Mood and Sleep in Parkinson's Disease

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Received Sep.1, 2005; accepted Dec. 21, 2005. From the Department of Psychiatry and Human Behavior, Butler Hospital (Drs. Borek and Kohn); and the Department of Neurology, Memorial Hospital of Rhode Island (Dr. Friedman), Brown University, Providence, R.I.

Preliminary data from this study were presented at the 185th annual meeting of the American Psychiatric Association, May 21–26, 2005, Atlanta, Ga.

In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME article *were asked to complete a statement regarding all relevant financial relationships between themselves or their spouse/partner and any commercial interest (i.e., a proprietary entity producing health care goods or services) occurring within at least 12 months prior to joining this activity. The CME Institute has resolved any conflicts of interest that were identified. The disclosures are as follows: Dr. Kohn has received grant/research support from the National Alliance for Research on Schizophrenia and Depression (NARSAD) and serves on the speakers/advisory boards for Pfizer and Forest. Drs. Borek and Friedman have no significant commercial relationships to disclose relevant to the presentation.*

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Objective: To determine whether severity of depression and severity of anxiety were associated with particular types of sleep disturbance in patients with Parkinson's disease.

Method: 120 patients with a diagnosis of idiopathic Parkinson's disease were consecutively recruited from a movement disorders clinic from July 2004 to May 2005. Idiopathic Parkinson's disease was diagnosed by a board-certified neurologist (J.H.F) and defined by the presence of 3 of the 4 cardinal signs of Parkinson's disease: resting tremor, rigidity, bradykinesia, and postural instability. Patients were administered the Hamilton Rating Scale for Depression, Hamilton Rating Scale for Anxiety, Covi Anxiety Scale, Pittsburgh Sleep Quality Index (PSQI), and Epworth Sleepiness Scale (ESS). Patients were assessed for nightmares and rapid eye movement (REM) sleep behavior disorder (RBD) using a structured questionnaire and dream log. Multivariate analyses evaluated whether severity of depression and severity of anxiety correlated with the sleep outcome measures (PSQI, ESS, nightmares, and RBD).

Results: The mean ± SD age of the patients was 71 ± 10.8 years with a mean Parkinson's disease duration of 7.3 ± 4.7 years. Thirty-eight percent were female, 41.7% had a psychiatric history, 53.3% had nightmares, and 30% had clinically defined RBD. Severity of depression and severity of anxiety significantly correlated with poor sleep quality, daytime somnolence, and nightmares. Severity of depression contributed significantly to the overall variance in poor sleep quality and nightmares. Severity of anxiety contributed significantly to the overall variance in daytime somnolence.

Conclusions: Depressive and anxiety symptoms were associated with sleep disturbances in patients with Parkinson's disease. It is important to examine for the presence of depression and anxiety in patients presenting with sleep disorders, as depression and anxiety impair quality of life and are treatable conditions.

(J Clin Psychiatry 2006;67:958–963)

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. Although Parkinson's disease is primarily considered a movement disorder, the behavioral symptoms are common and constitute an important source of disability. Depression and anxiety are the most common psychiatric conditions that accompany Parkinson's disease. Depression occurs in 40% to 50% of patients,[1–3] and mild depression accounts for a large proportion of symptoms.[4] Anxiety disorders are reported to occur in up to 40% of patients with Parkinson's disease[5,6] and often coexist with depression. Sleep disorders are common as well and include sleep fragmentation, daytime somnolence, sleep apnea, nightmares, and rapid eye movement (REM) sleep behavior disorder (RBD).[7] RBD is a parasomnia characterized by loss of muscle atonia during REM sleep and prominent motor activity associated with dream mentation.[8] Patients enact their dreams, which are often violent in nature and involve being chased, being attacked, or defending oneself from attack.

We sought to determine whether the severity of depression and severity of anxiety correlated with particular types of sleep disturbance in patients with Parkinson's disease. To our knowledge, only 1 prior study examined the effect of both depression and anxiety on sleep in Parkinson's disease and was limited to evaluation of quality of sleep.[9] We wanted to examine whether depressive and anxiety symptoms were associated with sleep

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quality as well as other common sleep disturbances in Parkinson's disease, including daytime somnolence, nightmares, and RBD.

METHOD

Subjects

A consecutive series of 185 patients who attended the Movement Disorders Clinic at Memorial Hospital of Rhode Island were recruited from July 2004 to May 2005. Patients with a diagnosis of idiopathic Parkinson's disease were included in the study. Idiopathic Parkinson's disease was diagnosed by a board-certified neurologist (J.H.F.) and defined by the presence of 3 of the 4 cardinal signs of Parkinson's disease: resting tremor, rigidity, bradykinesia, and postural instability. Information on the diagnosis and details of patients' medication were obtained from medical records. Nursing home residents, patients with a Mini-Mental State Examination (MMSE)[10] score of 20 or below, and patients who could not communicate in English were excluded from the study. The MMSE score < 21 was chosen to exclude patients with moderate and severe cognitive impairment to ensure reliability of responses to self-assessments. The study protocol was approved by the Institutional Review Board at Memorial Hospital of Rhode Island. After complete description of the study to the subjects, written informed consent was obtained.

Psychiatric Assessments

Psychiatric history was obtained from each patient, including onset of the psychiatric disorder with respect to date of Parkinson's disease diagnosis. A geriatric psychiatrist (L.L.B.) performed the psychiatric evaluations. The severity of depression was measured with the 17-item Hamilton Rating Scale for Depression (HAM-D),[11] which has high validity in Parkinson's disease.[12] Scoring thresholds for depressive symptoms are as follows: very severe, ≥ 23; severe, 19 to 22; moderate, 14 to 18; mild, 8 to 13; normal, ≤ 7.[13] The severity of anxiety was measured with the Hamilton Rating Scale for Anxiety (HAM-A);[14] a score ≥ 14 indicates clinically significant anxiety.[15] The Covi Anxiety Scale (CAS)[16] was paired with the HAM-A to evaluate anxiety symptoms; a score of ≥ 7 (maximum score of 15) has been used to qualify patients for inclusion in treatment outcome studies.[16] The scoring thresholds for the HAM-D, HAM-A, and CAS have not been validated in the Parkinson's disease population. The patient's cognitive state was assessed with the MMSE.[10]

Sleep Assessments

The Pittsburgh Sleep Quality Index (PSQI)[17] evaluated the quality of sleep; a score > 5 indicates significant sleep disturbance.[17] The Epworth Sleepiness Scale (ESS)[18] measured daytime sleepiness; a score > 10 is considered clinically significant.[18] Nightmares were evaluated with the question "Have you had frightening or very disturbing dreams that wake you from sleep?"[19] The term *frightening dream* was used in order to maintain consistency of definition, since the term *nightmare* has different meanings to people and can include emotions other than fear, such as anger or grief.[19] Patients were asked to estimate their frequency of nightmares in the past year. A 1-month prospective daily dream log assessed dream content. The Nightmare Distress Scale (NDS)[20] evaluated the degree of waking distress associated with nightmares. The 13-item scale (maximum score of 56) is both reliable, based on the Cronbach α, and valid.[20] Posttraumatic stress disorder (PTSD) was diagnosed using DSM-IV criteria.[21] RBD was defined according to the clinical minimal diagnostic criteria of the International Classification of Sleep Disorders, Revised (ICSD-R)[8]: *limb or body movement associated with dream mentation* (criterion B) in the presence of at least 1 of the following (criterion C): (1) *Harmful or potentially harmful sleep behaviors* (2) *Dreams appear to be "acted out"* (3) *Sleep behaviors disrupt sleep continuity*. In our study, patients did not receive polysomnography (PSG). While PSG can reliably detect RBD, it is not necessary for diagnosis.[8] Information about nocturnal behavior was obtained from both patient and caregiver. Patients were asked to report the frequency of RBD episodes in the past year.

Neurologic Assessment

The motor disease severity of patients was assessed by a single rater (J.H.F.) according to the Hoehn and Yahr staging system,[22] which ranges from stage I (mild unilateral disease) to stage V (cannot stand or walk). The duration of Parkinson's disease was measured in years, from the year the diagnosis was made.

Statistical Analysis

Statistical analysis was carried out using means, standard deviations (SDs) and Pearson product moment correlation coefficients. Independent t tests and χ^2 tests were used on continuous and categorical variables, respectively. Multiple regression analyses were performed using the PSQI, ESS, nightmares, and RBD as dependent variables; HAM-D, HAM-A, CAS, age, gender, duration of Parkinson's disease, stage of Parkinson's disease, psychiatric history, sleep medication, levodopa (L-dopa), dopamine agonist, and PTSD were the independent variables. Nightmares and RBD were also used as independent variables when PSQI and ESS were the outcome measures. Backward regression analyses were conducted to determine the best predictor variables for each of the dependent variables; $p < .1$ was required to be retained in the model. All analyses were performed with SPSS version 12.0 for Windows (SPSS, Inc., Chicago, Ill.).

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Table 1. Patient Demographics (N = 120)

Clinical Features	Value
Age, mean ± SD (range), y	71 ± 10.8 (40–91)
Gender, N (%)	75 M (62.5); 45 F (37.5)
Hoehn and Yahr stage, mean ± SD (range)	2.5 ± 0.9 (1–5)
Duration of Parkinson's disease, mean ± SD (range), y	7.3 ± 4.7 (1–29)
Sleep medication, % (N)	23.3 (15 M; 13 F)
L-Dopa medication, % (N)	83.3 (61 M; 39 F)
Dopamine agonist medication, % (N)	46.7 (38 M; 18 F)
Psychiatric history, % (N)	41.7 (25 M; 25 F)*
Psychiatric disorder after Parkinson's disease onset, % (N)	18.3 (13 M; 9 F)
Nightmares, % (N)	53.3 (43 M; 21 F)
RBD, % (N)	30.0 (31 M; 5 F)†
PTSD, % (N)	3.3 (3 M; 1 F)

*p < .05.
†p < .01.
Abbreviations: F = female, M = male, PTSD = posttraumatic stress disorder, RBD = rapid eye movement (REM) sleep behavior disorder.

Table 2. Results of Sleep and Psychiatric Assessments in a Cohort of Patients With Parkinson's Disease

Rating Scale	Score, Mean ± SD (range)	Cutoff Score, %
PSQI	7.4 ± 3.9 (1–17)	
Score > 5		64.1
ESS	9.4 ± 5.5 (0–22)	
Score > 10		39.8
HAM-D	10.0 ± 5.8 (2–27)	
Score = 8–13		43.3
Score = 14–18		11.7
Score = 19–22		4.1
Score ≥ 23		4.2
HAM-A	9.3 ± 7.1 (0–34)	
Score ≥ 14		23.2
CAS	5.6 ± 2.3 (3–12)	
Score ≥ 7		30.8
MMSE	27.0 ± 2.5 (21–30)	
NDS	20.5 ± 8.0 (13–50)	

Abbreviations: CAS = Covi Anxiety Scale, ESS = Epworth Sleepiness Scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, MMSE = Mini-Mental State Examination, NDS = Nightmare Distress Scale, PSQI = Pittsburgh Sleep Quality Index.

RESULTS

Demographic Characteristics

Of the 185 patients consecutively contacted, 120 were recruited. Fifty-six patients did not meet inclusion criteria, and 9 refused to participate. The excluded patients were as follows: 21 were in a nursing home, 11 were too ill to participate, 8 did not meet criteria for idiopathic Parkinson's disease, 8 were unable to be contacted, 4 did not speak English, 3 had MMSE scores < 21, and 1 died.

The demographic characteristics of the study population appear in Table 1. Sleep medication consisted of benzodiazepines, zolpidem, quetiapine, amitriptyline, and trazodone. Fifty patients (41.7%) had a lifetime history of psychiatric disorders, including depression (N = 34), anxiety (N = 29), schizophrenia (N = 1), and bipolar disorder (N = 1). Female gender was significantly correlated with psychiatric history $\chi^2(120) = 5.4$, df = 1, $p < .05$. Sixteen patients developed depression, and 10 patients developed anxiety after onset of Parkinson's disease. The results of the sleep and psychiatric assessments appear in Table 2.

Figure 1. Frequency of Nightmares in a Cohort of Patients With Parkinson's Disease

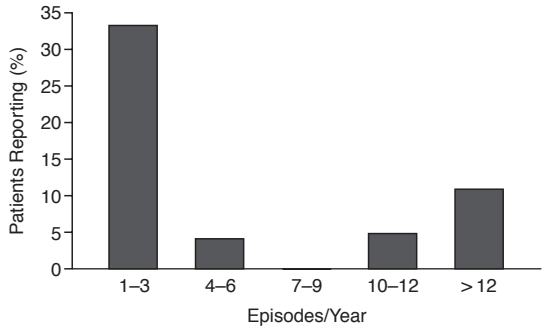
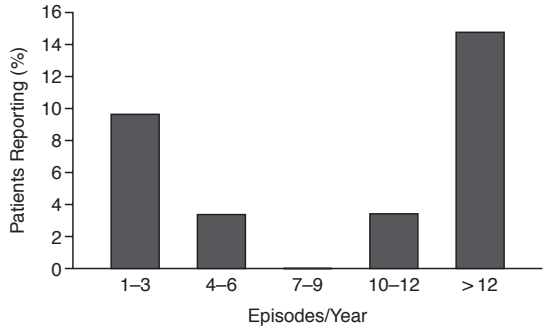


Figure 2. Frequency of RBD Episodes in a Cohort of Patients With Parkinson's Disease



Abbreviation: RBD = rapid eye movement (REM) sleep behavior disorder.

The frequency of nightmares is depicted in Figure 1. Forty patients (33%) reported having nightmares between 1 and 3 times a year. The frequency of RBD episodes is depicted in Figure 2. Seventeen patients (14.2%) reported having RBD episodes more than once per month, and of these, 9 (52.9%) had episodes at least 3 nights per week.

Predictors of Sleep Quality

Poor sleep quality (PSQI) significantly correlated with elevated depressive symptoms (HAM-D) $r = 0.60$, df = 118, $p < .001$; elevated anxiety symptoms (HAM-A) $r = 0.50$, df = 118, $p < .001$; increased anxiety (CAS) $r = 0.45$, df = 118, $p < .001$; duration of Parkinson's disease $r = 0.22$, df = 118, $p < .05$; psychiatric history $t = 3.5$, df = 117, $p < .001$; and sleep medication $t = 0.24$, df = 117, $p < .001$. Variables with nonsignificant findings ($p > .05$) were as follows: age, gender, stage of Parkinson's disease,

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L-dopa, dopamine agonist, nightmares, RBD, and PTSD. A backward linear regression analysis was carried out using PSQI scores as the dependent variable and HAM-D scores, HAM-A scores, CAS scores, duration of Parkinson's disease, psychiatric history, and sleep medication as independent variables. In the final model, HAM-D scores (β = 0.55, t = 8.0, $p < .001$) and sleep medication (β = –0.32, t = –4.6, $p < .001$) accounted for most of the variance in the correlation with PSQI scores ($R^2 = 0.46$, F = 50.1, df = 2,116; $p < .001$). None of the other variables remained significantly correlated.

Predictors of Daytime Somnolence

Daytime somnolence (ESS) significantly correlated with elevated depressive symptoms (HAM-D) r = 0.18, df = 118, $p < .05$; elevated anxiety symptoms (HAM-A) r = 0.19, df = 118, $p < .05$; duration of Parkinson's disease r = 0.19, df = 118, $p < .05$; dopamine agonist t = 2.3, df = 94, $p < .05$; nightmares t = 3.0, df = 118, $p < .01$; male gender t = 2.7, df = 118, $p < .01$; RBD t = 2.0, df = 118, $p < .05$; and PTSD t = 3.0, df = 8.5, $p < .05$. Variables with nonsignificant findings ($p > .05$) were as follows: age, stage of Parkinson's disease, CAS scores, psychiatric history, sleep medication, and L-dopa. A backward linear regression analysis was carried out using ESS scores as the dependent variable and HAM-D scores, HAM-A scores, duration of Parkinson's disease, dopamine agonist, nightmares, male gender, RBD, and PTSD as independent variables. In the final model, HAM-A scores (β = 0.31, t = 2.3, $p < .05$), male gender (β = –0.36, t = –2.8, $p < .01$), and duration of Parkinson's disease (β = –0.24, t = 2.0, $p < .05$) accounted for most of the variance in the correlation with ESS scores ($R^2 = 0.21$, F = 5.2, df = 3,59; $p < .01$). None of the other variables remained significantly correlated.

Predictors of Nightmares

Nightmares significantly correlated with elevated depressive symptoms (HAM-D) t = 2.7, df = 118, $p < .01$; elevated anxiety symptoms (HAM-A) t = 2.0, df = 118, $p < .05$; increased anxiety (CAS) t = 2.5, df = 118, $p < .05$; younger age t = –2.8, df = 118, $p < .01$; L-dopa $\chi^2(120) = 4.5$, df = 1, $p < .05$; psychiatric history $\chi^2(120) = 4.3$, df = 1, $p < .05$; and RBD $\chi^2(120) = 12.3$, df = 1, $p < .001$. Variables with nonsignificant findings ($p > .05$) were as follows: gender, duration of Parkinson's disease, sleep medication, dopamine agonist, and PTSD. A backward logistic regression analysis was carried out using nightmares as the dependent variable and HAM-D scores, HAM-A scores, CAS scores, age, L-dopa, psychiatric history, and RBD as independent variables. In the final model, RBD (odds ratio [OR] = 4.25, CI 95% 1.66 to 10.88, $p < .003$), HAM-D scores (OR = 0.89, CI 95% 0.82 to 0.97, $p < .008$), and L-dopa (OR = 0.27, CI 95% 0.08 to 0.87, $p < .03$) remained significantly correlated with nightmares ($\chi^2 = 24.3$, $p < .001$).

Predictors of RBD

RBD significantly correlated with male gender $\chi^2(120) = 12.2$, df = 1, $p < .001$; nightmares $\chi^2(120) = 12.3$, df = 1, $p < .001$; dopamine agonist $\chi^2(120) = 6.1$, df = 1, $p < .05$; and duration of Parkinson's disease t = 2.1, df = 50.5, $p < .05$. Variables with nonsignificant findings ($p > .05$) were as follows: HAM-D scores, HAM-A scores, CAS scores, age, stage of Parkinson's disease, psychiatric history, sleep medication, L-dopa, and PTSD. A backward logistic regression analysis was carried out using RBD as the dependent variable and male gender, nightmares, dopamine agonist, and duration of Parkinson's disease as independent variables. In the final model, the following variables remained significantly correlated with RBD ($\chi^2 = 29.8$, $p < .001$): male gender (OR = 6.10, CI 95% 1.98 to 18.83, $p < .002$), nightmares (OR = 4.59, CI 95% 1.77 to 11.96, $p < .002$), and duration of Parkinson's disease (OR = 0.91, CI 95% 0.82 to 0.99, $p < .04$).

Other Significant Findings

Nightmare distress significantly correlated with elevated depressive symptoms (HAM-D) r = 0.57, df = 118, $p < .001$; elevated anxiety symptoms (HAM-A) r = 0.54, df = 118, $p < .001$; and increased anxiety (CAS) r = 0.48, df = 118, $p < .001$. Stage of Parkinson's disease significantly correlated with increased depressive symptoms (HAM-D) r = 0.26, df = 118, $p < .01$; increased anxiety symptoms (HAM-A) r = 0.27, df = 118, $p < .01$; and greater anxiety (CAS) r = 0.18, df = 118, $p < .05$.

DISCUSSION

In this study, severity of depression and severity of anxiety were significantly associated with poor sleep quality, daytime somnolence, and nightmares in patients with idiopathic Parkinson's disease. Depressive symptoms and sleep medication were the most important risk factors for poor sleep quality. Previous studies found depression to be significantly associated with sleep disturbances in the Parkinson's disease population.[23–27] In contrast to our study, Menza and Rosen.[9] found that depression and anxiety did not contribute significantly to the overall variance in sleep quality; rather, age, L-dopa dose, and on/off phenomena were major determinants of sleep. The difference in our findings may be due, in part, to the different measures used to evaluate psychiatric symptoms. Menza and Rosen[9] used visual analog scales to assess depression and anxiety. These scales are self-rated and assess mood with a single item. In contrast, the HAM-D and HAM-A are physician-rated scales and evaluate severity of depression and anxiety with multiple items, providing a more detailed assessment of symptoms. Such measures may identify depression and anxiety more accurately. Unlike the study of Menza and Rosen, our study did not assess for on/off phenomena and L-dopa dose.

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Anxiety symptoms, male gender, and duration of Parkinson's disease were the most important risk factors for daytime somnolence. These variables accounted for only 21% of the variance, suggesting that other factors are important contributors to daytime sleepiness. These factors may include intrinsic abnormalities in Parkinson's disease, concurrent medical illness, and the effects of nocturnal sleep disturbance, which were not assessed. An association between male gender, duration of Parkinson's disease, and daytime sleepiness has been previously reported.[28] In our study, patients with greater anxiety symptoms had more daytime somnolence. This may be a consequence of the poor sleep quality experienced by patients with anxiety.

In contrast to other studies,[25,29] we found that neither sleep quality nor daytime somnolence was significantly associated with motor disease severity. Our findings agree with Tandberg et al.,[27] who also demonstrated lack of association between sleep disorders and stage of Parkinson's disease; rather, depressive symptoms were significantly correlated with sleep disorders. This finding suggests that depression may be a more important risk factor than disease severity for sleep disturbances in Parkinson's disease patients. Our finding of a significant association between stage of Parkinson's disease and severity of depression and anxiety suggests mood changes in Parkinson's disease are, in part, a reaction to motor disability.

Depressive symptoms, RBD, and L-dopa remained significant in predicting nightmares. Patients with depression may be more likely to report nightmares. In another study,[25] Parkinson's disease patients with higher depression scores had significantly more bad dreams compared with patients with lower depression scores. Previous studies found an association between L-dopa and nightmares in the Parkinson's disease population.[29,30]

RBD was the only sleep outcome measure that was not associated with depressive or anxiety symptoms. This finding is consistent with the ICSD-R diagnostic criterion for RBD stating that mental disorders are not associated with RBD symptoms.[8] Instead, we found male gender, nightmares, and duration of Parkinson's disease to be the most important risk factors for RBD. Previous studies demonstrated an overwhelming male predominance in RBD,[31–33] and Parkinson's disease duration has been associated with RBD.[33] In our study, the majority of RBD patients reported dreams that were aggressive and frightening in nature (unpublished data). These findings are consistent with the literature.[31–33]

Our data indicate that depression, anxiety, and nightmares are common in patients with idiopathic Parkinson's disease and often begin after onset of the disease. Approximately 40% of patients had a psychiatric history, and nearly half of these developed depression or anxiety after Parkinson's disease onset. Fifty-three percent of patients had nightmares. A review of the literature reveals a wide range in nightmare frequency in Parkinson's disease patients; estimates are between 5.7% and 32%.[29,30] One study reported a frequency similar to ours (48%), but this figure included patients with vivid dreams.[34] Our high frequency of nightmares is likely related to the use of prospective daily dream logs, in addition to retrospective self-reports, which increased detection of nightmares.

The majority of our patients had 1 to 3 nightmares a year, indicating that nightmares were uncommon. A study of nightmares in a normal control population found that only 8.3% of subjects had nightmares more than once a month.[35] In our study, patients with higher depression and anxiety scores were significantly more distressed by nightmares. Nightmare distress has been associated with depression and anxiety in normal control populations.[36,37]

The frequency of clinically defined RBD in our population (30%) is similar to that found in other studies[33,38] using polysomnography for RBD diagnosis.[38] In this study, the majority of patients with RBD had frequent episodes, occurring more than once a month, and half of these had episodes at least 3 nights per week. Frequent RBD episodes have been previously reported.[33]

Our results indicate that a high proportion of patients had significant problems with sleep quality (64.1%) and daytime somnolence (39.8%). This finding is consistent with studies showing a high prevalence of sleep disorders in Parkinson's disease patients.[28,29,34] The tendency of our patients to have mild depressive symptoms (43.3%), as rated by the HAM-D, is consistent with reports that most Parkinson's disease patients have less severe forms of depression.[4] However, in both the depression and anxiety rating scales, there is a wide range in scores, indicating the presence of clinically significant symptoms.

The strengths of this study are the relatively large sample and the comprehensive battery of evaluations examining both psychiatric symptoms and different aspects of sleep disturbance in Parkinson's disease patients. In particular, nightmares in Parkinson's disease have not previously been well characterized. To our knowledge, this is the first study to examine a potential association between depressive and anxiety symptoms and daytime somnolence, nightmares, and RBD in the Parkinson's disease population. Limitations of our study include lack of a healthy control group, the possibility of recall bias from use of questionnaires, and the fact that we did not use PSG to quantify sleep parameters. As PSG was not obtained, we may have underdiagnosed RBD; PSG has been shown to significantly increase the sensitivity of RBD diagnosis.[38] We did not include a healthy control group because our main focus was to evaluate potential associations between depression, anxiety, and sleep disturbances within the Parkinson's disease population.

Depression and anxiety are often underrecognized and undertreated clinically and not as well studied as the

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motor aspects of the disease.[39] Depression and anxiety contribute significantly to disability in Parkinson's disease,[40,41] and depression is the most important impairing factor for the quality of life in Parkinson's disease patients, even after accounting for motor disease severity.[42,43]

In conclusion, depression and anxiety may explain a significant part of sleep disorders in patients with Parkinson's disease. Future studies should investigate whether sleep disturbances improve in Parkinson's disease after treatment of depression and anxiety. While PSG is useful in identifying sleep apnea and RBD, it is not particularly valuable in assessing uncomplicated insomnia. Increased recognition and effective management of depression and anxiety are likely to improve the quality of life for Parkinson's disease patients.

Drug names: quetiapine (Seroquel), trazodone (Desyrel and others), zolpidem (Ambien).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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