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The Efficacy of Venlafaxine in Treatment of Depression in Parkinson`s Disease

Fuat Torun[1], Kemal Bayulkem[2], Sebahat Dilek Torun[3]

ÖZET:

Parkinson hastalığında depresyon tedavisinde Venlafaksin'in etkinliği

Amaç: Depresyon, Parkinson hastalığında (PH) ortalama %40-50 prevalans hızı ile en sık görülen ruhsal hastalıktır. PH de görülen depresyonun tedavisinde seçici serotonin ve norepinefrin geri alım inhibitörleri (SNRIs) kullanılmasına rağmen literatürde henüz bir çalışma bulunmamaktadır. Bu prospektif çalışmanın amacı bu hastalarda SNRI grubunda yer alan venlafaxinin terapötik etkisini araştırmaktır.

Yöntem: Bu çalışmaya depresyonu olan 14 fluktuasyonsuz PH'li hasta dahil edilmiştir. Bütün hastalara depresyonu değerlendirmek üzere Hamilton Depresyon Derecelendirme Ölçeği (HAM-D), Montgomery-Asberg Depresyon Ölçeği (MADRS), PH'yi değerlendirmek üzere Birleştirilmiş Parkinson Değerlendirme Ölçeği (UPDRS) ve Hoehn-Yahr Ölçeği (H+Y) uygulanmıştır. Bu hastalarda venlafaxin ile depresyonun tedavisi sırasında uygulanmakta olan antiparkinson ve diğer ilaç dozlarında bir değişiklik yapılmamıştır.

Bulgular: 8 haftalık çalışma sonucunda bütün hastalarda HAM-D ve MADRS toplam skorlarında istatistiksel olarak anlamlı düzelmeler görülürken, UPDRS ve H+Y değerlerinde istatistiksel olarak anlamlı bir farklılık görülmemiştir.

Sonuç: Bu çalışmanın sonucunda elde edilen verilere göre PH de görülen depresyonun tedavisinde venlafaxine tedavisinin etkili olabileceği düşünülmüştür.

Anahtar sözcükler: Venlafaksine, depresyon, Parkinson hastalığı

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ABSTRACT:

The efficacy of venlafaxine in treatment of depression in Parkinson`s disease

Objective: Depression is the most common psychiatric disorder appearing in Parkinson's Disease (PD) with an average prevalence rate almost 40-50 %. Selective serotonin and norepinephrine reuptake inhibitors (SNRIs) are currently used in the treatment of depression in patients with PD, but we have not found any studies in the literature regarding this treatment choice. The aim of this prospective study was to investigate the therapeutic efficacy of venlafaxine, which is a SNRI antidepressant, in the treatment of depression in Parkinson's disease.

Method: Fourteen non-fluctuating PD patients with depression were enrolled in the study. The Hamilton Depression Rating Scale (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), the Unified Parkinson's Disease Rating Scale (UPDRS), and the Hoehn-Yahr Scale (H+Y) were used to assess depression and Parkinsonism. Antiparkinson and other medications were unchanged during the study.

Results: After 8 weeks of venlafaxine treatment, statistically significant improvement was seen in total scores of HAM-D and MADRS in all patients. On the other hand, the changes in UPDRS scores and H+Y stages were not statistically significant.

Conclusion: The results of the study suggest that venlafaxine may be effective in the treatment of depression in patients with PD.

Key words: Venlafaxine, depression, Parkinson's disease

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[1]M.D., Department of Psychiatry, Ümraniye Training and Research Hospital, Istanbul-Turkey
[2]M.D., Department of Neurology, Medical School of Cerrahpaşa, Istanbul-Turkey
[3]M.D., M.P.H., Ph.D., Occupational Health Care Provider, Assistt Rehberlik ve Müsteri Hizmetleri A.S., Istanbul-Turkey

Yazışma Adresi / Address reprint requests to:
Dr. Fuat Torun, Department of Psychiatry Umraniye Training and Research Hospital Istanbul-Turkey

Telefon / Phone: +90-216-632-1818

Elektronik posta adresi / E-mail address: fuattorun@hotmail.com

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INTRODUCTION

Depression, is the most common psychiatric disorder appearing in Parkinson's disease (PD) with an average prevalence rate almost 40-50% (range 20-90%) (1-5). Most authors agree that both pathological and biological components play etiological roles in depression. It is known that the principal neurobiological pathology in PD is a depletion of dopamine in the striatum; however, reduced norepinephrine and particularly serotonin levels are also thought to play a role in depression. Therefore, there seems to be an overlap between the pathogenesis of depression and PD. In addition to loss of dopaminergic neurons, PD is accompanied by degeneration of noradrenergic neurons in the locus coeruleus, serotonergic neurons in the dorsal raphe, and cholinergic neurons in the nucleus basalis and their attendant projection systems. Differential degrees of pathology among these neuronal systems are thought to underlie the heterogeneous motor, psychiatric, and cognitive properties of PD (6,7).

For many years, it was thought that psychiatric phenomena in PD, particularly affective changes, were related to the lack of dopamine and motor impairment. After levodopa treatment became available in the 1960's, it became apparent that up to two-thirds of PD patients has persistent affective disorders, in spite of antiparkinsonian treatment and that most changes were amenable to antidepressant treatment (8).

Although tricyclic antidepressants (TCAs) improve the mood in patients with PD, they have a relatively high incidence of serious anticholinergic and cardiac side effects, particularly among elderly patients (9-12). Selective serotonin reuptake inhibitors (SSRIs) have a lower incidence of adverse effects than TCAs especially in geriatric patients (13). SSRIs are now commonly used to treat depression in PD, but some patients have reported an exacerbation of parkinsonian symptoms (14,15). At the same time, some extrapyramidal side effects were described in depressed patients treated with SSRIs (16-18). Another major problem is occurrence of serotonin syndrome in patients concurrently taking SSRIs and selegiline (19,20).

Recent review articles concerning the treatment of depression in elderly and/or PD patients indicate that medications such as venlafaxine, nefazadone, and mirtazapine may prove to be efficacious (20).

Venlafaxine is neither a SSRI nor a TCA. It is a 'mixed' antidepressant agent. It prevents the reuptake of both norepinepherine and serotonin, although it has more potency at the serotonin receptor. It does not exert effects at the histaminergic, muscarinic, or alpha-adrenergic receptors, although it may occasionally cause mild anticholinergic symptoms. The initial starting dose is 37.5 mg daily. It should be titrated slowly up to a maximum of 150 mg daily in elderly patients. It is also available as an extended release preparation. Venlafaxine should be used with caution in hypertensive patients since it can raise blood pressure (21).

The aim of this study was to determine the efficacy and tolerability of venlafaxine in the treatment of depression in PD patients.

MATERIAL and METHODS

Subjects

Twenty nine consecutive patients who are followed at the PD and Movement Disorders Clinic in Department of Neurology of the Medical School of Kocaeli University participated in this study.

All patients had at least two of the three cardinal features of PD (bradykinesia, rigidity, and tremor). Exclusion criteria were as follows: (1) stages IV and V in Hoehn and Yahr's staging; (2) any 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) use of antidepressant medications during the previous 3 months; (4) accompanying dementia as defined by DSM-IV criteria and supported by a Mini Mental State Examination score less than 24 (22); (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; (8) high blood pressure.

The patients were given full information about the study protocol and written informed consent was obtained. The Ethics Committee of the Medical Faculty of Kocaeli University approved the study, which was conducted in accordance with the Declaration of Helsinki.

Measurements

At the initial assessment, the study group was evaluated by using the Structured Clinical Interview for Axis I Disorders (SCID-I) for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (23). Before antidepressant treatment was initiated, HAM-D and MADRS were applied to all patients by a psychiatrist (FT). Both HAM-D and MADRS were repeated at week 4 and week 8 of treatment, as these scales tend to measure different aspects of depression.

The Hamilton Depression Rating Scale (HAM-D):

The HAM-D is an interview rating scale consisting of 17 items. The scale is used by determining the presence or absence of the symptoms in each item and ranking them as mild, moderate, or severe via the psychiatrist's question for the related item and assessing the answers. The total score of the scale is 0 to 51, obtained by summing the ratings (24). Validity of HAM-D in PD depression has been demonstrated (25). HAM-D has been tested to be valid and reliable in a Turkish sample (26).

The Montgomery-Asberg Depression Rating Scale (MADRS):

The MADRS is a ten-item diagnostic questionnaire which measures the severity of depressive episodes in patients with mood disorders. It was designed in 1979 by British and Swedish researchers as an adjunct to the HAM-D, and is intended to be more sensitive to the changes brought on by antidepressants and other forms of treatment than the HAM-D (27). It has been found to be valid and reliable in Turkish patients (28). MADRS is a validated screening and diagnostic scale for depression in PD (29).

Before enrollment, the patients underwent standard laboratory tests and ECG. Vital signs were measured on each visit. Motor performance was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) (30), and the Hoehn and Yahr Staging Scale (H+Y) (31).

Venlafaxine's application and dosage

Antiparkinsonian drugs and other medications were unchanged throughout the study. In addition to antiparkinsonian drugs, 6 of the patients were taking selegiline. The dose of venlafaxine was 37.5mg/day during the first week and 75 mg every morning for the remainder of the study. No other psychotropic medications were permitted during the course of the study. Response to treatment was defined as a >50% decrease in HAM-D and MADRS total scores.

Statistical Methods

The results of the descriptive analyses are given as the mean and standard deviations. Because the data did not meet the parametric test criteria, changes in HAM-D and MADRS scores throughout the treatment period were assessed by Friedman's test. Mean baseline and final visit UPDRS and Hoehn and Yahr Staging Scale scores were compared by using the Wilcoxon signed rank test. A p value of < 0.05 was considered as significant. Data were analyzed using SPSS 11.0 version.

RESULTS

Out of 29 patients who were followed in the section of PD and Movement Disorders in the Department of Neurology, 15 patients were excluded from the study (5 did not meet the criteria for depression, 3 had dementia, 3 had an abnormal ECG, 3 had high blood pressure, and 1 had been treated for depression). The mean age of the patients who were included (n=14) in the study was 63.0 ± 9.11 years (range 37–70). All of the patients who were included the study (7 men, 7 women) completed the study. The mean PD duration of patients was 6.08±3.71 years (range 1-13). All of the patients were receiving levodopa-benserazide therapy at a mean daily dose of 428.5±136.1mg/day. Seven patients were receiving entacapone 514.2±106.9 mg/day, 6 patients were taking selegiline 10 mg/day. Ten patients were taking dopamine agonists (6 patients were taking pergolide 0.79±1.02 mg/day and 4 were on bromocriptine treatment at a mean daily dose of 7.8±5.8 mg/day).

Mean HAM-D and MADRS scores at baseline assessment were 21.64±4.36 (median 20.5; min 16– max 30) and 29.14±5.10 (median 29; min 20- max 36) respectively. The mean HAM-D and MADRS total scores decreased steadily and consistently throughout the study period. Changes in all of the total scores at baseline, four, and eight weeks are presented in Table 1.

A ≥50% decrease in HAM-D and MADRS total scores from the baseline values was obtained in 13 (92.9%) of the patients at week 8.

Strict criteria for remission for HAM-D (HAM-D≤7) and MADRS (MADRS≤9) were met by 50.0% (n=7) and 57.1% (n=8) of the patients, respectively.

On the other hand, changes in daily living activities (DLA), motor and total UPDRS scores, and H+Y stages

Table 1: HAM-D and MADRS scores at baseline, at week 4 and at the final visit

Scales	Baseline		Week 4 (Week 8)		Final visit		p*
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	
HAM-D	21.64±4.36	20.5	12.93±0.74	12	7.57±2.59	7	<0.001
MADRS	29.14±5.10	29	18.57±1.55	18	9.57±4.16	9.5	<0.001

*Friedman Test

HAM-D: Hamilton Depression Rating Scale, MADRS: Montgomery-Asberg Depression Rating Scale.

Table 2: UPDRS and H+Y scores at baseline and at the final visit

Scales	Baseline Mean±SD	Final visit (8th week) Mean ±SD	p*
UPDRS			
DLA	16.71±9.95	16.86±9.82	0.884
Motor	21.29±8.39	20.57±8.63	0.201
Total	42.57±20.97	42.29±20.68	0.750
H+Y	2.43±0.85	2.36±0.74	0.650

* Wilcoxon signed rank test

H+Y: Hoehn and Yahr Stage, UPDRS: Unified Parkinson Disease Rating Scale, DLA: Daily Living Activities

were not statistically significant (Table 2).

Venlafaxine was well tolerated except for gastrointestinal side effects in four patients and mild hypertension in two patients. All side effects were temporary.

DISCUSSION

It is possible to say that venlafaxine is effective in the treatment of depression in PD, according to the results of this study. Venlafaxine (75 mg/day) did not worsen motor performance and ameliorated depression in depressed non-fluctuating PD patients. HAM-D and MADRS scores significantly improved from baseline at week 4 to the final visit (week 8) in all patients. In the literature we could not find any study regarding the efficacy of venlafaxine in the treatment of depression in PD. There is a placebo-controlled medication trial in depressed PD patients comparing a dual reuptake inhibitor (nortriptyline) and a SSRI (paroxetine CR) (32). In that trial, nortriptyline was found efficacious in the treatment of depression and paroxetine CR was not. There are two case reports about the remarkable effect of milnacipran, which is another SNRI antidepressant in the treatment of depression in PD refractory to SSRIs (33).

Venlafaxine is a dual reuptake inhibitor, which inhibits reuptake of both serotonin and norepinephrine. A PET study provided evidence of a loss of both dopamine and noradrenaline innervation of cortical and subcortical components of the limbic system in patients with PD and depression, perhaps providing a possible way of understanding our study results (34). These PET study results might help in understanding the functional anatomy of depression and have therapeutic implications. Another, speculative explanation for these results may lie in the role of norepinephrine transporters in the prefrontal cortex. The norepinephrine reuptake transporter is responsible for removing dopamine from the synapse in this area of the brain (35). The antidepressant effects associated with increasing norepinephrine levels may also be partly or largely due to the concurrent increase in dopamine in the prefrontal cortex (36).

In the present study daily living activities (DLA), motor and total UPDRS scores, and H+Y stages were unchanged. Several reports have described deterioration of parkinsonian motor symptoms with the addition of SSRI antidepressants (37,38), but there are no studies with respect to SNRIs. There is only a case report in the literature that illustrates the development of parkinsonian symptoms in association with milnacipran which is another SNRI antidepressant (39). We found no significant changes in UPDRS and H+Y scores with venlafaxine.

In the present study venlafaxine was generally well tolerated, except gastrointestinal side effects in four patients (2 patients were taking selegiline, but the side effects were moderate and temporary). Insomnia and sexual dysfunction were the other side effects. Venlafaxine should not be used in patients with uncontrolled hypertension, because it has a tendency to increase blood pressure. This hypertensive effect may be desirable in PD patients with postural hypotension (37); however, none of our patients had uncontrolled hypertension or postural hypotension. Venlafaxine should be avoided in agitated depressed PD patients. Moreover, venlafaxine does not have a flat dose-response curve like that of the SSRIs, so that escalating doses may continue to have therapeutic benefits (40,41).

In a publication concerning the possible interaction between antidepressants and selegiline, a monoamine oxidase-B inhibitor, 6 patients were taking selegiline, and none of them experienced serotonin syndrome (rigidity, tremor, incoordination and mental status changes) (42).

The limitations of this study are the small sample size and lack of placebo control. Replication of our findings, in prospective, double-blind, and placebo controlled studies with larger subject sizes, is needed to make more precise and reliable statements.

CONCLUSION

In conclusion, the results of our study suggest that

venlafaxine may be useful in the treatment of depression in patients with PD. In the present study venlafaxine at the dosage of 75 mg/day did not exacerbate parkinsonian symptoms. HAM-D and MADRS scores significantly improved from baseline to the final visit in all patients. In the present study DLA, motor and total UPDRS scores, and H+Y stages were unchanged. None of the participants experienced "serotonin syndrome." Venlafaxine should not be used in PD patients with uncontrolled hypertension and it is also important to check blood pressure frequently, even in patients with normal blood pressure during the venlafaxine treatment.

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