Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale

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A B S T R A C T

Background: Severity of PD is usually assessed by means of the motor and disability-based Hoehn and
Yahr staging (HY), or clinician and patient global perceptions. Scores of more detailed assessments, as the
MDS-UPDRS, have not been translated to a grading that allows assignment of score sections to severity
levels. The objective of the present study is to determine cut-off points for PD severity levels based on the
MDS-UPDRS.

Methods: International, observational study. Applied assessments were: HY, MDS-UPDRS, Clinical
Impression for Severity Index, and Clinical and Patient Global Impression of Severity. The coincidence in
severity level (mild, moderate, severe) of at least two clinical classifications plus the patient's gradation
was considered "the criterion of severity". Cut-off values for each MDS-UPDRS subscale was determined
by triangulation of: 1) percentile 90 of the subscale total score; 2) receiver operating characteristic (ROC)
analysis; and 3) ordinal logistic regression (OLR) model.

Results: Sample was composed of 452 consecutive PD patients without dementia, 55.3% males, age
65.1 ± 10.7 years and PD duration 8.7 ± 6.3 years. All HY stages were represented. The "criterion of severity",
classified 275 patients (60.8% of the sample) as: mild PD, 149 (54.2%); moderate, 82 (29.8%); and severe,
44 (16%). The following MDS-UPDRS cut-off points between mild/moderate and moderate/severe levels
were found: Part 1: 10/11 and 21/22; Part 2: 12/13 and 29/30; Part 3: 32/33 and 58/59; and Part 4: 4/5
and 12/13.

Conclusion: Cut-off points to classify PD patients as mild, moderate, or severe on the basis of their MDS-
UPDRS scores are proposed.

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1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that clinically evolves over time from subtle non-specific
non-motor manifestations of the premotor phase to the most advanced stages in which patients are severely disabled. Progressive disability is due to the combination of motor and non-motor problems and related complications that increase in number and severity throughout the course of the disease making the clinical management more complex and affecting patients' quality of life and independence [1–3].

Since the publication of the Hoehn and Yahr staging [4], measures to evaluate PD have evolved to comprehensive evaluations as, for example, the Movement Disorder Society- Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) [5] and the Non-Motor Symptoms Scale [6] or to assessments focused on a specific aspect such as the Parkinson’s Fatigue Scale [7] and the Parkinson’s Disease Dyskinesia Scale [8], among others. However, with the increasing complexity of the disorder there is an increased difficulty to determine the severity of the disease in a pragmatic and easily understandable manner [9] and a combination of several global self-reported and administered scales may be needed to approach this objective.

Global measures have the advantage of providing concise information on the overall health state and can be useful for patients selection (for example, cases with “mild disease” for a clinical trial) and decision-making (for example, assignment of a “very dependent” level for receiving social assistance). In short, the distribution of patients in such categories as mild, moderate, and severe, helps to determine in a pragmatic manner their global health status, facilitates the communication, and allows the decision making process.

The most frequently used global assessment for PD is the Hoehn and Yahr staging (HY) [4,10]. It is based on the disability resulting from motor impairment and balance dysfunction, but does not inform about some motor features and non-motor manifestations. It is widely used for description of PD patients groups and case selection for studies.

The generic Clinical Global Impression (CGI) [11] is a global measure mainly applied in psychiatry, but also used in PD as an outcome into clinical trials and other kind of studies. The CGI has two main components, respectively focused on severity (CGIS) and change (CGIC). The CGI has been criticized as inconsistent and too general [12], but is widely used. The CGIS can be adapted for patients self-assessment (PGIS), a strategy allowing comparisons between rater-based and patient-based evaluation [12].

A recent approach to global evaluation of PD is the Clinical Impression of Severity Index for PD (CISI-PD), a specific instrument based on the global clinical impression on four relevant aspects of PD: motor signs, disability, motor complications, and cognitive impairment, a combination that explained 92% of the CGIS variance [13]. The CISI-PD summarizes the evaluation carried out through the interview, examination, and application of other assessments.

The present study was aimed at determining, using agreed levels of severity among these professional- and patient-based generic scales, the cut-off points for the MDS-UPDRS subscales that could determine levels of disease severity of useful clinical application.

2. Methods

2.1. Design

Multicenter, international, observational, cross-sectional study.

2.2. Patients

Consecutive patients with diagnosis of PD by a neurologist with expertise in movement disorders, according to international criteria [14], were recruited. Patients suffering for other chronic disabling conditionsimpeding or interfering with the evaluation of PD impact were excluded from the study. Patients unable to directly answering written questionnaires were helped by a trained person out of the patient’s relationships and of the usual health professionals attending them. Patients with moderate or severe cognitive deterioration, according to MDS-UPDRS Part I – item 1 equal or greater than 3 and CISI-PD Cognition 4 or higher, were not included in the analysis.

Each participant site obtained approval from the local Ethics Committee or Institutional Review Board and patients had to give their signed consent to participate in the study.

2.3. Assessments

In addition to demographic and PD historical information, the following assessments were applied:

- MDS-UPDRS Spanish version [5,15], a comprehensive scale composed of four parts: Part I – Non-Motor Experiences of Daily Living, which includes thirteen items: six rater-based and seven for patient self-assessment; Part II – Motor experiences of daily living, with 13 patient-based items; Part III – Motor examination, including 18 items (33 scores); and Part IV – Motor complications, formed of six items on dyskinesia and fluctuations. Each item scores from 0 (normal) to 4 (severe) and for each part, total scores are obtained from the sum of the corresponding item scores.

HY, original version, that classifies the course of PD in five stages [4,10], is a tool that provides a clinical estimate of PD severity based on four outstanding PD aspects: motor signs, disability, motor complications, and cognitive status. Each domain scores from 0 (normal) to 6 (very severe) and the total range values from 0 to 24 points.

Global Impression of Severity. The 7-option clinician-based (CGIS) [11] and a 6-option patient-based global impression of severity (PGIS, with the option “severe” representing the collapse of the “markedly ill” and “severely ill”options that may be difficult to differentiate for patients) were included in the respective case report forms.

2.4. Data analysis

Descriptive statistics (central tendency and dispersion measures; proportions) were applied to characterize the variables in the sample. Levodopa-equivalent daily dose was calculated according to Tomlinson et al., 2010 [17]. Concordance among the four global evaluations was estimated by means of the Kendall’s coefficient of concordance. Given the different structure of the four scales, a value >0.60 was considered satisfactory. Percentage of agreement between the scales was also determined.

The global evaluations were transformed to three severity categories — mild, moderate, and severe — according to previous studies or response options wording: HY classification (stages 1 and 2, mild; stage 3, moderate; and stages 4 and 5, severe) [10]; CISI-PD [13]; CGIS (1–7, mild; 8–14, moderate; 15, severe) [16]; PGIS (2–3, mild; 4–5, moderate; 5–7, severe); and PGIS (1–2, mild; 3, moderate; 4–5, severe) (Table 1).

The coincidence in degree of severity of at least two of the three clinical classifications plus the patient’s gradation was adopted as “the criterion of severity” for this study. Comparison between groups broken down by these severity levels was carried out with the Kruskal–Wallis test. Bonferroni correction for multiple comparisons was applied.

Cut-off values for each MDS-UPDRS subscale by each severity level were determined by means of: 1) percentile 90 of the subscale total score; 2) receiver operating characteristic (ROC) analysis; and 3) ordinal logistic regression (OLR) model, calculating the probability curves for each category of severity and the cut-off points between these curves. The OLR was applied to ascertain the relationship between a continuous variable independent (the MDS-UPDRS subscales) and a dependent variable of ordinal type (the severity levels classification), allowing to obtain the cut-off points of the independent variable model logit associated with the ’v’ (that is, in the present study) categories of the dependent variable. As foreseeably the three described methods would not coincide in their results, a triangulation by average of the three corresponding values was planned to estimate the value most probably close to the true cut-off point for each situation.

3. Results

The sample for the present study, from 9 different centres of seven countries, was composed of 452 patients, 55.3% males, with age (mean ± SD) 65.1 ± 10.7 years (range: 22–91) and PD duration 8.7 ± 6.3 years (range: 0–40). HY staging was: 69 (15.3%) were in stage 1; 163 (36.0%) in stage 2; 133 (29.4%) in stage 3; 70 (15.5%) in stage 4; and 17 (3.8%) in stage 5. Additional characteristics of the sample are shown in Table 2.

Concerning treatment for PD, 86.5% of patients received levodopa, 57.5% dopamine agonists, 49% a combination of both; and 36.8% other anti-PD drugs such as MAO-B inhibitors or amantadine. Thirty-eight patients (8.4%) underwent functional surgery for PD.

Table 3 shows the distribution of the sample broken down by the PD severity levels (mild, moderate, severe) derived from the HY, CISI-PD, CGIS, and PGIS as described in the Data analysis section.
The correlation between these scales ranged from 0.84 (CGIS with CISI-PD levels) to 0.56 (HY with PGIS levels) and the Kendall’s coefficient of concordance among the four classifications was 0.65 ($p < 0.0001$). The percentage of agreement between their respective severity levels classifications ranged from 87% (HY with PGIS) to 95% (CISI-PD with CGIS).

For a definitive classification of patients, the “criterion of severity”, consisting in the agreement between at least two grading systems out of the three clinician-based (HY, CISI-PD, and CGIS) plus the PGIS was used. The “criterion”, classified 275 patients out of 452 (60.8% of the sample) as: mild PD, 149 (54.2%); moderate, 82 (29.8%); and severe, 44 (16%). Values of the variables in the study, broken down according to these severity levels, are shown in Table A (Supplementary material). All historic and evaluative values were significantly different between the established severity categories.

Cut-off points for the four MDS-UPDRS sections were determined by percentile 90, ROC analysis, and OLR (Table 4). As foreseen, the obtained cut-off values were not coincident, although differences between methods were only around 2–3 points. The mean values among the three methods (triangulation) offer a theoretical approach to the true cut-off point values (Table 4; Supplementary material, Figs. 1 and 2).

### 4. Discussion

Estimations about the severity of a chronic disease are necessary, but also may be elusive when a recognized objective marker of severity does not exist. In this situation, the estimates are based on subjective appraisal and clinical experience.

For neurodegenerative diseases and specifically for PD, the continuum between onset and advanced phases is very variable in the expression and rate of progression. Presence and severity of symptoms throughout time is heterogeneous, with a wide variability among patients, making difficult to define limits for disease severity graduation. As recently shown, a discrepancy between the gradation of motor and non-motor disorders is commonly observed [9,18].

However, having available a consistent method for classifying PD patients as mild, moderate, or severe would entail advantages for a diversity of settings from daily practice to social-health policy. Such method could be implemented on the appearance of specific symptoms, the number of symptoms, or thresholds reached in measures of severity or disability. Nonetheless, in the absence of a defined and appropriate anchor, the determination of cut-off values for these measures would be arbitrary.

Using global measures has the disadvantages of subjectivity and scant precision, but conceptually is more close to the intended classification. In the present study, we used a combination of this kind of measures resulting from the patient evaluation and clinical impression (HY, CISI-PD, CGIS) and patient self-assessment (PGIS). The coincidence in the gradation derived from estimations coming from both sources was considered “the criterion” to definitively setting a case as mild, moderate, and severe, as doctors and patients—simultaneously and independently—consider this is the severity level to which the patient can be assigned. This coincidence was possible in only 61% of the cases, due to the conditions imposed for the elaboration of the criterion, but is consistent and allows the extrapolation of the outcomes for the complete sample. It is worthy of note that neither neurologists nor patients knew about the elaboration of the criterion, but is consistent and allows the extrapolation of the outcomes for the complete sample. It is worthy of note that neither neurologists nor patients knew about the elaboration of the criterion, but is consistent and allows the extrapolation of the outcomes for the complete sample.

Part 4

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consistent statistical methods. This way, the severity level can be
which cut-offs for MDS-UPDRS scores could be assigned by
authors stated that future goals should include the de
minimal,” “mild,” “moderate,” and “severe” PD [19]. According to
this statement, the objective of the present study was to explore
whether different scores of the individual sections of the UPDRS
may suggest categorical levels of disease severity which may be of
utility at bedside use. To our knowledge, a similar gradation is not
available for the MDS-UPDRS and the present study would be,
therefore, the first attempt for furnishing such a clinically relevant
classification.

To have available a consistent method for classifying PD patients
as mild, moderate, or severe would entail advantages for a diversity
of settings from daily practice to social-health policy. Such method
could be implemented on the appearance of specific symptoms or
complaints, number of symptoms, or the threshold reached to
measures of severity or disability, but that task immediately seems
to be complex. We think that the concordance of global scores from
three clinical validated scales together with one scale of patient
self-evaluation could provide a reliable method for definition of
severity levels.

For trained clinicians is not difficult to link UPDRS motor scores
to a severity stage. As an example, Lang and co-workers stated that
patients with a Part III UPDRS score of 30 or below in off stage were
not enough disabled to undergo DBS whereas scores of 30 or above
in on stage reflect too much affectation to be considered a candi
date for surgery [20]. However such precision cannot be achieved by
other than experts in movement disorders and an objective limit
statistically determined would be welcome for clinical practice
daily use.

Concerning limitations of the study, future studies with other samples
and using a different approach can find other results, but the
sample size in our study, the strength of the statistical methods
applied, and the proximity of their results are promising. Triangu
lation, offering a balanced value among those coming from
different approaches, has a strong logical basis and has been pro
posed in other settings sharing a similar context of uncertainty on
the authentic value among several available [21,22]. Depression is a
common and core non motor symptom in PD impacting on pa
tients’ disability and quality of life. It may be argued that depression
can affect self-assessments. However, this symptom must be
considered into the gamut of non motor manifestations contrib
uting to the severity of the disease and cannot be excluded. To
diminish the impact of any circumstance influencing self
evaluation the cut-off scores were obtained only on data from
coincident gradation by patient and doctor. This way, potential bias
of patient self-evaluation was discarded or attenuated.

Forty per cent of patients did not meet “the criterion of severity”
established for this study. To determine the MDS-UPDRS cut-offs
these patients could not be considered. However, once the cut-off
points are settled they can be applied to any patient assessed by
means of the MDS-UPDRS.

In conclusion, we found through the agreement between clinician-based evaluations and patient self-assessment, a reliable
categorical classification of PD severity (mild, moderate, severe) to
which cut-offs for MDS-UPDRS scores could be assigned by
consistent statistical methods. This way, the severity level can be
directly determined from the scores of the MDS-UPDRS subscales
and this gradation may be of clinical utility. We propose the values
shown in the column “Triangulation cut-off values” in Table 4
to classify PD patients’ condition as mild, moderate, or severe on
the basis of their MDS-UPDRS scores.

Authors’ roles

1 — Conception and Design — Pablo Martinez-Martín, Marcelo Merello
Acquisition of data — Mario Alvarez; Tomoko Arakaki; Victor Campos Arillo; Pedro Chaná; William Fernández; Nélida Garretto; Juan Carlos Martínez-Castrillo; Mayela Rodríguez-Violante; Marcos Serrano-Dueñas; Diego Ballesteros
Analysis of data — Pablo Martinez-Martín, Carmen Rodríguez-Blázquez, Jose Manuel Rojo-Abuin
Interpretation of data — Pablo Martinez-Martín, Carmen Rodríguez-Blázquez, Jose Manuel Rojo-Abuin, Marcelo Merello
2 — Drafting of the manuscript — Pablo Martinez-Martín and Marcelo Merello Critical review of the draft — All the coauthors.
3 — Final approval of the submitted manuscript — All the coauthors.

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Pablo Martinez-Martín received honoraria from speaking en
gements at scientific meetings of Abbvie and Teva, and from serving in a scientific advisory board of Abbvie; grants from Carlos III Institute of Health [FIS], IMERSO, Reina Sofía Foundation, and Michael J. Fox Foundation. He is Chair of the IPMDS Committee for Development of Rating Scales. His employment is at Carlos III Institute of Health.

Carmen Rodríguez-Blázquez has nothing to declare. Her
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Mario Alvarez has no disclosures to declare. His employment is at National Centre of Neurological Restoration (CIERN).

Tomoko Arakaki has no disclosures to declare. Her employment is at, Hospital Ramos Mejía.

Victor Campos Arillo received honoraria from speaking en
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Marcelo Merello received honoraria from speaking engagements at scientific meetings of Lundbeck and GSK. Received grant support from Allergan and Pfizer and received honoraria as consultant for Medtronic. His employment is at Raul Carrea Institute for Neurological Research (FLENI).

Conflict of interest

The authors declare no conflict of interests for this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2014.10.026.

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