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A Validation Study of Depressive Syndromes in Parkinson's Disease

Sergio E. Starkstein, MD, PhD,[1,2]* Marcelo Merello, MD, PhD,[3] Ricardo Jorge, MD,[4] Simone Brockman, MA,[1,2] David Bruce, MD,[2,5] Gustavo Petracca, MD,[6] and Robert G. Robinson, MD[4]

[1]*School of Psychiatry and Clinical Neurosciences, University of Western Australia, Western Australia, Australia*
[2]*Department of Psychiatry, Fremantle Hospital, Western Australia, Australia*
[3]*Raul Carrea Institute of Neurological Research-FLENI, Buenos Aires, Argentina*
[4]*Department of Psychiatry, University of Iowa, Iowa City, Iowa*
[5]*School of Medicine and Pharmacology, University of Western Australia, Western Australia, Australia*
[6]*Instituto Neurológico de Buenos Aires, Argentina*

Abstract: The validity, sensitivity, and specificity of depressive symptoms for the diagnosis of major depression, minor depression, dysthymic disorder, and subsyndromal depression in Parkinson's disease (PD) were examined. A consecutive series of 173 patients with PD attending a Movement Disorders Clinic underwent a comprehensive psychiatric and neurological assessment. The symptoms of loss of interest/pleasure, changes in appetite or weight, changes in sleep, low energy, worthlessness or inappropriate guilt, psychomotor retardation/agitation, concentration deficits, and suicide ideation were all significantly associated with the presence of the DSM-IV depressed mood criterion for major depression. The symptoms of changes in appetite, changes in sleep, low energy, low self-esteem, poor concentration, and hopelessness were all significantly associated with the presence of the DSM-IV criterion of sad mood for dysthymic disorder. Thirty percent of our sample met DSM-IV diagnostic criteria for major depression, 20% met diagnostic criteria for dysthymic disorder, 10% met diagnostic criteria for minor depression, and 8% met clinical criteria for subsyndromal depression. Patients with either major or minor depression had significantly more severe deficits in activities of daily living, more severe cognitive impairments, and more severe Parkinsonism than patients with either dysthymic disorder or no depression. This study provides validation to the DSM-IV diagnostic criteria for major depression and dysthymic disorder for use in PD. The categories of minor and subsyndromal depression may need further validation. © 2007 Movement Disorder Society

Key words: Parkinson's disease; depression; dysthymia; anxiety

There is consistent evidence that depression in Parkinson's disease (PD) is associated with more severe cognitive and functional impairments,[1-3] a faster progression of illness, worse quality of life,[4] increased mortality,[5] and higher burden for caregivers[4,6] when compared with PD patients without depression. On the other hand, there is still debate on the most valid strategy to diagnose depression in PD. One of the main confounders is that frequent symptoms of depression such as psychomotor retardation, loss of energy, poor sleep, loss of appetite, and blunted facial expression are prominent symptoms of PD as well.

A NINDS/NIMH Work Group was recently conveyed to propose provisional diagnostic criteria for depression in PD.[7] The Work Group acknowledged that strict DSM-IV criteria are difficult to implement in PD because of the required attribution of specific symptoms of PD to the depressive syndrome. The question as to whether the phenomenology of depression in PD is similar to the phenomenology of depression among individuals with no neurological disease was also raised. Another important limitation is that the validity of major, minor, and dysthymic depressions as diagnosed with DSM-IV criteria has never been validated in separate

*Correspondence to: Dr. Sergio E. Starkstein, Education Building T-7, Fremantle Hospital, Fremantle, 6959 Western Australia, Australia. E-mail: ses@cyllene.uwa.edu.au

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samples of demented and nondemented patients with PD. The NINDS/NIMH Work Group[7] suggested that the validity of subsyndromal depression (a subtype of depression associated with significant functional deficits in elderly individuals without PD [9]) should also be examined in PD.

To summarize, whether the DSM-IV categories of major depression, minor depression, and dysthymic disorder, as well as the category of subsyndromal depression, are valid diagnoses in PD has not been established. One strategy is to examine the specific association between the clinical criteria for these types of depression and the presence of sad mood, and whether this association is significantly influenced by potential confounders such as age, severity of Parkinsonism, and magnitude of cognitive deficits. Therefore, the main aim for the present study was to examine the phenomenology of depression in PD and to assess the specificity of symptoms of depression for the diagnosis of major, minor, dysthymic, and subsyndromal depression in PD patients with or without dementia. Additional aims were to examine the impact of motor symptoms of PD and dementia upon the specificity of depressive symptoms, to examine phenomenological differences between PD patients with depression when compared with patients with "primary" depression, and to determine the frequency of "masked" depression in PD.

PATIENTS AND METHODS

We recruited a consecutive series of 173 patients with idiopathic PD, who attended at regular follow-up visits the Movement Disorders Clinic of a tertiary care medical institution in Buenos Aires, Argentina. All patients met the United Kingdom Parkinson's Disease Society Brain-Bank clinical criteria for idiopathic PD,[8] and underwent neuroimaging studies as part of their routine clinical care. None of them had focal lesions on computed tomography scans or magnetic resonance imaging, a history of neuroleptic medication use, or a history of lack of response to antiparkinsonian drugs.

We also examined 46 individuals aged over 60 years who visited the psychiatric clinic at our facility because of depressed mood. The inclusion criteria for this group included (1) a DSM-IV diagnosis of either major, minor, or dysthymic depression and (2) with no neurological disorder.

Neurological Examination

After the methodology of the study has been fully explained, informed written consent was obtained from all the participants. Patients were assessed by a neurologist (who was blind to the psychiatric data) with the Unified Parkinson's Disease Rating Scale (UPDRS).[9] Severity of illness was also assessed with the *Hoehn and Yahr stages*.[10] All patients were examined about 1 to 2 hours after they had taken their antiparkinsonian drugs, during the maximal benefit of the medication.

Psychiatric Examination

A psychiatrist blind to neurological findings assessed all patients with the following instruments: the Mini-Mental State Exam (MMSE)[11]; the Clinical Dementia Rating; and the Hamilton Depression Scale (HAM-D).[12] Dementia due to PD was diagnosed based on DSM-IV criteria. The Structured Clinical Interview for DSM-IV (SCID)[13] was administered to the patient and a first-degree relative. Based on the SCID responses, DSM-IV Axis I diagnosis of major depressive episode, dysthymic disorder, and the DSM-IV research diagnosis of minor depression disorder were made using the inclusive approach.[14] Major depression was diagnosed whenever the patient had five or more of the following symptoms during two or more weeks before the assessment, and at least one of the symptoms was either depressed mood or loss of interest or pleasure: (1) depressed mood, (2) diminished interest or pleasure, (3) decrease or increase in appetite and/or weight, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) loss of energy, (7) feelings of worthlessness or guilt, (8) poor concentration, and (9) suicidal ideation. The criteria for minor depression are the same as the criteria for major depression, except that at least two, but less than five of the symptoms are necessary. Finally, the criteria for dysthymic disorder were depressed mood for at least 2 years, and two or more of the following: (1) poor or increased appetite, (2) insomnia or hypersomnia, (3) loss of energy, (4) low self-esteem, (5) poor concentration, and (6) feelings of hopelessness. As suggested by the NINDS-NIMH Work-Group, we diagnosed subsyndromal depression based on Judd's criteria[15] (i.e. two or more depressive symptoms at SCID threshold or subthreshold levels, at least one of which must be depressed mood).

Statistical Analysis

Statistical analyses for continuous variables were carried out using uni- and multivariate analysis of variance (MANOVA) followed by post hoc comparisons. A receiver operating characteristics (ROC) curve was constructed to analyze sensitivity and 1-specificity for the number of symptoms of depression to identify clinically significant sad mood and loss of interest. Associations appearing in frequency distributions were tested using chi-square and Fisher's exact tests. Associations were

TABLE 1. *DSM-IV criteria for major depression and dysthymic disorder for patients with Parkinson's disease*

	Hoehn–Yahr I–II		Hoehn–Yahr III		Hoehn–Yahr IV–V	
	No sad mood	Sad mood	No sad mood	Sad mood	No sad mood	Sad mood
Number of patients	40	40	29	34	9	21
Major depression[a]						
Loss of interest/pleasure	1.3 (0.6)	2.5 (0.7)	1.6 (0.8)	2.5 (0.6)	1.6 (1.0)	2.3 (0.8)
Changes in appetite/ weight	1.1 (0.4)	1.8 (0.8)	1.0 (0.3)	1.7 (0.9)	1.3 (0.7)	1.6 (0.8)
Sleep changes	1.3 (0.7)	2.0 (0.9)	1.3 (0.7)	1.7 (0.8)	1.3 (0.7)	1.8 (1.0)
Psychomotor changes	1.3 (0.6)	2.0 (0.8)	1.4 (0.7)	2.1 (0.9)	1.6 (1.0)	2.1 (0.9)
Loss of energy	1.3 (0.6)	2.3 (0.7)	1.4 (0.7)	2.4 (0.7)	1.4 (0.7)	2.2 (0.8)
Worthlessness/guilt	1.0 (0.2)	2.0 (0.8)	1.1 (0.5)	1.7 (0.8)	1.2 (0.4)	1.9 (1.0)
Concentration deficits	1.2 (0.5)	2.3 (0.8)	1.5 (0.9)	2.4 (0.8)	1.4 (0.7)	2.4 (0.8)
Suicide ideation	1.1 (0.5)	1.5 (0.8)	1.0 (0.3)	1.7 (0.9)	1.2 (0.4)	1.6 (1.0)
Dysthymic disorder[b]						
Number of patients	39	21	31	12	13	5
Changes in appetite	1.1 (0.4)	1.5 (0.8)	1.1 (0.3)	1.8 (1.0)	1.3 (0.5)	1.8 (1.0)
Sleep changes	1.4 (0.6)	1.8 (0.9)	1.3 (0.6)	1.7 (0.9)	1.0 (0.5)	2.4 (0.9)
Low energy	1.4 (0.6)	2.4 (0.8)	1.3 (0.7)	2.3 (0.8)	1.4 (0.4)	2.8 (0.3)
Low self-esteem	1.1 (0.4)	1.7 (0.9)	1.0 (0.3)	1.7 (0.9)	1.2 (0.2)	2.2 (1.0)
Poor concentration	1.3 (0.6)	2.2 (0.8)	1.6 (0.8)	2.0 (0.8)	1.3 (0.5)	2.2 (0.9)
Hopelessness	1.1 (0.3)	2.4 (0.7)	1.0 (0.2)	1.7 (0.9)	1.0 (0.2)	2.4 (0.7)
Additional symptoms[c]						
Psychological anxiety	0.6 (0.7)	1.3 (0.9)	0.4 (0.7)	1.2 (0.8)	0.5 (0.8)	1.0 (0.9)
Autonomic anxiety	0.5 (0.6)	1.2 (0.8)	0.4 (0.6)	1.3 (0.8)	0.3 (0.7)	1.1 (1.0)

Numbers are means (SD).

[a]Effect for depressed mood: Wilks' Lambda = 0.59, df = 8,160, $P < 0$ .0001. Post hoc comparisons between patients with versus those without sad mood showed significant differences ($P < 0.0001$) for all individual items.

[b]Effect for sad mood: Wilks' Lambda = 0.43, df = 6,110, $P < 0.0001$. Post hoc comparisons between patients with versus those without sad mood showed significant differences ($P < 0.001$) for all individual items.

[c]Effect for depressed mood: Wilks' Lambda = 0.80, df = 2,166, $P < 0.0001$.

analyzed with a stepwise regression analysis. All *P* values are two-tailed.

RESULTS

Sad mood, as ascertained with the SCID item A1 (i.e. depressed mood most of the day, nearly every day for two or more weeks), was present in 88 patients (51%), absent in 66 patients (38%), and subthreshold in 19 patients (11%). Patients in the subthreshold category were included within the group with sad mood whenever they scored 2 or more on Item 1 of the HAM-D (i.e. a spontaneous report of sad feelings), whereas those with a score of 0 or 1 were included in the group with no sad mood. Based on this diagnostic scheme, 95 patients (55%) were included in the sad mood group, and 78 patients (45%) were included in the group with no sad mood.

Phenomenology of Depression in PD

We examined the specificity of the association between the DSM-IV criteria for major depression and the presence of sad mood with a two-way MANOVA, with depressed mood (present vs. absent) and Hoehn and Yahr stages (I–II vs. III vs. IV–V) as the grouping variables, and the remaining DSM-IV criteria for major depression as the dependent variables. There was a significant main effect for sad mood (Wilks' Lambda = 0.59, df = 8,160, $P < 0.0001$), no significant main effect for Hoehn and Yahr stages (Wilks' Lambda = 0.94, df = 16,320, $P = 0.89$), and no significant sad mood × Hoehn and Yahr stage interaction (Wilks' Lambda = 0.91, df = 16,320, $P = 0.61$). On individual comparisons, patients with sad mood had significantly higher scores on the symptoms of loss of interest/pleasure, changes in appetite/weight, insomnia, psychomotor agitation/retardation, loss of energy, worthlessness/inappropriate guilt, concentration deficits, and suicide ideation than patients with no sad mood (Table 1). The Cronbach's α coefficient (measuring internal consistency) for the nine DSM-IV criteria for major depression was 0.85, and α coefficients with individual items deleted ranged from 0.81 to 0.84. Corrected item-total correlations ranged from 0.43 (sleep changes) to 0.65 (sad mood). Finally, ROC statistics were calculated with sad mood (present vs. absent) as the classification variable, and the eight additional DSM-IV criteria for major depression as the criterion. The area under the curve was 0.84 (95% CI = 0.78–0.89, $P < 0.0001$), thus demonstrating high accuracy. A cutoff of four or more symptoms of depression had a high specificity (95%) but

a low sensitivity (51%) for the presence of significant sad mood. When the threshold was lowered to two or more symptoms of depression, the sensitivity increased to 81% but the specificity dropped to 76%.

We next examined the specificity of the association between the DSM-IV criteria for dysthymic disorder and sad mood with a two-way MANOVA, with sad mood (present vs. absent) and Hoehn and Yahr stages as the grouping variables, and the six remaining DSM-IV criteria for dysthymia as the dependent variables. There was a significant main effect for sad mood (Wilks' Lambda = 0.43, df = 6,110, $P < 0.0001$), no significant main effect for Hoehn and Yahr stages (Wilks' Lambda = 0.85, df = 12,220, $P = 0.14$), and a significant sad mood × Hoehn and Yahr stage interaction (Wilks' Lambda = 0.82, df = 12,220, $P < 0.05$; Table 1). On individual comparisons, patients with sad mood showed significantly higher scores on the symptoms of changes in appetite, changes in sleep, low energy, low self-esteem, poor concentration, and hopelessness when compared with patients with no sad mood. The Cronbach α coefficient for the seven DSM-IV criteria for dysthymia was 0.83, and α coefficients with individual items deleted ranged from 0.76 to 0.83. Corrected item-total correlations ranged from 0.41 (sleep changes) to 0.78 (sad mood). Finally, ROC statistics with sad mood (present vs. absent) as the classification variable and the additional DSM-IV criteria for dysthymia as the criterion showed an area under the curve of 0.96 (95% CI = 0.91–0.99, $P < 0.0001$), thus demonstrating high accuracy. A cutoff of two or more symptoms of depression had a high specificity (91%) and sensitivity (92%) for the presence of significant sad mood.

Anxiety is a frequent comorbid condition of depressed patients with PD,[16] but is not considered within the DSM-IV criteria for depression syndromes. The NINDS-NIMH Work Group suggested ascertaining the association between depression and the symptoms of psychological and autonomic anxiety in PD. We examined this association with a two-way MANOVA with depressed mood (present vs. absent) and Hoehn and Yahr stages (I–II vs. III vs. IV–V) as between-group factors and scores on items 10 and 11 on the HAM-D, which rate psychological and autonomic anxiety, respectively, as the dependent variables. There was a significant effect for sad mood (Wilks' Lambda = 0.80, df = 2,166, $P < 0.0001$), no significant effect for Hoehn and Yahr stage (Wilks' Lambda = 0.98, df = 4,332, $P = 0.72$), and no significant sad mood × Hoehn and Yahr stage interaction (Wilks' Lambda = 0.99, df = 4,332, $P = 0.87$; Table 1). This finding demonstrates that anxiety is significantly associated with sad mood and is not influenced by stage of illness.

APPENDIX 1. *Symptoms of major depression for patients with PD and elderly depressed individuals without PD*

	No PD group	PD group
Number of patients	44	44
Age (mean years)	64.4 (8.0)	68.6 (5.4)
Mini-Mental State Exam	25.6 (4.0)	25.9 (4.0)
Hamilton Depression Scale	18.0 (5.3)	18.5 (5.7)
Depressed mood	2.9 (0.2)	2.9 (0.2)
Loss of interest/pleasure	2.5 (0.6)	2.8 (0.4)
Sleep changes	2.2 (0.9)	2.0 (0.8)
Psychomotor changes	2.1 (0.8)	2.4 (0.8)
Loss of energy	2.5 (0.6)	2.6 (0.6)
Worthlessness/guilt	2.1 (0.9)	2.1 (0.8)
Concentration deficits	2.5 (0.7)	2.5 (0.7)
Suicide ideation	1.9 (0.9)	2.0 (0.9)

Numbers are means (SD).

Phenomenology of Depression in PD When Compared With Primary Depression

To further validate the syndrome of depression in PD, we compared the severity of the SCID items for major depression between PD patients with depressed mood and a consecutive series of 46 individuals with depressed mood and no PD. Thirty-two of these individuals had major depression, eight had dysthymia, and six had minor depression. This group was matched for MMSE scores (+2 points), HAM-D scores (+2 points), and gender with consecutive PD patients, with a score of 3 on the depressed mood SCID item. Two of the non-PD individuals could not be matched for HAM-D scores and had to be excluded, while six of the pairs included in the statistical analysis could not be matched for gender. Since non-PD individuals had a mean of 4 years of age lower than the PD group, age was entered as a covariate. A MANOVA with group (PD depressed mood vs. primary depression) as the independent variable and the eight DSM-IV clinical criteria for major depression as the dependent variables showed no significant overall effect (Wilks' Lambda = 0.87, df = 8,78, $P = 0.32$; Appendix 1).

Frequency and Clinical Correlates of Depression Syndromes in PD

Fifty-two patients (30%) met DSM-IV criteria for major depression, 34 patients (20%) met DSM-IV criteria for dysthymia, 18 patients (10%) met DSM-IV research criteria for minor depression, and 69 patients (40%) were not depressed. Masked major depression, defined as the presence of four or more criteria for major depression without depressed mood or loss of interest/

APPENDIX 2. *Demographic and clinical findings for PD patients with subsyndromal or no depression*

	No depression	Subsyndromal depression
Number of patients	55	14
Age (mean years)	67.4 (9.5)[a]	62.5 (11.8)
Education (mean years)	10.6 (5.4)	12.7 (5.9)
Duration of illness (mean years)	6.7 (5.4)	5.0 (2.3)
UPDRS		
Mentation (mean)	2.9 (3.1)	3.1 (2.4)
Daily life activities	10.3 (7.3)	12.0 (6.8)
Motor signs (mean)	16.6 (10.6)	21.0 (8.0)
Complications (mean)	2.2 (3.5)	1.6 (1.9)
Total scores (mean)	32.4 (19.7)	38.6 (16.3)
Hamilton Depression Scale	4.8 (3.8)	6.8 (3.7)
Mini-Mental State Exam	24.3 (5.0)	25.9 (3.7)
Gender (% females)	23 [42][b]	7 [50]
Hoehn and Yahr stages I–II	29 [53]	8 [57]
Hoehn and Yahr stage III	18 [33]	5 [36]
Hoehn and Yahr stages IV–V	8 [14]	1 [7]
Dementia[a] (% positive)	19 [35]	5 [36]

[a]Numbers are means (SD).
[b]Values in square brackets indicate percentages.

anhedonia,[17] was present in only 2 of the 173 patients (1%), whereas masked dysthymia, defined as the presence of two or more symptoms for dysthymia but no sad mood, was diagnosed in 6 of the 173 patients (3%). Criteria for subsyndromal depression were met by 14 of the 69 nondepressed patients (20%). There were no significant clinical or demographic differences between patients with subsyndromal depression and patients without depression (Appendix 2). Patients with major or minor depression had significantly higher scores on the UPDRS domains of mentation, activities of daily living, and motor symptoms, and significantly lower MMSE scores than did nondepressed or dysthymic patients (Table 2).

Dementia and Depression in PD

Patients with either major or minor depression had a significantly higher frequency of dementia than patients with dysthymia or no depression (Table 2). A two-way MANOVA with depressed mood (present vs. absent) and dementia (present vs. absent) as the grouping factors and the remaining DSM-IV criteria for major depression as the dependent variables showed the expected effect for

TABLE 2. *Demographic and clinical findings for PD patients with no minor, major ,or dysthymic depression*

	No depression	Minor depression	Major depression	Dysthymia
Number of patients	69	18	52	34
Age (mean years)	66.5 (10.0)	67.0 (11.3)	66.0 (9.1)	64.5 (10.7)
Education (mean years)	11.0 (5.5)	13.0 (4.4)	9.8 (4.8)	11.2 (4.9)
Duration of illness (mean years)	6.4 (5.1)	7.8 (4.7)	5.7 (4.3)	4.3 (3.4)
UPDRS				
Mentation[a] (mean)	2.9 (2.9)	5.1 (3.6)	6.3 (2.3)	4.5 (2.2)
Daily life activities[b]	10.6 (7.2)	14.7 (9.2)	15.1 (8.7)	9.8 (6.2)
Motor signs[c] (mean)	17.4 (10.2)	24.4 (11.0)	23.0 (9.9)	15.72(8.4)
Complications (mean)	2.1 (3.2)	3.0 (4.0)	2.7 (3.4)	2.3 (2.7)
Total scores (mean)	33.6 (19.2)	47.7 (22.6)	46.9 (19.9)	32.1 (14.1)
Hamilton Depression Scale[d]	5.2 (3.8)	9.3 (4.4)	18.3 (6.3)	11.1 (3.7)
Mini-Mental State Exam[e]	24.6 (4.8)	21.1 (8.1)	23.32 (5.9)	25.7 (4.2)
Levodopa (mg/day)	550 (417)	551 (256)	611 (323)	479 (359)
Bromocriptine (mg/day)	2.8 (6.8)	5.0 (10.6)	1.5 (3.7)	0
Selegiline (mg/day)	5.5 (7.9)	6.2 (7.4)	3.6 (7.4)	4.1 (7.5)
Anticholinergics	4 [6][f]	1 [6]	1 [2]	4 [12]
Gender (% females)	30 [43]	8 [44]	25 [48]	112 [32]
Hoehn and Yahr stages I–II	37 [54]	4 [22]	20 [38]	19 [56]
Hoehn and Yahr stage III	23 [33]	9 [50]	20 [38]	11 [32]
Hoehn and Yahr stages IV–V	9 [13]	5 [28]	12 [24]	4 [12]
Dementia[g] (% positive)	19 [30]	10 [62]	26 [53]	4 [11]
History of depression (positive)	11 [16]	3 [17]	7 [13]	9 [26]
Antidepressants	3 [4]	1 [6]	8 [15]	3 [9]
Benzodiazepines	12 [17]	3 [17]	10 [19]	9 [26]

Numbers are means (SD).
[a]$F(3, 169) = 14.0$, $P < 0.0001$ (all three depressed groups > nondepressed ($P < 0.01$); major depression > dysthymia ($P < 0.01$).
[b]$F(3, 169) = 4.67$, $P < 0.01$ (major and minor depression > dysthymia $P < 0.05$; major depression > no depression $P < 0.01$).
[c]$F(3, 169) = 6.32$, $P < 0.001$ (major and minor depression > dysthymia and no depression $P < 0.01$).
[d]$F(3, 169) = 75.2$, $P < 0.0001$ (all three depression groups > no depression $P < 0.001$).
[e]$F(3, 169) = 3.06$, $P < 0.05$ (major depression and minor depression < dysthymia $P < 0.05$).
[f]Values in square brackets indicate percentages.
[g]$X^2 = 31.1$, df = 12, $P = 0.001$ (major depression vs. dysthymia Fisher exact test $P = 0.001$; minor depression vs. dysthymia Fisher exact test $P = 0.01$).

APPENDIX 3. *DSM-IV criteria for major depression and dysthymic disorder for PD patients with or without dementia*

	No sad mood		Sad mood	
	No dementia	Dementia	No dementia	Dementia
Number of patients	47	31	59	36
Major depression				
Loss of interest/pleasure	1.3 (0.6)	1.7 (0.9)	2.4 (0.7)	2.5 (0.7)
Changes in appetite/weight	1.0 (0.3)	1.2 (0.6)	1.7 (0.8)	1.7 (0.9)
Sleep changes	1.3 (0.7)	1.2 (0.6)	1.8 (0.9)	2.0 (0.9)
Psychomotor changes	1.3 (0.6)	1.5 (0.8)	1.9 (0.8)	2.3 (0.8)
Loss of energy	1.3 (0.5)	1.4 (0.8)	2.2 (0.8)	2.6 (0.6)
Worthlessness/guilt	1.0 (0.2)	1.2 (0.5)	1.8 (0.8)	2.0 (0.9)
Concentration deficits	1.2 (0.5)	1.5 (0.9)	2.2 (0.8)	2.6 (0.6)
Suicide ideation	1.1 (0.4)	1.1 (0.4)	1.5 (0.8)	1.8 (1.0)
Dysthymic disorder				
Number of patients	51	32	30	9
Changes in appetite	1.1 (0.3)	1.2 (0.6)	1.7 (0.9)	1.5 (1.0)
Sleep changes	1.3 (0.7)	1.3 (0.4)	1.8 (0.9)	2.0 (1.0)
Low energy	1.5 (0.7)	1.3 (0.7)	2.3 (0.9)	2.7 (0.7)
Low self-esteem	1.1 (0.5)	1.0 (0.1)	1.8 (0.9)	1.7 (1.0)
Poor concentration	1.3 (0.7)	1.5 (0.8)	2.2 (0.9)	1.8 (0.9)
Hopelessness	1.0 (0.4)	1.0 (0.4)	2.3 (0.9)	1.8 (0.9)

Numbers are means (SD).

depressed mood (Wilks' Lambda = 0.50, df = 8,162, $P < 0.0001$), no significant effect for dementia (Wilks' Lambda = 0.92, df = 8,162, $P = 0.09$), and no significant sad mood by dementia interaction (Wilks' Lambda = 0.96, df = 8,162, $P = 0.59$; Appendix 3). A similar analysis for the DSM-IV criteria for dysthymic disorder showed the expected significant effect for sad mood (Wilks' Lambda = 0.49, df = 6,113, $P < 0.0001$), no significant effect for dementia (Wilks' Lambda = 0.97, df = 6,113, $P = 0.79$), and no significant sad mood by dementia interaction (Wilks' Lambda = 0.91, df = 6,113, $P = 0.10$; Appendix C).

The Specificity of Loss of Interest/Pleasure for Depression Syndromes in PD

Four of the 52 patients (8%) with major depression and 6 of the 18 patients with minor depression (33%) had loss of interest or pleasure in the absence of depressed mood (Fisher's exact test, $P = 0.01$). We next examined the association between loss of interest/pleasure and the remaining DSM-IV criteria for major depression. Patients with a score of 2 (i.e., sub threshold) on the SCID item rating loss of interest/pleasure were recoded as 1 whenever they scored 0 or 1 on the HAM-D item rating loss of interest (item 7), and 3 whenever they scored 2 or more (i.e. loss of interest in activities, hobbies, or work). Loss of interest/anhedonia was present in 58 of the 95 patients (61%) with sad mood, when compared with 15 of the 78 patients (19%) without sad mood ($X^2 = 56.1$, df = 2, $P < 0.001$). A two-way MANOVA with loss of interest/pleasure (present vs. absent) and Hoehn–Yahr stages as the grouping variables and the remaining DSM-IV criteria for major depression as the dependent variables showed a significant main effect for loss of interest/pleasure (Wilks' Lambda = 0.72, df = 8,160, $P < 0.0001$), no significant main effect for Hoehn and Yahr stages (Wilks' Lambda = 0.93, df = 16,320, $P = 0.80$), and no significant sad mood × Hoehn and Yahr stage interaction (Wilks' Lambda = 0.91, df = 16,320, $P = 0.53$). On individual comparisons, patients with loss of interest/pleasure showed significantly higher scores on all the remaining DSM-IV items for major depression when compared with patients with no loss of interest/pleasure (Appendix 4). Finally, ROC statistics were calculated with loss of interest or pleasure (present vs. absent) as the classification variable, and the seven additional DSM-IV criteria for major depression as the criterion. The area under the curve was 0.88 (95% CI = 0.82–0.92, $P < 0.0001$), thus demonstrating high accuracy. A cutoff of 2 or more symptoms of depression had a high sensitivity (91%) but a lower specificity (73%) for the presence of significant loss of interest/pleasure.

Motor Signs and Symptoms of Depression

We examined the association between motor symptoms of PD and depressive symptoms using a stepwise regression analysis, with HAM-D total score as the dependent variable and the UPDRS motor items as the independent variables. The main finding was that the overall UPDRS-Motor section score accounted for 11% of the variance with HAM-D scores ($R^2 = 0.11$, $P < 0.001$), but gait was the only motor variable significantly

APPENDIX 4. *DSM-IV criteria for major depression and loss of interest*

	Hoehn–Yahr I–II		Hoehn–Yahr III		Hoehn–Yahr IV–V	
	No interest loss	Loss of interest	No interest loss	Loss of interest	No interest loss	Loss of interest
Sad mood	1.7 (0.9)	2.6 (0.7)	1.8 (0.9)	2.3 (0.8)	2.0 (1.0)	2.5 (0.7)
Changes in appetite/weight	1.2 (0.5)	1.8 (0.5)	1.1 (0.7)	1.6 (0.9)	1.4 (0.9)	1.5 (0.8)
Sleep changes	1.5 (0.8)	2.0 (0.8)	1.5 (0.7)	1.6 (0.9)	1.3 (0.8)	2.0 (1.0)
Psychomotor changes	1.4 (0.7)	2.0 (0.7)	1.5 (0.9)	2.1 (0.9)	1.9 (0.9)	2.0 (0.9)
Loss of energy	1.5 (0.7)	2.3 (0.8)	1.4 (0.7)	2.5 (0.7)	1.4 (0.6)	2.4 (0.8)
Worthlessness/guilt	1.3 (0.6)	1.9 (0.5)	1.2 (0.7)	1.7 (0.9)	1.3 (0.9)	2.0 (1.0)
Concentration deficits	1.5 (0.7)	2.2 (0.8)	1.5 (0.8)	2.4 (0.8)	1.7 (0.9)	2.4 (0.8)
Suicide ideation	1.2 (0.5)	1.6 (0.8)	1.2 (0.6)	1.7 (0.9)	1.3 (0.6)	1.7 (1.0)

Numbers are means (SD).

correlated with depression scores ($R^2 = 0.08$, $P < 0.0001$). Similar results were obtained when the HAM-D item 1 (i.e. sad mood) was used as the dependent variable (overall $R^2 = 0.11$, $P < 0.001$, gait $R^2 = 0.08$, $P < 0.0001$).

DISCUSSION

We examined the specificity of symptoms of depression in a series of 173 patients with PD and there were several important findings. First, all the DSM-IV clinical criteria for major depression and dysthymia were significantly associated with sad mood, and this association was not influenced by stage of illness or presence of dementia. Moreover, there were no significant differences on the severity of symptoms of depression when PD patients with sad mood were compared with elderly individuals with sad mood, but no PD matched for MMSE and HAM-D scores. Second, 30% of our sample met DSM-IV criteria for major depression, 20% met the clinical criteria for a dysthymic disorder, 10% met the clinical criteria for minor depression, and 8% met Judd's criteria for subsyndromal depression. Third, the frequency of depression diagnosed based on the presence of loss of interest without sad mood was significantly higher for minor as compared to major depression, suggesting that the diagnosis of minor depression is less specific for the presence of sad mood than major depression. Fourth, patients with either major or minor depression had significantly more severe functional impairments, more severe Parkinsonism, and a higher frequency of dementia than patients with dysthymia or no depression.

Before further comments, several limitations of our study should be pointed out. First, our sample consisted of patients attending a Movement Disorders Clinic for regular care, which may have biased our sample toward more severe cases. This factor and our use of the inclusive approach for symptom attribution may partially account for the relatively high frequency of major depression in our study. The NINDS-NIMH Work Group[7] suggested that the inclusive approach may be more reliable and easier to implement in both clinical and research settings. Among hospitalized older adults, Koenig et al.[18] found that the exclusive approach missed over 45% of the patients identified by the inclusive approach with severe impairment from their depressive symptoms. A high frequency of depression was also reported in epidemiological studies that included PD patients living in the community.[19] Second, blinding was limited by the presence of a question on depression on the UPDRS, and by the evidence of severity of Parkinsonism for the psychiatrist. Nevertheless, parkinsonian signs explained only 11% of the variance with depression scores. Third, we used sad mood as the gold standard, given that this criterion is the most relevant for the diagnosis of major depression among patients with neurological disorders.[20-22] Finally, the sample with subsyndromal depression was relatively small, and findings for this group should be considered preliminary.

The important question of how to diagnose depression in PD remains an unsolved dilemma. The NINDS-NIMH Work Group stressed the need for clinical research that "(1) accounts for symptom overlap among depression, motor symptoms, and other comorbidities in PD; (2) considers the full spectrum of depressive disturbances in PD; and (3) leads to development of standards for diagnosing depression in PD."[7] To our knowledge, ours is the first study to examine the validity of the DSM-IV criteria for major depression, minor depression, and dysthymia, and to examine the frequency and clinical correlates of subsyndromal depression in PD. When patients were divided into subgroups based on the presence of sad mood, we found that all the remaining DSM-IV clinical criteria for major depression and dysthymia were significantly associated with the presence of sad mood and had strong internal validity. On the other hand, 33% of patients with minor depression were diagnosed based on

the presence of loss of interest but no sad mood when compared with only 8% of patients with major depression. This finding suggests that the category of minor depression may include a relatively large proportion of individuals with apathy rather than a "true" affective disorder.

Only 14 patients (8% of the participants) met Judd's criteria for subsyndromal depression. The NINDS-NIMH Work Group suggested that subsyndromal depression could be clinically relevant; but we could not find demographic or clinical differences between patients with subsyndromal depression and those without depression. This finding suggests that the category of subsyndromal depression is of dubious clinical relevance in PD. The NINDS-NIMH Work Group also suggested assessing several psychiatric symptoms, such as psychological and autonomic anxiety, that are commonly observed among depressed patients with PD but are not included within the DSM-IV diagnostic criteria for depressive syndromes. We found a significant association between psychological and autonomic anxiety and the presence of sad mood in PD, suggesting that anxiety could be added to the diagnostic criteria for both major depression and dysthymia in PD. Finally, the NINDS-NIMH Work Group raised the concern that using the DSM-IV criteria for major depression and dysthymia could exclude half of PD patients with clinically significant depression. We found masked major depression (defined as meeting four or more criteria for major depression in the absence of sad mood or loss of interest/pleasure) in only 2 of the 173 participants, whereas masked dysthymia (defined as two or more symptoms for dysthymia but no sad mood) was found in only 6 of the 173 patients. Taken together, these findings suggest that the use of DSM-IV diagnostic criteria for major depression and dysthymia may not exclude a large proportion of PD patients with clinically significant depression. Given our use of the inclusive strategy to diagnose depression, we expected a significant impact of stage of illness upon the severity of symptoms of major depression and dysthymia. However, this hypothesis was not empirically supported, demonstrating that symptoms of depression are not significantly influenced by stage of illness. We examined the association between motor symptoms of PD and depressive symptoms, using a stepwise regression analysis with HAM-D total scores as the dependent variable and the UPDRS motor items as independent variables. The main finding was that motor items accounted for 11% of the variance with HAM-D scores, but gait was the only motor variable significantly correlated with depression scores.

Based on validated DSM-IV criteria, the frequency of major depression in our sample was 30%, the frequency of dysthymia was 20%, and the frequency of minor depression was 10%. A recent meta-analysis reported a probable prevalence of 31% for major depression in PD.[23] Patients with either major or minor depression had significantly worse scores on the mentation, activities of daily living, and motor sections of the UPDRS when compared with nondepressed or dysthymic PD patients. Duration of PD was similar for all four groups, suggesting that patients with major or minor depression may have a faster progression of cognitive, functional, and motor deficits than do dysthymic or nondepressed PD patients.

Since most studies that examined the validity of depressive symptoms in PD have excluded patients with cognitive deficits, the phenomenology of depression among PD patients with dementia remains unknown. This is an important limitation given that the majority of patients with PD will eventually develop dementia at some stage of the illness.[24] We found that comorbid dementia had no significant impact upon the DSM-IV clinical criteria for major depression or dysthymia, suggesting that these criteria may be used in PD regardless of the presence of dementia.

In conclusion, this is to our knowledge the first study to validate diagnostic criteria for major depression, minor depression, and dysthymic disorder for both demented and nondemented patients with PD. Our findings suggest that major depression and dysthymia in PD should be diagnosed using the full diagnostic criteria for each disorder, as listed in the DSM-IV. Presence of anxiety could be included as an additional criterion for both major depression and dysthymia. Minor depression may be diagnosed using the DSM-IV criteria but only when sad mood is present. Finally, subsyndromal depression should not be used in PD until further validation.

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