Chapter 1
Depression, Apathy, Anhedonia, and Fatigue in Parkinson's Disease

Marianna Amboni, Gabriella Santangelo, and Paolo Barone

Depression in PD

Definition and Pathophysiology

Definition

Depression is a common neuropsychiatric disorder characterized by the persistence and pervasiveness of a spectrum of symptoms that can variously aggregate. These symptoms include: depressed mood, loss of interest/pleasure, loss or gain in weight or appetite, insomnia or hypersomnia, psychomotor agitation, fatigue, feelings of worthlessness or guilt, diminished ability to think or concentrate, indecisiveness, thoughts of death, and suicidal ideation.

M. Amboni, MD, PhD
Neuroscience Section, Department of Medicine and Surgery,
Center for Neurodegenerative Diseases, University of Salerno
Via S. Allende, 1, Baronissi, Salerno 84081, Italy

Division of Neurology, IDC Hermitage-Capodimonte,
Via Cupa Delle Tozzole, 2, Naples 80131, Italy
e-mail: marianna.amboni@libero.it

G. Santangelo, PhD
Department of Psychology, Second University of Naples,
Viale Ellittico 31, Caserta 81100, Italy
e-mail: gabriella.santangelo@unina2.it

P. Barone, MD, PhD (✉)
Neuroscience Section, Department of Medicine and Surgery,
Center for Neurodegenerative Diseases, University of Salerno
Via S. Allende, 1, Baronissi, Salerno 84081, Italy
e-mail: pbarone@unisa.it

H. Reichmann (ed.), *Neuropsychiatric Symptoms of Movement Disorders*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-3-319-09537-0_1

Depressive disorders are common in Parkinson's disease (PD) (see section "Epidemiology") and impact negatively on disability [1, 2] and quality of life [3], accounting for approximately 40 % of the variability in quality of life scores [4]. Symptoms of depressive disorders in PD span across a spectrum of severity and of variety, but no distinctive profile has been identified [5]; nevertheless guilt or feelings of failure are not common, and the risk to commit suicide is low despite the frequent suicidal ideation [6]. Mood disorders in PD include major depression, minor depression, dysthymic disorders, and subthreshold depression [7, 8]; subthreshold (or subsyndromal) depression in PD identifies a clinical picture of depressive symptoms that does not meet the criteria for major depression, minor depression, or dysthymic disorder but nonetheless has a clinical relevance; furthermore patients with PD suffering from depressive symptoms only during off states may be diagnosed as having subthreshold depression [9].

Despite the importance of recognizing mood disorders in PD, their diagnosis is greatly complicated since physical or cognitive symptoms of the neurological disorder overlap with symptoms of depression. The application of the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) [10] (Table 1.1) for the diagnosis of depression in PD might generate an overdiagnosis, due to the overlapping of the DSM-IV criteria with somatic and cognitive symptoms of PD. Furthermore, little is known about the contribution of either apathy or anhedonia or their association in the diagnosis of depression in PD. The diagnostic criteria for depression in PD were reviewed by the workgroup established by the National Institute for Neurological Disease and Stroke and the National Institute of Mental Health in 2006 [7]. The workgroup recommended using an inclusive approach in assessing symptoms when using the DSM criteria to diagnose depression to enhance reliability. An inclusive approach means considering all symptoms as related to depression, regardless of their overlap with PD or other medical conditions. Briefly, the workgroup recommended:

I. The diagnosis of depression in PD should be made according to DSM-IV criteria using an inclusive approach. Subthreshold depression should be included.
II. The timing of assessing should be specified (on versus off periods).
III. Informants should be used for cognitively impaired patients.
IV. Decreased interest should be omitted as core affective symptom when diagnosing minor or subthreshold depression.

The workgroup concluded that the recommended guidelines for diagnosing depression in PD require further assessment and validation as research tools and in clinical practice.

Pathophysiology

Two major pathophysiological and not mutually exclusive mechanisms have been proposed for depression in PD: (1) a nonspecific reactive comorbid depression in PD, patients develop depression as a reaction to a chronic debilitating illness, and (2) specific comorbid depression in PD, depression is related to the pathophysiology of PD.

Table 1.1 Diagnostic and statistical manual of mental disorders 4th edition criteria for major and minor depression

Major depressive episode
A. Persistence and general pervasiveness of five or more of nine potential symptoms during the same 2-week period that represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure that is present most of the day, nearly every day, as indicated by either subjective report or observation made by others
1. Depressed mood
2. Markedly diminished interest or pleasure in all, or almost all, activities
3. Loss or gain in weight or appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate or indecisiveness
9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. Symptoms do not meet criteria for a DSM mixed episode (presence of phenomena of both a manic and a depressed episode)
C. Symptoms cause clinically significant distress or functional impairment
D. Symptoms are not due to the direct physiological effects of a substance or a general medical condition
E. Symptoms are not better accounted for by bereavement
Minor depressive episode
Requires only two of the nine symptoms above, but one must be either depression/sadness or loss of interest/pleasure

The finding that depression can develop in any stage of PD and even may antecede the onset of motor symptoms [11] would not support the first hypothesis; in addition, when compared with subjects affected by other chronic conditions matched for disability, PD patients show more severe depressive symptoms [12]. Therefore, even if motor and nonmotor disability in PD might contribute to depression, it cannot be considered the unique determinant, suggesting that the cause of depression is intrinsic to the pathophysiology of PD. A combination of dopaminergic, noradrenergic, and serotoninergic system dysfunction has been thought to underlie the development of depression in PD [13, 14].

Studies on dopamine transporter (DAT) availability in depressed PD patients have produced conflicting results. Depression in PD has been associated with higher loss of striatal dopamine transporter availability [15, 16] maybe due to greater dopaminergic degeneration in PD patients with depressive symptoms as compared with PD patients without. Other studies have found an association between depressive symptoms and increased dopamine transporter availability [17, 18]. These inconsistencies might be due to methodological heterogeneities among studies and/or to the finding that striatal dopaminergic dysfunction in PD may be itself heterogeneous, related with some depressive symptoms but not all [19]. Apart from such discrepancies, these results confirm the pivotal role exerted by dopaminergic pathways in the occurrence of depression in PD.

In addition to dopamine, other monoamines seem to have a role in the pathogenesis of depression in PD. In a recent positron emission tomography (PET) study, serotonin transporter binding was found increased in PD patients with depressive symptoms in limbic structures and caudal raphe nuclei, suggesting a lower serotonin availability [20]. Accordingly, another study, using transcranial sonography, has shown reduced echogenicity of the dorsal raphe in subjects with depression preceding PD motor onset [21]. Finally, in regard to noradrenergic contribution, another PET study found loss of dopamine and noradrenaline innervations in the locus coeruleus and in limbic areas in depressed PD patients [22], and, consistently, a neuropathological study demonstrated neuronal loss and gliosis in the noradrenergic locus coeruleus [23].

In line with this model of dysfunctional monoamine pathways projecting to cortical areas, altered brain metabolism or blood flow in the frontal cortex has been associated with depression in PD [24–27]. Accordingly, structural neuroimaging techniques have shown gray matter loss and white matter abnormalities in the prefrontal, temporal, and some limbic regions in depressed PD patients [28, 29]. Finally a very recent resting-state functional magnetic resonance study (RS fMRI) revealed reduced functional connectivity in the prefrontal-limbic network in PD patients with depression as compared with PD patients without [30].

Epidemiology

Depressive disorders are common in PD and may even precede the diagnosis of PD in up to 30 % of patients [31–33]. In addition, subjects with depression were found to be 3.14 times more likely to develop PD [34]. Estimates of prevalence of depression in PD vary considerably in published studies mostly due to the heterogeneity of population included and to the criteria used for defining depression in PD (e.g., DSM-IV criteria, clinical rating scales, etc.). In a large systematic review of the prevalence of depression in PD including 36 studies, the weighted prevalence of major depressive disorder was 17 %, minor depression 22 %, dysthymia 13 %, and clinically significant depression 35 % [35]. Prevalence of depressive symptoms and of major depression of more recent studies is reported in Table 1.2. Depressive disorders in PD patients as well as in the general population develop in the context of multiple interacting risk factors. PD-specific risk factors for depression include more severe motor symptoms, greater PD-related disability, more advanced disease stage, longer disease duration, higher levodopa equivalent dosage, presence of hallucinations, cognitive impairment, sleep disorders, and dysautonomia [44–48]. In addition, older age, longer duration, and increased severity of PD were found to contribute to care dependency in patients with untreated depression [49].

A recent cross-sectional study, aimed at building a model for risk factors of depression in PD, found that three PD-specific factors (longer disease duration, more severe motor symptoms, levodopa use) and six nonspecific factors (female gender,

Table 1.2 Frequency rates of depressive symptoms/depression in PD [36–43]

Study	Population	Depressive symptom frequency (%)	Major depression frequency (%)	Scale/criteria used for assessing depressive symptoms/depression
Barone et al. (2007) [36]	1,023 PD patients	27.8	9.2	BDI, HAM/DSM IV
Farabaugh et al. (2009) [37]	158 PD patients	58	NA	HANDS
Riedel et al. (2010) [38]	1,449 PD patients	33.6	NA	MADRS
Inoue et al. (2010) [39]	105 PD patients	38	4.7	BDI/DSM IV
Nègre-Pagès et al. (2010) [40]	450 PD patients	40	NA	HADS
van der Hoek et al. (2011) [41]	256 PD patients	36.3	12.9	BDI
Yamanishi et al. (2013) [42]	117 PD patients	56	NA	BDI
Weerkamp et al. (2013) [43]	73 nursing home residents with PD	45	NA	BDI

BDI Beck Depression Inventory, *HAM* Hamilton Depression Rating scale, *DSM IV* Diagnostic and Statistical Manual of Mental Disorders 4th edition, *NA* not assessed, *HANDS* Harvard Department of Psychiatry/National Depression Screening Day Scale, *MADRS* Montgomery-Asberg Depression Rating Scale, *HADS* Hospital Anxiety and Depression Scale

personal or family history of depression, worse disability, and more affected cognition) were significantly associated with depression; interestingly, nonspecific factors were more strongly related to depression than PD-specific factors [50].

Assessment Tools

In clinical practice, the use of depressive symptom rating scales can improve identification of depression in parkinsonian patients without substituting clinical criteria [51]. Clinician-rated depression scales such as the 24-item and 17-item Hamilton Depression Rating Scale (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), and item depression of the Unified Parkinson's Disease Rating Scale (UPDRS) and self-reported scales such as the Beck Depression Inventory (BDI) and 30-item and 15-item Geriatric Depression Scale (GDS) are considered to be valid in PD [52–64].

Recently, the Patients Health Questionnaire-9 has shown to be an adequate instrument for screening depression in PD [65, 66].

A recent study compared the performance of six self-reported (BDI-II, GDS-30, Center for Epidemiologic Studies Depression Rating Scale-Revised, Inventory of Depressive Symptoms Self Report (IDS-SR), PHQ-9, part I of UPDRS) and three clinician-rated (HAMD-17, Inventory of Depressive Symptomatology-Clinician-Rated, and MADRS) depression scales in community-based parkinsonian patients against psychiatric diagnosis based on DSM-IV-TR criteria [51]. The finding revealed that all self-reported scales, mainly BDI-II, and clinician-rated scales had strong psychometric properties and thus may be useful for depression screening with their cutoff. The study also provided information about the time needed to complete self-report depression scales in PD, and therefore it is a useful guide for the clinician to choose the most appropriate depression rating scale [51].

PD Nonmotor-Associated Features

There is controversy about the relationship between depression and cognitive dysfunctions in PD patients. Three possible patterns emerge: (1) depression influences cognition in PD, in this case depression would influence the severity of cognitive impairment [44, 67–76]; (2) depression and cognition are independent, although many symptoms of the two conditions might overlap in PD [31, 77–80]; and (3) cognitive dysfunctions, that are related to PD neuropathology, are the substrate of a depressive disorder in PD, in this case a distinct pattern of cognitive impairment (quality) would be associated with depression.

The relationship between depression and executive dysfunctions is generally considered as depression affecting severity of cognition. However, frontal dysfunctions related to neuropathology of PD might be responsible for depressive symptoms, especially considering that DSM-IV criteria for major depression diagnosis do not separate anhedonia from apathy. Santangelo et al. [81] found that depressed PD patients with high level of apathy and/or anhedonia scored significantly lower on frontal tasks than patients with depressed mood (DSM-IV, criterion 1) and nondepressed patients. These findings suggest that the combination of apathy, anhedonia, and frontal lobe dysfunctions might contribute to the overdiagnosis of depression in PD. Varanese et al. [82] found that apathy was not associated with executive impairment in PD patients. These findings support the idea that apathy and depression are two independent nonmotor symptoms of PD.

Management

Treatment options for depressive symptoms in PD should be based on the specific characteristics of the patient. The first step should include a review of all drugs taken by the patient in order to identify and possibly eliminate those medications

that could contribute to affective symptoms; then, the optimization of dopaminergic treatment should be considered, since this strategy is often effective in cases of subthreshold (e.g., "off"-related nonmotor fluctuations including depression) and mild depression. In regard to dopaminergic treatment, a number of open-label studies have suggested that both pramipexole and ropinirole exert antidepressant effect in PD patients [83–86]. A recent large 12-week randomized, double-blind, placebo-controlled study in PD, enrolling patients with depressive symptoms (15-item GDS score ≥5 or UPDRS Part I depression item score ≥2), compared pramipexole (0.375–3 mg/day, $N=139$) and placebo ($N=148$) and showed that pramipexole significantly improved BDI scores ($p=0.01$) and UPDRS motor scores ($p=0.003$); statistical analysis, adjusting for UPDRS, suggested a direct effect of pramipexole on depression [87]. A randomized, placebo-controlled, double-blind study of ropinirole extended-release preparation [88] also showed improvement on BDI scores as compared to placebo; nevertheless, the primary outcomes of this study were motor fluctuations; therefore, patients were not selected according to criteria for depression. Similarly, a double-blind, randomized, placebo-controlled study aimed at assessing rotigotine efficacy on early motor dysfunction and sleep problems in PD [89] found, as additional efficacy outcome, greater improvement with rotigotine than placebo on BDI-II scores and on mood/cognition domain score of nonmotor symptoms scale (NMS).

The evidence-based data regarding the therapeutic efficacy of antidepressants for treating depression in PD are still equivocal. A systematic review and meta-analysis of ten studies showed uncertainty and lack of strong evidence supporting the clinical efficacy of selective serotonin reuptake inhibitors (SSRIs) for depression in PD [90]. A successive evidence-based review concluded that tricyclic antidepressants (TCA) are likely efficacious and possibly useful; nevertheless side effects are common [91]. Recently, a large randomized, double-blind, placebo-controlled trial of antidepressants in PD has provided Class I evidence that both paroxetine (SSRI) and venlafaxine (a serotonin and norepinephrine reuptake inhibitor, SNRI) significantly improve depression in subjects with PD without worsening motor function [92]. Double-blind, placebo-controlled studies of antidepressant drugs in PD are summarized in Table 1.3.

Non-pharmacological interventions for depression in PD include cognitive behavior therapy (CBT) and repetitive transcranial magnetic stimulation (rTMS). The largest study on CBT for depression in PD was a 10-week randomized controlled trial of 80 patients that showed significant improvement in the treated group as compared with the control group [98]. rTMS has been proposed as a technique to improve mood in PD, but results are still preliminary and potentially confounded by the possible effect on motor and cognitive function. A double-blind sham-controlled study of the left prefrontal rTMS showed significant improvement on depression scales [99]. In double-blind studies, comparing dorsolateral prefrontal cortex (DLPFC) rTMS and fluoxetine (using placebo and sham rTMS, respectively), both interventions resulted comparably efficacious in improving depressive symptoms [100, 101].

Table 1.3 Antidepressants in PD: double-blind, placebo-controlled studies [92–97]

Study	*N*	Drug	Daily dose (mg)	Results	Worsening parkinsonism
Wermuth et al. (1998) [93]	18/19	Citalopram/placebo	10	Citalopram = placebo	No
Leentjens et al. (2003) [94]	6/6	Sertraline/placebo	50	Sertraline = placebo	No
Weintraub et al. (2010) [95]	28/27	Atomoxetine/placebo	80	Atomoxetine = placebo	No
Devos et al. (2008) [96]	16/15/17	Desimipramine/citalopram/placebo	75	Improvement for both drugs	No
			20		
Menza et al. (2009) [97]	18/17/17	Paroxetine/nortriptyline/placebo	37.5	Improvements for nortriptyline but not for paroxetine	No
			75		
Richard et al. (2012) [92]	42/34/39	Paroxetine/venlafaxine/placebo	40	Improvement for both drugs	No
			225		

Apathy in PD

Definition and Pathophysiology

Definition

Apathy refers to a combination of behavioral, emotional, and cognitive features that originate from reduced interest/motivation in goal-directed behaviors and from lack of emotional responsiveness. The clinical picture of apathy is characterized by loss of self-activation or self-initiated behavior, indifference, impassibility, and flattened affect.

Apathy is one of the most common nonmotor symptoms in PD, occurring since early stages of disease, and increasing in frequency as the disease progresses (see section "Epidemiology"). It has been associated with decreased quality of life and poor performances on activity of daily living [102]. The diagnosis of apathy in PD is challenging since it is commonly associated with disorders such as depression, cognitive impairment, and fatigue; in addition, many features of such disorders overlap with symptoms of apathy.

Recently two sets of diagnostic criteria have been validated in PD [103, 104]. The criteria used in these two studies are similar and include: (1) diminished motivation compared to baseline level of functioning; (2) reduction of goal-directed behavior, goal-directed cognitive activity, and emotion; (3) symptoms sufficiently severe to cause significant impairment of personal, social, or occupational function; and (4) symptoms not attributable to the effects of physical disability, level of consciousness, or medication.

Pathophysiology

The pathophysiological mechanism underlying apathy in PD is still not fully understood. Apathy is probably related with a dysfunction in the mesocorticolimbic circuit including the ventral striatum, anterior and posterior cingulate (AC, PC), and inferior prefrontal gyrus since these structures are key components of the brain motivational and reward system [105]. Recently, a morphological magnetic resonance imaging (MRI) study on 55 PD patients [106] showed that high apathy scores were correlated with low gray matter (GM) density in the right PC gyrus and the bilateral inferior frontal gyrus; based on the involvement of the cingulate and premotor cortices, the authors suggested that "autoactivation" processing deficits could be associated with apathy in PD. Consistently, in an 11C-raclopride PET study, apathy scores after deep brain stimulation of the subthalamic nucleus (STN-DBS) in PD patients correlated with a decreased dopamine transmission particularly in the dorsolateral and orbitofrontal cortex, AC and PC [107], suggesting that apathy in PD would be underlied by greater mesocorticolimbic dopaminergic denervation. The involvement of mesocorticolimbic networks in apathy has been further corroborated by a recent fluorodeoxyglucose PET study on 45 PD patients neither depressed nor demented [108]; in addition, this study found a negative correlation

between metabolism within the bilateral posterior lobe of the cerebellum and apathy scores on AES, supporting the view of a topographic segmentation of the cerebellum, with some structures implicated in motivation and behavioral regulation. Finally, further evidence suggesting that mesocorticolimbic dopaminergic denervation would have a key role in the pathogenesis of apathy derived from studies on DBS in PD patients. STN-DBS can induce or worsen apathy in some parkinsonian patients [107, 109]: reduction of dopaminergic agents and/or stimulation of the associative and limbic regions has been proposed as mechanisms underlying apathy after surgery [110].

Epidemiology

Apathy is one of the most common nonmotor symptoms of PD, with prevalence rates ranging from 13.9 to 70 % and a mean prevalence of 35 % (for a recent review see Santangelo et al. [111]). Several factors may contribute to variable prevalence rates found across studies. First, apathy frequently occurs with depression and with cognitive impairment, particularly dysexecutive syndromes; thus, studies not excluding depression and/or dementia could overestimate its frequency. Second, apathy rate can vary based on the PD population studied (e.g., community sample versus tertiary movement disorders clinic sample). Finally, apathy frequency might be biased by the different tools used for diagnosis (e.g., specific, nonspecific scales, clinical criteria, etc.).

Apathy is common in PD since early stages. Recently, Pedersen and colleagues [112] reported an apathy prevalence rate of 22.9 % in 175 newly diagnosed PD patients with a prevalence of "pure apathy" (i.e., apathy without comorbid depression and dementia) of 14.3 %.

In regard to the mutual relationship among apathy, motor symptoms, and nonmotor symptoms in PD, a recent 4-year longitudinal study showed that at follow-up, apathetic PD patients were more frequently depressed and demented than never-apathetic patients; moreover, dementia at baseline and a more rapid decline in speech and axial symptoms during follow-up were independent risk factors for incident apathy [113] (see also section "PD nonmotor-associated features"). Finally, two recent studies found that patients with right predominant PD motor laterality were at higher risk of suffering from apathy as compared with those with left predominant motor symptoms [114, 115].

Assessment Tools

In clinical practice and research, several rating scales are available to identify and measure severity of apathy in PD patients. Among questionnaires, Apathy Evaluation Scale (AES) [116], Apathy Scale (AS) [117], Lille Apathy Rating Scale (LARS) [118],

Apathy Inventory (AI) [119], Item 7 of the Neuropsychiatric Inventory (NPI) [120], and Item 4 (motivation/initiative) of the UPDRS [121] can be used in PD patients.

Recently, a task force commissioned by the Movement Disorders Society (MDS) [122] reviewed the psychometric properties of the abovementioned scales and reported that both AS and apathy items of UPDRS fulfilled criteria for "recommended scale" for screening apathy, but Item 4 of the UPDRS can be only used as a screening question with caution because it consists of a single item [52]. The AES has good internal consistency [123], and it has been classified as "suggested scale" because only information on reliability but not on validity is now available. The AI has been poorly studied, and it has been classified as "listed scale"; its brevity may make it an attractive and useful instrument to measure apathy in PD. The LARS was developed for PD patients; it has good internal consistency, adequate test-retest, inter-rater reliability, good sensitivity, and specificity in PD population [124]. It is the longest of the all available apathy rating scales, and it was classified as a "suggested scale" by MDS review. The Item 7 of the NPI showed good inter-rater agreement, but other clinimetric properties were not investigated in PD; therefore, it can be considered as a "suggested scale."

PD Nonmotor-Associated Features

Three prospective studies found a close relationship between cognitive dysfunction and apathy. In particular, dementia [113] and reduced inhibitory control assessed by means of Stroop Test [125] were found to be independent risk factors for incident apathy, whereas apathy may be a predictive factor for cognitive decline over time in non-demented, nondepressed PD patients [126]. The association between apathy and executive/frontal dysfunction is consistently found in PD patients at early and advanced stages of disease [82, 112, 117, 123, 125, 127–129]. Few studies investigated other cognitive domains such as memory and visuospatial functions in apathetic PD patients yielding discordant results: some authors found that apathetic patients performed worse than non-apathetic patients on the memory subtest of the Cambridge Cognitive Examination (CAMCOG) [123], on Grober and Buschke 16-item recall test [126], and on paired associative learning test [117], silhouette recognition task [112], and praxis subtest of CAMCOG [123]. Other studies did not find similar results [128]. A recent study showed a significant association between the apathy and affective component of Theory of Mind (ToM) [130], which is the ability of processing inferences about other people's emotions and feelings.

Management

There are no approved drugs for managing apathy. Since apathy is closely related to depression and cognitive impairment, first, possible comorbid depression should be treated in patients with apathy. Because of the association with depression and

cognitive impairment, pharmacologic agents most frequently administered to apathetic patients include dopaminergic drugs and acetylcholinesterase inhibitors.

Previous small open-label trials have suggested that dopaminergic agents could be effective in improving apathy in PD patients [131, 132]. A recent meta-analysis of seven randomized, double-blind, placebo-controlled trials of pramipexole, using the UPDRS Part I as a secondary outcome measure, showed that patients who had a baseline UPDRS Part I Item 4 score >0 (motivation, $N=570$), motivational symptoms improved in 63.2 % of patients taking pramipexole compared to 45.0 % of those taking placebo (weighted OR 2.06; $p<0.001$) [133]. Very recently, in a post hoc analysis of RECOVER study ($N=287$), Chaudhuri and collaborators [134] found significant improvement from baseline on apathy items of NMSS ("lost interest in surroundings," "lost interest in doing things") in the rotigotine group as compared with the placebo group. In addition, in a randomized, placebo-controlled trial ($N=37$, PD patients treated with STN-DBS), Thobois and collaborators [135] found that the dopamine agonist piribedil is effective in treating apathy.

Apart from dopaminergic agents, a randomized controlled trial evaluating efficacy of atomoxetine, a selective norepinephrine reuptake inhibitor, for treatment of clinically significant depressive symptoms in PD patients and with apathy as a secondary outcome measure, showed no benefit for either depression or apathy [95].

In regard to acetylcholinesterase inhibitors, an open-label controlled study of galantamine ($N=41$) in PD patients with dementia found significant improvement in the primary cognitive outcome measures but also in the apathy section of the NPI ($p=0.006$) [136]. Nevertheless, a subsequent double-blind, placebo-controlled study in nondemented PD subjects ($N=54$) designed to assess cognitive improvement as primary outcome did not find significant difference in apathy measures [137].

Finally, two ongoing randomized, placebo-controlled trials are evaluating efficacy of acetylcholinesterase (rivastigmine) [ClinicalTrials. gov identifier: NCT00767091; http://clinicaltrials.gov/ct2/show/NCT00767091] and MAO-B inhibitors (rasagiline) [ClinicalTrials.gov identifier: NCT00755027; http://clinicaltrials.gov/ct2/show/NCT00755027] on apathetic symptoms in PD patients.

Anhedonia in PD

Definition and Pathophysiology

Definition

Anhedonia is defined as a lowered ability to experience physical and social pleasure. It is recognized to be a core symptom of major depression [10] and is frequent in several psychiatric diseases including abstinence/intoxication with substances of abuse and schizophrenia [138, 139].

Anhedonia includes two types of pleasure deficits: anticipatory and consummatory [140]. Anticipatory anhedonia refers to the inability to experience pleasure at the thought of a future reward ("wanting"), whereas consummatory anhedonia reflects

the inability to experience pleasure while the subject is engaged in an enjoyable experience ("liking").

In PD anhedonia has been seen as a symptom that can be part of various syndromes, such as depression, dementia, or apathy [122, 141]. To date, anhedonia in PD lacks an unambiguous and generally accepted definition, and its identification is based on specific rating scales (see section "Assessment tools"). Recent studies [142, 143] suggest that PD patients may have intact "consummatory" pleasure and altered "anticipatory" pleasure that has been frequently found associated with apathy.

Pathophysiology

Some recent studies have suggested that distinct neural networks would be involved in anticipatory and consummatory anhedonia in PD; the former type might be underlied by a dysfunction in the dopaminergic mesolimbic system including the ventral striatum and anterior cingulate cortex [22], whereas the latter one might be associated with alteration in the dopaminergic prefrontal cortex circuits [142, 144]. It is worth noting that the neural circuit involved in anticipatory anhedonia is the same that has been linked to apathy (see section "Pathophysiology of apathy") maybe suggesting that anticipatory anhedonia could be a symptom of apathy (reduced "wanting").

Epidemiology

Anhedonia is common in PD with a prevalence ranging from 15 % up to 79.7 % in PD patients with depression [84, 145–148]. As for depression and apathy, most prevalence differences across studies depend on methodological issues (e.g., tool and cutoff used for defining anhedonia, overlapping with other neuropsychiatric disorders, type of PD population studied).

Most studies conducted in PD patients [81, 84, 142–145, 147, 148] with the exception of one [146] suggest a significant relationship between anhedonia and other neuropsychiatric symptoms, namely, depression, apathy, and, to a less extent, cognitive dysfunction (see section "PD nonmotor-associated features").

In regard to the possible relationship between anhedonia and motor symptom severity, some studies reported an association [84, 145] and others did not [144, 146]; this inconsistency might be due to the different PD stages of the population included in these studies.

Assessment Tools

The identification of anhedonia is difficult since it may occur on its own or as part both of depression and apathetic syndrome [122]. However, in clinical practice and research, the clinician may use several questionnaires developed for measuring

severity of anhedonia in patients with psychiatric diseases. The Chapman Scales for Physical and Social Anhedonia were used in one study on PD patients and were considered to have several shortcomings for this type of patients: the scales include items characterized by a very complex syntactic structure and were too long for patients with bradyphrenia [146]. Moreover, their clinimetric properties have not been fully investigated. The Chapman Scales were classified as listed by MDS task force [122]. To provide a short scale validated and easily applicable in clinical setting, Santangelo et al. [144] explored the clinimetric properties of the Snaith-Hamilton Pleasure Scale (SHAPS) and found it to be a reliable tool to evaluate apathy in patients with PD and other forms of parkinsonism. More recently, the psychometric properties of the Japanese version of SHAPS were also investigated [149].

PD Nonmotor-Associated Features

Several studies evidenced a strong association between anhedonia and apathetic or depressive syndromes in PD patients, indicating that reduced hedonic tone may be considered a feature of apathy [123] and of depression [81, 84, 145, 147]. Conversely, Isella et al. [146] did not find relationship between anhedonia, depression, and apathy. Increasing age, apathy, and cognitive dysfunctions were found contributing factors to anhedonia severity [144]. Recently, significant association between apathy and anxiety trait was reported [148].

As for association between anhedonia and cognitive deficits, one study on a small sample of PD patients revealed no significant correlation between anhedonia and score on frontal tasks [146]. Otherwise, Santangelo et al. [81] reported that patients with anhedonia performed worse than nondepressed patients without apathy or anhedonia on cognitive tasks tapping visuoconstructional and frontal functions. In addition, significant correlations were found between anhedonia and score on Frontal Assessment Battery (FAB) in patients with PD and other forms of parkinsonism [144]. The relationship between anhedonia and frontal dysfunctions might support the idea that anhedonia may depend on frontal lobe dysfunctions arising from alteration of prefrontal dopamine circuits.

Management

A number of open-label studies suggest that dopaminergic agents may be effective in improving hedonic tone (for a recent review see Assogna et al. [141]). Most trials focused on pramipexole may be due to its preferential action on D_3 dopaminergic receptors in the mesolimbic and prefrontal neural circuits; overall, such studies [84, 145, 147, 150] found that pramipexole was effective on depression, anhedonia, and motor symptoms. In particular, Reichmann and collaborators [150] found that PD patients switched from other dopamine agonists to pramipexole had a significant

improvement on depression and anhedonia thus suggesting that such beneficial effects would not be simply reactive responses to motor improvement but specific effects of the treatment. Nevertheless, since these studies were open label, further randomized, double-blind, placebo-controlled trials are needed to confirm these results.

Finally, very recently, in a post hoc analysis of RECOVER study ($N = 287$), Chaudhuri and collaborators [134] found significant improvement from baseline on the anhedonia item of NMSS ("difficulty experiencing pleasure") in the rotigotine group as compared with the placebo group.

Fatigue in PD

Definition and Pathophysiology

Definition

Fatigue has been commonly defined as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion. It is characterized by difficulty in initiating and sustaining mental and physical activities. Despite fatigue is one of the most common and disabling symptoms in neurological disorders, its identification and understanding is hampered by the lack of standard definition [151].

Fatigue is common in PD (see section "Epidemiology"). Although several features of fatigue in PD have been described, it is still unclear whether fatigue can be considered either a motor or nonmotor symptom [152]. Its identification is challenging due to the overlap with other common symptoms of PD like depression, apathy, sleep problems, and autonomic dysfunction. In addition, the presence of different components of fatigue (mental, physical) further complicates its recognition. Based on the fact that PD patients generally describe their fatigue as different from the fatigue, they had experienced prior PD onset, and Brown et al. [153] proposed an operational definition of fatigue in PD as a "feeling of abnormal and overwhelming tiredness and lack of energy, distinct both qualitatively and quantitatively from normal tiredness." To date, identification of fatigue in PD is based on specific rating scales (see section "Assessment tools").

Pathophysiology

The pathophysiology of fatigue in PD is still poorly understood [154]. Fatigue is commonly subdivided into a peripheral and a central component; peripheral fatigue is commonly observed in diseases involving the peripheral nervous system like myasthenia gravis, whereas central fatigue is frequently observed in several chronic diseases of the central nervous system including PD. Several findings suggest that fatigue in PD might have a minor peripheral contribution and a major component underlied by central mechanisms [154]. It is worth noting that central fatigue features in PD may overlap with a number of nonmotor symptoms like depression, apathy,

and sleep problems thus complicating the understanding of its pathophysiology. Few neuroimaging studies have addressed the pathophysiological mechanisms of central fatigue. By means of a single-photon emission computed tomography (SPECT) study, Abe and collaborators [155] reported that fatigue in PD correlated with reduced cerebral blood flow in the frontal lobe in absence of significant correlation between fatigue and depression. More recently, a PET study aimed at evaluating the dopaminergic and serotonergic contribution to fatigue in PD [156] showed that fatigue was mainly associated with denervation of serotonergic terminals in both dorsal and ventral striatum and in the thalamus; furthermore fatigue was associated with reduced dopaminergic transmission in the extra-striatal region, namely, the insula. Taken together these results could suggest that fatigue in PD would be associated with dysfunction in striatal serotonergic and extra-striatal dopaminergic neural circuits and in their projections to the frontal lobe.

Finally, fatigue in PD has been associated with abnormal primary motor cortex excitability [157], suggesting that altered cortical plasticity might be responsible for physical fatigue that would share both clinical features and pathophysiological mechanisms with bradykinesia and sequence effect.

Epidemiology

Fatigue in PD is a frequent symptom with a prevalence rate ranging from 28 to 77.6 % (Table 1.4). Most variability on frequency rates is due to methodological issues (e.g., different assessment tools, overlap with other PD symptoms, PD population studied). Fatigue can be present in every stage of disease and even may antecede the onset of motor symptoms in approximately one third of patients [164]. Fatigue has been identified as one of the most disabling symptoms in PD and has been found as an important determinant of worse quality of life [165].

Several factors have been variably associated with fatigue: female gender, postural instability gait difficulties (PIGD) phenotype, and many nonmotor symptoms like depression, anxiety, apathy, sleep disturbances, and autonomic impairment [163–165]. In addition, fatigue has been associated with reduced physical activity [166], though it is still not clear whether fatigue determines reduced physical activity or a sedentary lifestyle can favor the onset of fatigue.

Finally, available data in literature do not allow to find a definite relationship between fatigue and disease severity due to the controversial results.

Assessment Tools

Since fatigue has a multidimensional character, it is difficult to measure [167]. In clinical setting, it is possible to use several questionnaires from those generic which evaluate fatigue in a holistic manner to those specifically designed for PD [168].

Table 1.4 Frequency rates of fatigue in PD [158–163]

Study	Population	Fatigue frequency	Scale used for assessing fatigue
Friedman and Friedman (1993) [158]	58 PD patients	67 %	Fatigue severity questionnaire
Karlsen et al. (1999) [159]	233 PD patients	44.2 %	Rating scale for low energy in the NHP, 7-point scale devised to evaluate fatigue
Herlofson and Larsen (2003) [160]	66 PD patients	50 %	Fatigue severity scale
Alves et al. (2004) [161]	233 PD patients followed over a period of 8 years (from 1993 to 2001)	35.7 % at baseline 55.7 % at last follow-up	Rating scale for low energy in the NHP, 7-point scale devised to evaluate fatigue, fatigue severity scale
Skorvanek et al. (2013) [162]	165 PD patients	77.6 %	Multidimensional fatigue inventory
Beiske et al. (2013) [163]	176 PD patients	28 %	Fatigue questionnaire

NHP Nottingham Health Profile

Recently, a task force commissioned by MDS revealed that only four scales are recommended to use for PD patients [169]: the Fatigue Severity Scale (FSS) [170], the PD-specific 16-item Parkinson Fatigue Scale (PFS-16) [153], the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) [171], and the Multidimensional Fatigue Inventory (MFI) [172].

The FSS includes physical and mental aspects of fatigue, was validated for PD populations, and is useful to screen and measure severity of fatigue [169, 173].

The PFS-16 is the first specific scale for measuring fatigue in PD. This scale evaluates only physical aspects of fatigue and has very good internal consistency and discriminant and convergent validity [174].

The FACIT-F was designed for assessing anemia-associated fatigue in oncological patients; it seems to be able to discriminate between fatigued and non-fatigued PD patients [173] and shows promise in PD as reported in a recent systematic review of measurement properties of self-report fatigue questionnaires [175].

The MFI was recently validated in PD and is reliable and valid to assess fatigue [176].

More recently, other questionnaires have been investigated. The Fatigue Impact Scale for Daily Use (D-FIS) [177] is a unidimensional scale of fatigue impact, and it was validated in PD; its psychometric properties were good: it showed adequate internal consistency and no floor and ceiling effect [178]. The Modified Fatigue Impact Scale (MFIS) was validated in PD patients without dementia: it showed high internal consistency, strong convergent validity, and adequate divergent validity [179].

In conclusion, although fatigue is a nonmotor symptom reducing quality of life in PD at several stages of disease, until now no multidimensional questionnaire was

validated in PD. Future studies should investigate specific aspects of fatigue in PD to allow the development of questionnaires that reflect both generic and PD-specific symptoms of fatigue.

PD Nonmotor-Associated Features

Several studies reported a relationship of fatigue with depression [158, 159, 180, 181], whereas others found high level of fatigue in nondepressed PD patients [161, 182]. Fatigue is associated with anxiety (both trait and state) [164, 183] and with sleep disorders [184]. However, some studies revealed that fatigue could not be attributable to excessive daytime sleepiness or poor sleep [164]. In a study, fatigue was related to cardiovascular sympathetic dysfunctions and with orthostatic hypotension [185]. The abovementioned associations might suggest that fatigue in PD is a nonmotor symptom. Finally fatigue was found to be associated with poor decision making evaluated by Iowa Gambling Task [186], with high level of apathy [182, 187] and to reduce quality of life in PD patients as evidenced in several studies [160, 182, 188]. More recently, fatigue was investigated in drug-naïve PD patient and was found to be associated with high level of depression and difficulties with activities of daily living (ADL) [189].

Management

Management of fatigue in PD is often complicated by the coexistence of several contributing factors like depression, anxiety, sleep disorders, and autonomic dysfunction; thus, the first treatment option should be identifying and possibly treating such symptoms.

In regard to medications with a specific action on fatigue in PD, most studies have evaluated the effect of dopaminergic drugs. Previous studies have suggested beneficial effect of levodopa and pergolide [190, 191]. More recently, methylphenidate, a dopamine transporter blocker, at a dose of 10 mg three times a day, has been found to be effective in improving fatigue in a randomized, placebo-controlled study ($N=36$) [192]. In addition, in a post hoc analysis of RECOVER study ($N=287$), Chaudhuri and collaborators [134] found significant improvement from baseline on the fatigue item of NMSS ("fatigue or lack of energy") in the rotigotine group as compared with the placebo group, though such benefit was associated with improvement also on depression, apathy, and anhedonia not allowing to support a specific action of rotigotine on fatigue. Finally, a sub-study of ADAGIO ($N=1105$) has shown that rasagiline was associated with significantly less progression of fatigue compared with placebo over a 9-month period [193].

References

1. Kuhn W, Heye N, Muller TH, et al. The motor performance test series in Parkinson's disease is influenced by depression. J Neural Transm. 1996;103:349–54.
2. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Effect of psychiatric and other non-motor symptoms on disability in Parkinson's disease. J Am Ger Soc. 2004;52:784–8.
3. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry. 2000;69:308–12.
4. Global Parkinson's Disease Survey Steering Committee. Factors impacting on quality of life in Parkinson's disease: results from an international study. Mov Disord. 2002;17:60–7.
5. Leentjens AF. Depression in Parkinson's disease: conceptual issues and clinical challenges. J Geriatr Psychiatry Neurol. 2004;17:120–6.
6. Kummer A, Cardoso F, Teixeira AL. Suicidal ideation in Parkinson's disease. CNS Spectr. 2009;14:431–6.
7. Marsh L, McDonald WM, Cummings J, Ravina B. Provisional diagnostic criteria for depression in Parkinson's disease: report of an NINDS/NIMH Work Group. Mov Disord. 2006;21:148–58.
8. Starkstein SE, Merello M, Jorge R, Brockman S, Bruce D, Petracca G, Robinson RG. A validation study of depressive syndromes in Parkinson's disease. Mov Disord. 2008;23:538–46.
9. Chen JJ, Marsh L. Depression in Parkinson's disease: identification and management. Pharmacotherapy. 2013;33:972–83.
10. American Psychiatric Association. Diagnostic and statistical manual of mental disorder. 4th ed. Washington: American Psychiatry Association; 1994.
11. Leentjens AF, Van den Akker M, Metsemakers JF, Lousberg R, Verhey FR. Higher incidence of depression preceding the onset of Parkinson's disease: a register study. Mov Disord. 2003;18:414–8.
12. Ehmann TS, Beninger RJ, Gawel MJ, Riopelle RJ. Depressive symptoms in Parkinson's disease: a comparison with disabled control subjects. J Geriatr Psychiatry Neurol. 1990;3:3–9.
13. Brooks DJ, Piccini P. Imaging in Parkinson's disease: the role of monoamines in behavior. Biol Psychiatry. 2006;59:908–18.
14. Eskow Jaunarajs KL, Angoa-Perez M, Kuhn DM, Bishop C. Potential mechanisms underlying anxiety and depression in Parkinson's disease: consequences of L-DOPA treatment. Neurosci Biobehav Rev. 2011;35:556–64.
15. Hesse S, Meyer PM, Strecker K, Barthel H, Wegner F, Oehlwein C, et al. Monoamine transporter availability in Parkinson's disease patients with or without depression. Eur J Nucl Med Mol Imaging. 2009;36:428–35.
16. Weintraub D, Newberg AB, Cary MS, Siderowf AD, Moberg PJ, Kleiner-Fisman G, et al. Striatal dopamine transporter imaging correlates with anxiety and depression symptoms in Parkinson's disease. J Nucl Med. 2005;46:227–32.
17. Felicio AC, Moriyama TS, Godeiro-Junior C, Shih MC, Hoexter MQ, Borges V, et al. Higher dopamine transporter density in Parkinson's disease patients with depression. Psychopharmacology (Berl). 2010;211:27–31.
18. Ceravolo R, Frosini D, Poletti M, Kiferle L, Pagni C, Mazzucchi S, Volterrani D, Bonuccelli U. Mild affective symptoms in de novo Parkinson's disease patients: relationship with dopaminergic dysfunction. Eur J Neurol. 2013;20:480–5.
19. Koerts J, Leenders KL, Koning M, Portman AT, van Beilen M. Striatal dopaminergic activity (FDOPA-PET) associated with cognitive items of a depression scale (MADRS) in Parkinson's disease. Eur J Neurosci. 2007;25:3132–6.
20. Politis M, Wu K, Loane C, Turkheimer FE, Molloy S, Brooks DJ, et al. Depressive symptoms in PD correlate with higher 5-HTT binding in raphe and limbic structures. Neurology. 2010;75:1920–7.

21. Walter U, Hoeppner J, Prudente-Morrissey L, et al. Parkinson's disease-like midbrain sonography abnormalities are frequent in depressive disorders. Brain. 2007;130:1799–807.
22. Remy P, Doder M, Lees A, Turjanski N, Brooks D. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain. 2005;128:1314–22.
23. Frisina PG, Haroutunian V, Libow LS. The neuropathological basis for depression in Parkinson's disease. Parkinsonism Relat Disord. 2009;15:144–8.
24. Mayberg HS, Starkstein SE, Sadzot B, et al. Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease. Ann Neurol. 1990;28:57–64.
25. Ring HA, Bench CJ, Trimble MR, et al. Depression in Parkinson's disease. A positron emission study. Br J Psychiatry. 1994;165:333–9.
26. Cardoso EF, Maia FM, Fregni F, et al. Depression in Parkinson's disease: convergence from voxel-based morphometry and functional magnetic resonance imaging in the limbic thalamus. Neuroimage. 2009;47:467–72.
27. Matsui H, Nishinaka K, Oda M, et al. Minor depression and brain perfusion images in Parkinson's disease. Mov Disord. 2006;21:1169–74.
28. Feldmann A, Illes Z, Kosztolanyi P, et al. Morphometric changes of gray matter in Parkinson's disease with depression: a voxel-based morphometry study. Mov Disord. 2008;23:42–6.
29. Kostic VS, Agosta F, Petrovic I, et al. Regional patterns of brain tissue loss associated with depression in Parkinson disease. Neurology. 2010;75:857–63.
30. Luo C, Chen Q, Song W, Chen K, Guo X, Yang J, Huang X, Gong Q, Shang HF. Resting-state fMRI study on drug-naïve patients with Parkinson's disease and with depression. J Neurol Neurosurg Psychiatry. 2013;260(11):2754–60.
31. Santamaria J, Tolosa E, Valles A. Parkinson's disease with depression: a possible subgroup of idiopathic parkinsonism. Neurology. 1986;36:1130–3.
32. Ishihara L, Brayne C. A systematic review of depression and mental illness preceding Parkinson's disease. Acta Neurol Scand. 2006;113:211–20.
33. Lieberman A. Depression in Parkinson's disease – a review. Acta Neurol Scand. 2006;113:1–8.
34. Shen CC, Tsai SJ, Perng CL, Kuo BI, Yang AC. Risk of Parkinson disease after depression: a nationwide population-based study. Neurology. 2013;81:1538–44.
35. Reijnders JS, Ehrt U, Weber WE, et al. A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord. 2008;23:183–9.
36. Barone P, et al. Depression and antidepressant use in Parkinson's disease: results from the PRODEST-PD study. Abstract P1122 poster presented at 11th Congress of EFNS, Brussels. 26 Aug 2007.
37. Farabaugh AH, Locascio JJ, Yap L, Weintraub D, McDonald WM, Agoston M, Alpert JE, Growdon J, Fava M. Pattern of depressive symptoms in Parkinson's disease. Psychosomatics. 2009;50:448–54.
38. Riedel O, Klotsche J, Spottke A, et al. Frequency of dementia, depression, and other neuropsychiatric symptoms in 1,449 outpatients with Parkinson's disease. J Neurol. 2010;257:1073–82.
39. Inoue T, Kitagawa M, Tanaka T, Nakagawa S, Koyama T. Depression and major depressive disorder in patients with Parkinson's disease. Mov Disord. 2010;25:44–9.
40. Nègre-Pagès L, Grandjean H, Lapeyre-Mestre M, Montastruc JL, Fourrier A, Lépine JP, Rascol O, DoPaMiP Study Group. Anxious and depressive symptoms in Parkinson's disease: the French cross-sectional DoPaMiP study. Mov Disord. 2010;25:157–66.
41. van der Hoek TC, Bus BA, Matui P, van der Marck MA, Esselink RA, Tendolkar I. Prevalence of depression in Parkinson's disease: effects of disease stage, motor subtype and gender. J Neurol Sci. 2011;310:220–4.
42. Yamanishi T, Tachibana H, Oguru M, Matsui K, Toda K, Okuda B, Oka N. Anxiety and depression in patients with Parkinson's disease. Intern Med. 2013;52:539–45.
43. Weerkamp NJ, Tissingh G, Poels PJ, Zuidema SU, Munneke M, Koopmans RT, Bloem BR. Nonmotor symptoms in nursing home residents with Parkinson's disease: prevalence and effect on quality of life. J Am Geriatr Soc. 2013;61:1714–21.

44. Starkstein SE, Preziosi TJ, Berthier ML, Bolduc PL, Mayberg HS, Robinson RG. Depression and cognitive impairment in Parkinson's disease. Brain. 1989;112:1141–53.
45. Dissanayaka NNW, Sellbach A, Silburn PA, O'Sullivan JD, Marsh R, Mellick GD. Factors associated with depression in Parkinson's disease. J Affect Disord. 2011;132:82–8.
46. Becker C, Brobert GP, Johansson S, Jick SS, Meier CR. Risk of incident depression in patients with Parkinson disease in the UK. Eur J Neurol. 2011;18:448–53.
47. Gallagher DA, Schrag A. Psychosis, apathy, depression and anxiety in Parkinson's disease. Neurobiol Dis. 2012;46:581–9.
48. Riedel O, Heuser I, Klotsche J, Dodel R, Wittchen HU, GEPAD Study Group. Occurrence risk and structure of depression in Parkinson disease with and without dementia: results from the GEPAD Study. J Geriatr Psychiatry Neurol. 2010;23:27–34.
49. Riedel O, Dodel R, Deuschl G, Klotsche J, Förstl H, Heuser I, Oertel W, Reichmann H, Riederer P, Trenkwalder C, Wittchen HU. Depression and care-dependency in Parkinson's disease: results from a nationwide study of 1,449 outpatients. Parkinsonism Relat Disord. 2012;18:598–601.
50. Leentjens AF, Moonen AJ, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE, Köhler S. Modeling depression in Parkinson disease: disease-specific and nonspecific risk factors. Neurology. 2013;81:1036–43.
51. Williams JR, Hirsch ES, Anderson K, Bush AL, Goldstein SR, Grill S, Lehmann S, Little JT, Margolis RL, Palanci J, Pontone G, Weiss H, Rabins P, Marsh L. A comparison of nine scales to detect depression in Parkinson disease: which scale to use? Neurology. 2012;78:998–1006.
52. Starkstein SE, Merello M. The unified Parkinson's disease rating scale: validation study of the mentation, behavior, and mood section. Mov Disord. 2007;22:2156–61.
53. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62.
54. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382–9.
55. Leentjens AF, Verhey FR, Lousberg R, Spitsbergen H, Wilmink FW. The validity of the Hamilton and Montgomery-Åsberg depression rating scales as screening and diagnostic tools for depression in Parkinson's disease. Int J Geriatr Psychiatry. 2000;15:644–9.
56. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606–13.
57. Leentjens AF, Verhey FRJ, Luijckx GJ, Troost J. The validity of the Beck Depression Inventory as a screening and diagnostic instrument for depression in patients with Parkinson's disease. Mov Disord. 2000;15:1221–4.
58. Naarding P, Leentjens AFG, van Kooten F, Verhey FRJ. Disease-specific properties of the Hamilton Rating Scale for depression in patients with stroke, Alzheimer's disease, and Parkinson's disease. J Neuropsychiatry Clin Neurosci. 2002;14:329–48.
59. McDonald WM, Holtzheimer PE, Haber M, Vitek JL, McWhorter K, Delong M. Validity of the 30-item geriatric depression scale in patients with Parkinson's disease. Mov Disord. 2006;21:1618–22.
60. Silberman CD, Laks J, Capitao CF, Rodrigues CS, Moreira I, Engelhardt E. Recognizing depression in patients with Parkinson's disease: accuracy and specificity of two depression rating scale. Arq Neuropsiquiatr. 2006;64:407–11.
61. Weintraub D, Oehlberg KA, Katz IR, Stern MB. Test characteristics of the 15-item geriatric depression scale and Hamilton depression rating scale in Parkinson disease. Am J Geriatr Psychiatry. 2006;14:169–75.
62. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1983;17:37–49.
63. Visser M, Leentjens AF, Marinus J, Stiggelbout AM, van Hilten JJ. Reliability and validity of the Beck depression inventory in patients with Parkinson's disease. Mov Disord. 2006;21:668–72.
64. Ertan T, Kiziltan G, Uygucgil H. Reliability and validity of the Geriatric Depression Scale in depression in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2005;76:1445–7.

65. Thompson AW, Liu H, Hays RD, et al. Diagnostic accuracy and agreement across three depression assessment measures for Parkinson's disease. Parkinsonism Relat Disord. 2011;17:40–5.
66. Chagas MH, Tumas V, Rodrigues GR, Machado-de-Sousa JP, Filho AS, Hallak JE, Crippa JA. Validation and internal consistency of Patient Health Questionnaire-9 for major depression in Parkinson's disease. Age Ageing. 2013;42:645–9.
67. Mayeux R, Stern Y, Rosen J, Leventhal J. Depression, intellectual impairment, and Parkinson disease. Neurology. 1981;31:645–50.
68. Starkstein SE, Bolduc PL, Mayberg HS, et al. Cognitive impairments and depression in Parkinson's disease: a follow up study. J Neurol Neurosurg Psychiatry. 1990;53:597–602.
69. Kuzis G, Sabe L, Tiberti C, Leiguarda R, Starkstein SE. Cognitive functions in major depression and Parkinson disease. Arch Neurol. 1997;54:982–6.
70. Cubo E, Bernard B, Leurgans S, Raman R. Cognitive and motor function in patients with Parkinson's disease with and without depression. Clin Neuropharmacol. 2000;23:331–4.
71. Anguenot A, Loll PY, Neau JP, Ingrand P, Gil R. Depression and Parkinson's disease: study of a series of 135 Parkinson's patients can. J Neurol Sci. 2002;29:139–46.
72. Norman S, Troster AI, Fields JA, Brooks R. Effects of depression and Parkinson's disease on cognitive functioning. J Neuropsychiatry Clin Neurosci. 2002;14:31–6.
73. Uekermann J, Daum I, Peters S, Wiebel B, Przuntek H, Müller T. Depressed mood and executive dysfunction in early Parkinson's disease. Acta Neurol Scand. 2003;107:341–8.
74. Stefanova E, Potrebic A, Ziropadja L, Maric J, Ribaric I, Kostic VS. Depression predicts the pattern of cognitive impairment in early Parkinson's disease. J Neurol Sci. 2006;248:131–7.
75. Tröster AI, Paolo AM, Lyons KE, Glatt SL, Hubble JP, Koller WC. The influence of depression on cognition in Parkinson's disease: a pattern of impairment distinguishable from Alzheimer's disease. Neurology. 1995;45:672–6.
76. Tröster AI, Stalp LD, Paolo AM, Fields JA, Koller WC. Neuropsychological impairment in Parkinson's disease with and without depression. Arch Neurol. 1995;52:1164–9.
77. Beliauskas LA, Glantsz RH. Depression type in Parkinson's disease. J Clin Exp Neuropsychol. 1989;11:597–604.
78. Taylor AE, Saint-Cyr JA, Lang AE, Kenny FT. Parkinson's disease and depression: a critical reevaluation. Brain. 1986;109:279–92.
79. Huber SJ, Paulson GW, Shuttleworth EC. Relationship of motor symptoms, intellectual impairment, and depression in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1988;51:855–8.
80. Silberman CD, Laks J, Capitão CF, et al. Frontal functions in depressed and nondepressed Parkinson's disease patients: impact of severity stages. Psychiatry Res. 2007;149:285–9.
81. Santangelo G, Vitale C, Trojano L, Longo K, Cozzolino A, Grossi D, Barone P. Relationship between depression and cognitive dysfunctions in Parkinson's disease without dementia. J Neurol. 2009;256:632–8.
82. Varanese S, Perfetti B, Ghilardi MF, Di Rocco A. Apathy, but not depression, reflects inefficient cognitive strategies in Parkinson's disease. PLoS ONE. 2011;6:e17846.
83. Rektorova I, Rektor I, Bares M, et al. Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. Eur J Neurol. 2003;10:399–406.
84. Lemke MR, Brecht HM, Koester J, Kraus PH, Reichmann H. Anhedonia, depression, and motor functioning in Parkinson's disease during treatment with pramipexole. J Neuropsychiatry Clin Neurosci. 2005;17:214–20.
85. Barone P, Scarzella L, Marconi R, Antonini A, Morgante L, Bracco F, Zappia M, Musch B, Depression/Parkinson Italian Study Group. Pramipexole versus sertraline in the treatment of depression in Parkinson's disease: a national multicenter parallel-group randomized study. J Neurol. 2006;253:601–7.
86. Rektorova I, Balaz M, Svatova J, et al. Effects of ropinirole on nonmotor symptoms of Parkinson's disease: a prospective multicenter study. Clin Neuropharmacol. 2008;31:261–6.

87. Barone P, Poewe W, Albrecht S, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2010;9:573–80.
88. Pahwa R, Stacy MA, Factor SA, Lyons KE, Stocchi F, Hersh BP, Elmer LW, Truong DD, Earl NL, EASE-PD Adjunct Study Investigators. Ropinirole 24-h prolonged release: randomized, controlled study in advanced Parkinson disease. Neurology. 2007;68:1108–15.
89. Trenkwalder C, Kies B, Rudzinska M, Fine J, Nikl J, Honczarenko K, et al. Rotigotine effects on early morning motor function and sleep in Parkinson's disease: a double-blind, randomized, placebo-controlled study (RECOVER). Mov Disord. 2011;26:90–9.
90. Skapinakis P, Bakola E, Salanti G, Lewis G, Kyritsis AP, Mavreas V. Efficacy and acceptability of selective serotonin reuptake inhibitors for the treatment of depression in Parkinson's disease: a systematic review and meta-analysis of randomized controlled trials. BMC Neurol. 2010;10:49.
91. Seppi K, Weintraub D, Coelho M, et al. The movement disorder society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson's disease. Mov Disord. 2011;26 Suppl 3:S42–80.
92. Richard IH, McDermott MP, Kurlan R, et al. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. Neurology. 2012;78:1229–36.
93. Wermuth L, Sorensen PS, Timm B, et al. Depression in idiopathic Parkinson's disease treated with citalopram: a placebo-controlled trial. Nordic J Psychiatry. 1998;52:163–9.
94. Leentjens AF, Vreeling FW, Luijckx GJ, Verhey FRJ. SSRIs in the treatment of depression in Parkinson's disease. Int J Geriatr Psychiatry. 2003;18:552–4.
95. Weintraub D, Mavandadi S, Mamikonyan E, et al. Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. Neurology. 2010;75:448–55.
96. Devos D, Dujardin K, Poirot I, et al. Comparison of desipramine and citalopram treatments for depression in Parkinson's disease: a double-blind, randomized, placebo-controlled study. Mov Disord. 2008;23:850–7.
97. Menza M, Dobkin RD, Marin H, et al. A controlled trial of antidepressants in patients with Parkinson disease and depression. Neurology. 2009;72:886–92.
98. Dobkin RD, Menza M, Allen LA, et al. Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial. Am J Psychiatry. 2011;168:1066–74.
99. Pal E, Nagy F, Aschermann Z, Balazs E, Kovacs N. The impact of left prefrontal repetitive transcranial magnetic stimulation on depression in Parkinson's disease: a randomized, double-blind, placebo-controlled study. Mov Disord. 2010;25:2311–7.
100. Boggio PS, Fregni F, Bermpohl F, et al. Effect of repetitive TMS and fluoxetine on cognitive function in patients with Parkinson's disease and concurrent depression. Mov Disord. 2005;20:1178–84.
101. Fregni F, Santos CM, Myczkowski ML, et al. Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 2004;75:1171–4.
102. Pedersen KF, Larsen JP, Alves G, Aarsland D. Prevalence and clinical correlates of apathy in Parkinson's disease: a community-based study. Parkinsonism Relat Disord. 2009;15:295–9.
103. Starkstein SE, Merello M, Jorge R, Brockman S, Bruce D, Power B. The syndromal validity and nosological position of apathy in Parkinson's disease. Mov Disord. 2009;24:1211–6.
104. Drijgers RL, Dujardin K, Reijnders JS, Defebvre L, Leentjens AF. Validation of diagnostic criteria for apathy in Parkinson's disease. Parkinsonism Relat Disord. 2010;16:656–60.
105. Duffy JD. The neural substrates of motivation. Psychiatr Ann. 1997;27:24.
106. Reijnders JS, Scholtissen B, Weber WE, Aalten P, Verhey FR, Leentjens AF. Neuroanatomical correlates of apathy in Parkinson's disease: a magnetic resonance imaging study using voxel-based morphometry. Mov Disord. 2010;25:2318–25.
107. Thobois S, Ardouin C, Lhommee E, Klinger H, Lagrange C, Xie J, et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. Brain. 2010;133(Pt 4):1111–27.

108. Robert G, Le Jeune F, Lozachmeur C, Drapier S, Dondaine T, Péron J, Travers D, Sauleau P, Millet B, Vérin M, Drapier D. Apathy in patients with Parkinson disease without dementia or depression: a PET study. Neurology. 2012;79:1155–60.
109. Lhommèe E, Klinger H, Thobois S, Schmitt E, Ardouin C, Bichon A, Kistner A, Fraix V, Xie J, AyaKombo M, Chabard'es S, Seigneuret E, Benabid AL, Mertens P, Polo G, Carnicella S, Quesada JL, Bosson JL, Broussolle E, Pollak P, Krack P. Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours. Brain. 2012;135(Pt 5):1463–77.
110. Starkstein SE. Apathy in Parkinson's disease: diagnostic and etiological dilemmas. Mov Disord. 2012;27:174–8.
111. Santangelo G, Trojano L, Barone P, Errico D, Grossi D, Vitale C. Apathy in Parkinson's disease: diagnosis, neuropsychological correlates, pathophysiology and treatment. Behav Neurol. 2013;27:501–13.
112. Pedersen KF, Alves G, Brønnick K, Aarsland D, Tysnes OB, Larsen JP. Apathy in drug-naïve patients with incident Parkinson's disease: the Norwegian ParkWest study. J Neurol. 2010;257:217–23.
113. Pedersen KF, Alves G, Aarsland D, Larsen JP. Occurrence and risk factors for apathy in Parkinson disease: a 4-year prospective longitudinal study. J Neurol Neurosurg Psychiatry. 2009;80:1279–82.
114. Cubo E, Benito-Leo'n J, Coronell C, Armesto D, ANIMO Study Group. Clinical correlates of apathy in patients recently diagnosed with Parkinson's disease: the ANIMO study. Neuroepidemiology. 2012;38:48–55.
115. Harris E, McNamara P, Durso R. Apathy in patients with Parkinson disease as a function of side of onset. J Geriatr Psychiatry Neurol. 2013;26:95–104.
116. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res. 1991;38:143–62.
117. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 1992;4:134–9.
118. Sockeel P, Dujardin K, Devos D, Deneve C, Destee A, Defebvre L. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2006;77:579–84.
119. Robert PH, Clairet S, Benoit M, et al. The apathy inventory: assessing apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. Int J Geriatr Psychiatry. 2002;17:1099–105.
120. Cummings JL, Mega M, Gray K, Rosenburg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44:2308–14.
121. Fahn S, Elton RL, members of the UPDRS committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. Recent developments in Parkinson's disease. Florham Park: McMillan Health Care; 1987. p. 153—63.
122. Leentjens AF, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE, Weintraub D, Sampaio C, Poewe W, Rascol O, Stebbins GT, Goetz CG. Apathy and anhedonia rating scales in Parkinson's disease: critique and recommendations. Mov Disord. 2008;23:2004–14.
123. Pluck GC, Brown RG. Apathy in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2002;73:636–42.
124. Zahodne LB, Young S, Kirsch-Darrow L, Nisenzon A, Fernandez HH, Okun MS, Bowers D. Examination of the Lille Apathy Rating Scale in Parkinson disease. Mov Disord. 2009;24:677–83.
125. Santangelo G, Vitale C, Picillo M, Moccia M, Erro R, Pisano G, Pezzella D, Cuoco S, Longo K, Pellecchia MT, Amboni M, De Rosa A, De Michele G, Trojano L, Barone P. Relationship between apathy and cognitive dysfunctions in de novo, untreated Parkinson's Disease patients : a prospective longitudinal study. Eur J Neurol. 2014 May 22 [Epub ahead of print].

126. Dujardin K, Sockeel P, Delliaux M, Deste'e A, Defebvre L. Apathy may herald cognitive decline and dementia in Parkinson's disease. Mov Disord. 2009;24:2391–7.
127. Isella V, Melzi P, Grimaldi M, Iurlaro S, Piolti R, Ferrarese C, Frattola L, Appollonio I. Clinical, neuropsychological, and morphometric correlates of apathy in Parkinson's disease. Mov Disord. 2002;17:366–71.
128. Zgaljardic DJ, Borod JC, Foldi NS, Rocco M, Mattis PJ, Gordon MF, Feigin AS, Eidelberg D. Relationship between self- reported apathy and executive dysfunction in nondemented patients with Parkinson disease. Cogn Behav Neurol. 2007;20:184–92.
129. Grossi D, Santangelo G, Barbarulo AM, Vitale C, Castaldo G, Proto MG, Siano P, Barone P, Trojano L. Apathy and related executive syndromes in dementia associated with Parkinson's disease and in Alzheimer's disease. Behav Neurol. 2013;27:515–22.
130. Santangelo G, Vitale C, Trojano L, Errico D, Amboni M, Barbarulo AM, Grossi D, Barone P. Neuropsychological correlates of theory of mind in patients with early Parkinson's disease. Mov Disord. 2012;27:98–105.
131. Czernecki V, Pillon B, Houeto JL, Pochon JB, Levy R, Dubois B. Motivation, reward, and Parkinson's disease: influence of dopa therapy. Neuropsychologia. 2002;40:2257–67.
132. Czernecki V, Schipbach M, Yaici S, Levy R, Bardinet E, Yelnik J, Dubois B, Agid Y. Apathy following subthalamic stimulation in Parkinson disease: a dopamine responsive symptom. Mov Disord. 2008;23:964–9.
133. Leentjens AF, Koester J, Fruh B, Shephard DT, Barone P, Houben JJ. The effect of pramipexole on mood and motivational symptoms in Parkinson's disease: a meta-analysis of placebo-controlled studies. Clin Ther. 2009;31:89–98.
134. Chaudhuri RK, Martinez-Martin P, Antonini A, Brown RG, Friedman JH, Onofrj M, Surmann E, Ghys L, Trenkwalder C. Rotigotine and specific non-motor symptoms of Parkinson's disease: post hoc analysis of RECOVER. Parkinsonism Relat Disord. 2013;19:660–5.
135. Thobois S, Lhommée E, Klinger H, Ardouin C, Schmitt E, Bichon A, Kistner A, Castrioto A, Xie J, Fraix V, Pelissier P, Chabardes S, Mertens P, Quesada JL, Bosson JL, Pollak P, Broussolle E, Krack P. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. Brain. 2013;136(Pt 5):1568–77.
136. Litvinenko IV, Odinak MM, Mogil'naya VI, Emelin AY. Efficacy and safety of galantamine (reminyl) for dementia in patients with Parkinson's disease (an open controlled trial). Neurosci Behav Physiol. 2008;38:937–45.
137. Grace J, Amick MM, Friedman JH. A double-blind comparison of galantamine hydrobromide ER and placebo in Parkinson disease. J Neurol Neurosurg Psychiatry. 2009;80:18–23.
138. Stevens A, Peschk I, Schwarz J. Implicit learning, executive function and hedonic activity in chronic polydrug abusers, currently abstinent polydrug abusers and controls. Addiction. 2007;102:937–46.
139. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophr Res. 2007;93:253–60.
140. Gard D, Germans Gard M, Kring A, John O. Anticipatory and consummatory components of the experience of pleasure: a scale development study. J Res Pers. 2006;40:1086–102.
141. Assogna F, Cravello L, Caltagirone C, Spalletta G. Anhedonia in Parkinson's disease: a systematic review of the literature. Mov Disord. 2011;26:1825–34.
142. Weintraub D, Cary M, Stern M, et al. Daily affect in Parkinson disease is responsive to life events and motor symptoms. Am J Geriatr Psychiatry. 2006;14:161–8.
143. Jordan LL, Zahodne LB, Okun MS, Bowers D. Hedonic and behavioral deficits associated with apathy in Parkinson's disease: potential treatment implications. Mov Disord. 2013;28:1301–4.
144. Santangelo G, Morgante L, Savica R, et al. Anhedonia and cognitive impairment in Parkinson's disease: Italian validation of the Snaith-Hamilton Pleasure Scale and its application in the clinical routine practice during the PRIAMO study. Parkinsonism Relat Disord. 2009;15:576–81.
145. Reichmann H, Brecht MH, Koster J, Kraus PH, Lemke MR. Pramipexole in routine clinical practice: a prospective observational trial in Parkinson's disease. CNS Drugs. 2003;17:965–73.

146. Isella V, Iurlaro S, Piolti R, Ferrarese C, Frattola L, Appollonio I, et al. Physical anhedonia in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2003;74:1308–11.
147. Lemke MR, Brecht HM, Koester J, Reichmann H. Effects of the dopamine agonist pramipexole on depression, anhedonia and motor functioning in Parkinson's disease. J Neurol Sci. 2006;248:266–70.
148. Matsui K, Tachibana H, Yamanishi T, Oguru M, Toda K, Okuda B, Oka N. Clinical correlates of anhedonia in patients with Parkinson's disease. Clin Neurol Neurosurg. 2013;115:2524–7.
149. Nagayama H, Kubo S, Hatano T, Hamada S, Maeda T, Hasegawa T, Kadowaki T, et al. Validity and reliability assessment of a Japanese version of the Snaith-Hamilton pleasure scale. Intern Med. 2012;51:865–9.
150. Reichmann H, Odin P, Brecht HM, Koster J, Kraus PH. Changing dopamine agonist treatment in Parkinson's disease: experiences with switching to pramipexole. J Neural Transm Suppl. 2006;71:17–25.
151. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. Neurology. 2013;80:409–16.
152. Fabbrini G, Latorre A, Suppa A, Bloise M, Frontoni M, Berardelli A. Fatigue in Parkinson's disease: motor or non-motor symptom? Parkinsonism Relat Disord. 2013;19:148–52.
153. Brown RG, Dittner A, Findley L, Wessely SC. The Parkinson fatigue scale. Parkinsonism Relat Disord. 2005;11:49–55.
154. Berardelli A, Conte A, Fabbrini G, Bologna M, Latorre A, Rocchi L, Suppa A. Pathophysiology of pain and fatigue in Parkinson's disease. Parkinsonism Relat Disord. 2012;18(S1):226–8.
155. Abe K, Takanashi M, Yanagihara T. Fatigue in patients with Parkinson's disease. Behav Neurol. 2000;2:103–6.
156. Pavese N, Metta V, Bose SK, Chaudhuri KR, Brooks DJ. Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. Brain. 2010;133:3434–43.
157. Lou JS, Benice T, Kearns G, Sexton G, Nutt J. Levodopa normalizes exercise related cortico-motoneuron excitability abnormalities in Parkinson's disease. Clin Neurophysiol. 2003;114:930–7.
158. Friedman J, Friedman H. Fatigue in Parkinson's disease. Neurology. 1993;43:2016–8.
159. Karlsen K, Larsen JP, Tandberg E, Jørgensen K. Fatigue in patients with Parkinson's disease. Mov Disord. 1999;14:237–41.
160. Herlofson K, Larsen JP. The influence of fatigue on health-related quality of life in patients with Parkinson's disease. Acta Neurol Scand. 2003;107:1–6.
161. Alves G, Wentzel-Larsen T, Larsen JP. Is fatigue an independent and persistent symptom in patients with Parkinson disease? Neurology. 2004;63:1908–11.
162. Skorvanek M, Nagyova I, Rosenberger J, Krokavcova M, Ghorbani Saeedian R, Groothoff JW, Gdovinova Z, van Dijk JP. Clinical determinants of primary and secondary fatigue in patients with Parkinson's disease. J Neurol. 2013;260:1554–61.
163. Beiske AG, Loge JH, Hjermstad MJ, Svensson E. Fatigue in Parkinson's disease: prevalence and associated factors. Mov Disord. 2010;25:2456–60.
164. Hagell P, Brundin L. Towards an understanding of fatigue in Parkinson disease. J Neurol Neurosurg Psychiatr. 2009;80:489–92.
165. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, PRIAMO Study Group, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009;24:1641–9.
166. Elbers R, van Wegen EE, Rochester L, Hetherington V, Nieuwboer A, Willems AM, et al. Is impact of fatigue an independent factor associated with physical activity in patients with idiopathic Parkinson's disease? Mov Disord. 2009;24:1512–8.
167. Friedman J, Brown R, Comella C, Garber C, Krupp L, Lou J, et al. Fatigue in Parkinson's disease: a review. Mov Disord. 2007;22:297–308.
168. Falup-Pecurariu C. Fatigue assessment of Parkinson's disease patient in clinic: specific versus holistic. J Neural Transm. 2013;120:577–81.

169. Friedman JH, Alves G, Hagell P, Marinus J, Marsh L, Martinez-Martin P, Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins G, Schrag A. Fatigue rating scales critique and recommendations by the Movement Disorders Society task force on rating scales for Parkinson's disease. Mov Disord. 2010;25:805–22.
170. Krupp LB, La Rocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46:1121–3.
171. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the functional assessment of cancer therapy (FACT) measurement system. J Pain Symptom Manage. 1997;13:63–74.
172. Smets EMA, Garseen B, Bonke B, Dehaes JCJM. The multidimensional fatigue inventory (MFI). Psychometric properties of an instrument to assess fatigue. J Psychosom Res. 1995;39:315–25.
173. Hagell P, Ho¨glund A, Reimer J, Eriksson B, Knutsson I, Widner H, Cella D. Measuring fatigue in Parkinson's disease: a psychometric study of two brief generic fatigue questionnaires. J Pain Symptom Manage. 2006;32:420–32.
174. Grace J, Mendelsohn A, Friedman JH. A comparison of fatigue measures in Parkinson's disease. Parkinsonism Relat Disord. 2007;13:443–5.
175. Elbers RG, Rietberg MB, van Wegen EE, Verhoef J, Kramer SF, Terwee CB, Kwakkel G. Self-report fatigue questionnaires in multiple sclerosis, Parkinson's disease and stroke: a systematic review of measurement properties. Qual Life Res. 2012;21:925–44.
176. Elbers RG, van Wegen EE, Verhoef J, Kwakkel G. Reliability and structural validity of the Multidimensional Fatigue Inventory (MFI) in patients with idiopathic Parkinson's disease. Parkinsonism Relat Disord. 2012;18:532–6.
177. Fisk JD, Doble SE. Construction and validation of a fatigue impact scale for daily administration (D-FIS). Qual Life Res. 2002;11:263–72.
178. Martinez-Martin P, Catalan MJ, Benito-Leon J, Moreno AO, Zamarbide I, Cubo E, van Blercon N, Arillo VC, Pondal M, Linazasoro G, Alonso F, Ruiz PG, Frades B. Impact of fatigue in Parkinson's Disease: the fatigue impact scale for daily use (D-FIS). QualLife Res. 2006;15:597–606.
179. Schiehser DM, Ayers CR, Liu L, Lessig S, Song DS, Filoteo JV. Validation of the modified fatigue impact scale in Parkinson's disease. Parkinsonism Relat Disord. 2013;19:335–8.
180. Dooneief G, Mirabello E, Bell K, Marder K, Stern Y, Mayeux R. An estimate of the incidence of depression in idiopathic Parkinson's disease. Arch Neurol. 1992;49:305–7.
181. Havlikova E, Rosenberger J, Nagyova I, Middel B, Dubayova T, Gdovinova Z, et al. Clinical and psychosocial factors associated with fatigue in patients with Parkinson's disease. Parkinsonism Relat Disord. 2008;14:187–92.
182. Miwa H, Miwa T. Fatigue in patients with Parkinson's disease: impact on quality of life. Intern Med. 2011;50:1553–8.
183. Shulman LM, Taback RL, Bean J, Weiner WJ. Comorbidity of the nonmotor symptoms of Parkinson's disease. Mov Disord. 2001;16:507–10.
184. Friedman JH, Fernandez HH. The nonmotor problems of Parkinson's disease. Neurologist. 2000;6:8–27.
185. Nakamura T, Hirayama M, Hara T, Hama T, Watanabe H, Sobue G. Does cardiovascular autonomic dysfunction contribute to fatigue in Parkinson's disease? Mov Disord. 2011;26:1869–74.
186. Sáez-Francàs N, Hernández-Vara J, Corominas-Roso M, Alegre J, Jacas C, Casas M. Relationship between poor decision-making process and fatigue perception in Parkinson's disease patients. J Neurol Sci. 2014;337(1–2):167–72.
187. Sáez-Francàs N, Hernández-Vara J, Corominas Roso M, AlegreMartín J, CasasBrugué M. The association of apathy with central fatigue perception in patients with Parkinson's disease. Behav Neurosci. 2013;127:237–44.

188. Havlikova E, Rosenberger J, Nagyova I, Middel B, Dubayova T, Gdovinova Z, et al. Impact of fatigue on quality of life in patients with Parkinson's disease. Eur J Neurol. 2008;15:475–80.
189. Kang SY, Ma HI, Lim YM, Hwang SH, Kim YJ. Fatigue in drug-naïve Parkinson's disease. Eur Neurol. 2013;70:59–64.
190. Lou JS, Kearns G, Benice T, Oken B, Sexton G, Nutt J. Levodopa improves physical fatigue in Parkinson's disease: a double-blind, placebo-controlled, crossover study. Mov Disord. 2003;18:1108–14.
191. Abe K, Takanashi M, Yanagihara T, Sakoda S. Pergolide mesylate may improve fatigue in patients with Parkinson's disease. Behav Neurol. 2001–2002;13:117–21.
192. Mendonça DA, Menezes K, Jog MS. Methylphenidate improves fatigue scores in Parkinson disease: a randomized controlled trial. Mov Disord. 2007;22:2070–6.
193. Stocchi F, The ADAGIO Investigators. Benefits of treatment with rasagiline for fatigue symptoms in patients with early Parkinson's disease. Eur J Neurol. 2014;21(2):357–60.