Effect of Reboxetine on Depression in Parkinson's Disease Patients

Matthias R. Lemke, M.D.

Background: Depression occurs frequently in patients with Parkinson's disease and appears to be associated with increased disability and reduced quality of life. Pharmacologic treatment with tricyclic antidepressants or serotonin reuptake inhibitors may produce adverse effects on cognition or motor functions in Parkinson's disease patients. The efficacy of reboxetine, a novel norepinephrine reuptake inhibitor, has been shown in major depressive disorder, with specific effects on motivation and negligible effects on psychomotor and cognitive function.

Method: The effects of reboxetine on depression were investigated in 16 patients with idiopathic Parkinson's disease in an open, prospective study. Prior antidepressant medication was stopped because of lack of efficacy or intolerable side effects. Severity of depressive symptoms was assessed by the Hamilton Rating Scale for Depression, the Self-Rating Depression Scale, the Snaith-Hamilton Pleasure Scale, and the Social Adaptation Self-Evaluation Scale during the study period of 4 weeks.

Results: A significant improvement in depression scores was observed after 4 weeks ($z = -3.31$, $p < .008$). In 1 subject, reboxetine treatment was discontinued because of psychotic symptoms. Seven patients experienced transient side effects, including restlessness, insomnia, and increased sweating. There were no significant changes in parkinsonian motor symptoms or dosage of levodopa.

Conclusion: Reboxetine appears to be effective and well tolerated in Parkinson's disease patients receiving 4 weeks of treatment of moderate-to-severe depression. There are good theoretical and clinical reasons, including pharmacologic specificity of effects and low incidence of side effects, to consider reboxetine for treatment of depression in Parkinson's disease.

(J Clin Psychiatry 2002;63:300–304)

Received Nov. 1, 2000; accepted Aug. 23, 2001. From the Department of Psychiatry, University of Kiel, Kiel, Germany.

Supported by a Research Grant from the Faculty of Medicine, University of Kiel (Motor Phenomena in Depression).

Dr. Lemke has received funding for clinical trials and symposia from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Lilly, Pharmacia, and Sanofi-Synthelabo.

The author thanks L. Friege, Ph.D., for support in statistical methods and all doctors and patients involved for their cooperation in this investigation.

Corresponding author and reprints: Matthias R. Lemke, M.D., Department of Psychiatry, University of Kiel, Niemannsweg 147, D-24105 Kiel, Germany (e-mail: mrlemke@psychiatry.uni-kiel.de).

Depression is the most common mental change in Parkinson's disease and occurs in approximately 40% to 50% of Parkinson's disease patients.[1] The profile of depressive symptoms in Parkinson's disease differs from idiopathic depression; symptoms include elevated levels of dysphoria, pessimism about the future, irritability, and sadness without guilt. The presence of depression in Parkinson's disease determines quality of life[2,3] and may correlate with functional impairment.[4] Depressed patients with Parkinson's disease have greater frontal lobe dysfunction, including reward and motivational systems, and greater involvement of dopaminergic and noradrenergic systems than nondepressed Parkinson's disease patients.[5] Forebrain dopaminergic systems play a key role in motivation and the incentive to act,[6] and abnormalities reduce effects of reward mechanisms, resulting in anhedonia and loss of motivation. Depressed Parkinson's disease patients have a remarkable cell loss in the locus ceruleus, the source of norepinephrine, compared with nondepressed patients.[5]

Antidepressants are effective in relieving depressive symptoms in Parkinson's disease,[7] but their use may be limited by unwanted side effects. Tricyclics can be associated with anticholinergic side effects, and serotonin reuptake inhibitors may worsen parkinsonian motor functions.[8] The efficacy and tolerability of reboxetine, a norepinephrine reuptake inhibitor, have been shown in major depressive disorder, dysthymia,[9] and in a single case report of depression in Parkinson's disease.[10] This novel antidepressant shows negligible effects on psychomotor and cognitive function[11] and may be especially effective in improving negative self-perception and lack of motivation toward action.[12] An open trial was performed to assess the effects and tolerability of reboxetine treatment of depression in

Parkinson's disease after prior treatment with tricyclic antidepressants or serotonin reuptake inhibitors was stopped.

METHOD

In this open trial, consecutive patients were selected at the Department of Psychiatry, University of Kiel (Germany) from the inpatient unit, outpatient section, and liaison service. Patients were included if they fulfilled the following criteria: diagnosis of idiopathic Parkinson's disease (presence of 2 of 3 cardinal symptoms [tremor, bradykinesia, rigidity] and levodopa responsiveness) and a stable antiparkinsonian drug regimen with levodopa 2 weeks before initiation of reboxetine treatment, DSM-IV criteria for major depressive disorder, and moderate-to-severe depression based on a 17-item Hamilton Rating Scale for Depression (HAM-D)[13] score > 17. Self-rated depression was documented using the Self-Rating Depression Scale (SDS)[14]; anhedonia, using the Snaith-Hamilton Pleasure Scale (SHAPS-D[15,16]; range, 0–14, with higher values indicating greater anhedonia); and social activity level, using the Social Adaptation Self-Evaluation Scale (SASS)[17] (range, 0–60, with lower values indicating greater impairment). Parkinson's disease was staged according to criteria developed by Hoehn and Yahr (range, 0–5; stage 1 = unilateral involvement, stage 5 = confinement to bed/wheelchair).[18] Motor symptoms were scored using the Unified Parkinson's Disease Rating Scale part III, motor function (UPDRS-III[19]; range, 0–56, with higher numbers indicating greater impairment).

All patients had received at least 1 prestudy treatment with antidepressant medication, which was discontinued because of insufficient clinical improvement or intolerable side effects. The following exclusion criteria applied: elevated blood pressure, cardiac arrhythmia, epileptic seizure disorder, or other neuropsychiatric disorders that included psychotic features and dementia. All patients gave informed consent after the study procedure and possible unwanted drug effects were fully explained.

All other antidepressant medication was discontinued before start of treatment with reboxetine. Reboxetine was started at a dosage of 2 mg once a day. The reboxetine dosage was increased until improvement was noted or intolerable side effects occurred. Depending on tolerability, concomitant treatment with zolpidem or diazepam for problems with sleep was initiated if clinically necessary.

Severity of depression was evaluated using the HAM-D, SHAPS-D, SDS, and SASS. Psychopathologic symptoms were assessed at baseline (T0) using the HAM-D, and treatment with reboxetine was started. Subsequent ratings were completed on days 7 (T1), 14 (T2), 21 (T3), and 28 (T4) by a research psychiatrist (M.R.L.). Adverse effects, tolerability, and neurologic symptoms were observed on these days as well. Laboratory tests for routine hematology and blood and urine biochemistry were also performed on these days. The results are presented as mean ± SD. Statistical comparisons between pretreatment and posttreatment scores were made using the Wilcoxon signed rank test. Levels of significance were corrected by Bonferroni adjustment (type I error) since multiple parameters (i.e., 6) were compared. Therefore, the upper level for significance to reject the null hypothesis was set at $p < .008$ (Bonferroni correction, $p < .05/6$).

RESULTS

Sixteen patients, satisfying the inclusion criteria, entered the study. Main characteristics such as age, severity of motor impairment, prior medication, dosages of reboxetine and levodopa, and total HAM-D scores for the 15 patients who completed the study are depicted in Table 1. Unsuccessful antidepressant treatment prior to the experimental period was discontinued. The starting dose of reboxetine was 2 mg daily for all subjects. The daily dose was gradually increased to a mean of 6.13 mg (range, 4–8 mg) at T4. Three patients were receiving concomitant treatment with zolpidem (mean daily dosage = 3.4 mg; range, 2–5 mg) at T4.

Mean total HAM-D scores at T4 (12.20 ± 3.27) showed a mean decrease of 32.28% (range, 6.25–50) compared with values at T0 (18.60 ± 2.99) ($z = –3.31$, $p < .008$). Changes in HAM-D factor scores are shown in Figure 1. At T4, scores for the HAM-D inhibition (2.33 ± 1.17), anxiety (2.80 ± 2.39), and somatic symptoms (3.05 ± 1.50) factors were reduced by 62.17% ($z = –3.40$, $p < .008$), 38.27% ($z = –2.41$, $p < .008$), and 45.54% ($z = –2.93$, $p < .008$), respectively, expressed as percentage decrease from baseline scores at T0 (inhibition, 6.0 ± 1.51; anxiety, 4.47 ± 1.64; and somatic symptoms, 5.60 ± 1.40). However, the mean score for the HAM-D agitation factor did not show significant alterations between T0 (2.60 ± 1.35) and T4 (2.40 ± 1.05) ($z = –0.72$, $p > .008$).

Compared with baseline levels, there were no significant differences in SDS scores (T0, 53.86 ± 5.94; T4, 47.14 ± 6.85; $z = –2.29$, $p > .008$), but significant changes in SHAPS-D scores (T0, 6.13 ± 2.79; T4, 3.21 ± 1.36; $z = –3.08$, $p < .008$), and SASS scores (T0, 20.60 ± 5.22; T4, 30.21 ± 4.33; $z = –3.06$, $p < .008$) were found after the treatment period with reboxetine.

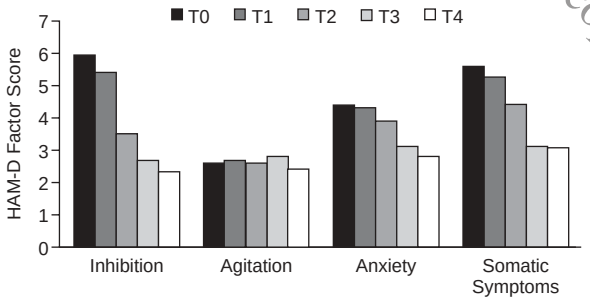
In 1 patient, treatment with reboxetine was discontinued prematurely due to manifestation of delusions and visual hallucinations. In all patients, blood count and biochemistry showed no significant changes during the study period. No effects on urinary functions were observed. Differences in total UPDRS-III motor scores between T0 (18.06 ± 2.71) and T4 (17.13 ± 2.82) ($z = –2.12$, $p > .008$) and levodopa dosages between T0 (373.33 ± 88.37) and T4 (376.66 ± 79.88) ($z = –2.43$, $p > .008$) were not statistically significant. Two patients presented

Table 1. Main Characteristics of Parkinson's Disease Patients (N = 15), Medication, and Treatment Response[a]

								Reboxetine Treatment			Total HAM-D[d] Score	
Patient	Age (y)	Sex	Duration of Illness (y)	Stage of Motor Impairment[b]	UPDRS-III Score[c]	Levodopa (mg/d)	Prior Medication	Maximum Dose (mg/d)	Adverse Effects	Concomitant Medication	Pretreatment	Posttreatment
1	68	F	2	2	20	350	Amitriptyline	4	Sweating	…	14	8
2	57	F	1	2	23	400	Amitriptyline Paroxetine	8	Insomnia, restlessness	Zolpidem …	21	10
3	75	F	3	2.5	19	350	Fluoxetine	6	…	…	21	12
4	63	M	4	3	18	300	Amitriptyline	6	Tremor, agitation	…	15	12
5	63	M	3	3	20	450	Doxepin	4	…	…	22	15
6	72	F	2	2	12	400	Trimipramine	4	…	…	16	7
7	66	M	6	2.5	21	550	Amitriptyline Fluoxetine	8	Tremor, restlessness, sweating, insomnia	Zolpidem	26	16
8	65	M	3	3	18	500	Amitriptyline	8	Restlessness	…	19	12
9	59	F	1	2	14	300	Doxepin	6	…	…	18	9
10	73	F	5	3	19	250	Doxepin Fluoxetine	4	Tremor, agitation	…	15	15
11	61	F	4	2.5	16	450	Sertraline	6	Sweating	…	18	9
12	67	M	3	2	17	350	Amitriptyline	8	…	…	20	18
13	66	M	2	2	19	250	Citalopram	8	Insomnia	Zolpidem	19	11
14	73	M	3	3	18	300	Paroxetine	6	…	…	19	13
15	75	F	4	2	17	400	Fluoxetine	6	…	…	17	10

[a]Abbreviations: HAM-D = Hamilton Rating Scale for Depression, UPDRS-III = Unified Parkinson's Disease Rating Scale part III, motor function.
[b]As defined by Hoehn and Yahr.[18] Range, 0–5; stage 1 = unilateral involvement, stage 5 = confinement to bed/wheelchair.
[c]Range, 0–56; higher numbers indicate greater impairment.
[d]17 items. Range, 0–52; higher numbers indicate greater severity of depression.

Figure 1. Effect of Reboxetine on Hamilton Rating Scale for Depression (HAM-D)[13] Scores in Depressed Parkinson's Disease Patients (N = 15)[a]



[a]Mean HAM-D factor scores at different timepoints (T0 = before treatment, T1–T4 = 1–4 weeks after initiation of treatment) during treatment with reboxetine.

with transient increase of hand tremor. Slight agitation, the feeling of restlessness, and sweating occurred temporarily in 7 patients and were reversible after modification of dosage.

DISCUSSION

In the present study, the efficacy and tolerability of reboxetine were investigated in Parkinson's disease patients with depression. In these patients, prestudy treatment with other antidepressants was stopped because of lack of efficacy or intolerable side effects. Scores of observer-rated, but not self-rated depression, and of anhedonia and self-assessed social impairment were significantly lower after 4 weeks of treatment. Scores for the HAM-D inhibition, anxiety, and somatic symptoms factors, but not the agitation factor, were significantly reduced. There were no significant changes in motor symptoms or dosage of antiparkinsonian medication during the study period. In 1 patient, treatment was discontinued because of occurrence of psychotic symptoms.

The selection of the right antidepressant medication in Parkinson's disease should be based on the following considerations: (1) Is the medication effective in treatment of depressive symptoms associated with Parkinson's disease? (2) Does the medication affect parkinsonian motor symptoms? (3) Does the concomitant antiparkinsonian medication need adjustment? There is a lack of systematic clinical trials investigating these issues. Only few double-blind studies exist, and in most investigations depressive and parkinsonian symptoms are not assessed with standardized instruments.[5,20]

Tricyclic antidepressants have been shown to be efficacious in treatment of depression in Parkinson's disease. However, their use is largely avoided because of their risk of anticholinergic side effects, including worsening of cognitive functions and orthostatic hypotension.[1] Selective serotonin reuptake inhibitors have efficacy comparable to that of tricyclic antidepressants, but a better safety profile. They are considered first-line treatment of depression in Parkinson's disease.[21] However, these drugs have been repeatedly reported in case reports as potential inducers of parkinsonian motor symptoms or of the rare serotonergic syndrome.[1] In the present study, treatment

with reboxetine did not significantly change motor functions of Parkinson's disease patients. However, we can not conclude from these results that motor functions were equal before and after the study period, because type II error cannot be excluded by this study design. Case reports indicate that the antidepressant mirtazapine may have beneficial effects on different types of tremor.[22] Effects of antidepressants on parkinsonian motor dysfunction need further systematic studies in larger samples.

Efficacy and tolerability of reboxetine, a norepinephrine reuptake inhibitor, have been shown in major depression and dysthymia.[9] A recently published case study[10] reported efficacious and well-tolerated treatment of depression in Parkinson's disease with reboxetine. Reboxetine may be especially effective in improving negative self-perception and lack of motivation toward action.[23] Lack of motivation to act is a characteristic symptom in depressed Parkinson's disease patients and may be related to greater frontal lobe dysfunctions including reward and motivational systems and greater involvement of dopaminergic and noradrenergic systems in depressed than in nondepressed Parkinson's disease patients.[5] In our study, reboxetine was effective in treatment of depression including inhibition and somatic symptoms, anhedonia, and social activities. All patients received stable dosages of levodopa, which were not significantly altered during the treatment with reboxetine. Further studies about the course of depression in Parkinson's disease patients treated with other antiparkinsonian medication, including novel dopamine agonists, are needed. In the present trial, all patients received treatment with tricyclics or serotonin reuptake inhibitors prior to reboxetine treatment. Further studies are necessary to evaluate the effects of first-line treatment with reboxetine in Parkinson's disease. Parkinson's disease patients included in the present study suffered from moderate Parkinson's disease, and effects in advanced Parkinson's disease need further evaluation.

The sensitivity to medication effects may be higher in elderly patients. The dosage of reboxetine was increased balancing therapeutic and unwanted effects. The main adverse effects, seen in only a few patients, were mild-to-moderate agitation, sweating, and insomnia. Most of these effects were temporary and reversible after adjustment of dosage. The medication with reboxetine had to be discontinued in 1 patient because of development of hallucinations and delusions. It remains uncertain whether these psychotic symptoms occurred spontaneously or were related to pharmacodynamic or pharmacokinetic effects of the antidepressant medication. No alterations in cognitive or psychomotor functions were reported. There are insufficient data regarding the clinical significance of depression scores in Parkinson's disease patients and the appropriate length of the study periods. Because of comorbidity, even small changes may be clinically significant. Efficacy of treatment may increase with longer study periods. However, these issues need to be studied further. Because of the open study design, which included lack of both a control group and blinding, selection and treatment biases may have influenced the results of this trial. However, this is the first reported series of depressed Parkinson's disease patients who have been treated with reboxetine; this study showed that reboxetine seems to be reasonably well tolerated in a small number of patients with Parkinson's disease when taken over 4 weeks. Randomized, double-blind studies will further clarify the efficacy and tolerability of reboxetine in these patients.

On the basis of this trial, selection of reboxetine as antidepressant medication in Parkinson's disease can be considered for the following reasons: (1) Reboxetine appears to be effective in treatment of depression in Parkinson's disease, a finding that needs to be shown in randomized, controlled clinical trials. (2) In the present trial, reboxetine did not seem to affect parkinsonian motor symptoms. (3) Concomitant antiparkinsonian medication did not need adjustment.

In conclusion, there are good theoretical and clinical reasons, including pharmacologic specificity of effects and low incidence of side effects, to consider reboxetine for treatment of depression in Parkinson's disease. On the basis of this open trial, assumed effects of reboxetine on motivation and social functioning, and established noradrenergic mechanisms involving reward and motivational systems in depressed Parkinson's disease patients, further, systematic controlled studies are warranted to evaluate the effects of reboxetine in the treatment of depression associated with Parkinson's disease.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), diazepam (Valium and others), doxepin (Sinequan and others), fluoxetine (Prozac and others), mirtazapine (Remeron), paroxetine (Paxil), sertraline (Zoloft), trimipramine (Surmontil), zolpidem (Ambien).

REFERENCES

1. Allain H, Schuck S, Mauduit N. Depression in Parkinson's disease [editorial]. BMJ 2000;320:1287–1288
2. Kuopio AM, Marttila RJ, Helenius H, et al. The quality of life in Parkinson's disease. Mov Disord 2000;15:216–223
3. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry 2000; 69:308–312
4. Brown RG, MacCarthy B, Gotham AM, et al. Depression and disability in Parkinson's disease: a follow-up of 132 cases. Psychol Med 1988;18: 49–55
5. Cummings JL. Depression and Parkinson's disease: a review. Am J Psychiatry 1992;149:443–454
6. Taylor AE, Saint-Cyr JA. Depression in Parkinson's disease: reconciling physiological and psychological perspectives. J Neuropsychiatry Clin Neurosci 1990;2:92–98
7. Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. BMJ 1995;310:1433–1438
8. Richard IH, Kurlan R, for the Parkinson Study Group. A survey of antidepressant drug use in Parkinson's disease. Neurology 1997;49:1168–1170
9. Burrows GD, Maguire KP, Norman TR. Antidepressant efficacy and tolerability of the selective norepinephrine reuptake inhibitor reboxetine:

a review. J Clin Psychiatry 1998;59(suppl 14):4–7
10. Lemke MR. Reboxetine treatment of depression in Parkinson's disease [letter]. J Clin Psychiatry 2000;61:872
11. Hindmarch I. The effects of antidepressants on psychomotor function with particular reference to reboxetine. Eur Neuropsychopharmacol 1997;7 (suppl 1):S17–S21
12. Dubini A, Bosc M, Polin V. Noradrenaline-selective versus serotonin-selective antidepressant therapy: differential effects on social functioning. J Psychopharmacol 1997;11:S17–S23
13. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
14. Zung WWK, Richards CB, Short MJ. Self-rating scale in an outpatient clinic. Arch Gen Psychiatry 1965;13:505–515
15. Snaith RP, Hamilton M, Morley S, et al. A scale for the assessment of hedonic tone: the Snaith-Hamilton Pleasure Scale. Br J Psychiatry 1995; 167:99–103
16. Franz M, Lemke MR, Meyer T, et al. German version of the Snaith-Hamilton-Pleasure Scale (SHAPS-D): anhedonia in schizophrenic and depressive patients. Forschr Neurol Psychiatr 1998; 66:407–413
17. Bosc M, Dubini A, Polin V. Development and validation of a social functioning scale, the Social Adaptation Self-evaluation Scale. Eur Neuro psychopharmacol 1997;7(suppl 1):S57–S70
18. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427–442
19. Fahn S, Elton RL, and members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, et al, eds. Recent Developments in Parkinson's Disease, vol 2. New York, NY: Macmillan; 1987:153–164
20. Klaassen T, Verhey FR, Sneijders GH, et al. Treatment of depression in Parkinson's disease: a meta-analysis. J Neuropsychiatry Clin Neurosci 1995;7:281–286
21. Zesiewicz TA, Gold M, Chari G, et al. Current issues in depression in Parkinson's disease. Am J Geriatr Psychiatry 1999;7:110–118
22. Pact V, Giduz T. Mirtazapine treats resting tremor, essential tremor, and levodopa-induced dyskinesias [letter]. Neurology 1999;53:1154
23. Dubini A, Bosc M, Polin V. Do noradrenaline and serotonin differentially affect social motivation and behaviour? Eur Neuropsychopharmacol 1997;7(suppl 1):S49–S55