

# Sertraline in Parkinson's Disease

Okan Dođu M.D.<sup>1</sup>, Serhan Sevim M.D.<sup>1</sup>, Özmen Metin<sup>2</sup>

## ABSTRACT:

### SERTRALINE IN PARKINSON'S DISEASE

**Objective:** Depression is the most common psychiatric disorder in Parkinson's disease (PD). Selective serotonin reuptake inhibitors (SSRIs) are currently used for treating depression in PD. Many cases of extrapyramidal side effects and exacerbation of PD symptoms due to SSRIs have been reported. The aim of the present study was to investigate the effect of sertraline on motor performance and depressive symptoms in a group of depressed PD patients. **Method:** Twentyfive, nonfluctuating PD patients with depression or dysthymic disorder according to the DSM-IV criteria were enrolled in the study. Montgomery-Asberg Depression Rating Scale (MADRS), Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn-Yahr Scale were used for the assessments of depression and parkinsonism respectively. Cognitive functions were assessed by Kökmen's Short Test of Mental Status. Patients were given 50mg/d sertraline for 12 weeks. **Results:** Twentyone patients (12 men, 9 women) completed the study (mean age±SD: 65.09±10.3 years, mean PD duration±SD: 44.2±27.2 months). Mean baseline MADRS score (24.8±7.36) was significantly reduced (18.04±5.9) (p=0.000) and UPDRS score remained stable. One patient did show an increase of parkinsonian tremor. Three patients excluded from the study due to side effects of sertraline and one patient did not come to the final visit was excluded from the study. **Conclusion:** The results of the present study suggest that sertraline does not worsen motor performance and may be useful in the treatment of depression in PD.

**Key Words:** Parkinson's disease, depression, selective serotonin reuptake inhibitors, sertraline

**Bull Clin Psychopharmacol 2002;126-129**

## INTRODUCTION

Depression is the most common psychiatric disturbance in patients with Parkinson's disease (PD) (1). According to the published studies, the prevalence of depression ranges between 20 to 90% (2). The average rate of depression in PD was found 40% (1). The discrepancy between the rates of depression in PD may be due to differences in definitions of depression applied or in the rating scales used. The half of the patients with depression in PD met criteria for major depression and the other half met criteria for dysthymic disorder (1). Selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat depression in PD but there have been no controlled trials available evaluating their safety and efficacy in this condition. In addition, many cases of extrapyramidal side effects including parkinsonism, dystonia, myoklonus and dyskinesia related to SSRIs have been reported (3). There are also studies showing that SSRIs could exacerbate parkinsonian symptoms in PD (4). The serotonin syndrome may also occur in patients concurrently taking SSRIs and selegiline (5,6).

Sertraline is a relatively selective serotonin reuptake inhibitor with some dopamine reuptake inhibitor activity (7). There are some reports claiming that sertraline has a good tolerability and efficacy in the treatment of depression in PD (8) but also some others showing that sertraline can induce parkinsonism (9,10).

In this study we aimed to investigate the effect of sertraline on motor performance and depressive symptoms in a group of depressed patients with PD.

## METHOD

### Subjects

A total of 25 consecutive non-fluctuating PD patients with depression were recruited from the Movement Disorder Clinic at Mersin University Hospital. PD was diagnosed according to the criteria of the UK Parkinson's Disease Society Brain Bank (11). All patients had at least two of four cardinal features of PD (bradykinesia, rigidity, tremor and postural instability) and either major depression or dysthymic disorder meeting Diagnostic and Statistical Manual of Mental

<sup>1</sup>Department of Neurology, <sup>2</sup>Department of Psychiatry, Mersin University School of Medicine, Mersin / İçel, Turkey.

Address reprint requests to: Okan Dođu M.D., Department of Neurology, Mersin University School of Medicine, Zeytinbahçe Cad. 33070 Mersin / İçel, Turkey. Phone: +90 (324) 337 4300 Fax: +90 (324) 337 4305 E-mail: okandogu@mersin.edu.tr

Date of acceptance: 24.06.2002

Disorders, 4th edition, revised (DSM-IV-TR) criteria. Depression was evaluated by Montgomery-Asberg Depression Rating Scale (MADRS) which is a validated screening and diagnostic scale for depression in PD (12). Parkinsonian symptoms were assessed by Unified Parkinson's Disease Rating Scale Part III (UPDRS) (13) and Hoehn-Yahr scale (14). The UPDRS is currently a standard and widely used scale for Parkinson's disease research. It has successfully met criteria for inter-rater reliability and validity. The UPDRS is composed of 42 items that includes four sections (I. Mentation, behavior and mood; II. Activities of daily living; III. Motor examination and IV. Complications of therapy) and 42 items. Each item in the first three sections are rated from 0 (normal) to 4 (severe). The Part III of the UPDRS has 14 items for evaluating bradykinesia, tremor, rigidity, speech, facial expression, postural stability and gait. Patients were evaluated for cognitive state by using Turkish version of Kökmen's Short Test of Mental Status (STMS) (15). The cut-off score for the STMS is 29 and the patients below this score were considered demented and were excluded from the study. The patients were given full information about the study protocol and they gave informed consent were obtained. During the study period the doses of antiparkinsonian medications were held constant. The possible effect of sertraline on motor performance in PD may lead to difficulties in evaluating patients therefore patients with motor fluctuations were not included in the study. In order to avoid interaction between selegiline and sertraline, patients on selegiline were not included in the study.

After baseline assessments, patients with depression took 50 mg oral sertraline in each morning for 12 weeks. Patients underwent an evaluation at a final visit 12 week later. Each evaluation was performed at 10.00 AM. All the measurements were carried out by an trained neurologist who was blind to the aim of the study.

Statistical analysis was performed with SPSS 9.05 software. The results of descriptive analysis are given as the mean and standard deviations. Mean baseline and final visit UPDRS and MADRS scores were compared by using Wilcoxon Rank test.  $p < 0.05$  was set as point of significance.

## RESULTS

A total of 21 depressed PD patients (12 men, 9 women) completed the study. Mean age was

65.09±10.3 years and mean PD duration was 44.2±27.2 months. Of these, 18 were receiving levodopa-benserazide at a mean daily dose of 377.9±245.6 mgs. In addition to levodopa, 7 (33.3%) patients were on piribedil, 6 (28.6%) patients were on pergolide and 2 (9.5%) patients were on lisuride therapy. Eight (38.1%) patients were not taking dopamine agonist therapy. Mean Hoehn-Yahr stage was 1.92±0.6 (range 1-3). Add-on therapy with sertraline did not significantly change UPDRS scores ( $p > 0.05$ ) (Table 1). Analysis of UPDRS subscores for rigidity, bradykinesia and tremor also did not demonstrate any worsening (Table 1). In one patient (4.7%) we found an increased parkinsonian tremor (UPDRS tremor subscore was 9 at baseline and 14 at final visit). MADRS scores significantly improved from baseline to final visit ( $p = 0.000$ ). MADRS scores were ameliorated in 15 subjects, were unchanged in two subjects, and same in one subject.

Three patients excluded from the study due to side effects of sertraline. One patient discontinued after the first dose because of the abdominal pain and nausea. Another two discontinued after one week due to side effects of nausea and vomiting. Another patient did not come to the final visit and was excluded from the study.

## DISCUSSION

In this open-label trial, we found that sertraline at a dose of 50 mg/day did not worsen motor performance in depressed nonfluctuating PD patients. In addition, in these patients sertraline significantly reduced depressive symptoms assessed by MADRS. Sertraline was generally well tolerated, but three (12%) of 25 patients discontinued medication because of side effects.

In one patient (4.7%), we observed an increased parkinsonian tremor. The tremor returned to baseline score in one month after cessation of the sertraline. There are some reports on worsening of motor function after the use of SSRIs such as fluoxetine, paroxetine and fluvoxamine (4,16-20). There are also studies evaluating fluoxetine, sertraline and paroxetine on motor symptoms and depression in PD and found no significant increase in parkinsonian symptoms (21-23). Methodological differences can explain these varying results. In some studies, the primary endpoint was the antidepressant efficacy of the SSRIs in patients

**Table 1. MADRS, UPDRS and UPDRS bradykinesia, rigidity and tremor subscores at baseline and at final visit.**

	Baseline (Mean±S.D.)	Endpoint (Mean±S.D.)	Z	P
MADRS	24.8±7.36	18.04±5.90	3.817	0.000
UPDRS	24.52±10.8	24.04±10.71	0.843	0.39 (NS)
UPDRS-Bradykinesia subscore	10.66±5.18	10.8±5.34	1.134	0.25 (NS)
UPDRS-Rigidity subscore	3.47±1.83	3.61±1.85	1.340	0.18 (NS)
UPDRS-Tremor subscore	4.47±4.55	4.76±4.55	1	0.317 (NS)

NS= not significant

with PD, whereas in others the aim was to assess the effect on motor performance. The worsening of parkinsonism or de novo developing of parkinsonism were sometimes reported only in isolated cases.

In this study a patient showed marked deterioration of tremor with the use of sertraline. The exact mechanism of such effect is not known. In a study of evaluating the effects of add-on therapy with fluoxetine in patients with PD, Monastruc et al. (22) found no significant increase of parkinsonian symptoms after a 1-month treatment but also interestingly found reduced tremor subscores. They could not make a clear explanation for this surprising result. Some authors concluded that SSRIs-induced worsening of motor function could be explained by dopamine-antagonistic activity of such compounds (24,25). Di Rocco et al. (9) performed an in vivo study of the effect of sertraline on dopamine metabolism and found that in animals pre-treated with sertraline, striatal dopamine, dopamine

metabolites and serotonin metabolite 5-hydroxy indol acetic acid (5-HIAA) levels were significantly decreased compared to control animals. They concluded that sertraline had an effect on dopamine metabolism, which may alter function in the striatum and induce a parkinsonian syndrome.

In conclusion, present study suggests that sertraline at the dosage of 50 mgs/d does not exacerbate parkinsonian symptoms. The deterioration of parkinsonian tremor in one single patient was reversible with the withdrawal of the drug. The results of the study also suggest that sertraline may be useful in the treatment of depression in patients with PD. The limitations of this study are the small sample size and possibility of placebo effect, which is common in any medication trial. Thus, controlled trials on larger populations are needed to confirm both efficacy of sertraline and the effect on parkinsonism in depressed patients with PD.

## References:

- Cummings JL. Depression and Parkinson's disease; A review. *Am J Psychiatr* 1992;149:443-454.
- Gotham AM, Brown RG, Marsden CD. Depression in Parkinson's disease: a quantitative and qualitative analysis. *J Neurol Neurosurg Psychiatry* 1988;51:1498-1502.
- Leo RJ. Movement disorders associated with the serotonin selective reuptake inhibitors. *J Clin Psychiatry* 1996;57:449-454.
- Chouinard G, Sultan S. A case of Parkinson's disease exacerbated by fluoxetine. *Hum Psychopharmacol* 1992;7:63-66.
- Suchowersky O, de Vries JD. Interaction of fluoxetine and selegiline. *Can J Psychiatry* 1990;35:571-572.
- Garcia-Monco JC, Padierna A, Beldarrain MG. Selegiline, fluoxetine, and depression in Parkinson's disease. *Mov Disord* 1995;10:352.
- Bolden-Watson C, Richelson E. Blockade by newly-developed antidepressants of biogenic amine uptake in to rat brain synaptosomes. *Life Sci* 1993;52:1023-1029.
- Hauser RA, Zesiewicz TA. Sertraline for the treatment of depression in Parkinson's disease. *Mov Disord* 1997;12:756-759.
- Di Rocco A, Brannan T, Prikhojan A, Yahr MD. Sertraline induced parkinsonism. A case report and in-vivo study of the effect of sertraline on dopamine metabolism. *J Neural Transm* 1998;105:247-251.
- Pina Latorre MA, Modrego PJ, Rodilla F, Catalan C, Calvo M. Parkinsonism and Parkinson's disease associated with long-term administration of sertraline. *J Clin Pharm Ther* 2001;26:111-112.
- Lees AJ. The relevance of Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988;51:144-147.
- Leentjens AF, Verhey FR, Lousberg R, Spitsbergen H, Wilmink FW. The validity of the Hamilton and Montgomery-Asberg depression rating scale as screening and diagnostic tools for depression in Parkinson's disease. *Int J Geriatr Psychiatry* 2000;15:644-649.
- Fahn S, Alton RL, and members of the UPDRS development committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB., eds. *Recent developments in Parkinson's disease*. Vol 2. New York Mc Millan, 1987:153-163.
- Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967;17:427-442.
- Kökmen E, Naessens JM, Offord KP. Short Test of Mental Status: descriptive and preliminary results. *Mayo Clin Proc* 1987;62:281-288.
- Jimenez-Jimenez FJ, Tejeiro J, Martinez-Junquera G, Cabrera-Valdivia F, Alarcon J, Garcia Albea E. Parkinsonism exacerbated by paroxetine. *Neurology* 1994;44:2406.
- Jansen Steur ENH. Increase of Parkinson disability after fluoxetine medication. *Neurology* 1993;43:211-213.
- Simons JA. Fluoxetine in Parkinson's disease. *Mov Disord* 1996;11:581-582.
- Arya DK, McKenzie J, Worral N. Exacerbation of extrapyramidal symptoms with paroxetine. *Aust N Z J Psychiatry* 1995;29:521-522.
- Meco G, Bonifati V, Fabrizio E. Worsening of parkinsonism with fluvoxamine: two cases. *Hum Psychopharmacol* 1994;9:439-441.
- Caley CF, Freidman JH. Does fluoxetine exacerbate Parkinson's disease? *J Clin Psychiatry* 1992;53:278-282.

22. Montastruc JL, Fabre N, Blin O, Senard JM, Rascol O, Rascol A. Does fluoxetine aggravate Parkinson's disease? A pilot prospective study. *Mov Disord* 1995;10:355-357.
23. Dell'Agenlo G, Cearvolo R, Nuti A, Bellini G, Piccini D, D'Avino C, Dell'Osso L, Bonucelli U. SSRIs do not worsen Parkinson's disease: evidence from an open-label, prospective study. *Clin Neuropharmacol* 2001;24:221-227.
24. Arya DK. Extrapiramidal symptoms with selective serotonin reuptake inhibitors. *Brit J Psychiatry* 1994;165:728-733.
25. Brod TM. Fluoxetine and extrapyramidal side effects. *Am J Psychiatry* 1989;146:1352-1353.