



CONSENSUS STATEMENT

Advanced Parkinson's disease: Clinical characteristics and treatment (part 1)[☆]

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KEYWORDS

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Abstract

Introduction: A large percentage of patients with Parkinson's disease (PD) develop motor fluctuations, dyskinesias, and severe non-motor symptoms (NMS) within 3 to 5 years of starting dopaminergic therapy, and these motor complications are refractory to treatment. Several authors refer to this stage of the disease as advanced PD.

Objective: To define the clinical manifestations of advanced PD and the risk factors for reaching this stage of the disease.

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Non-motor scales;
Quality of life scales

PALABRAS CLAVE

Enfermedad de
Parkinson avanzada;
Factores de riesgo;
Fenotipo clínico;
Escalas de valoración
motora;
Escalas de valoración
no motora;
Escalas de calidad de
vida

Development: This consensus document has been prepared by using an exhaustive literature search and by discussion of the contents by an expert group on movement disorders of the Sociedad Española de Neurología (Spanish Neurology Society), coordinated by two of the authors (JK and MRL).

Conclusions: Severe motor fluctuations and dyskinesias, axial motor symptoms resistant to levodopa, and cognitive decline are the main signs in the clinical phenotype of advanced PD.

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Enfermedad de Parkinson avanzada. Características clínicas y tratamiento (parte I)

Resumen

Introducción: Un porcentaje importante de pacientes con enfermedad de Parkinson (EP) desarrollan complicaciones motoras en forma de fluctuaciones motoras, discinesias y síntomas no motores al cabo de 3–5 años del inicio del tratamiento que resultan de difícil control terapéutico. Esta fase de la enfermedad ha sido definida por algunos autores como fase avanzada de la EP.

Objetivo: Definir las características clínicas y los factores de riesgo que condicionan que una EP evolucione a un estadio avanzado.

Desarrollo: Este documento de consenso se ha realizado mediante una búsqueda bibliográfica exhaustiva y discusión de los contenidos llevadas a cabo por un grupo de expertos en trastornos del movimiento de la Sociedad Española de Neurología coordinados por dos de los autores (JK y MRL).

Conclusiones: La presencia de fluctuaciones motoras y discinesias graves, síntomas motores axiales resistentes a la levodopa y síntomas no motores, como los trastornos cognitivos, representan las principales manifestaciones fenotípicas de una EP avanzada.

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Introduction

Parkinson's disease (PD) is a progressive degenerative disease for which no curative treatment currently exists. Most drugs used to treat PD are intended to re-establish striatal dopamine levels in these patients. This is done by administering the dopamine precursor levodopa. More recently, dopaminergic agonists have been employed for the same purpose. These treatments lessen patients' symptoms considerably in addition to improving quality of life parameters over 5 to 8 years. However, by the end of this period, most patients will develop neuropsychiatric and motor complications (fluctuations and dyskinesia). In some cases, they may also present significant cognitive impairment that can be difficult to manage. These complications probably reflect a combination of factors among which disease progression, i.e. the evolution of the degenerative process, is the most important variable. In order to provide appropriate treatment to patients in an advanced stage of PD, it is necessary to understand the clinical characteristics defining patients who are candidates for certain treatments. This article reviews clinical characteristics that define these patients, risk factors that have been linked to more rapid PD progression, and the motor and non-motor assessment scales used in these cases.

Clinical characteristics of advanced PD

Definition of advanced PD phenotype, motor signs, and non-motor signs

Definition of advanced PD

No regulated studies evaluating disease progression in the pre-levodopa period are currently available. Hoehn and Yahr established a mean time to disability onset of 7 years.¹ Subsequent studies have provided more complete information about the progression of motor symptoms and reduction in quality of life. In patients receiving no treatment, the yearly increase on the Unified Parkinson's Disease Rating Scale (UPDRS) total is estimated at between 8 and 10 points (5–6 on the motor subscale), with more marked progression in the first years after the onset of motor symptoms.^{2–4}

PD is said to be advanced when conventional treatment does not provide the patient with an adequate level of motor control. Patients generally experience alternating periods of good and deficient control over symptoms (motor fluctuations with delayed onset of response, end-of-dose deterioration, dose failures, and unpredictable responses). Furthermore, periods of poor motor control may be accompanied by NMS. NMS that are not related to 'off' periods may also appear; such symptoms depend on the patient's age and the disease's progression timeline. In addition to motor fluctuations, patients experience involuntary movements

(dyskinesia) which may come to be extremely disabling.^{5,6} The time period for a patient to reach an advanced stage of PD varies greatly, but the timeline is more than 10 years from diagnosis for most patients. A small minority will experience rapid progression (less than 5 years). Even more infrequently, some patients will remain in intermediate stages for an indefinite length of time.⁵

Motor symptoms in advanced PD

The most frequent motor symptoms in advanced PD are the complications categorised as dyskinesias and motor fluctuations. Some meta-analyses have estimated a 40% probability of developing motor fluctuations and dyskinesia after 4 to 6 years of levodopa treatment.⁷ Other individual studies have shown that the percentage of patients with motor fluctuations and dyskinesia may vary between 10% and 60% at 5 years of progression, and that this percentage reaches 80% to 90% in the final years.⁸

Motor fluctuations are predictable at first, but become more complex as the disease progresses. The most frequent fluctuations are end of dose deterioration (wearing-off) in which the drug effect ceases in a shorter time; longer latency to response (delayed-on); dose failure (no-on); nocturnal or morning akinesia; and unpredictable complex motor fluctuations.⁹

Dyskinesias are another motor symptom in advanced PD. While they typically manifest as choreic movements, they may also be dystonic or ballistic. Dyskinesias may affect any part of the body and they can be disabling, painful, or both. The main risk factors for developing dyskinesias are young age at onset, disease duration, and levodopa dosage.^{10,11} Peak-dose dyskinesias are the first to appear. They manifest as orofacial, cervical, and limb choreic movements. Onset coincides with the peak plasma concentration of levodopa and its maximum therapeutic effect. Biphasic dyskinesias are choreic or ballistic movements of the lower limbs, and they appear both when the drug is taking effect and when it is wearing off. They may be accompanied by autonomic symptoms. Dyskinesias that appear during 'off' periods tend to be dystonic.⁹

Apart from motor complications, advanced PD is also characterised by motor symptoms that respond poorly or not at all to dopaminergic treatment. These symptoms include gait disorders, postural disorders, lack of stability, dysphagia, and dysarthria, and they cause severe disability. Freezing of gait (FOG) in these patients leads to falls. Estimates indicate that more than 80% of all patients with a 15 to 20-year history of PD experience FOG; the resulting falls cause bone fractures in up to 35% of these cases.^{12,13} Impaired gait, posture, and balance seem to be due in part to degenerative changes in the pedunculopontine nucleus (PPN), which would explain why such impairments do not respond to dopaminergic treatment and why deep brain stimulation of this nucleus elicits partial improvement.¹⁴ Recall that doctors have described cases of FOG during 'on' periods in which freezing disappeared after the levodopa dose was decreased. Dysarthria and dysphagia both have a negative effect on these patients' quality of life. Retrospective studies have established that the latency time between disease onset and the appearance of these symptoms is 7 years for dysarthria and 11 for dysphagia.¹⁵

NMS in advanced PD

NMS are very frequent in PD. In fact, they were mentioned by James Parkinson himself in his "Essay on the Shaking Palsy" in which he lists the presence of sleep disorders, urinary incontinence, constipation, and delirium in these patients.¹⁶

The appearance of NMS results from both neurodegeneration and the presence of deposits of alpha-synuclein protein in different areas of the nervous system. These areas may include non-dopaminergic structures of the brainstem (locus coeruleus, dorsal raphe nucleus, dorsal vagal nucleus); the cholinergic basal ganglia, olfactory bulb, anterior olfactory nucleus, neocortical and limbic areas, and the thalamus and diencephalic nuclei; and the peripheral sympathetic ganglia and sympathetic/parasympathetic efferent pathways.¹⁷ Clinical-pathological correlations have not yet been established for many of these NMS.

NMS may present at any stage of the disease, and they may also precede motor symptoms by several years.^{18,19} In any case, NMS intensify as the disease progresses, and they may be incapacitating in advanced stages of PD once patients have developed the complete motor phenotype.²⁰

As disease progresses, patients' sleep disorders intensify along with cognitive and autonomic impairments. Sleep disorders in patients with advanced PD manifest as difficulty falling asleep, frequent awakenings, REM sleep behaviour disorder (RBD), inversion of the sleep-wake cycle, and excessive daytime somnolence.²¹ The presence of RBD is often associated with visual hallucinations,²² neuropsychiatric changes, and cognitive impairment. In fact, presence of RBD in patients with PD and no dementia is a predictor of dementia onset.²³

Psychiatric disorders secondary to dopaminergic treatment frequently appear in the intermediate to advanced stages of PD. Notable examples include impulse control disorders (ICDs) (gambling, pathological shopping, hypersexuality)²⁴ or behavioural changes such as performing complex stereotyped tasks (collecting or building useless objects).²⁵ These disorders have a particular association with use of dopaminergic agonists; to a lesser extent, they have also been described with levodopa.

Patients with advanced PD who present severe speech and gait disorders, depression, and poor response to levodopa treatment are at greater risk for developing dementia. Nevertheless, the most crucial factors in the development of dementia are the patient's age and duration of disease.²⁶ Visual hallucinations are frequently associated with the development of dementia in PD. The underlying pathology of dementia in PD is not well understood, but it is due in part to degeneration of the basal nucleus of Meynert. This in turn leads to cholinergic deficit, and may contribute to the psychotic symptoms that are often present in these patients.

Autonomic symptoms are very common in advanced stages of PD. Orthostatic hypotension may contribute to falls and genitourinary problems; constipation may be related to the presence of Lewy bodies in peripheral autonomic nerves.

Other NMS include depression, anxiety, apathy, and pain. As the disease progresses, pain is a very common symptom and may in fact be the patient's main complaint. Pain may be categorised in different ways, including musculoskeletal pain, dystonic pain, neuropathic pain, and central pain syndrome. Pain frequently fluctuates, increasing in 'off' periods

and decreasing during 'on' periods. This suggests that dopaminergic pathways are involved.²⁷ This also occurs in other NMS that appear or intensify with decreased motor control, including depression, anxiety, fatigue, apathy, dysphagia, and perspiration.²⁸

Conclusions and recommendations

1. PD is considered advanced if the patient experiences a fluctuating clinical state with alternating periods of good and poor symptom control. These fluctuations may affect both motor and NMS and they cannot be controlled using conventional therapy.
2. Advanced PD gives rise to motor symptoms that respond poorly or not at all to oral levodopa. Symptoms include gait disorders, postural disorders, lack of stability, dysphagia, and dysarthria, and they cause severe disability.
3. Appearance of non-motor complications and the development of disabling NMS (such as dementia, autonomic symptoms, pain, or psychiatric symptoms) are typical in patients with advanced PD.

Risk factors affecting development of an advanced PD phenotype

The timeline for progression to advanced PD varies from patient to patient. Once patients reach that stage, the illness follows a steady course and both physical and cognitive disability increase as a series of other complications appear.²⁹

Kempster et al.²⁹ analysed the relationship between age and the presence of several of the clinical characteristics that manifest in the advanced phase of PD, including frequent falls, visual hallucinations, dementia, and need for institutional living. They found a direct relationship between age at PD onset and appearance of complications, that is, the older the age of onset, the sooner complications will appear. However, once complications are present, time until death does not depend on the patient's age at PD onset. Hallucinations mark the beginning of this period, and together with dementia, they are correlated to increased density of cortical Lewy bodies. PD progression accelerates in patients over 70, and this factor is independent from disease duration and from age at onset. In contrast, the progression rate in early to intermediate stages is affected by age at onset and by other prognostic factors.

Age

Population studies and hospital series have shown that age is a fundamental factor in PD progression.²⁶ PD onset in elderly patients is associated with accelerated progression,^{26,30–43} more marked motor function impairment,⁴⁰ decreased response to levodopa,²⁹ increased frequency of axial deficits with falls and FOG,^{40–42} and a higher risk of dementia.³¹ In contrast, younger patients with PD will experience slower disease progression and increased prevalence of motor complications.^{29,31,44,45} The age at which the speed of disease progression changes has not yet been established; different series cite cut-off points ranging from 50 to 60 years.^{26,29–38,46}

Sex

Some studies suggest that the course of PD in women is slower than in men,^{32,42,43} and also more benign, with a higher prevalence of dyskinesias.^{42,44} These findings have not been confirmed by other authors.⁴⁴

Disease duration

Longer disease duration implies an increased risk of presenting complications.³⁰

Motor phenotype

In 1967, Hoehn and Yahr observed that the presence of tremor was generally associated with a more benign course of the disease.¹ Even the first population studies highlighted that early appearance of postural instability and difficulty walking were indicative of poor prognosis⁴⁷ involving early-onset cognitive impairment and dementia.^{36,40,42,48}

Axial deficits evolve more rapidly than any other type of motor impairment, and they seem to provide the best index of disease progression.³³ Axial symptoms have been linked to degenerative processes reaching the extranigral structures of the brainstem. Elderly patients with PD will experience faster disease progression owing to the interaction between the neurodegenerative process specific to PD (as it extends to other structures in the brainstem and basal forebrain) and the degeneration specific to ageing in non-dopaminergic systems.²⁶ Severe motor impairment at baseline (high scores on UPDRS-III) also predicts a more rapid rate of deterioration and increased functional impairment during the first 10 years after disease onset.³²

Olfactory changes

Olfactory changes are present in 90% of patients with PD. These changes typically appear years before motor symptoms do, and many authors regard them as a presymptomatic marker of PD.^{49,50} They are also regarded as a prognostic marker since researchers have described a correlation between severity of hyposmia and PD.⁵¹ In addition, a correlation has also been found between olfactory changes at disease onset and increased risk of developing visual hallucinations and cognitive decline.⁵¹

Recent neuroimaging studies show that patients with severe hyposmia present cerebral hypometabolism with a distribution identical to that described in subjects with PD, which indicates a close relationship between those 2 entities.^{52,53} MRI volumetric studies have also shown a link between olfactory changes and atrophy of such limbic system structures as the amygdala, which confirms the clinical observation that severe hyposmia is associated with subsequent development of dementia.

REM sleep behaviour disorder

Appearance of RBD is associated with a higher risk of developing neurodegenerative diseases, especially in cases of α -synucleinopathies (dementia with Lewy bodies [MCI] and PD). It seems to be caused by a dysfunction affecting the catecholaminergic neurons of the locus coeruleus as well as cholinergic neurons of the dorsolateral PPN. Up to half the subjects with idiopathic RBD develop PD 15 years after diagnosis, and it is therefore considered a potential presymptomatic marker of the disease.^{54–57} Iranzo et al.

described substantia nigra (SN) hyperechogenicity in transcranial ultrasound scans and altered dopamine transport in ^{123}I -FP-CIT SPECT imaging in subjects with RBD. These findings indicate that this patient subgroup presents an increased risk of developing PD.⁵⁷

The presence of RBD is also associated with a more aggressive form of the disease, more severe motor and autonomic symptoms, and a higher incidence of hallucinations and cognitive impairment.^{23,58–60} On the other hand, the presence of RBD in subjects with PD is associated with specific cognitive deficits²³ that do not exist in subjects with PD and no RBD or in healthy controls. This association between RBD and cognitive impairment has also been confirmed by other authors^{37,60–62} and it may be related to the dysfunction of specific brainstem nuclei and their cortical projections.

Hallucinations and psychosis

Psychotic symptoms in PD include visions, feeling watched, simple or complex hallucinations, and delusions. These symptoms indicate a poor prognosis and they are associated with increased mortality rate, institutionalisation of the patient, and development of dementia.^{37,60,62–64}

Moreover, older age of onset, longer disease duration, and the presence of RBD contribute to a higher risk of hallucinations. Younger patients who suffer from depression associated with PD are also at a greater risk of developing hallucinations.⁶³

Although the dosage and the type of dopaminergic drug may affect the appearance of hallucinations, researchers do not know if all psychotic symptoms are drug-induced.⁶⁵ Hallucinations are usually chronic and progressive. Their prevalence and severity increase with time and they tend to persist; the percentage of remission is very low despite use of specific treatment.^{60,61}

Presence of cognitive decline or dementia

As dementia is a clinical manifestation of advanced PD, it is interesting to know which factors cause dementia in patients with PD. The risk of developing dementia is clearly related to age at PD onset,^{40,66–72} increased severity of motor symptoms,^{40,41} early appearance of axial symptoms,^{40–42} higher olfactory decline,^{51,62} presence of RBD,^{23,60} hallucinations,^{60–62} early changes in the semantic fluency, and the presence of MAPT H1/H1 genotype.^{33,72}

Some initial cognitive changes in PD reflect only dysfunction of the frontostriatal dopaminergic pathways that are dependent on the enzymatic activity of catechol-O-methyltransferase (COMT Val158Met) and dopaminergic drugs.⁷²

Impulse control disorder

Treatment with dopaminergic agonists, lower age, pre-morbid sensation-seeking personality, impulsiveness, prior history of anxiety and depression requiring treatment, and a personal or family history of addiction (mainly gambling and alcoholism) point to an increased risk of developing an ICD. According to results from the multicentre study completed by Voon et al.,²⁴ patients with different forms of ICDs also had higher scores on dyskinesia scales.

Identifying clinical phenotypes

One pathogenic basis that may explain the presence of different clinical phenotypes in PD has to do with the possible interaction of nigrostriatal degeneration and corticostriatal pathways with extrastriatal pathology and genetic polymorphisms.⁷³ Numerous studies have focused on identifying and characterising subgroups with homogeneous and clearly differentiated profiles. However, before drawing any valid conclusions, we must first consider possible errors originating from the following:

1. Diagnostic errors. Several clinico-pathological series have described a PD diagnostic error rate ranging from 20% to 24%. This indicates that many studies have included patients who did not have PD.
2. Differences in patient selection and referrals (specialty hospitals, tertiary hospitals, or unselected population samples).
3. Methods. The review includes both retrospective and prospective studies that may or may not include control groups; some studies are cross-sectional.
4. The study parameters, evaluation method, follow-up time, and time of inclusion compared to PD onset also vary.
5. Phenotypic analysis. The methods for forming subgroups vary. Some studies separate patients arbitrarily according to a priori criteria. Others apply differing statistical methods: cluster analysis or latent profile analysis (LPA), with different statistical values and error levels.
6. Analysis of the age factor. There are no standard criteria for determining the point at which a case of PD is regarded as early-onset.
7. Very few longitudinal studies make use of pathology testing.
8. Potential interactions between drugs and phenotypes are not analysed.
9. Genetic factors are not included systematically.

The existence of this variability inspired a prospective observational study in which many European and American centres are participating in order to identify or confirm biomarkers in PD. To this end, the study uses a standardised procedure to record epidemiological, clinical, analytical, genetic, and neuroimaging data in patients with PD and compare them to data from healthy subjects, applying a uniform statistical method.⁷⁴

Established clinical profiles Van Rooden et al.⁴⁵ analysed studies that had been published as of April 2009 and identified the following well-defined clinical phenotypes:

1. Patients older than 60 at PD onset (age range, 61–72.9) experiencing more rapid disease progression, more severe decline in motor function, bradykinetic-rigid syndrome, and higher frequency of axial symptoms.
2. Patients younger than 60 at PD onset (range, 50–59) with slower disease progression, milder motor impairment, an increased number of complications (motor fluctuations and dyskinesias) and no cognitive development.

The same group⁷³ applied a cluster analysis to data gathered in 2 European longitudinal studies (PROPARK and ELEM) of 2 similar prevalent PD cohorts. Both motor and NMS were

examined, and researchers identified 4 subgroups in each of the cohorts.

- Group 1 (49%): relatively young patients with an earlier age at onset, shorter treatment time at lower doses of levodopa, and mild impairment in all clinical areas.
- Group 2 (13%): patients with early-onset PD presenting severe and frequent motor complications, sleep disturbances, and depressive symptoms. These patients displayed longer disease duration with a longer course of dopaminergic treatment. They also received higher doses of levodopa than did patients with other PD subtypes. This group contained a relatively high percentage of women.
- Group 3 (30%): relatively elderly patients with PD, older age at onset, intermediate severity of non-dopaminergic symptoms, and mild and infrequent motor complications.
- Group 4 (8%): patients severely impaired across all domains except for tremor; motor complications are prominent, but less severe than in group 2. Disease onset occurs later in life; levodopa treatment duration is prolonged, and women make up a large percentage of this group.

Groups 3 and 4 display prominent axial symptoms, cognitive impairment, autonomic dysfunction, psychosis, daytime drowsiness and depression, and an older age at onset than other PD subtypes.

Regardless of age, tremor-dominant patient groups experience slower disease progression and less cognitive impairment than other groups. In contrast, non-tremor-dominant patients more commonly experienced depression, cognitive impairment,^{39,45,75} apathy, and hallucinations.⁷⁶ On establishing a correlation between clinical signs and neuropathological changes, the authors found that in non-tremor-dominant forms of PD, the loss of dopaminergic neurons on the ventrolateral part of the SN is more intense, as is dopaminergic loss in the posterior putamen. In tremor-dominant PD, the loss of dopaminergic neurons in the SN is greater in the medial region.⁷⁵ Selikhova et al.⁷⁷ completed a retrospective study of 242 patients with neuropathological confirmation of PD and analysed their possible clinical subtypes according to symptoms at onset and PD progression. These authors established 4 subgroups:

1. Patients aged <55 years at onset (25%).
2. Patients with tremor-dominant PD (31%).
3. Patients with non-tremor-dominant PD (36%).
4. Patients with rapidly progressing PD and no dementia who died within 10 years of disease onset (8%).

Among the patients in the first group with more motor fluctuations and longer disease duration, survival times were longer; falling, hallucinations, and cognitive impairment all appeared late in the course of PD. Tremor-dominant forms of PD did not have long survival times and there were no differences in time elapsed prior to the onset of falls and hallucinations. However, there is clearly an association between the non-tremor-dominant pattern and cognitive impairment.

The group with rapidly progressing PD consisted of older patients with more frequent depression and early-onset

axial motor symptoms (gait freezing and falls); 70% experienced tremors at onset that responded well to dopaminergic drugs. The non-tremor-dominant subgroup showed significantly more cortical Lewy bodies than any other group. It also had more cortical β -amyloid plaques and amyloid angiopathy than groups with early-onset PD and tremor-dominant PD. There is a correlation between onset of bradykinesia with cognitive impairment and the presence of Lewy bodies in the neocortex.

Rajput et al.⁷⁸ carried out a 39-year-long clinical longitudinal follow-up (1968–2006) in 166 patients with PD and identified 3 different clinical phenotypes: a phenotype with tremor as the dominant symptom (tremor-dominant forms), an akinetic-rigid form, and another combined-type form. Patients with tremor-dominant phenotype were younger at onset (55 vs 65 for akinetic-rigid forms), and presented a milder course of the disease, slower progression to Hoehn and Yahr stage 4, and a higher rate of motor fluctuations (46% in tremor-dominant cases and 26% in akinetic-rigid cases). Dementia was more common in cases with combined phenotypes and less frequent in tremor-dominant forms.

Biomarkers predicting progression of PD to an advanced stage

Uric acid Low blood levels of UA are a biomarker for risk of developing PD and for PD progression.^{72,79–82} In the DATATOP [58] study,⁸² researchers observed that high urate levels in patients' serum and cerebrospinal fluid (CSF) were related to slower disease progression and a longer delay before patients needed levodopa treatment. In contrast, low serum levels of UA prior to diagnosis increased the risk of developing the disease. After diagnosis, low blood and CSF levels of UA were related to more rapid progression of dementia and a sharper decrease in striatal dopamine transporter labelling according to the SPECT scan.^{72,79–82} This correlation is more evident in men than in women.⁷³ In the PRECEPT study, those patients with recent PD onset and no dopaminergic treatment who had high plasma levels of UA at baseline went longer periods before requiring treatment. They also presented lower UPDRS scores and less marked reduction in DAT tracer uptake according to the SPECT scan. Researchers also observed a higher percentage of patients with SWEDD.⁸¹

All studies suggest that UA may act as a neuroprotective agent based on its potential antioxidant effects; as a result, low levels of UA may cause a patient's condition to evolve more rapidly towards advanced stages of PD.

Measuring amyloid- β and tau in CSF A transversal study by Alves et al.⁷⁶ revealed that patients with PD have levels of amyloid- β that are lower than in healthy subjects, but higher than in patients with Alzheimer disease (AD). In addition, patients with AD presented a sharper decrease in amyloid- β levels and an increase in levels of total tau protein (T-tau) and phosphorylated tau protein (P-tau). Siderowf et al.⁸³ carried out the first longitudinal study of the relationship between a CSF biomarker (amyloid- β 1–42 [$A\beta_{1-42}$], P-tau_{181p} and T-tau) and cognitive decline in patients with PD. They showed that a low baseline value of $A\beta_{1-42}$ was associated with more rapid cognitive decline. Levels of P-tau and T-tau showed no significant associations with cognitive decline. In summary, this study showed that decreased levels of $A\beta_{1-42}$

in CSF (cut-off point ≤ 192 pg/mL) was a strong independent predictor of overall cognitive decline in patients with PD. *MAPT H1/H1 genotype and the COMT Val158Met polymorphism* The presence of the COMT Val158Met polymorphism and the MAPT H1/H1 genotype has been linked to cognitive impairment and dementia in PD.³²

Foltynie et al. analysed the relationship between the COMT Val158Met polymorphism and executive function in patients with PD and determined that reduced enzymatic activity (higher level of prefrontal dopamine) was linked to poorer cognitive performance.⁶⁸ However, when analysed alongside other variables (sex, treatments, age, disease duration, degree of motor impairment and premorbid intelligence quotient), the COMT genotype itself had no influence on performance of executive functions. This cognitive change does not progress to dementia. It may be related to impairment of the posterior cortical functions due to a change in the parietal–temporal–occipital structures, and its prognosis would therefore be different.

The MAPT H1/H1 genotype is one of the most important factors for predicting development of dementia that manifests as deficiencies in tasks performed by the temporal and parietal lobes. This genotype probably results in a change in tau protein transcription that promotes protein aggregation. The presence of cortical Lewy bodies containing tau protein and alpha-synuclein would support the hypothesis that the 2 proteins would interact by forming fibrils and deposits in cortical areas. This is a crucial step in the development of dementia.

Neuroimaging studies Functional and structural neuroimaging studies allow researchers to assess NS degeneration and dopamine deficiency in the striatum in the first case and atrophy of certain brain structures in the second. *Studies on cardiac innervation* The change in postganglionic cardiac innervation resulting from PD can be shown using SPECT techniques with ¹³¹I-metaiodobenzylguanidine (MIBG) that evaluate tracer uptake by measuring the myocardium/mediastinum index, and positron emission tomography with 6-¹⁸F-fluorodopamine (F-dopa), which measures tracer concentrations in the myocardium (septal and lateral walls).

Most authors have found no correlations between myocardial uptake of MIBG and age, sex, disease duration, or H&Y stage, but the former does seem to be correlated with motor phenotype. Myocardial uptake is more abnormal in bradykinetic-rigid forms with more severe bradykinesia.^{84,85} There is a relationship between nigrostriatal damage (DAT-scan), extranigral damage (¹³¹I-MIBG) and the H&Y stage, which may indicate parallel development of neurodegeneration.

Dopaminergic function studies In PET studies with [¹⁸F]-Fluorodopa (18F-DOPA), striatal uptake of the tracer may already be altered in asymptomatic patients and there is a marked association between striatal uptake of the tracer, disease progression, and motor disability.^{86–88}

At symptom onset, most patients with PD present decreases in uptake of ¹⁸F-DOPA in the contralateral putamen. These decreases correlate to patients' UPDRS scores. However, there is no clear relationship between variations in striatal tracer uptake and changes in symptom severity. This discrepancy is due to the presence of compensatory mechanisms^{89–92} occurring in the early stages of the dis-

ease. Such mechanisms maintain dopaminergic function by increasing presynaptic dopamine synthesis (increased ¹⁸F-DOPA uptake on PET scans) and decreasing dopamine transporter levels as seen on the DATSCAN. These findings were discovered in asymptomatic bearers of the LRRK2 mutation who were assessed periodically before any PD symptoms appeared.^{90,91}

Functional neuroimaging studies in patients with motor complications De la Fuente-Fernández et al.⁹³ have reported that patients with motor fluctuations have a more pronounced decrease (28%) in ¹⁸F-DOPA uptake in the putamen than do patients without motor fluctuations. That group⁹⁴ also analysed DAT's important role by showing that low levels of DAT uptake are also associated with the presence of fluctuations since they allow greater oscillations of the dopamine levels in striatal dopaminergic synapses.

Conclusions and recommendations

1. Defining the course of PD in each patient, and the disease's different phenotypes, is fundamental to elaborating personalised treatment plans. To achieve this end, doctors need well-conducted prospective studies and knowledge of the prognostic biomarkers that indicate that a patient is at risk for developing the clinical manifestations of advanced PD.
2. The evidence available to date strongly suggests that age at disease onset, motor symptom severity, hyposmia, early onset of axial symptoms and hallucinations, and association with RBD or depression are factors indicating a more severe prognosis with faster PD progression.
3. Uric acid levels in serum, A β _{1–42} in the CSF, and presence of the MAPT H1/H1 genotype are especially important prognostic markers. They may be able to indicate patients likely to experience rapid progression, especially those at risk for dementia.
4. Neuroimaging techniques permit earlier and more precise detection of structural and functional changes occurring in PD even in its early stages. In the future, they will enable us to detect patients with higher probabilities of progressing to an advanced PD phenotype. This combination of biomarkers will eventually be used to determine Parkinson's Disease at Risk Syndrome (PARS) as we group the markers indicating an elevated risk for developing PD into 4 different levels: prediagnostic, pre-motor, preclinical, and prephysiological.⁹⁵

Scales for evaluating changes in motor function, gait, dyskinesia, and quality of life in advanced PD

Evaluating impairment and disability in PD patients and the effect of different types of treatment requires the use of scales with well-defined clinimetric properties (validity, reliability, sensitivity).

Overall assessment

The Columbia University Rating Scale (CURS) was often used prior to the publication of the Unified Parkinson Disease Rating Scale (UPDRS) in 1981. Although few studies examine the clinimetric properties of these scales, available evidence suggests that they are valid and reliable even though the factor structure cannot be defined. One modified ver-

sion called the Sydney scale seems to be equally valid and reliable.⁹⁶ The third version of UPDRS (introduced in 1987) is the most widely used scale for analysing the clinical condition of a patient with PD. A number of studies have analysed the structure and clinimetric properties of version 3 of this scale, and it has been used in multiple clinical trials.^{97,98} The questionnaire can be administered in 10 to 20 minutes, and it includes a total of 55 items divided into 4 sections (I. Mentation, behaviour, and mood; II. Activities of daily living [ADL]; III. Motor examination; and IV. Complications of therapy). The scale's strong points are its widespread use, its analysis of all clinical aspects of the disease with particular emphasis on motor functions, and its clinimetric properties, validity, and reliability. Its disadvantages are that the text contains multiple ambiguities, inappropriate instructions for evaluators, certain metric deficiencies, and no evaluation parameters for NMS, which are now considered increasingly important. With this in mind, a working group from the Movement Disorders Society (MDS) decided to revise and update the scale in 2001.⁹⁹ The new expanded version (MDS-UPDRS) has a more well-defined clinimetric profile. This version now includes 65 items, but it still has 4 sections: I. Non-motor experiences of daily living; II. Motor experiences of daily living; III. Motor examination; and IV. Motor complications. All items have 5 possible responses with a common scale of 0 to 4 (0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe). Several items in part I and all items in part II are framed in questionnaire format and can be filled in by the patient or a carer. This being the case, no more than 30 minutes should be needed to complete the questionnaire. It includes 20 questions for the patient or carer, instructions for each item, and an appendix with complementary scales. Compared to the previous version, the new version shows high internal consistency, a stable factor structure, and good correlation with the original version.¹⁰⁰ Using partial scores for each section rather than summing up total scores is recommended when analysing results. Clinically relevant scoring changes to the UPDRS were published in 2010.¹⁰¹ A change of 2.5 points on the motor subscale is considered minimal, with changes of at least 5.2 points considered moderate and those reaching 10.8 points, large. The values indicating minimal, moderate, or large changes to the total UPDRS score are 4.3, 9.1, and 17.1 points, respectively.

The Hoehn and Yahr scale (H&Y) is the most widely used scale for establishing the degree of PD progression using simple stages.¹⁰² It is used as a gold standard for testing other scales. The Schwab and England disability scale,⁹⁶ another standard assessment instrument, has been used in a number of studies. Researchers analysed the clinimetric properties of both scales in 2006 and concluded that they had a good level of acceptability and appropriate construct validity, but that content validity was unsatisfactory.¹⁰³ UPDRS-II (ADL) measures the impact of PD on activities of daily living among patients with the disease. A multiple linear regression analysis showed that partial scores on the ADL subscale were more closely and reliably correlated to disease duration than scores on other sections, after adjusting for age at disease onset. The robust association between ADL scores and disease duration suggests that this subscale is the best marker of disease progression compared to signs and symptoms evaluated by other sections of the UPDRS. The score on the ADL

section correlates well with the H&Y scale, and the minimum clinically relevant change is estimated at +2 points.¹⁰⁴

CISI-PD (Clinical Impression of Severity Index for PD) is a simple, easy-to-use instrument with four domains (motor signs, disability, motor complications, and cognitive status). It lets doctors measure the clinical impression of disease severity directly related to the patient's motor situation, disease duration, and depression, and it rounds out the data provided by the H&Y or S&E scales.^{105,106}

The Intermediate Scale for Assessment of Parkinson's disease (ISAPD) and the subsequent Short Parkinson's Evaluation Scale (SPES) were developed in order to have relatively rapid, simple, and valid scales for use in daily practice and in clinical research. They have not been validated independently. The ISAPD has moderate to good correlations with the H&Y, UPDRS, and S&E, excellent internal consistency, and good interobserver reliability. It can be completed in 7 to 10 minutes⁹⁶ and its authors have only evaluated it in a single study. SPES is also a quick and easy test (7–10 minutes). Many of its psychometric properties resemble those of the UPDRS, but this test contains fewer items as well as fewer sublevels, resulting in more homogeneous sections. Inter-investigator reliability and internal consistency are good, but this was only shown by the article written by the test developers.^{12,107} The SCOPA-Motor Scale (S-MS) was created to improve specific clinimetric aspects of the SPES by changing response options, moving the item on dysphagia from the disability section to the motor assessment section, and including a section examining motor complications. It contains 21 items in 3 domains: motor examination, disability, and complications. The scale has been validated in Spanish.¹⁰⁸ It is consistent, valid, and considerably shorter than the UPDRS. The ceiling and floor effects are satisfactory except in the 'complications' section; the same is true of the UPDRS-IV.

Gait assessment

The UPDRS and SPES/Scopa scales include only 3 items for assessing gait in patients with PD; under some circumstances, this may be insufficient. The Rating Scale for Gait Evaluation in Parkinson's disease (RSGE-PD) was developed in 1997 (versions 1.0 and 2.0) for the purpose of selective gait analysis.¹⁰⁹ It includes 4 domains: socioeconomic data, functional ability, examination (doctor's findings) and complications (side effects of levodopa). It delivers a holistic evaluation of the complex motor activity of walking. The test is easy to perform, does not require complex technological material, and can be completed in 10 minutes. This scale's clinimetric properties have been shown to be acceptable, and version 2.0 has undergone external validation.¹¹⁰ Another scale specifically evaluating gait in PD was published in 2004, but it requires specially trained personnel and sophisticated computer infrastructure.¹¹¹

FOG phenomena affect about half of all patients in advanced stages of PD. UPDRS includes only one item evaluating FOG, but it also measures the intensity of the FOG episode according to whether or not it provokes a fall. At present, the only validated scale that quantifies FOG severity and evaluates the effectiveness of specific treatment is FOG-Q, a subjective scale.^{112,113} It features 6 questions and the total score ranges from 0 to 24. In addition to

quantifying FOG severity, it analyses different types of FOG (start hesitation, turning hesitation, reaching a target, narrow passages). This scale is at least as reliable as item 14 of the UPDRS scale, and it provides better evaluation of the drug effect, and a better test-retest correlation in addition to identifying nearly twice as many cases with FOG. This scale's limitations are related to the difficulty of discriminating between freezing and akinesia and the difficulties a patient may have in identifying FOG episodes. To resolve these problems, researchers developed a new version of the scale (FOG-Q II) using video demonstrations. The new version is still pending validation.

Assessing dyskinesias

The two most widely used scales with good clinimetric properties for assessing dyskinesias are AIMS (abnormal involuntary movement scale) and the Rush dyskinesia scale. AIMS assesses the severity of abnormal involuntary movements for different parts of the body, during resting or active times. It consists of 10 items scored on a 5-point Lickert scale. One of this scale's weaknesses is that it does not discriminate between different types of involuntary movements. It was developed for the purpose of analysing late-onset dyskinesias, and therefore stresses oral–buccal–lingual movements, which are less apparent in PD than those of the trunk and extremities.¹¹⁴ The Rush scale examines the degree of interference caused by dyskinesia using 3 standard motor processes (such as walking, getting dressed, and drinking from a cup), scored from 0 to 4. It also describes the type of dyskinesia, indicating which one is the most incapacitating. Both are widely used and available in translated versions, but these translations have not been validated on the country level. Two new scales, PDYS-26 (Parkinson Disease Dyskinesia Scale) and UDysRS (Unified Dyskinesia Rating Scale) demonstrate excellent clinimetric properties, but they have only been used in the centres where they were developed.¹¹⁵

Motor and non-motor fluctuations can be detected using the QUICK self-assessment (19 items) that was validated in 2008.¹¹⁶ We recommend that patients with motor complications keep a diary so that doctors can analyse their functional situation throughout the day and determine the appropriate treatment approach. Hauser developed patient diaries in the year 2000, and they were validated in 2004.¹¹⁷ The Scopa-DC (diary card) has good clinimetric properties. It analyses 5 items (walking, changing position, using hands, involuntary movements, and night-time sleep quality) at 6 times during the day with scores ranging from 0 to 3. The information it provides about the patient's 'off' times is not as clear as in the Hauser diaries, but it does let us assess the effectiveness of treatment.¹¹⁸

Based on this analysis, we conclude that reliable scales for detecting motor complications and establishing the extent of the patient's motor impairment and dependence are available.

Quality of life assessment

Given the wide range of clinical manifestations of PD (sensory, motor, coordination, cognitive, and behavioural changes) and the treatments available for certain associated disorders, achieving control over some symptoms and signs

may provoke significant adverse effects that decrease the patient's well-being and quality of life.^{118,119} Health-related quality of life (HRQoL) is defined as a patient's perception of the impact and consequences of disease on his or her life.¹²⁰ Assessing and quantifying this concept is fundamental in order to observe the disease's impact on a patient, and to measure the effect of different types of treatment.

Comparing HRQoL in the general population with that in patients with PD may be an interesting option. However, PD-oriented scales cannot be used for that purpose because the questions they contain are too specific. Using generic scales may therefore be a viable option for assessing QoL in PD compared to QoL in the general population. EuroQoL-5D (EQ-5D) is a generic CVRS scale that has been subjected to extensive validation. It shows high levels of sensitivity, internal consistency, and reliability in both the general population and in patient groups. The instrument may be administered quickly and its feasibility is good. The test contains 5 items, each of which has 3 possible scaled responses. High scores indicate a poorer perception of health. An analogue visual scale is also used to assess current overall state of health. The EQ-5D has been widely used in studies of patients with PD.^{121–124} The content of the EQ-5D scale is appropriate for patients with PD. It also correlates to the UPDRS scale and can differentiate between PD stages. Studies have shown that it is sensitive to therapeutic interventions in patients with PD.¹²³

The Parkinson's Disease Questionnaire 39 (PDQ-39) and its short version (PDQ-8) are 2 specific scales used to measure HRQoL in patients with PD. PDQ-39 consists of 39 items grouped in 8 subscales. Each item receives a score between 0 (never) and 4 (always).¹²⁵ PDQ-39 has a validated Spanish-language version.¹²⁶ Items on the scale were obtained as a result of exhaustive interviews with patients with PD. PDQ-39 has no significant ceiling or floor effects, and it has been shown to have high internal consistency. The scale is able to distinguish between PD stages.^{127,128} Its content is appropriate and complete, although it contains no items for a few important areas (sleep, sexual function).¹²⁹ PDQ-8 includes 8 items, each of which represents a subscale on PDQ-39. The total score is obtained by summing the scores from all 8 items and transposing the score to a scale of 0 to 100. Here, higher scores reflect a poorer HRQoL.¹³⁰ It has been validated in a number of languages (including Spanish), and by multiple authors.¹³¹ While PDQ-8 demonstrates low reliability and validity compared to PDQ-39, there is no evidence of its having a ceiling or floor effect, and internal consistency, test–retest reliability, and internal correlation are all satisfactory. Also, PDQ-8 has a higher feasibility than PDQ-39,¹³² and the minimum clinically important difference has been calculated.¹³³ Due to having content appropriate for patients with PD, good clinimetric properties, and having been used by numerous research groups, it is recommended by the Movement Disorder Society Task Force.¹³⁴

The Parkinson's Disease Quality of Life Scale (PDQUALIF) is an instrument including 33 items grouped in 7 domains: social/role function, self-image/sexuality, sleep, outlook, physical function, independence, and urinary function, plus an item examining the patient's global HRQoL. Each item is scored on a 5-point Lickert scale. Testing time is between 10 and 15 minutes.¹²³ PDQUALIF places particular emphasis on non-motor deficits and disabilities and raises many questions related to social factors in quality of life. This is

the only questionnaire with items referring to fatigue or ability to drive, and these factors have an important effect on the decline in quality of life in patients with PD.¹³⁵ PDQUALIF displays good clinimetric properties and may be used in conjunction with the UPDRS motor scale to evaluate non-motor impairment and social functioning. Nevertheless, PDQUALIF has only been used by its developers, and the Movement Disorder Society Task Force suggests rather than recommends using it.¹³⁴

Conclusions and recommendations

1. No articles have rigorously established which scores or score ranges for the different scales listed previously (motor and ADL scales) are useful in determining if a patient has advanced-stage PD.
2. Generally speaking, criteria indicating advanced PD may be H&Y stage ≥ 3 , S&E score $\leq 70\%$, score ≥ 30 on the UPDRS motor subscale, and UPDRS IV score ≥ 3 for dyskinesias and ≥ 2 for fluctuations ('off' time exceeding 25% of total waking time). We should point out that a patient would not have to obtain scores in the listed ranges on all of the scales in order to be identified as having advanced PD. A score in the pathological range on any of the scales may be sufficient to indicate a subject with advanced PD, although results from different tests will probably be similar.

Scales for assessing NMS in advanced PD

NMS are common in PD. A number of studies have reported non-motor symptom prevalence ranging from 21% at time of diagnosis to 88% some 7 years later.¹³⁶ They include autonomic dysfunction, mood alterations, fatigue, sleep disorders, and neuropsychiatric symptoms. Patients display increasing NMS as the disease progresses, but certain symptoms such as hyposmia, constipation, depression, and RBD may even manifest during the premotor phase of the disease.^{18,137,138} NMS have a large impact on the patient's quality of life and psychosocial function, and they can lead to a patient's being institutionalised.¹³⁹ Nevertheless, a very high percentage of these NMS may go undetected due to a lack of specific, valid instruments created to identify them.¹⁴⁰

There are no practical, reliable instruments for evaluating the wide spectrum of NMS in PD. Different scales, including the Non-Motor Symptom Questionnaire (NMSQuest)¹⁴¹ and the Non-Motor Symptom Scale (NMSS),¹⁴² have recently been developed to detect and evaluate NMS. The UPDRS has also been revised, and the new MDS-UPDRS has successfully passed its clinimetric tests. More complete than the original UPDRS, it contains new items examining NMS in PD and requires input from patients and their carers in order to assess these symptoms.¹⁰⁰ Part I (non-motor experiences of daily living) includes 13 items that examine mental and psychological state, sleep disorders, autonomic dysfunction, pain, dopamine dysregulation syndrome, and fatigue. This instrument has been recommended and it is easy to use.

Evaluating autonomic dysfunction

Hypersalivation, difficulty swallowing, and constipation are very common autonomic dysfunctions in PD.¹⁴³ They have a negative impact on quality of life and no clear correlation to motor symptoms. These symptoms may be assessed using techniques such as videofluoroscopy swallowing studies or colonic motility studies for constipation, but the tests are expensive, require specific equipment and trained operators, and are not feasible for all clinics and researchers.¹⁴⁴ Other validated scales are also available. While they are easy to use and demonstrate good clinical correlation, their validity in PD patients is limited. The purpose of this review is to evaluate existing scales for hypersalivation, dysphagia, and constipation in PD.¹⁴⁵

In a recent review ordered by the MDS, researchers studied 3 types of scales: scales broken down by symptom, global scales addressing dysautonomia and NMS, and lastly, single items from comprehensive scales. They evaluated the different clinimetric properties for each scale (content validity, readability and comprehension, internal consistency, construct validity, acceptability/floor and ceiling effects, test–retest reliability, agreement, responsiveness, interpretability, minimum clinically important difference, time to administer, and administration burden). After the assessment, scales were categorised as 'recommended' if they were regarded as valid, reliable, and sensitive; if they had been used in clinical studies by groups other than those that created them; and if they had been used in PD populations. Scales meeting some but not all requirements were categorised as 'suggested'.¹⁴⁵

Three of the symptom-based scales were chosen for evaluating hypersalivation: DSFS (Drooling Severity and Frequency Scale),¹⁴⁶ DSS (Drooling Severity Scale),¹⁴⁷ and SCS-PD (Sialorrhea Clinical Scale for PD).¹⁴⁸ All of the above were categorised as 'suggested'. DSFS is widely used and specific for PD, but its clinimetric correlation is insufficient. The only advantage of the DSS is that it was designed for PD, and while SCS-PD shows good consistency, validity, and applicability to PD (in a small sample), it has not been evaluated by outside researchers. Two of the dysphagia scales were categorised as 'suggested': SDQ (Swallowing Disturbance Questionnaire)¹⁴⁹ and SWAL-QOL (Generic Scale for Dysphagia-Related Outcomes Quality of Life).^{150–152} The first was evaluated in a group of PD patients only and many of its clinimetric properties were not studied; the second is widely used, but it has not been validated for PD. Lastly, with regard to constipation as a symptom, none of the scales met the criteria for being considered either 'suggested' or 'recommended'.¹⁴⁵

Specific scales have been evaluated for the entire autonomic dysfunction spectrum of PD, although clinimetric properties have not been examined in all cases. Researchers have identified 2 global scales for non-motor and autonomic dysfunction disorders that meet 'recommended' criteria: SCOPA-AUT (Scales for Outcome in PD-Autonomic)^{18,153} and NMSQuest (Nonmotor Symptoms Questionnaire for PD).¹⁴¹ The NMSS (Nonmotor Symptoms Assessment Scale for PD),¹⁴² which had only been used by the original study group, was categorised as 'suggested'.

Within the third group, referring to single items from comprehensive scales,¹⁰⁰ items 6 and 7 on UPDRS (salivation and swallowing) were not rated. Although inter-examiner

reliability is good for these items, clinimetric assessment is limited. Items 2 (swallowing) and 12 (bowel function) on the UMSARS scale were not used as they are not specific to PD and do not focus on dysautonomia.¹⁴⁵

Many of the currently existing scales have not been totally or even partially validated for this disease. Similarly, while analogue visual scales are widely used, none has been validated for PD. These scales should be validated precisely because they are easy to use and widely available. Depending on the circumstances, some of the less-specific non-motor scales (SCOPA-AUT and NMSQuest) may be used as rapid means of evaluating symptoms such as hypersalivation, difficulty swallowing, and constipation, but their ability to measure such symptoms is limited. Until researchers have access to validated forms of more detailed scales measuring disease severity, symptom progression, and response to treatment, physiological measurements will also be needed (videofluoroscopy, colonic motility studies, etc.).¹⁴⁵

Conclusions and recommendations Very few scales specifically evaluate hypersalivation, difficulty swallowing, or constipation.

Depending on the situation, non-motor scales such as SCOPA-AUT, NMS Quest, and MDS-UPDRS I can easily be used to identify and measure frequency of sialorrhoea, dysphagia, and constipation, but their ability to detect quantitative changes may be limited.

NMSS may be used as a comprehensive instrument for evaluating treatment response.

Until scales measuring disease severity, symptom progression, and response to treatment have been validated for PD, doctors must include physiological measurements (videofluoroscopy, colonic motility studies, etc.).

Assessing sleep disorders

Sleep disorders are common in patients with PD, affecting more than 75% of the total.¹⁵⁴ The most frequent disorders are insomnia, sleep fragmentation, daytime drowsiness, RBDs, sleep apnoea syndromes, neuropsychiatric disorders, restless leg syndrome, and sporadic limb movements disorder.^{18,137,155} In advanced phases of PD, daytime drowsiness and bouts of sleepiness may significantly affect daily life. It is therefore important to recognise and evaluate these disorders using the patient's medical history and the appropriate scales.¹⁵⁶ Neurophysiological studies including polysomnography, the Multiple Latency Sleep Test and the Maintenance of Wakefulness Test are expensive. Most hospitals do not have access to these tests, and since some sleep disorders fluctuate, many cases will not be identified.

A number of scales have been used to measure sleep and wakefulness, but only a few have been validated for their specific clinimetric properties in the PD population. The MDS recently sponsored a working group that completed a systematic literature review to examine these scales and evaluate their utility in PD. The group determined that of a total of 48 scales, only 6 could be categorised as 'recommended'. The PD sleep scale (PDSS)¹⁵⁷ and the Pittsburgh sleep quality index (PSQI)¹⁵⁸ are useful for evaluating sleep disorders and insomnia and measuring their severity. SCOPA sleep is recommended for identifying general sleep disorders and detecting and measuring the severity of daytime drowsiness.¹⁵⁹ The Epworth Sleepiness Scale (ESS)¹⁶⁰ and the

Inappropriate Sleep Composite Score (ISCS) are both recommended for detecting and measuring bouts of daytime sleepiness and their severity. The Stanford sleepiness scale (SSS)¹⁶¹ is indicated for assessing drowsiness and measuring its severity at a specific time. All the above scales are useful for evaluating different aspects of sleep or daytime drowsiness, although each has been shown to have specific advantages and limitations in PD patients. None of the scales may be used to diagnose a specific disorder (for example, certain types of insomnia, RBD, RLS, or sleep-related respiratory disorders). Researchers need new scales that better reflect specific treatments and quantify treatment response in sleep disorders.¹⁶²

Conclusions and recommendations

- All 6 scales (PDSS, PSQI, SCOPA-Sleep, ESS, ISCS, and SSS) evaluate night-time sleep and daytime drowsiness in patients with PD and rate the severity of symptoms. These scales do not focus on other specific sleep disorders such as restless leg syndrome, RBDs, or sleep apnoea.
- Some aspects of these scales have not been correctly examined: the effect of medications on sleep, presence of other sleep disorders or motor/NMS, and the fluctuations of the motor state.
- None of the scales is a substitute for the complete history provided by the patient or carer, nor can they replace polysomnography in certain cases.
- The study group recommends further research to determine whether self-administered scales (PSQI, ESS, and SCOPA) may be filled in by patients' carers or domestic partners.

Assessing cognitive impairment

Cognitive impairment and dementia merit a special section among NMS of PD.⁷⁰ Cognitive impairment is one of the most frequent non-motor complications in PD, and it occurs to a greater or lesser extent in most patients. Types of cognitive impairment include attention deficit, executive dysfunction, visuospatial changes, verbal fluency impairment, and memory disorders without dementia. In any case, dementia affects up to 40% of patients with PD, and this figure is 6 times higher than the dementia prevalence in the general population. Its cumulative presence over a period of many years varies between 60% and 80%.^{70,163}

One very important step is determining which instruments will be useful for early identification of the different cognitive changes that may present over the course of the disease. With this in mind, a detailed neuropsychological examination will be required to determine the extent and the pattern of cognitive impairment as the disease progresses.

The National Institute of Neurological Disorders and Stroke-Parkinson's disease (NINDS) proposes completing a review of easy-to-use scales for gathering useful data that can be applied to patients at all stages of PD. NINDS classifies scales in 4 categories according to their purpose:

1. Screening scales intended to detect a potential new disorder.
2. Scales measuring severity of the disorder in the domain of interest.

3. Scales sensitive to longitudinal change.
4. Diagnostic instruments.

The use of different scales may explain why data from different studies carried out to date is so heterogeneous. Widely-used studies such as the Mattis Dementia Rating (MDRS) and the Mini Mental State Examination (MMSE) are incomplete for the PD population. Four scales have been specifically designed for PD (Mini Mental Parkinson [MMP], Scales for Outcomes of Parkinson's Disease Cognition [SCOPA-COG], Parkinson's Disease Cognitive Rating Scale [PD-CRS], and Parkinson Neuropsychometric Dementia Assessment [PANDA]). Of these 4, SCOPA-COG and PDCRS have undergone extensive and rigorous validation processes. *Mini Mental Status Examination* MMSE is the most commonly used dementia screening test. It provides information about cognitive performance across multiple domains.¹⁶⁴ It evaluates the following cognitive functions: orientation in space/time, registration and recall, attention and calculation, oral and written language, and visuospatial/constructive commands. Although MMSE shows a low sensitivity to the executive dysfunction that characterises PD, it has been included as an instrument for diagnosing PD with dementia (PD-D) based on its widespread use, universal applicability, and quick and easy administration procedure. Some researchers propose using 26 as a cut-off point in order to correct the test's low sensitivity to executive function loss in PD.¹⁶⁵

The MMP and Panda scales were designed as brief tests for detecting cognitive impairment. They have not yet undergone clinimetric assessments.¹⁶⁶

Montreal Cognitive Assessment (MoCA) Developed as a screening instrument, MoCA has a structure similar to that of the MMSE. It assesses cognitive performance in multiple domains. It is known for its high sensitivity (but not specificity) for differentiating between PD patients with mild cognitive impairment and those without cognitive impairment. MoCA assesses domains having to do with PD and has a short administration time (10–15 minutes). This instrument is more sensitive than the MMSE and equivalent to SCOPA-COG. It can be used to screen for cognitive impairment and determine its severity, and it can also identify patterns of cortical and subcortical changes.¹⁶⁷

Addenbrooke's Cognitive Examination (ACE-R) Similar to MoCA, ACE-R is a useful scale for patient screening because it is easy to administer and does not require specific training. Its cut-off point for diagnosing dementia has not been determined, and the test has not been widely used in clinical trials.¹⁶⁸

Scales for Outcomes in Parkinson's Disease-COGnition (SCOPA-COG) SCOPA-COG evaluates cortical and subcortical functions.¹⁶⁹ Designed for cognitive assessments in patients with PD, the test is easy to administer and requires little time. The test evaluates specific alterations in cognitive impairment that are frequent in PD (executive function and processing speed changes), and the scale's contents are acceptably reliable and valid. Its limitations are that it only evaluates 4 cognitive domains (memory, attention, executive functions, and visuospatial skills). Its ability to assess cortical cognitive function is limited.

Parkinson's Disease Cognitive Rating Scale PDCRS also evaluates cortical functions to provide a better description

of the different forms of cognitive impairment that may be present from the earliest stages of the disease.¹⁷⁰

Its sensitivity and specificity for diagnosing dementia in PD is 94%, and the scale can distinguish between control populations, PD without dementia, mild cognitive impairment, and dementia. The test battery was specifically developed for PD. Its limitations are that administration takes 17 minutes in patients without dementia and 26 in PD with dementia.

A recent independent evaluation of psychometric properties in PDCRS showed that it correlated well with both the MMSE and SCOPA-COG and that levels of acceptability, internal consistency, construct validity, and precision were satisfactory.¹⁷¹ While both PDCRS and SCOPA-COG have relatively long administration times, PDCRS is shorter (17 min vs 45 min), which suggests that it may also be useful for daily practice. Both scales are highly sensitive and able to detect initial cognitive changes in PD, which may be subtle.

Mattis Dementia Rating Scale (MDRS)

MDRS includes items and subscales that are sensitive to frontal–subcortical changes in PD, and therefore to executive dysfunction as well. It may be used in longitudinal studies and it describes the severity of the dementia. Its main weaknesses are lack of items that are sensitive to cortical dysfunction and low sensitivity to visuoconstructive disorders. In addition, its long administration time is cumbersome for daily practice.¹⁷²

Short Screen for Parkinson's Disease with Dementia (PDD-SS) Not many scales have been specifically designed to detect dementia in PD. MMP is a screening test derived from the MMSE that has not yet undergone extensive clinimetric evaluation. Its administration time is 10 minutes. Another scale intended for screening PD with dementia is PANDA, a test requiring more than 10 minutes to administer. Data regarding its acceptability and construct validity are lacking, but its total score shows age and education effects. We have already mentioned the MDRS as being useful, although somewhat impractical for routine clinical use. The PDD-SS is a new scale developed for early detection of cognitive impairment in PD.¹⁷³

PDD-SS¹⁷³ is a valid, precise, and rapid neuropsychological instrument that identifies mild to moderate dementia in PD. The test can be administered in 5 minutes and it is not affected by age, education, or motor condition severity. The scale includes items related to those cognitive domains most affected beginning in the earliest stages of PD (memory, executive function, visuospatial abilities, and cognitive and psychiatric symptoms such as hallucinations and apathy). The questionnaire lists 4 yes/no questions that either patients or carers may answer; scores range from 0 to 33, with higher scores indicating the best status. It is highly sensitive (96%) and specific (81.3%) for diagnosing PD with dementia. Its administration time indicates that it may be regarded as the first test specifically developed for PD.

Conclusions and recommendations MDS recommendations for evaluating mild cognitive impairment associated with PD indicate the following scales¹⁷⁴:

- PDCRS. Evaluating cortical–frontal–subcortical cognitive impairment, this instrument is designed to

discriminate cognitively functional patients with PD from those with associated impairment and dementia. Application time is 15 minutes.

- MoCA: this instrument is more sensitive than the MMSE and equivalent to SCOPA-COG. It can be used to screen for cognitive impairment and determine its severity. Estimated application time is 10 minutes.
- SCOPA-COG: evaluates cognitive impairment in PD. One advantage is that a version is available for the Spanish population, with validation studies showing acceptable results. However, the test may have poorer sensitivity for identifying patients with PD who do not have dementia, but are at risk for developing it. Estimated application time is 15 minutes.
- MDRS: evaluates cortical–subcortical impairment. Does not examine cortical or visuospatial functions. The test has been widely used and validated. Estimated application time is 20 minutes.

Evaluation of NMS in motor fluctuations

Another very interesting topic in advanced PD is use of scales that detect NMS during 'wearing-off' times. This is classified as a modality of motor fluctuation. We should note that some NMS are poorly identified because of their variety, because the patient may not associate NMS with PD fluctuations, or because the doctor may be less concerned about NMS than about motor symptoms. Nevertheless, NMS are known to be frequent and incapacitating, especially anxiety, bradyphrenia, fatigue, akathisia, and perspiration. Symptoms are generally more frequent during 'off' times, but they can also manifest during the 'on' or 'pre-on' times.¹⁷⁵

A battery of scales can be used to assess these NMS in PD: SCOPA, designed to validate scales examining every clinical domain of PD and disease progression on a yearly basis; the SMN scale; and part I of UPDRS. Overall, these scales are valid, reliable, and detailed, and they evaluate typical characteristics of NMS.¹⁷⁶ Nevertheless, these scales are unable to describe non-motor symptoms completely. They will require a diary (not yet available) which the patient will use to assess the full range of NMS manifestations and their severity on a day-by-day basis rather than relying on memory (static instruments). Without such diaries, patients with PD and fluctuating symptoms cannot give a detailed description of the NMS that impact their quality of life.

Conclusions and recommendations

- The SCOPA, NMSS, and MDS-UPDRS I scales are good instruments for evaluating a wide variety of NMS.
- These scales do not completely describe NMS in patients with motor fluctuations.
- We recommend that patients use diaries to record NMS and compare their timing to the motor fluctuations they experience.

Evaluation of neuropsychiatric symptoms

Neuropsychiatric symptoms are very common in advanced PD and they may also manifest in the initial stages of the disease. They are responsible for a significant decrease in the quality of life of both patient and carer, and evaluating

these symptoms before and after treatment is important. The most frequent neuropsychiatric symptoms are depression, apathy, visual hallucinations, and ICDs. Suicide risk should also be assessed, but there are no specific scales for patients with PD.

- *Evaluating apathy*: the Starkstein Apathy Scale and the Frontal System Behaviour Scale (FRSBE) are recommended for measuring apathy, executive dysfunction, and loss of inhibition.^{177,178}
- *Evaluating depression*: depression is present in up to 90% of patients with PD and it is not clearly linked to the severity of motor symptoms. The HADS questionnaire may also be recommendable.^{179,180} Other validated scales include the Beck Depression Inventory, the Geriatric Depression Scale, and the Montgomery-Åsberg Depression Rating Scale.^{181–183}
- *Evaluating ICDs*: these adverse effects of dopaminergic drugs (mainly dopaminergic agonists) may appear in up to 14% of all patients. We recommend using the QUIP¹⁸⁴ and Punding scales.¹⁸⁵
- The Columbia Suicide Severity Rating Scale has been validated in the general population.¹⁸⁶ One study assessed risk of suicide in PD using the Paykel Scale.¹⁸⁷

Conclusions and recommendations

- Neuropsychiatric symptoms are very frequent in all stages of PD, and they have a significant effect on the quality of life of both patients and carers.
- The scales listed for measuring apathy (FRSBE and Starkstein) are generally recommended. The HADS questionnaire and the Montgomery-Åsberg scale have both been validated for depression. Lastly, ICD may be assessed using either the Punding Scale or QUIP.
- When evaluating neuropsychological function in a patient with PD, we recommend including a complementary medical history drawn up by reliable carer. This provides additional information enabling better assessment of the patient's cognitive state and better detection of any neuropsychiatric manifestations.

Conflicts of interest

The authors have no conflicts of interest to declare.

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