from baseline to the final visit were noted, specifically in the placebo group whilst no significant change was observed in PD patients who had subjective fatigue from baseline. Previously, Lou et al. [121] described a reduction in physical fatigue in patients using levodopa, reaffirming that fatigue could have a dopaminergic etiology.

Similarly reflecting the overarching dopaminergic origins of apathy, a 2002 study showed that apathy levels (AS) of a group of PD patients without dementia or depression improved significantly under L-Dopa treatment [45].

7.1.1.2. Rotigotine. In the RECOVER trial, rotigotine was effective for both fatigue and apathy measured by the NMSS

Table 4. Therapeutic interventions for fatigue in Parkinson's disease: randomized clinical trial, meta-analysis, and open-label studies.

Intervention	Study reference	Study design	Outcome measures	Results
Pharmacological				
Levodopa	Schifitto et al. 2008	RCT n = 361 patients* 42 weeks	FSS	No effect
Levodopa-carbidopa intestinal gel infusion (LCIG)	Martinez-Martin et al., 2015	Open label n = 87* 24 weeks	NMSS sleep/fatigue	Improvement of NMSS sleep/fatigue domain scores (LCIG> apomorphine)
	Dafsari et al., 2019	Open label n = 173* 24 weeks	NMSS sleep/fatigue	Improvement of NMSS sleep/fatigue domain scores (LCIG) or DBS STN > apomorphine)
Rotigotine	Wang et al., 2018	Meta-analysis of 8 RCT n = 1675	NMSS sleep/fatigue	Improvement of NMSS sleep/fatigue domain scores
	Ray Chaudhuri et al., 2013	RCT n = 287* 5 to 12 weeks		
Apomorphine	Martinez-Martin et al., 2015	Open label n = 87* 24 weeks	NMSS Sleep/fatigue domain	No effect
Doxepin	Rios Romenets et al. 2013	RCT pilot study n = 18* 6 weeks	FSS	Improvement of fatigue
Methylphenidate	Mendonça et al., 2007	RCT n = 36* 6 weeks	FSS, MFI	No effect
Modafinil	Ondo et al., 2005	RCT n = 40* 4 weeks	FSS	In a subset of PD patients (n = 16) improved physical fatigue
	Lou et al. 2009	Randomized controlled study n = 19* 8 weeks	MFI	Reduced physical fatigue
Caffeine	Postuma et a. 2012	RCT n = 61* 6 weeks	FSS	No effect
Rasagiline	Rascol et al. 2011	Post Hoc analysis of ADAGIO trial n = 1176* 72 weeks	PFS	Improvement of fatigue
	Lim et al. 2015	RCT pilot n = 30* 12 weeks	MFIS	Improvement of fatigue
Memantine	Ondo et al. 2011	RCT followed by an open label extension n = 40* 16 weeks	FSS	No effect
Non-Pharmacological				
STN-DBS	Dafsari et al., 2019	Open label n = 173* 24 weeks	NMSS sleep/fatigue	Improvement of NMSS sleep/fatigue domain scores
Vestibular stimulation	Wilkinson t al. 2019	RCT n = 33* 4 weeks	FSS	Improvement of fatigue
Acupuncture	Kluger et al. 2016	RCT n = 94* 6 weeks	MFIS	No effect
Exercise	Canning et al 2012	RCT n = 20* 6 weeks	VAFS	Trend to improvement

Abbreviations: RCT = Randomized Control Trial, STN DBS = Subthalamus Deep Brain Stimulation, MFI = Multidimensional Fatigue Inventory, FSS = Fatigue Severity Scale, NMSS = Non-motor Symptoms Scale, PFS = Parkinson Fatigue Scale, MFIS = Modified Fatigue Impact Scale, VAFS = Visual Analog Fatigue Scale
* Total number of participants enrolled

in PD patients, compared with placebo after 1–8 weeks of titrations, 4 weeks of maintenance, and 30 days of follow-up posterior the medication was discontinued. In this cohort of patients, fatigue was reduced from 77% to 60% of patients, and there was significant improvement in 4 (items 7, 8, 10, 11) out of the 7 individual items in the mood/apathy domain as compared to controls [122]. In another randomized study, rotigotine improved the total 'mood/apathy' domain score of the NMSS (secondary outcome) in the high-dose group compared with placebo [104]. In this same study, a post-hoc analyses of items 7, 8, 11, 12 of the 'mood/apathy' domain NMSS improved in the combined score for both the low- and high-dose rotigotine groups compared with placebo [104]. However, there was no improvement in the primary outcome of the self-reported AS scores between the groups. The authors postulated that this might be due to better sensitivity

Table 5. Therapeutic interventions for apathy in Parkinson's disease: randomized clinical trial, meta-analysis, and open-label studies.

Intervention	Study reference	Study design	Outcome measures	Results
Pharmacological				
Levodopa	Czenecki et al., 2002	Open label n = 23 PD (in both 'on' and 'off' states vs 28 controls)	AS	Improvement of AS apathy for those under levodopa treatment
Levodopa-carbidopa intestinal gel infusion (LCIG)	Martinez-Martin et al., 2015	Open label n = 87* 24 weeks	NMSS mood/apathy domain	Improvement of NMSS mood/apathy domain scores (apomorphine > LCIG)
	Dafsari et al., 2019	Open label n = 173* 24 weeks	NMSS mood/apathy domain	Improvement of NMSS mood/apathy domain scores (apomorphine > IJLI or DBS STN)
Rotigotine	Hauser et al., 2016	RCT n = 122* 5 to 19 weeks	AS NMSS mood/apathy domain	No changes in AS score Improvement of NMSS mood/apathy domain scores
	Ray Chaudhuri et al., 2013	RCT n = 287* 4 weeks	NMSS mood/apathy domain	Improvement of NMSS mood/apathy domain scores in post-hoc analysis
Pramipexole	Leentjens et al., 2009	Meta-analysis of 7 RCT n = 1296*	UPDRS Part I item 4	Improvement of motivational symptoms
	Oguro et al., 2014	Open label, case-control n = 36* 8 weeks	Modified apathy scale	Pramipexole together with levodopa improved apathy
Ropinirole	Czernecki et al., 2008	Open label n = 8* 6 weeks	AS AI	Improvement of apathy in patients who had stopped all dopaminergic therapy after STN DBS
Piribedil	Thobois et al., 2013	RCT n = 37* 12 weeks	AS	Improvement of apathy in PD patients with apathy after DBS STN
Apomorphine	Martinez-Martin et al., 2011	Open label n = 17*	Item 8 of the NMSS mood/apathy domain	Improvement of NMSS mood/apathy (and especially Item 8) domain scores on apomorphine compared to control
	Martinez-Martin et al., 2015	Open label n = 87* 24 weeks	NMSS mood/apathy domain	Improvement of NMSS mood/apathy domain scores (apomorphine > LCIG)
Methylphenidate	Moreau et al., 2012	RCT n = 81* 12 weeks	LARS	Improvement of apathy in the subgroup of apathetic patients (N = 7)
Rivastigmine	Devos et al., 2014	RCT n = 101* 24 weeks	LARS	Improvement of apathy
Non-pharmacological				
rTMS	Oguro et al., 2014	Randomized double-blind, sham-controlled cross-over study n = 15* Area of stimulation: SMA 12 days	AS (Japanese translated)	Improvement of apathy
	Maruo et al., 2013	Randomized double-blind, cross-over study with sham stimulation n = 21* Area of stimulation: M1 3 days	AS	No improvement of apathy
	Fernandez and Bowers et al, 2016	Randomized sham-controlled double-blinded trial n = 24* Area of stimulation: Left prefrontal cortex 10 days	AES	Improvement of apathy immediately after rTMS, but no between-group differences.
Activity Therapy	Butterfield et al. 2017	Open label n = 34* 6–10 weeks (6-weeks of intervention)	AES	Improvement of apathy

Abbreviations: RCT = Randomized Control Trial, rTMS = Repetitive transcranial magnetic stimulation, AES = Apathy Evaluation Scale, AS = Starkstein Apathy Scale, LARS = Lille Apathy Rating Scale, AI = Apathy Inventory
* Total number of participants enrolled

and insight to apathy by caregivers, than by patients themselves.

Wang et al. conducted a meta-analysis on eight randomized placebo-controlled trials looking at the effect of rotigotine for the treatment of NPS [123]. The studies included a total of 1,675 PD patients, using NMSS to assess sleep/fatigue and mood/apathy. Three studies (Trenkwalder et al. 2011; Antonini et al. 2015 and Hauser et al.2016) [104,124,125]

showed a significant improvement of the sleep/fatigue domain in PD patients using rotigotine compared with the control group, but these items were not analyzed separately. Pertaining to apathy, this meta-analysis reported a significant improvement using NMSS in the studies by Antonini et al. (2015), Hauser et al. (2016), and Chung et al. [104,125,126]. It seems rotigotine could act on both dopaminergic and serotonergic receptor subtypes, improving not only fatigue and apathy but other NMS too [123].

7.1.1.3. Pramipexole. There is some controversy on the potential benefit of pramipexole on fatigue, since Shannon et al. reported fatigue as an adverse effect of its use [127], though the finding was not statistically significant. Later, Hauser et al. compared different versions of pramipexole, the immediate and the extended release, with placebo, showing that pramipexole was associated with the worsening of fatigue in PD patients [128]. Akihiko Morita et al. performed a multicenter cross-sectional study in 350 non-demented PD Japanese patients comparing the effect of dopaminergic treatment on fatigue, using the PFS [89]. Pramipexole was significantly more frequently used in PD patients without fatigue who were in an early stage of the disease, a finding that could be attributed to its agonist effect in D3-receptors, which are related with a good response of fatigue [89].

Regarding apathy, a 2009 meta-analysis of seven RCTs found that pramipexole has a beneficial effect on motivation (assessed with the UPDRS Part I item 4) [129]. When 22 participants with apathy but without depression were analyzed in a head-to-head comparison study examining the differential effects of dopamine agonists on NPS of PD [130], there was a significantly lower frequency of apathy in the pramipexole group (3.4%) compared to the ropinirole (8.5%) and levodopa (9.9%) groups, respectively. In another study, 1.5 mg daily of pramipexole together with L-DOPA improved apathy in PD patients within 8 weeks, compared with monotherapy with L-DOPA [131].

7.1.1.4. Ropinirole. In an open-label study, ropinirole was effective in improving apathy (AS) by 54% in eight patients who had stopped all dopaminergic therapy after STN DBS [46]. However, there are no clinical trials exploring the effect of ropinirole on fatigue in PD.

7.1.1.5. Piribedil. In 12-week double-blind randomized controlled trial of piribedil (a D2 and D3 receptor agonist) vs. placebo of 37 patients with apathy (AS score > 14) following STN DBS and initial withdrawal of dopamine agonist treatment, the apathy score was reduced on follow-up by 34.6% (n = 19) on piribedil 300 mg/day compared to 3.2% on placebo [105].

7.1.2. Monoamine oxidase inhibitors (MAOi)

7.1.2.1. Rasagiline. In a sub-study of the ADAGIO trial [88], the effects over fatigue of rasagiline 1 mg and 2 mg doses were compared with placebo using the PFS at baseline and at 72 weeks follow-up in early PD patients. Greater progression on severity of fatigue from baseline to follow-up was seen in the placebo group compared with the treatment arm ($p < 0.01$ for rasagiline 1 mg and $p < 0.001$ for 2 mg). This trial showed that rasagiline effectively slowed the progression of fatigue in early PD patients compared to placebo at follow-up, but it is important to notice that fatigue was not the main outcome. Later, Lim et al. compared rasagiline 1 mg with placebo at 12 weeks follow-up in 30 PD patients using the MFIS, with significant improvement in average MFIS scores for rasagiline compared to placebo groups [132].

7.1.3. Antidepressant medication

7.1.3.1. Doxepin. Doxepin, a tricyclic antidepressant with histaminergic antagonistic action, has been used successfully as treatment for insomnia in elderly patients. Ríos Romenets et al. conducted a randomized pilot study comparing non-pharmacologic treatment or doxepin (10 mg daily) versus placebo in a cohort of 18 PD patients who suffered from insomnia and as a secondary outcome, severity of fatigue was measured. The results showed that doxepin improved fatigue severity (FSS) compared with placebo and insomnia severity as well ($p < 0.03$) [133]. Although the results were positive, the number of participants was small and with a short follow up, for which larger studies focus on the effect of doxepin over fatigue are necessary.

7.1.3.2. Selective serotonin re-uptake inhibitors (SSRIs). Evidence for use of antidepressants to treat apathy in PD has been conflicting. In several studies, SSRIs have been reported to increase apathy in PD [134–136]. There are few quality studies that clarify the efficacy or differential indications of antidepressants in PD which prevents the existence of clear recommendations.

7.1.3.3. Bupropion. The noradrenaline–dopamine reuptake inhibitor bupropion increases the concentration of both neurotransmitters by having a weak and relatively selective effect on their pre-synaptic re-uptake [137,138]. It has been reported to improve motivation scores in patients with apathy syndrome, though not specifically in PD [139]. One Spanish review for antidepressants in PD concluded that Bupropion was likely useful for apathy in this population but acknowledged that evidence is at best Class IV (consensus or expert opinion only) with limited evidence to make firm recommendations [140].

7.1.3.4. Milnacipran. The selective serotonin and noradrenaline reuptake inhibitor (SNRI), Milnacipran, initially administered twice daily at 30 mg/day until subsequent adjustments as appropriate up to 60 mg/day from the second week over 12 weeks, improved apathy (reflected by AES) in an open-label trial among 8 PD patients with minimal side effects [141].

7.1.4. Psychostimulants

7.1.4.1. Modafinil. Although modafinil is often used as a treatment for excessive daytime sleepiness (EDS), there have been several studies looking into the effectiveness of this medication on fatigue in PD. Ondo et al. found no significant effect of modafinil on fatigue reported outcomes [142]. However, in other study with a smaller cohort of PD patients (n = 19), it was shown that modafinil was associated

with an improvement of physical fatigue compared with placebo, but there was no effect on mental fatigue [143,144]. It is not clear how modafinil improves fatigue, but in animal models, it seems to increase dopamine release in the nucleus accumbens by local GABAergic mechanisms and increases extracellular dopamine concentration in the prefrontal cortex [144].

7.1.4.2. Methylphenidate. Mendonça et al. performed a randomized, double-blind, placebo-controlled trial of methylphenidate in 36 PD patients, who received either methylphenidate (10 mg three times daily) or placebo for 6 weeks, using FSS and MFI total score to assess fatigue. At follow-up, no statistically significant differences were found between methylphenidate and placebo over fatigue in any score [86]. As such, the use of methylphenidate in relation to fatigue will require further analysis most with a larger cohort of patients. On other hand, methylphenidate (5 mg per day) was found to be beneficial for apathy in a case report [145] and in a small group of 7 patients treated with high doses of methylphenidate (1 mg/kg) for 90 days after STN DBS [146]. However, the assessment of apathy was a secondary outcome in the latter study.

7.1.4.3. Caffeine. Postuma et al. conducted a randomized controlled trial evaluating the effects of caffeine on motor and NMS with 61 PD patients, split between caffeine and a placebo arm. The patients receiving caffeine showed improvements in motor symptoms measured with UPDRS III but did not show improvements in fatigue impact on ADL nor fatigue severity, depression, and sleep disturbances [147].

7.1.5. Rivastigmine

In a double-blind placebo-controlled study of 31 PD patients who have moderate to severe apathy (evaluated with the LARS) but without dementia or depression, transdermal cholinesterase inhibitor rivastigmine (9.5 mg/day) was shown to significantly improve apathy after 6 months [51,148].

7.1.6. Antiglutamatergic drugs

7.1.6.1. Memantine. Memantine has been used for other NPS in PD, such as depression and anxiety, with modest benefit [149]. Ondo et al. carried out a single-center, double-blind, placebo-controlled pilot trial of memantine in 34 PD patients. Despite memantine titrated to 20 mg/day it was well tolerated, with fatigue severity and influence over ADL found not to be different compared with placebo after an 8 weeks follow-up [150].

7.1.6.2. Amantadine. Amantadine was found beneficial to ameliorate fatigue in other neurological conditions, such as multiple sclerosis [151]. Later, Rodriguez-Moran et al. described that the proportion of PD patients suffering fatigue measured with D-FIS, MFI, and VAFS was significantly lower in those who were on amantadine combined with dopaminergic therapy compared to other therapies [152]. As this favorable result was a secondary outcome, further trials focusing on the effects of amantadine on fatigue in PD are needed.

7.1.7. Advanced therapies

7.1.7.1. Apomorphine. The impact of chronic subcutaneous apomorphine infusion (Apo) was analyzed by Martinez Martin et al. in 2011 in a multicenter trial across Europe, showing a positive effect on fatigue and apathy in 17 PD later-stage patients measured with NMSS from baseline to 6 months of follow-up [153]. More recently, a larger cohort of patients were analyzed in EuroInf, a multicenter study comparing apomorphine and intrajejunal levodopa infusion (IJLI), resulting in better outcomes on fatigue for IJLI rather than Apo and more significant improvement on apathy for Apomorphine compared with IJLI [154]. The subsequent EuroInf 2 study, which compared deep brain stimulation, apomorphine, and levodopa infusion, did not find significant improvement in fatigue scores in PD patients in the apomorphine group compared with IJLI and DBS; however, fatigue and apathy were not analyzed independently, but only within their NMSS domains [155].

7.1.7.2. Intrajejunal levodopa infusion. Statistically significant improvement of fatigue scores from baseline to 6 months follow-up was described in a pilot multi-center study of intrajejunal levodopa infusion (IJLI); nevertheless, no correlation of improvement in fatigue item and QoL was found [156]. Consistent with earlier studies, GLORIA, EuroInf, and EuroInf 2 affirmed the benefits of IJLI on fatigue and apathy through longer follow-ups [154,155,157].

7.2. Non-pharmacological treatment

7.2.1. Bilateral subthalamic deep brain stimulation (STN DBS)

Largely used as an efficient treatment option for motor symptoms in PD, the benefits of DBS in ameliorating the burden of NMS in PD patients, specially fatigue, have recently been explored. Chou et al. described a cohort of 17 patients, who underwent bilateral STN DBS, completing the PFS and the Epworth Sleepiness Scale (ESS) before and 6 months post-surgery. No significant changes were observed in the severity of fatigue after bilateral DBS STN and ESS. However, the number of participants was small, and they were not selected based on fatigue but on motor symptoms [158]. Later, Dafsari et al. and the EuroInf 2 study described the effects of bilateral STN DBS on NMS in PD showing a strong benefit on fatigue at follow-up compared to baseline, with significant improvement in QoL [155,159].

Evidence pertaining to the impact of STN DBS on apathy in PD has been scanty and inconsistent. Pre-clinical studies in rodents have found chronic STN DBS to have profound and complex effects on behavioral motivation [160], reminiscent of apathy, which may contribute to the development of some apathetic symptoms independent of dopaminergic neurodegenerative processes or reduction in dopamine replacement therapy [161]. A 2006 study compared a series of 15 PD patients with a control group and concluded that poststimulation apathy (AES) results directly from STN DBS [106]. In 2009, the same group demonstrated that apathy could be induced by STN DBS in PD and not merely an effect of decreased levodopa post-DBS, with postoperative cortical metabolic abnormalities seen on ^{18}FDG-PET [162]. However,

the findings of a recent parallel open-label study (EARLYSTIM) yielded no significant change in apathy scores (ASBPD and AS) during the 2 years following STN DBS [163]. The worsening of apathy in 25% of patients 6 years after STN DBS was also thought to likely indicate disease progression, rather than the direct influence of DBS [164].

7.2.2. Transcranial direct current stimulation (tDCS)

In tDCS, a weak electrical current is delivered through two scalp electrodes by a portable battery-powered stimulator, thus modulating intrinsic neuronal activity in a polarity-specific manner and effecting cortical excitability [165]. In one randomized double-blind parallel study, 23 patients with PD were included and randomized to either tDCS plus occupational therapy or sham tDCS plus occupational therapy. Both groups received eight sessions of 20 minute of true tDCS or sham for two consecutive weeks; daytime sleepiness and fatigue were evaluated with ESS and FSS. Although tDCS did not improve daytime sleepiness just after the end of the sessions, or even at 3 months follow-up, a modest positive effect on fatigue was observed in patients receiving true tDCS compared to those on sham just after the treatment, which was not sustained at 3 months [157,158]. In future, longer follow-ups are recommended in studies exploring the effects of tDCS.

7.2.3. Repetitive transcranial magnetic stimulation (rTMS)

In rTMS, short low-frequency (≤1 Hz), high-frequency trains, or varying bursts of stimulation (such as the theta burst stimulation (TBS)) are administered through a coiled wire placed on the scalp, resulting in a magnetic-induced electric field which modifies cortical plasticity, with consequent changes in neuronal activity [165]. There are no specific studies regarding the effect of rTMS on fatigue in PD, although in general, rTMS has been probed to have some benefits for motor symptoms in PD but not for NMS [158,166]. In one study, rTMS stimulation improves the score in the Stroop test, which reflects attention and executive function associated with the frontal lobe [167], and was found to be significantly correlated with the AS score in PD [168,169].

A 2013 double-blind, placebo-controlled cross-over RCT of bilateral M1 foot area stimulation (high-frequency real rTMS) performed for 3 consecutive days did not significantly improve AS scores (n = 10) compared to that of sham stimulation (sham-rTMS) (n = 11) [170]. Similar findings were found in the ReStore Study done by Fernandez and Bowers examining the effect of high-frequency rTMS stimulation over the left prefrontal area in 16 PD patients with apathy (compared to that of sham treatment in 8 patients) daily for 10 days over a 2-week period: significant improvements in apathy (assessed with the modified AES) in both groups which was maintained over 3 months, but with no between-group differences [171]. A Japanese study in 2014, however, showed that rTMS stimulation over the supplementary motor area for 15 PD patients significantly improved both apathy (AS) and depression as compared to those given placebo stimulation [172].

7.2.4. Vestibular stimulation

Recently it has been proposed that caloric vestibular stimulation (CVS) may increase functional neuronal connectivity through the activation of cortical and subcortical ascending pathways involved in PD symptoms. One study compared CVS with placebo, reporting significant improvement of NMS such fatigue, in the CVS arm after 8 weeks of twice-daily treatment, and this improvement persisted after the treatment. Interestingly, most benefits occurred at 5 weeks after cessation of CVS. Even though the benefits returned to baseline after 6-month follow-up, this seems to be a promising non-invasive therapy and further studies with longer time of treatment are warranted [173].

7.3. Other therapies

7.3.1. Massage therapy

Traditional Japanese massage, which uses common massage techniques such as kneading, rubbing, tapping, and shaking in specific points in the body, has been proven to produce favorable outcomes in NMS of PD, used frequently as a complementary therapy. In addition, periodic session of massages may improve NMS such as fatigue in PD patients, suggesting that the stretch reflex and the muscle spindles stimuli during massage are associated with relaxation, and this could play a role relieving symptoms like fatigue [174].

7.3.2. Acupuncture

Acupuncture has been used as complementary treatment for many other conditions such as multiple sclerosis and cancer, with significant improvement of fatigue. In PD patients, both alternatives of acupuncture, the traditional and the sham were probed to be efficient to ameliorate the fatigue burden, which can be result of a placebo effect [175,176].

7.3.3. Exercise

Exercise has been tested by Canning et al. (2012), showing a trend of improvement on fatigue in PD patients who tried treadmill sessions [177]. However, Winward et al. (2012) did not find any changes in fatigue at follow-up, although they used a different exercise protocol than the former [178].

7.3.4. Activity therapy

In 2016, Butterfield et al. tested the effectiveness of the Parkinson's Active Living (PAL) program, one of the first behavioral therapy essentially a telephone-based 6-week activity scheduling and monitoring treatment regime integrating external cueing, which is designed to specifically target apathy in PD. Reduction in apathy levels, as reflected by the AES, was highly significant from baseline to post-intervention, with a moderate positive impact on patients' self-rated QoL (PDQ39) [179].

7.3.5. Multi-sensory stimulation/snoezelen

The objective of Multi-Sensory Stimulation/Snoezelen is to maintain or improve wellbeing by providing positive stimulation of the five senses (visual, auditory, tactile, olfactory, and gustatory stimulation). This behavioral intervention has been demonstrated in two high-quality randomized controlled trials to be effective for apathy in elderly patients with dementia, but no studies specific to PD patients have been identified [180].

8. Summary and key messages

Both fatigue and apathy remain two of the commonest and most disabling, yet often under-appreciated and under-recognized, NMS in PD. The span of these two NMS is considerable, ranging from the premotor stage to advanced and palliative PD, with a clear negative impact on quality of life and caregiver burden. Their pathophysiology remains largely unclear but seems to be linked to diverse factors, such as deficits in the prefrontal-ACC circuits, degeneration of multiple neurotransmitter pathways, primarily dopaminergic and serotoninergic, abnormal activity and connectivity of limbic-cortical circuits, and elevated levels of inflammatory markers in the central nervous system. Several scales have been developed to correctly assess both symptoms, while only the FSS and the Apathy Scale are 'recommended', the PFS is probably the best one for evaluation of fatigue in PD, and the newly developed MDS-NMS allows assessment of both using the same tool. To date, no specific treatment for fatigue and apathy in PwP has been found, although there are some promising pharmacological interventions such as Rivastigmine and apomorphine infusion (for apathy); and doxepin, rasagiline, and IJLI (for fatigue), for which further studies are needed. In addition, brain stimulation, vestibular stimulation, and DBS-STN appear to have beneficial effects. A holistic approach for both symptoms is needed in order to have an optimal management.

9. Expert opinion

Fatigue and apathy remain at the forefront of challenging symptoms in PD, not only pertaining to diagnosis but also especially relevant in relation to treatment. Given the relevance of both fatigue and apathy to QoL and caregiver burden in PD, an emphasis should be put on proper methods in identifying and addressing them. Based on the current evidence the most appropriate identification methods for assessing fatigue and apathy are the PFS and the AS, respectively. However, given the nature of both symptoms, great care should always be taken when assessing patients as there is significant clustering of fatigue and apathy within different NMS in PD, and with each other.

Further complicating the situation is the lack of clearly effective treatment strategies for these two debilitating NPS. The treatment for apathy is largely hampered by the lack of use of appropriate outcome measures, exemplified by the often used NMSS where apathy is not separated from the other items in the mood/cognition domain (now improved in the MDS-NMS being signposted as a specific domain), and by failing to make apathy a primary outcome of clinical trials. The same, although to a lesser extent, can be said for fatigue. Yet in this latter symptom, better evidence is available for at least some treatments. For instance, some dopaminergic medications appear to improve fatigue. Curiously, however, most pathophysiological and observational studies have reasoned against a dopaminergic origin of fatigue. This apparent discrepancy can be explained by the mechanisms outlined below.

The cause of fatigue and apathy in PD is complex and despite many advances in recent years, both in animal models and in PwP, the exact pathophysiology remains unclear. The latter is likely partly caused by the lack of uniform definitions of both fatigue and apathy in PD. This also causes problems when interpreting the results of clinical trials and observational studies. The heterogeneity in symptom definition is further underpinned by the use of largely non-enriched PD cohorts, exemplified by the use of random cross-sectional selection of PD participants in clinical research, without selecting the relevant ones in whom fatigue and apathy are key problems and who are most likely to respond to treatment.

Efforts regarding this have already been made by introducing the concept of specific NMS-dominant phenotypes in PD, for tailored interventional drug trials [181]. This would not require the development of novel instruments for fatigue and apathy in PD as many of tools have already shown their validity and usefulness, but we feel an endeavor should be made toward enriched study cohorts within the core concept of personalized medicine [1,182]. To this end, Cummings and his team have also recently published recommendations on the framework of clinical trials on apathy [183].

An early and holistic palliative approach is also recommended in tackling both fatigue and apathy in PD, such as setting up the interdisciplinary clinic model for both PwP and caregivers [184]. Close liaison between the different disciplines in the care plan facilitates communication and provides additional support for Pw Pwith fatigue and apathy, particularly regarding the integration of palliative care [185].

In five years from now, we expect clinical trials will focus on these crucial NMS since their management remains an unmet need and use of better signposting of both features with validated scales will provide enriched cohorts to study new interventional products and non-pharmacological measures. Key partners in patient charities, industry-based initiatives as well as policymakers' needs to drive such trials, which may also include repurposing of existing medications thus avoiding the huge bench to bedside costs of developing new molecules. Signals providing beneficial effects on fatigue are already available from several dopaminergic and non-dopaminergic agents and funding to initiate and complete large-scale studies providing level 1 evidence for management of fatigue and apathy in PD should be a major research strategy and priority in the 2020s [1,8,30,44,48,182].

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ORCID

Claudia Lazcano-Ocampo http://orcid.org/0000-0001-6646-5159

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