

Efficacy of Sertraline in the Treatment of Depression in Patients with Parkinson's Disease

Parkinsonlu Hastaların Depresyon Tedavisinde Sertralinin Etkinliği

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ABSTRACT Objective: We investigated the efficacy and safety of sertraline in the treatment of depression in patients with Parkinson's disease (PD) without motor oscillations. Sertraline has less potential for pharmacokinetic drug interactions than other antidepressants and this feature ensures a tolerability profile especially in the elderly. **Material and Methods:** Sixteen patients with PD who were diagnosed with major depression according to DSM-IV criteria were included in this open-label trial for 8th weeks. Anti-parkinsonian medications have not been modified throughout the study period. Initial sertraline dose was 25 mg for the first week and then increased to 50 mg given every morning. For assessment of depression, Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HAM-D) were used and Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn-Yahr Scale were used for parkinsonism. **Results:** BDI and HAM-D scores decreased significantly ($p=0.000$) and clinical global assessment of efficacy revealed "good" or "excellent" responses in all patients. Mean parkinsonian disability, as assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr Stage scales, remained unchanged throughout the study in the group as a whole. **Conclusion:** Although these preliminary results need to be confirmed in large placebo-controlled trials, 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: Depression; parkinson disease; serotonin; sertraline

ÖZET Amaç: Bu çalışmada, motor osilasyonları olmayan parkinsonlu hastaların depresyon tedavisinde sertralinin etkinliğini ve güvenilirliğini araştırdık. Diğer antidepressanlara göre sertralinin farmakokinetik olarak ilaç etkileşim potansiyeli daha düşüktür. Bu nedenle sertralin özellikle yaşlılarda uygun bir tolerabilite profiline sağlamaktadır. **Gereç ve Yöntemler:** Sekiz haftalık bu açık çalışmaya Parkinson hastalığı olan ve DSM-IV kriterlerine göre major depresyon teşhisi konulan 16 hasta dahil edildi. Çalışma boyunca hastaların aldığı anti-parkinson ilaçları değiştirilmedi. Başlangıç sertralin dozu ilk hafta boyunca 25 mg, daha sonra her sabah 50 mg olacak şekilde verildi. Hastalardaki depresyonu değerlendirmek üzere Beck Depresyon Envanteri (BDI) ve Hamilton Depresyon Ölçeği (HAM-D), parkinsonu değerlendirmek üzere de Birleşik Parkinson Hastalığı Değerlendirme Ölçeği (UPDRS) ve Hoehn & Yahr ölçeği uygulanmıştır. **Bulgular:** BDI ve HAM-D skorları istatistiksel olarak anlamlı düzeyde azaldı ($p=0.000$) ve klinik global izlem değerlendirmesi tüm hastalarda "iyi" ya da "mükemmel" cevaplar ortaya koydu. UPDRS ve Hoehn & Yahr ölçeği ile değerlendirilen ortalama parkinson özürüllük ölçülerindeki değişme istatistiksel olarak anlamlı değildi. **Sonuç:** Her ne kadar bu ön sonuçların geniş plasebo-kontrollü çalışmalar ile doğrulanması gerekiyorsa, ortaya çıkan sonuçlar sertralinin motor performansta kötüleşmeye yol açmadığını ve Parkinson hastalığı olanlarda görülen depresyonun tedavisinde kullanılabileceğini göstermektedir.

Anahtar Kelimeler: Depresyon; parkinson hastalığı; serotonin; sertralin

It is well known that physical disability has a clear effect on health-related quality of life in patients with Parkinson's disease (PD) and has been consistently the focus of therapeutic research. However, it is becoming increasingly apparent that psychiatric disorders have a considerable impact on the quality of life. Previous studies have shown that 40% of reduction in the quality of life in PD can be explained by depression.¹ Depression is one of the most common psychiatric disturbances in PD, with an average prevalence of about 40% (range, 25%-70%).¹⁻⁴

Depression is particularly important in these patients because, in addition to the personal suffering, it is associated with faster progression of physical symptoms,⁵ greater decline in cognitive skills,⁶ and inability to care for oneself.⁷ Different criteria and screening tools have been used when diagnosing depression in patients with PD, resulting in variable estimates of the occurrence of this condition. Additionally, clinical overlapping between the signs and symptoms of depression and some of those of PD (e.g. fatigue, slowness) causes the discrepancy. Several studies have failed to find a clear association between the severity of depression and motor disability. Depression may precede or occur simultaneously with cognitive impairment and in 25% of PD patients, and it precedes the onset of motor symptoms.⁸

Although functional impairment, as well as sociological and psychological factors, has an influence on the mood in PD, some evidence suggests that organic factors involved in the etiopathogenesis of depression in PD. Norepinephrine and serotonin deficits have been implicated in the neurochemical basis of this disorder.

Degeneration has been reported in the mesolimbic system, tegmental ventral area, locus coeruleus, and serotonergic nucleus. Depression in PD has been associated with lower levels of 5-HIAA (5-hydroxy-indolacetic acid) in cerebrospinal fluid,^{9,10} mesencephalic hypoacogenicity,¹¹ and frontomedial hypometabolism in 18-F-glucose PET scan.^{12,13} Additionally, decrease of dopamine in PD may contribute to increased risk of depression, but dopa-

minergic agents alone do not alleviate the depressive symptoms.¹⁴ Levodopa has no effect on depression although it improves motor symptoms. Therefore, it is not possible to suggest that attempts to establish an association between depression and altered dopamine metabolism in PD have yielded satisfactory results.

Tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs) are the mainstays of treatment of depression in patients with PD. Several studies demonstrated the usefulness of TCAs in the treatment of depression in PD, but they have a relatively high incidence of serious anti-cholinergic side effects, especially in the elderly population and are contraindicated in patients who experienced heart blocks or conduction abnormalities, severe arrhythmias or a recent myocardial infarction.¹⁵

Many clinicians prefer to use SSRIs for the treatment of PD-associated depression.^{16,17} SSRIs have some benign side effects. They do not change cardiac conduction.¹⁵ Moreover, SSRIs do not block the alpha-adrenergic system or decrease the threshold of the seizures.¹⁸ Some members of the Parkinson's Study Group (PSG) suggest that SSRIs may worsen motor function in PD.¹⁹ However, majority of these physicians continued using SSRIs, indicating that this potential risk may be overcome by their benefits. In addition, the serotonin syndrome may also occur in patients taking SSRIs and selegiline concurrently.²⁰

Sertraline which is a relatively selective SSRI with some dopamine re-uptake inhibitor activity may be particularly useful in PD.²⁰⁻²² Besides these properties, sertraline has a low potential for pharmacokinetic interactions with other drugs and a good tolerability profile in elderly patients.

In this prospective, open-label trial, we aimed to evaluate whether sertraline should have a place in the treatment of PD patients with depression. Thus, in the present study, we examined the effect of this drug on mood and motor impairments in a group of PD patients with depression.

MATERIAL AND METHODS

Sixteen consecutive parkinsonian patients with a history of mood disorder according to the results of structured interviews and DSM-IV criteria for depression^{23,24} were included in this study. The diagnosis of PD was established by a neurologist based on the presence of at least two of three cardinal signs (bradykinesia, rigidity, and tremor) plus unequivocal response to levodopa. Exclusion criteria were as follows: (1) stages IV and V in Hoehn and Yahr's staging;²⁵ (2) Axis I diagnosis other than a depressive disorder, including any current (within 3 months) diagnosis of alcohol or drug abuse/dependence (with the exception of nicotine dependence) (3) patients taking antidepressive medications during the previous three months; (4) accompanying dementia as defined by DSM-IV criteria and supported by the Mini Mental State Examination;²⁶ (5) a history of drug toxicity causing hallucinations, delirium, or confusional events; (6) a history of stroke, cranio-cerebral injury, or encephalitis; (7) any concomitant serious medical illness.

The patients were informed about the study protocol and they gave their informed consents. The study protocol was approved by the Ethics Committee of the Kocaeli University Faculty of Medicine.

Before enrollment, standard laboratory tests and electrocardiogram ECG were performed in all patients. Vital functions, blood pressure and pulse rate were measured on each visit. Motor performance was assessed using Unified Parkinson's Disease Rating Scale (UPDRS), and the Hoehn and Yahr Staging Scale.²⁷

All patients had a diagnosis of major depression (based on DSM-IV criteria), Beck Depression Inventory (BDI) score of ≥ 9.27 and HAM-D score of ≥ 8.28 . BDI and HAM-D were used as the main measures of antidepressive efficacy of sertraline.⁸ The Clinical Global Assessment of Efficacy (CGA-E) was also used as an additional measure of drug efficacy.

The initial dose of sertraline was 25 mg for the first week; then it was administered at a dose of 50 mg every morning. Anti-parkinsonian medication

remained unmodified during the trial unless necessary. Assessments were performed at baseline and on the 4th and 8th weeks of treatment. The scales were always administered by the same investigator. The patients were first asked whether they have experienced any adverse effects, and afterwards, the occurrence of a list of symptoms indicating adverse events were specifically questioned.

STATISTICAL ANALYSIS

The statistical analysis was performed using SPSS 11.0 software. Changes in the scores were analysed using Wilcoxon rank test. $P < 0.05$ was set as the significance level.

RESULTS

The study included a total of 16 patients (five males, 11 females). All patients completed the study. The mean age of the patients was 63.56 ± 9.88 years (range, 45-79 years) and mean duration of PD from the onset of the motor impairment was 101.6 ± 78.2 months (range, 9-312 months). The patients were given optimal anti-parkinsonian drug treatment during the three months prior to the clinical trial. The patients were receiving levodopa at a mean dose of 375.0 ± 133.6 mg/day (range, 300-875 mg/day) for a mean of 4.7 ± 6.0 years, along with a decarboxylase inhibitor (six patients carbidopa, six patients benserazide). Eight patients were taking selegiline: Five patients were receiving 10 mg/day, one patient 15 mg/day, another two patients 5 mg/day. Fourteen patients were taking dopamine agonists (eight patients were taking bromocriptine 6.4 ± 4.2 mg/day, and four were on pergolide treatment at a mean dose of 1.06 ± 4.2 mg/day).

Only one patient had a moderate wearing-off phenomenon; thus, special care was taken to assess his motor state during his best 'on' periods. In other two patients, mild peak-dose dyskinesia was observed at baseline and on day-30, but not on successive examinations.

The results are summarized in Table 1. The mean baseline HAM-D was 22.06 ± 5.60 and it improved to 7.94 ± 2.90 at the end of the study period (8th weeks) ($p = 0.000$). The mean baseline BDI

TABLE 1: Scores at baseline and final visit (8th week) (n=16)

	Baseline	Final visit	p
BDI	24.44 ± 10.11	10.38 ± 5.73	0.000
HAM-D	22.06 ± 5.60	7.94 ± 2.90	0.000
UPDRS			
DLA	17.60 ± 10.43	17.50 ± 10.10	0.837
Motor	22.88 ± 9.80	22.94 ± 10.30	0.750
Total	45.90 ± 23.10	45.40 ± 22.60	0.502
H+Y	2.50 ± 0.89	2.40 ± 0.92	0.414

BDI, Beck Depression Inventory; HAM-D, Hamilton Depression Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale; DLA, Daily Living Activities; H+Y, Hoehn and Yahr Stage.

was 24.44 ± 10.11 and it improved to 10.38 ± 5.73 at the end of the study (p= 0.000). Fifty percent or greater improvement in HAM-D and BDI was observed in 93.75% (n= 15) and 68.75% (n= 11) of the patients, respectively. Strict criteria for remission for HAM-D (HAM-D ≤8) and BDI (BDI≤9) were met by 37.5% and 43.75% of the patients, respectively.

The mean UPDRS was 45.90 ± 23.10 at baseline and it showed a reduction to 45.40 ± 22.60 at the end of the study (p= 0.502).

Three patients experienced side effects such as insomnia, anorexia, abdominal pain, increased perspiration, and restlessness, however developed tolerance within two weeks. These patients were receiving selegiline along with sertraline. However, these adverse reactions were mild and transient. None of the patients experienced serotonin syndrome. During the final visit, all of the patients were receiving sertraline at a dose of 50 mg/day.

DISCUSSION

The results of the present study showed that sertraline at a dose of 50 mg/day was effective in the treatment of depression in PD patients; and 93.75% (n= 15) and 68.75% of the patients (n= 11) showed 50% or greater improvement in the scores of HAM-D and BDI, respectively.

Clinical global assessment of efficacy indicated that the improvement ranged from “good” to “excellent” in 12 out of 16 patients which is in accordance with previous trials.²⁰ The major advan-

tage of SSRIs is that they are associated with fewer serious side effects than TCAs. Among SSRIs, sertraline offers several advantages that may allow greater tolerability in the elders. Plasma levels of sertraline changes with the dose administered and is mostly not affected by the age of the patient. Furthermore, sertraline causes less inhibition of the P450 IID6 isoenzyme than does fluoxetine or paroxetine, thereby it conveys less potential for drug-drug pharmacokinetic interactions with other medications metabolized by this enzyme.²⁰

Although rigorous clinical trial data are lacking regarding the use of SSRIs and TCAs in the treatment of depression in PD, their use is widespread in clinical practice. Some studies indicate an exacerbation of parkinsonism during SSRIs treatment in PD patients with depression whereas other reports suggest that these drugs do not affect motor function. Clinician may be concerned that SSRIs may worsen the patient's motor function by decreasing dopamine release in nigrostriatal pathways; however, clinical trial data and clinical experience supporting this consideration are limited. A database review of 199 PD patients treated with antidepressant medications failed to identify any significant difference in the frequency of extrapyramidal symptoms between different classes of antidepressants.³¹ In another study with a follow-up period of six months, 310 PD patients completed the study and worsening of tremor was observed in some patients, however the authors concluded that active management of depression with sertraline appeared to have a positive impact on parkinsonism.²²

Evidence that SSRIs do not worsen PD comes from an open-label prospective study.³² They compared the effect of four SSRIs (citalopram, fluoxetine, fluvaxamine and sertraline) on motor performance and the influence on depression in 65 non-demented, non-fluctuating PD patients with depression. Evaluation of the extra-pyramidal and depressive symptoms was performed by the use of UPDRS, BDI and HAM-D at baseline and on months 1, 3 and 6. UPDRS scores were not significantly modified by add on therapy with any drug.

Depressive symptoms showed significant improvement with all SSRIs. These findings suggested that SSRIs ameliorated depression without significantly worsening the extra-pyramidal symptoms.

In another study, sertraline at the same dose, induced an improvement in upper limb akinesia in depressed patients with PD.³³ Another study demonstrated deterioration of parkinsonian motor symptoms after treatment with fluoxetine at a dose of 20 mg/day.³⁴ Two PD patients with depression in whom parkinsonism was worsened by the use of paroxetine have also been reported.³⁵ A detailed retrospective study reported an increase in motor symptoms in only five of 58 patients with PD treated with SSRIs (two with fluoxetine and three with sertraline).³⁶

Extrapyramidal reactions and SSRIs were reviewed in a study.³⁷ The proposed hypothesis for the development of extrapyramidal reactions by SSRIs includes the inhibition of the extrapyramidal dopaminergic activity by serotonin. Extrapyramidal reactions include dystonia, dyskinesia, akathisia, exacerbation of PD and possibly the neuroleptic malignant syndrome. The majority of the symptoms occur within the first month of treatment.

We found no statistically significant change in UPDRS and H+Y scores when sertraline was added to treatment. In a study, no change in UPDRS scores was reported in a group of 15 patients with PD and depression, after treatment with sertraline 50 mg/day.²⁰ Another study in 54 idiopathic PD patients with depressive disorders, treated with sertraline reported that there were no statistically significant changes in UPDRS.²¹

A research on the possible interaction between antidepressants and selegiline reported that such an interaction may result in "serotonin syndrome".

This syndrome is usually diagnosed considering the change in mental status, the presence of myoclonus, sweating, hyperreflexia, incoordination and fever. In our study, eight patients were taking selegiline and none of them experienced "serotonin syndrome". A review of 4568 patients taking deprenyl and an antidepressant found that less than 1% of the patients had symptoms of the "serotonin syndrome".¹⁹ However, there is some evidence that the impairment of motor function is more common in PD patients with depression taking SSRIs and deprenyl.²⁰ Hence, the risk of serotonin syndrome is minimal and should not preclude treatment of a patient with depression. The concomitant use of selegiline and SSRIs seems generally well tolerated. Caution is nevertheless advised when combining an SSRI or a TCA with selegiline.³⁷ The lack of drug interaction would be explained by the exclusive monoamineoxidase-A metabolism of serotonin, whereas selegiline is relatively selective for monoamineoxidase-B inhibitor.

In the present study, sertraline was generally well tolerated with mild and transient side effects including gastrointestinal symptoms, insomnia, anorexia, abdominal pain, increased perspiration, and restlessness.

In conclusion, the present study suggests that sertraline at a dose of 50 mg/day improves depression without exacerbating the parkinsonian symptoms. Sertraline was generally well tolerated, side effects were mild and transient and none of the patients experienced a "serotonin syndrome". The limitations of this study were small sample size and lack of a placebo-controlled design. We suppose that placebo-controlled trials on larger populations are required to confirm both the efficacy of sertraline and its effect on parkinsonism in PD patients with depression.

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