Comparable data were not obtained in this study because of the limitation of gathering this information retrospectively from charts or video clips. However, referral bias (to a neuro-ophthalmological clinic vs. a movement disorders clinic) clearly influences the reported accompanying neurological features in Keane's survey compared to our own.

We were not able to evaluate the etiological background or prognosis in our patients with PGD in this retrospective analysis of the phenomenological features of gait abnormalities on our PMD patients. Our data are also limited by the relatively long duration of symptoms. It is our unsubstantiated impression that certain gait patterns described in series derived from acute hospital care settings, such as hemiparetic and paraparetic forms, tend to remit or may evolve to other types, such as buckling or dystonic. As indicated above, our movement disorders specialty clinic setting likely results in important referral biases with more prolonged, recalcitrant, or difficult-to-diagnose cases being seen more often than the easily diagnosed or short-lived cases.

Despite these limitations, this is the largest series of patients with PMD evaluated for the nature of their gait abnormalities. We noted a small number of different clinical features in patients with PMD as compared to PGD patients and certain gait features were more typical of those with a pure PGD, especially buckling of the knee, astasia–abasia, and bizarre gait. The reliability of our finding that excessive slowing of movement is more common in those with a PGD is uncertain given the number of comparisons we made and this will need to be confirmed in other clinical populations.

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Validity of Hamilton Depression Inventory in Parkinson's Disease

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Abstract: **Studies investigating the assessment of depression in Parkinson's disease (PD) are limited. We examined the concurrent validity and the internal consistency of the Hamilton Depression Inventory (HDI) and compared it to the Hamilton and Geriatric Depression Scales. PD patients (n = 79) were recruited from neurology clinics. Diagnosis of depressive disorder was made according to DSM-IV criteria. Receiver operating characteristic curves were used to calculate sensitivity, specificity, and positive and negative predictive values. The HDI exhibited an optimal cutoff for discriminating between depressed and nondepressed PD patients of 13.5/14.0 and is a valid instrument to use in the setting of PD.** © 2007 Movement Disorder Society

Key words: Hamilton Depression Inventory; Geriatric Depression Scale; Hamilton Depression Rating Scale; depression; Parkinson's disease; validity

Depression in Parkinson's disease (PD) is common and can be assessed by utilizing various rating scales with PD-specific cutoff scores.[1] Studies examining the validity of depression rating scales in PD are limited. The user-rated scales, Beck Depression Inventory (BDI)[2] and

Geriatric Depression Scale (GDS),[3] have been studied in PD. Both versions of the GDS (15 and 30) appear to show utility,[4,5] although limited confirmatory data exist. BDI poorly dichotomizes PD patients with and without depression.[6]

The Hamilton Depression Inventory (HDI)[7] is a relatively new user-rated version of the Hamilton Depression Rating Scale (HAMD).[8] HDI has been validated and used in the general population, showing similar performance to other scales such as HAMD and BDI.[9] The HDI 17-item version (HDI-17) consists of 17 items with multiple questions, which provide greater fidelity in evaluating clinical symptoms compared to the existing user-rated scales. The HDI-17 scoring system ranges from 0 to 52 and allows half-point values to increase accuracy. While HAMD is the most widely used depression rating scale generally and a scale extensively utilized in PD research, there have been no previous examinations of the HDI in the context of PD.[10] In the current study, we investigate the concurrent validity and the internal consistency of HDI-17 in PD and compare it to the GDS-15 and HAMD-17 for usefulness in assessing depression in PD patients.

PATIENTS AND METHODS

We recruited a consecutive series of patients diagnosed with idiopathic PD according to the U.K. Brain Bank criteria[11] from two neurology clinics in Brisbane. Inclusion criteria were Caucasian ancestry; residents of Brisbane; and ability to complete the questionnaires by themselves or with assistance. Patients with signs of dementia (Mini Mental State Examination, or MMSE < 24) were excluded. This study was approved by Princess Alexandra Hospital and the University of Queensland Human Research Ethics Committees.

HDI-17 and GDS-15 were mailed to participants. Within 2 weeks of mail-out, interviews were conducted by a psychiatrist or a trained research assistant at the patient's residence, blinded to the user-rated instrument results. The severity of PD was determined using the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr (HY) scale. All patients were screened for a current depressive disorder. Subjects screened positive if they fulfilled the criteria for major depression, minor depression, or dysthymia according to the Diagnostic and Statistical Manual, 4th edition (DSM-IV).[12] This was evaluated using the Mini-International Neuropsychiatric Interview (MINI-plus),[13] which was used as the gold standard in this study. Extensive validity testing has demonstrated the usefulness of MINI-plus as a research diagnostic tool against DSM-IV criteria evaluated using structured clinical interview for DSM-IV

(SCID).[13] The diagnosis of minor depression (participants having a current episode of at least 2 weeks of depressive symptoms but with fewer than the five items required for major depressive disorder) was derived from examining the results obtained from MINI-plus interview and adhering to the DSM-IV–proposed research diagnostic criteria. HAMD-17 was also performed at the interview applying the inclusive method.[14]

The receiver operating characteristic (ROC) curves were drawn and data for sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were obtained for a range of cutoff scores. ROC curves were used to derive the following parameters: the optimal discriminatory cutoff score (the score yielding the maximum sum of sensitivity and specificity); the diagnostic cutoff score (the score yielding a maximum sum of specificity and PPV); the screening cutoff score (the score providing a maximum sum of sensitivity and NPV). Internal consistency of the scales was assessed using Cronbach's alpha and split-half correlation coefficients. All statistical analyses were performed using the software packages SPSS and Stata.

RESULTS

One hundred fourteen patients met the inclusion criteria, with 79 consenting and completing the study. Table 1 presents the descriptive patient demographic and disease status parameters for participants. There were no significant differences in these parameters between participants and nonparticipants.

Table 2 illustrates results for different cutoff scores used to discriminate current depressive disorder (i.e., major depression or minor depression or dysthymia) and major depression. The cutoff scores of 13.5/14.0 for HDI-17, 6/7 for GDS-15, and 12/13 for HAMD-17 show optimal discrimination between the patients with and without any depressive disorder for the three instruments. Cutoff scores of 15.5/16.0 for HDI-17, 9/10 for

TABLE 1. *Demographics details for participating patients and detailed results*

Total number of participants (male/female)	79 (42/37)
Age (yr)	67 ± 10
Age at onset of PD symptoms (yr)	59 ± 12
Average MMSE	28 ± 2
HY stage: % mild (stages 1.0–2.0) to moderate (stages 2.5–3.0)/% severe stages (4.0–5.0)	91/9
Mean total UPDRS (range)	42 (8–103)
Current depressive disorder, n [M/F]	18 (23%) 10/8
Major depression, n [M/F]	9 (11%) 5/4
Minor depression, n [M/F]	5 (6%) 3/2
Dysthymia, n (%) [M/F]	4 (5%) 2/2

TABLE 2. *Receiver operating characteristic curve analysis: validity results for HDI-17, GDS-15, and HAMD-17*

Cutoff	Sensitivity		Specificity		Positive predictive value		Negative predictive value	
	I	II	I	II	I	II	I	II
HDI-17								
11.5/12.0	0.83	0.89	0.80	0.73	0.56	0.30	0.94	0.98
12.0/12.5	0.78	0.89	0.80	0.74	0.54	0.31	0.93	0.98
12.5/13.0	0.78	0.89	0.84	0.77	0.58	0.33	0.93	0.98
13.0/13.5	0.78	0.89	0.87	0.80	0.64	0.36	0.93	0.98
13.5/14.0[a]	0.78	0.89	0.90	0.83	0.70	0.40	0.93	0.98
14.0/14.5	0.72	0.89	0.92	0.86	0.72	0.44	0.92	0.98
14.5/15.0	0.67	0.89	0.93	0.89	0.75	0.50	0.91	0.98
15.0/15.5	0.61	0.89	0.95	0.91	0.79	0.57	0.89	0.99
15.5/16.0[b]	0.61	0.89	0.97	0.93	0.85	0.62	0.89	0.99
16.0/16.5	0.56	0.78	0.97	0.94	0.83	0.64	0.88	0.97
16.5/17.0	0.50	0.78	0.97	0.94	0.82	0.64	0.87	0.97
17.0/17.5	0.44	0.67	0.97	0.96	0.80	0.67	0.86	0.96
GDS-15								
4/5	0.94	1.00	0.75	0.67	0.53	0.28	0.98	1.00
5/6	0.89	1.00	0.82	0.74	0.59	0.33	0.96	1.00
6/7[a]	0.89	1.00	0.87	0.79	0.67	0.38	0.96	1.00
7/8	0.83	0.89	0.90	0.81	0.71	0.38	0.95	0.98
8/9[b]	0.72	0.89	0.93	0.87	0.76	0.47	0.92	0.98
9/10	0.50	0.78	0.98	0.96	0.90	0.70	0.87	0.97
HAMD-17								
9/10	0.94	1.00	0.74	0.64	0.52	0.27	0.98	1.00
10/11	0.89	1.00	0.80	0.71	0.57	0.31	0.96	1.00
11/12	0.89	1.00	0.89	0.81	0.70	0.41	0.96	1.00
12/13[a]	0.89	1.00	0.93	0.84	0.80	0.45	0.97	1.00
13/14	0.83	1.00	0.95	0.89	0.83	0.53	0.95	1.00
14/15	0.83	1.00	0.98	0.90	0.94	0.56	0.95	1.00
15/16	0.78	1.00	0.98	0.91	0.93	0.60	0.94	1.00
16/17	0.67	1.00	0.98	0.94	0.92	0.70	0.91	1.00
18/19[b]	0.55	1.00	1.00	0.99	1.00	0.90	0.88	1.00
20/21	0.50	0.89	1.00	0.99	1.00	0.89	0.87	0.99
21/22	0.39	0.78	1.00	1.00	1.00	1.00	0.84	0.97

I, results for current depressive disorder (i.e., major depression, minor depression, or dysthymia); II, results for current major depression.
[a]Maximum sum of sensitivity and specificity for depressive disorder.
[b]Maximum sum of sensitivity and specificity for major depression.

GDS-15, and 14/15 HAMD-17 were the optimal diagnostic cutoffs and cutoff values of 11.5/12.0 for HDI-17, 4/5 for GDS-15, and 9/10 HAMD-17 the optimal screening cutoffs for any depressive disorder. Comparisons of the areas under the curves (AUCs) from the three ROC curves, using the ROCCOMP command in Stata, revealed no significant differences at $P < 0.05$ (Fig. 1). However, HAMD-17 exhibited the largest AUC (0.96; Fig. 1), suggesting superiority to the two user-rated scales. Out of the two user-rated scales, HDI-17 exhibited a lower AUC to GDS-15. Similar trends were observed when major depression was the outcome of interest (Fig. 2). The optimal cutoff values that discriminate between patients with and without major depression are as follows: 15.5/16.0 for HDI-17; 8/9 for GDS-15, and 18/19 for HAMD-17. A gender comparison of all three scales suggested that the optimal cutoff scores for discriminating depressive disorder in PD may differ between male and female. The optimal cutoff values for

male versus female were 14.5/15.0 versus 13.5/14.0, 6/7 versus 7/8, and 12/13 versus 14/15 for HDI-17, GDS-15, and HAMD-17, respectively. The Cronbach's alpha coefficients were 0.85 for HDI-17 and GDS-15 and 0.86 for HAMD-17. The split-half correlation coefficients were
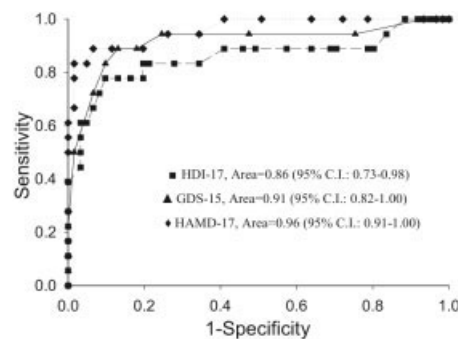

FIG. 1. ROC curves according to diagnosis of major/minor depression or dysthymia for HDI-17, GDS-15, and HAMD-17.
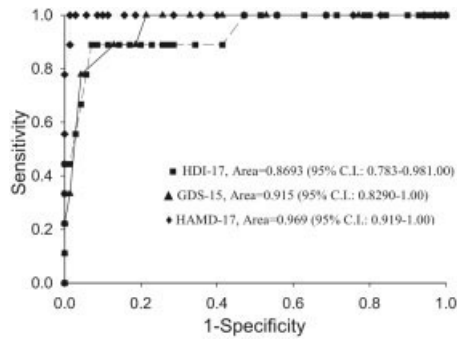
FIG. 2. ROC curves according to diagnosis of major depression for HDI-17, GDS-15, and HAMD-17.

0.83 for HDI-17, 0.77 for GDS-15, and 0.78 for HAMD-17.

DISCUSSION

Our findings suggest that HDI-17 is an appropriate scale to dichotomize PD patients into those with and without depressive disorder (i.e., major depression, minor depression, or dysthymia) in PD. The scale can be utilized for both screening and diagnostic purposes with specific cutoff scores. The optimal cutoff score obtained for PD to differentiate between patients with and without major depression is similar to that derived for the general population.[7] Compared to HAMD-17 and GDS-15, HDI-17 exhibited inferior AUC. The sensitivity and NPV at the optimal cutoff point for discrimination between depressed and nondepressed subjects were lower for HDI-17; however, the specificity and the PPV were slightly higher for HDI-17 than for GDS-15. All three scales demonstrated high internal consistency. Our study is limited to nondemented PD patients screened with the MMSE. Further validity testing is recommended in PD patients utilizing a DSM-IV diagnosis of dementia. We also note that gender-specific cutoff scores should be utilized when dichotomizing subjects. The observed differences in optimal cutoff scores between male and female were not uniform for all instruments; the optimal cutoff is lower for female when using the HDI-17, whereas for the other two scales, optimal cutoffs for female were higher in comparison to male. However, these results should be considered cautiously given the limited power of our study to detect gender differences (male, 42; female, 37).

Our study replicates the previous study by Leentjens and colleagues[10] investigating the validity of HAMD-17 in PD; however, we provide slightly different results. Leentjens and colleagues[10] suggested an optimal cutoff of 13/14 with sensitivity of 0.88 and specificity of 0.89 for HAMD-17. We obtained a slightly lower cutoff of

12/13 as the optimal cutoff with sensitivity of 0.89 and specificity of 0.93. This may reflect the fact that our study included a larger proportion of subjects with more severe PD symptoms (9% with HY severe compared to 1% in Leentjens and colleagues[10]). We also note that the HAMD-17 was not performed blinded to the gold-standard MINI-plus, and this was a limitation of our study.

Our study also allows a comparison in validity assessments with the work of Weintraub and colleagues,[5] who have previously examined the validity of GDS-15 in PD. Our optimal cutoff scores were slightly higher. Weintraub and colleagues[5] suggested an optimal cutoff of 4/5 to dichotomize depressive disorder (sensitivity, 0.88; specificity, 0.85) and a cutoff of 6/7 to determine major depression (sensitivity, 0.89; specificity, 0.93). In our study, we derived an optimal cutoff value of 6/7 for depressive disorder and 8/9 for major depression at similar sensitivity and specificity. The differences in the study population and the study method may account for these disparities. The participants in the study by Weintraub and colleagues[5] were almost all male with a mild degree of PD (mean UPDRS total score, 24.5). The participants in our study were consecutively recruited patients (53% male) with mild- to moderate-stage PD (mean UPDRS total score, 42.3). We also note that compared to our study, the previous study did not include patients with dysthymia and GDS-15 was both self- and rater-administered.

It is important to study the validity of user-rated scales to assess depression in PD due to time, energy, and higher costs involved with observer-rated testing, specifically in research studies with large sample sizes (e.g., risk factor studies). We provide novel information of the validity of another user-rated instrument in comparison to its observer-rated version (HAMD) and a widely utilized user-rated instrument (GDS-15). Our data provide cutoff values to dichotomize PD patients appropriately into those with and without major depression and major or minor depressive disorder or dysthymia, as defined in the DSM-IV criteria. These cutoffs are valid specifically in the research context, as the definition of depression may differ according to specific research study rationales. Our comparison of the user-rated scales suggests that the GDS-15 may be better suited for wide scale use due to its brevity and slightly higher sensitivity; yet we emphasize that none of these instruments can substitute for a professional clinical diagnosis. Nevertheless, all instruments should be compared (within the context of PD) to other available user-rated scales such as BDI[2] and the Center for Epidemiological Studies Depression Rating Scale,[15] with careful attention to the definition of depression. Moreover, the performance of all scales

needs to be tested for sensitivity to changes in affective status over time. Such assessment tools will be crucial in the setting of longitudinal clinical trials investigating response to antidepressive therapies in patients with PD.

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Proteasome Inhibitor Model of Parkinson's Disease in Mice Is Confounded by Neurotoxicity of the Ethanol Vehicle

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Abstract: **Defects in the ubiquitin-proteasome system have been implicated in Parkinson's Disease (PD). Recently, a rat model of PD was developed using a synthetic proteasome inhibitor (PSI), (Z-lle-Glu(O*t*Bu)-Ala-Leu-al). We attempted to transfer this model to mouse studies, where genetics can be more readily investigated due to the availability of genetically modified mice. We treated C57BL/6 (B6) mice with six intraperitoneal injections of 6 mg/kg PSI in 50 μl of 70% ethanol over a 2-week-period. We found significant decreases in nigrostriatal dopamine in PSI-treated mice compared with saline-treated mice. However, we observed similar decreases in the ethanol-treated vehicle control group. Administration of ethanol alone led to significant long-term alterations in dopamine levels. Ethanol significantly eclipses the effects of PSI in the dopamine system, and therefore is a confounding vehicle for this model.** © 2007 Movement Disorder Society

Key words: Parkinson's disease; proteasome; PSI; mouse model; ethanol; neurotoxicity.

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. It is a relentlessly progressive degenerative disease of the nigrostriatal system and results from the selective degeneration of dopamine neurons in the substantia nigra of the brain. The consequent deficiency in striatal dopamine gives rise to the characteristic symptoms of the disease including tremor, bradykinesia, rigidity, and postural instability.