Anhedonia, Depression, and Motor Functioning in Parkinson's Disease During Treatment With Pramipexole

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Anhedonia, a core symptom of depression, correlates with motor alterations in major depressive disorder and has been assumed to be frequent in depressed patients with Parkinson's disease (PD). In the present study, the authors assessed for the first time frequency of anhedonia in patients with idiopathic Parkinson's disease (N = 657) and the relationship of anhedonia and parkinsonian motor deficits during treatment with pramipexole. Mild depression was present in 47% of the patients and moderate to severe depression in 22%. Anhedonic individuals included 45.7% of all patients and 79.7% of depressed Parkinson's disease patients. Anhedonic Parkinson's disease patients had greater motor deficits, restrictions in activities of daily living, and depression compared to nonanhedonic patients. Frequency of anhedonia and depression was significantly reduced during treatment with pramipexole. Future studies should further investigate antianhedonic efficacy of dopamine agonists including pramipexole in depressed patients with Parkinson's disease.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2005; 17:214–220)

Depressive symptoms occur in about 45% of patients with Parkinson's disease (PD). They reduce subjective and objective quality of life independent of motor deficits.[1] Diagnosis of depression in Parkinson's disease patients relies particularly on subjectively experienced symptoms, including anhedonia, the reduced capacity to experience pleasure.

It has been postulated that experiencing joy and pleasure depends on dopaminergic reward mechanisms in the limbic system, which are thought to be the basis of motivation, drive, and activation.[2] In Parkinson's disease, degeneration of dopaminergic neurons involves motor structures, including basal ganglia, but also structures of the limbic system.[3] Degenerative processes in Parkinson's disease may affect dopaminergic reward mechanisms and lead to anhedonia, loss of motivation, avolition and apathy.[4] These pathophysiological mechanisms could explain effects of pramipexole, a novel dopamine agonist, on anhedonia and depression found in animal experiments[5,6] and patients with major depressive disorder.

Anhedonia, a core symptom of depression,[7] correlates

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with motor retardation in patients with major depressive disorder.[8] Anhedonia has been assumed to be a frequent symptom in depressed patients with Parkinson's disease.[9] Like in major depressive disorder, anhedonia may also have an impact on motor functioning and activities of daily living in Parkinson's disease. However, to our knowledge, no data exist regarding frequency and relevance of anhedonia in Parkinson's disease.

Therefore, the aim of this open study was to investigate depressive symptoms in Parkinson's disease and test the hypotheses that anhedonia is more frequent in patients with Parkinson's disease compared with healthy comparison subjects, that anhedonic patients with Parkinson's disease show more severe parkinsonian symptoms compared to nonanhedonic patients and that anhedonia is reduced during treatment with pramipexole.

METHODS

In this prospective, observational, open study, we included patients (N = 657) with clinical diagnosis of Parkinson's disease (presence of 2 of 3 cardinal features [tremor, bradykinesia, rigidity] and *L*-dopa responsiveness) at 298 study sites (in- and outpatients) if pramipexole as an add-on to L-dopa was clinically indicated (T1). Dosage was adjusted depending on efficacy and tolerability in weekly intervals allowing a maximal dose of 3 × 1.5 mg/day. Neurological and psychiatric examinations were performed at baseline (T1) and at the end of a maintenance period of 9 weeks on an average (T2). Exclusion criteria were psychotic symptoms (delusions, hallucinations, etc.), moderate to severe dementia and contraindications for pramipexole treatment including hypersensitivity to the drug. Healthy volunteers (N = 50) were recruited for comparison from employees of the University of Kiel and their relatives. Comparison subjects were excluded if they had any psychiatric or neurological disease at present or had a history of such a disease which was assessed by a standardized interview (MINI)[10] and motor scales (ESE)[11] and clinical examination.

For staging of the disease, we applied the Hoehn and Yahr Scale (ranging from 0 to 5; stage 1 = unilateral symptoms, stage 5 = restricted to wheelchair or bed if unsupported by others).[12] Trained observers rated severity of motor and nonmotor symptoms of Parkinson's disease using the Short Parkinson's Evaluation Scale (SPES) (range = 0 to 98, higher values representing more severe symptoms) and SPES subscales motor functioning, psychopathogy, depression, and activities of daily living.[13] Subjects were categorized as depressed on the basis of SPES depression scores (0 = no, 1 = mild, 2 = moderate, 3 = severe depressive symptoms). Anhedonia was assessed by the German version of the self-rating Snaith-Hamilton Pleasure Scale (SHAPS-D) (range = 0–14, higher values representing more severe anhedonia; cutoff score for anhedonia≥3).[14,15]

Statistical analysis included descriptive statistics and testing for normal distribution. We analyzed group differences using chi-square tests and unpaired and paired t tests (two-tailed). The upper limit for significance to reject H_0 was $p<0.05$. We analyzed correlations using Spearman correlation coefficient (r_s) (two-tailed, pairwise exclusion of missing data) where the upper level of significance to reject H0: $r_s = 1$ was set at $p<0.05$. In order to clarify the factor structure of the SHAPS-D in patients with Parkinson's disease, we performed a principal component analysis of the 14 items and evaluated the reliability of SHAPS-D with Cronbach alpha as measure of the internal consistency.

RESULTS

Each study site recruited 2.2 patients on average (SD 3.2, range = 1–40). The characteristics of all patients included are given in Table 1 and Figure 1. Most patients (86%) received comedication in addition to antiparkinson therapy. In addition, patients were treated with tri- and/or tetracyclic antidepressants (7.1%), hypnotics (3.6%), se-

TABLE 1. Characteristics of Parkinson's Disease Patients Included (mean SD, comorbid diseases >5%) and Healthy Comparison Subjects

	Patients (n = 657)	Comparison Subjects (n = 50)
Age (years)	67.7 ± 9.2	63.3 ± 7.4
Gender (female/male)	44/56 (%)	48/52 (%)
Comorbidity		
Hypertension	18.6 (%)	12.4 (%)
Coronary heart disease	14.8 (%)	8.9 (%)
Diabetes mellitus	7.6 (%)	6.8 (%)
SPES		
Total score	60.12 ± 13.53	
Motor functioning	30.14 ± 6.94	
Activities of daily living	16.50 ± 4.69	
Psychopathology	5.06 ± 1.60	
Depression	1.94 ± 0.78	

SD = standard deviation

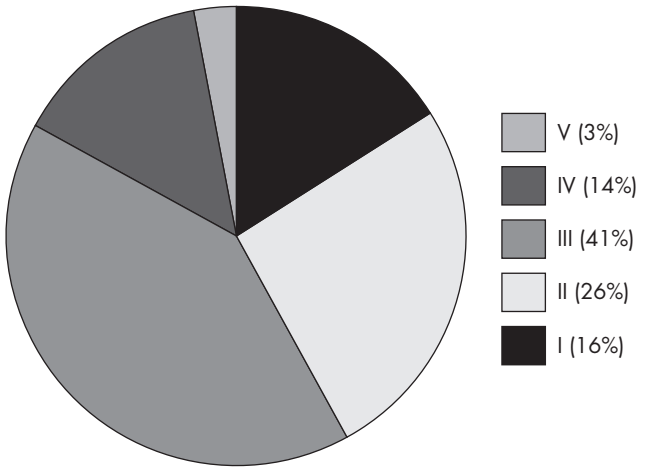
lective serotonin and/or norepinephrine reuptake inhibitors (3.4%), St. John´s Wort (2.2%), MAO-inhibitors (0.3%), and neuroleptics (0.3%).

All patients with Parkinson's disease (95.28% [N = 626]) included in the study (N = 657) completed the SHAPS-D Questionnaire. Cronbach alpha, a test for internal consistency, was 0.92 in nondepressed Parkinson's disease patients and 0.90 in depressed Parkinson's disease patients. Factor analysis (principal component analysis) showed significant loading of all items of the SHAPS-D on one factor which explained 75% of the total variance.

Snaith-Hamiltion Pleasure Scale-D scores (1.62 ± 1.57) of healthy volunteers (N = 50; age 63.3 ± 7.4 years, 48% female) differed significantly from scores (3.39 ± 3.68, $p<0.001$) of patients with Parkinson's disease (N = 626, age 67.7 ± 9.2 years). Analyzing depressed and nondepressed Parkinson's disease patients separately, we did not find a significant difference in SHAPS-D scores between healthy comparison subjects and nondepressed patients with Parkinson's disease (N = 488; 2.51 ± 4.02, $p>0.05$), but significantly higher scores in depressed patients with Parkinson's disease (N = 138; 6.52 ± 4.02, $p<0.0001$). Anhedonia was present in 79.7% of Parkinson's disease patients with depression.

We did not find a significant correlation between age and SHAPS-D scores either in the whole sample (N = 626; $r = 0.071$, $p = 0.07$) or in depressed (N = 138; $r = 0.136$, $p = 0.1107$) or nondepressed (N = 488; $r = 0.015$, $p = 0.7446$) patients with Parkinson's disease. Patients in earlier stages of the disease (Hoehn and Yahr < = 2) had anhedonia less often, compared with patients in more advanced (>2) stages (chi-square 20.81, df = 4, $p<0.001$).

FIGURE 1. Distribution of Stage I to V (Hoehn & Yahr) in the Total Sample of Parkinson's Disease Patients (N = 657)



We divided the total sample (N = 626) using the previously defined[12,13] cutoff score of ≥3 into an anhedonic subgroup (N = 286; 45.7%, score≥3) and a nonanhedonic subgroup (N = 340; 54.3%, score<3). Table 2 shows characteristics of the two subgroups and differences between them.

On the basis of SPES depression scores (0 = no, 1 = mild, 2 = moderate, 3 = severe depressive symtoms), 31% of the patients showed no depression, 47% mild, and 22% moderate to severe depression. We dichotomised the study population (N = 626) into a moderately to severely depressed subgroup (score≥2, N = 138, 22%) and a non- to mildly depressed subgroup (score<2, N = 488, 78%). Table 3 gives characteristics of the two subgroups and differences between them. If patients with mild depressive symptoms were included (score≥1), we allocated 69% to the depressed and 31% to the nondepressed subgroup.

The relationship between anhedonia (SHAPS-D) and symptoms of Parkinson's disease (SPES) is presented as a correlation matrix in Table 4. Significance of correlation did not change when we calculated partial correlation for age as the control variable. We calculated partial correlation between various variables and SHAPS-D for depression and motor functioning as control variables. When we controlled for depression, correlation between SHAPS-D and SPES total ($r_s = 0.23$, $p>0.05$), activities of daily living (ADL) ($r_s = 0.08$, $p>0.05$), and SPES motor functioning ($r_s = 0.16$, $p>0.05$) was not statistically significant. When we controlled for motor functioning, correlation was not significant between SHAPS-D and SPES total ($r_s = 0.11$, $p>0.05$), ADL ($r_s = 0.07$, $p>0.05$), but significant between SHAPS-D and depression ($r_s = 0.49$, $p>0.000$).

Dosage was adjusted depending on efficacy and tolerability in weekly intervals allowing a maximal dose of 3×1.5 mg/day. At T2, the average dose of pramipexole was 1.0 ± 0.6 mg/day (range = 0.3 to 4.2). Anhedonia was present in N = 286 (45.7%) patients at T1 and N = 160 (25.5%) at T2. In depressed PD patients (N = 138), frequency of anhedonia significantly decreased from 74.3% to 45.3% ($\chi 2 = 34.30$, df = 1, $p<0.001$), and in nondepressed Parkinson's patients (N = 488) from 34.6% to 18.3% ($\chi 2 = 60.377$, df = 1, $p<0.001$), respectively. Frequency of depression at T1 and T2 is depicted in Figure 2.

DISCUSSION

In the present study, we investigated for the first time frequency and severity of anhedonia in patients with Parkinson's disease compared to healthy comparison subjects, the relationship of anhedonia and severity of Parkinson's disease, and the course of anhedonia and depression during treatment with pramipexole. We found that 45.7% of all patients and 79.7% of depressed Parkinson's disease patients suffered from anhedonia. Anhedonic patients with Parkinson's disease showed significantly more severe motor deficits, more severe depression, and more restrictions in their activities of daily living. Frequency of anhedonia and depression was significantly reduced during treatment with pramipexole.

Anhedonia

Although it has been assumed that anhedonia is an important psychopathological feature of Parkinson's disease,[16] to our knowledge, no empirical data about frequency and severity of anhedonia have been available up to now. Anhedonia can be assessed and quantified as a subjectively experienced phenomenon independent of cultural or demographic characteristics using the SHAPS-D. We have translated this scale from the English original introduced by Snaith et al.[15] and showed its validaty and reliability before.[14] We are the first to apply the SHAPS-D to the examination of anhedonia in a large group of patients with Parkinson's disease. Of the 657 patients recruited, 626 patients completed the SHAPS-D questionnaire. This rate of 95.3% gives an in-

TABLE 2. Demographic and Psychometric Data (means ± SD) of Parkinson's Disease Patients (n = 626) With (score ⩽ 3) and Without (score <3) Anhedonia Measured Using the Snaith-Hamilton Pleasure Scale (SHAPS-D)

	ShAPS-D < 3 N = 340	SHAPS-D ⩾ 3 N = 286	
f/m	145/195	136/150	
Age	67.08 ± 8.95	68.04 ± 9.41	
SPES	55.34 ± 11.39	65.03 ± 13.47	T = −9.75, p < 0.0000
Motor functioning	28.00 ± 6.06	32.42 ± 7.00	T = −8.46, p < 0.0000
Psychopathology	4.42 ± 1.20	5.74 ± 1.60	T = −11.78, p < 0.0000
Depression	1.63 ± 0.64	2.30 ± 0.75	T = −12.04, p < 0.0000
ADL	15.16 ± 4.22	17.86 ± 4.52	T = −7.67, p < 0.0001
Stage (Hoehn & Yahr)	3.12 ± 1.00	3.40 ± 1.09	T = −2.09, p < 0.004

SPES-subscales: motor functioning, psychopathology, depression, activities of daily living (ADL)[11]

TABLE 3. Demographic and Psychometric Data (mean ± SD) of Nondepressed (SPES rating <2) and Depressed (SPES rating 2) Parkinson's Disease Patients (n = 626) Assessed Using the Short-Parkinson-Evaluation-Scale (SPES)

	Nondepressed N = 138	Depressed N = 488	
f/m	70/68	275/213	
Age	67.37 ± 9.13	68.81 ± 9.29	
SHAPS-D	2.05 ± 3.05	6.52 ± 4.02	T = −12.65, p < 0.000
SPES	57.17 ± 11.08	68.94 ± 14.16	T = −9.17, p < 0.000
Motor functioning	28.96 ± 6.40	33.76 ± 7.14	T = −7.13, p < 0.000
ADL	15.78 ± 4.25	18.54 ± 4.95	T = −6.46, p < 0.000
Stage (Hoehn & Yahr)	3.49 ± 0.96	4.05 ± 1.01	T = −5.71, p < 0.000

SPES-subscales: motor functioning, psychopathology, depression, activities of daily living (ADL)[11]; SD = standard deviation

TABLE 4. Correlation Between Anhedonia (SHAPS-D) and Symptoms of Parkinson's Disease (SPES) in Patients With Idiopathic Parkinson's Disease (correlation coefficient r_s)

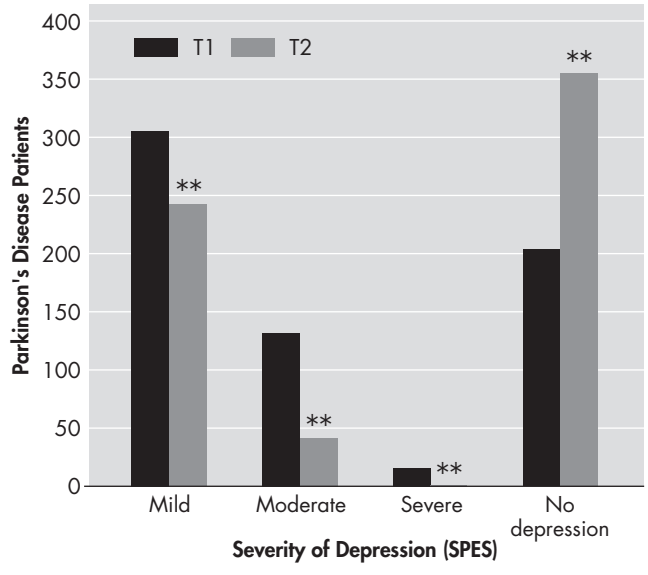
	SPES	MOTOR	ADL	PSYCHO	DEPR
SHAPS-D	0.39	0.35	0.29	0.48	0.50
SPES		0.90	0.89	0.64	0.43
MOTOR			0.71	0.47	0.33
ADL				0.53	0.30
PSYCHO					0.75

Significance for all correlations: p<0.000; SPES-subscales: motor functioning (MOTOR), psychopathology (PSYCHO), depression (DEPR), and activities of daily living (ADL)[11]

dication of the excellent applicability in this clientele. The analysis of the internal consistency of the SHAPS-D proves the reliability of the scale in patients with Parkinson's disease. This corresponds with previous findings in depressed and schizophrenic patients and healthy volunteers, respectively. Our data support the finding of a one-dimensional structure of SHAPS-D which we found in other populations before[14] and confirm findings with the original version.[15] The SHAPS-D has been found to be a useful change measure regarding subjectively experienced anhedonia in Parkinson's disease patients.

The significant correlation with depressiveness indicates valid recording of anhedonia as a core symptom of depression.[14,15] In addition, compared to healthy comparison subjects, anhedonia was not greater in nondepressed, but was greater in depressed Parkinson's disease patients. Previous studies reported anhedonia in 72% of patients with major depressive disorder.[8] In this study, anhedonia was present in 45.7% of all Parkinson's disease patients and in 79.7% of Parkinson's disease patients with depression. Therefore, severity of depression needs to be controlled for in future studies. Because 45.7% of the patients were anhedonic, our data confirm the assumption that anhedonia represents a frequent symptom[16] in patients suffering from advanced Parkinson's disease who were treated with the dopamine agonist pramipexole as add-on to *L*-dopa.

FIGURE 2. Frequency of Mild, Moderate and Severe Depression in Parkinson's Patients (N = 657) at the Time of Inclusion (baseline, T1) and at the End of the Study Period (T2) (* <0.05, **p<0.01)



Depression

Depression in Parkinson's disease may manifest secondary as a reaction to motor deficits and impairment of daily activities and social functioning. However, there are also indications of a primary manifestation of depression in Parkinson's patients involving monoaminergic pathways between brain stem nuclei and prefrontal and orbito-frontal cortical areas.[16] Findings on the prevalence of depression in Parkinson's disease vary considerably due to selection of the sample and method of assessing depression. The results of metaanalyses suggest a prevalence of about 45%.[17,18] Based on SPES ratings, we found mild depression in 47% and moderate to severe depression in 22% of the patients. Most previous studies report data from inpatient populations, whereas our patients were mostly outpatients with moderate to severe Parkinson's disease. Self-ratings revealed anhedonia, a core symptom of depression, in 45.7% of all patients and 79.7% of depressed Parkinson's disease patients. In future studies, these results need to be replicated using standardized observer- and self-rated depression scales. The nature of our Parkinson's disease population is biased to those enrolled in the open, observational trial with pramipexole. Epidemiological studies are needed to determine frequency of anhedonia and depression in PD patients using standardized diagnostic interviews.

In the survey by Richard and Kurlan,[19] neurologists of the Parkinson Study Group reported prescription of antidepressants in 26% of their patients with Parkinson's disease. In our study, 13% of the patients were treated with antidepressants. These findings indicate that antidepressant therapy may apply to patients with moderate and severe depression. Our data support previous surveys and the clinical impression that depression in Parkinson's disease is undertreated. Tri- and tetracyclic compounds are prescribed twice as often as the newer selective reuptake inhibitors. Selective serotonin reuptake inhibitors may cause worsening of motor symptoms. Therefore, neurological signs should be monitored carefully in cases where they are used as antidepressants in Parkinson's patients. Bupropion, a dopamine-selective antidepressant, appears to be effective in depression associated with Parkinson's disease. Since depression reduces quality of life of Parkinson's disease patients independently from the motor deficits,[20] future studies are needed to investigate the indication to treat mild depression in Parkinson's disease using newer

antidepressants with a more favorable side effect profile and specific effects of new dopamine agonists.

In patients suffering from major depressive disorder, we previously proved a close relationship between anhedonia and motor changes.[8] The results of the present study confirm that anhedonic patients with Parkinson's disease are more depressed, have more motor deficits and show more severe restrictions in the activities of daily living. Partial correlations, however, indicate that depressiveness represents a confounding variable in the relationship between anhedonia and motor functioning. Therefore, our results show the relevance of depression for deficits in motor function and daily activities and support the necessity of adequate antidepressant treatment in patients with Parkinson's disease.

Pramipexole

The degenerative process in Parkinson's disease involves dopaminergic neurons in the substantia nigra, in the limbic system and in other brain regions[3] and therefore may affect motivation and drive.[2] Anhedonia and depressiveness may warrant treatment with dopamine agonists. Animal experiments have shown specific effects of pramipexole, a nonergot dopamine agonist, on behavioral parameters thought to correspond to anhedonia and depression.[5] In addition, pramipexole appears to have antidepressive properties in patients with major depressive disorder.[21] In our study, anhedonia and depression were reduced during treatment with pramipexole as add-on to *L*-dopa. Our investigation has the known limitations of an open study design, and multiple study sites may increase the risk of site variations. A selection bias and spontaneous remission of symptoms cannot be excluded. Effects on depression should be tested using specific observer- and self-rated depression scales. Specificity of the effects of pramipexole on depression and anhedonia needs to be further evaluated in double-blind, controlled trials. However, the scope and strength of this study shows the course of anhedonia in a large number of patients during pramipexole treatment under routine conditions.

CONCLUSION

In conclusion, SHAPS-D is a practical, reliable instrument to assess anhedonia in patients with Parkinson's disease, as anhedonia is a frequent symptom in these patients. Anhedonic patients with Parkinson's disease have more severe motor deficits and restrictions in their activities of daily living than do nonanhedonic patients. Because of the high frequency and clinical relevance of anhedonia and the antidepressive and antianhedonic properties of pramipexole, further studies of efficacy and effectiveness of dopamine agonists in depression and anhedonia in patients with Parkinson's disease are warranted.

This study was supported by Boehringer Ingelheim, Germany.

The authors thank all doctors and patients involved for their cooperation in this investigation.

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