Fluoxetine does not impair motor function in patients with Parkinson's disease: correlation between mood and motor functions with plasma concentrations of fluoxetine/norfluoxetine

Fluoksetin ne remeti motornu funkciju kod bolesnika sa Parkinsonovom bolešću: korelacija raspoloženja i motorne funkcije sa koncentracijom fluoksetina/norfluoksetina u plazmi

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Abstract

Background/Aim. Selective serotonin reuptake inhibitors are the most commonly chosen antidepressants in patients with Parkinson's disease (PD). The aim of our study was to assess the influence of fluoxetine (Flu) on motor functions in patients with PD. Methods. In this prospective, controlled, open-label study, 18 patients with PD and mild depression ([10 ≤ Hamilton Rating Scale for Depression (HDRS) ≤ 23]) without dementia ([25 ≤ Mini-Mental State Examination (MMSE)]) were treated with Flu. Both single and repeated dose effects of Flu were assessed on days 1–80. Plasma concentrations of Flu and norfluoxetine (NORFlu) were correlated with the results of selected motor function performance scores: The Unified Parkinsons Disease Rating Score (UPDRS), Finger Tapping Test (FTT) and Purdue Pegboard Test (PPT). Severity of PD, depression and dementia were evaluated using standard tests ([Hoehn and Yahr stages (HY), Hoehn and Yahr stages (HY), activity of daily living (ADL), UPDRS, HDRS, MMSE]). Results. Steady-state for Flu/NORflu was reached after 18 days of treatment. Such a plateau correlated with significant improvements in both scores of depression and Parkinson’s disability (HDRS, UPDRS and ADL, respectively). In addition, FTT and PPT scores also increased until day 18, with further slight fluctuations around the plateau. Optimal motor performances correlated with Flu concentrations of approximately 60–110 μg/L. Conclusion. Flu (20 mg/day) significantly reduced depression in PD patients while it did not impair their motor performances. Because substantial placebo effects may arise in studies of PD and depression, large, prospective, randomized, placebo-controlled clinical trials are warranted.

Key words: parkinson disease; motor activity; depressive disorder; fluoxetine; treatment outcome.

Apstrakt

Uvod/Cilj. Selektivni inhibitori ponovnog preuzimanja serotonina su antidepresivi koji se najčešće koriste u lečenju oboljelih od Parkinsonove bolesti (PB). Cilj ovog istraživanja bio je da se proceni uticaj fluoksetina (Flu) na motorne funkcije bolesnika sa PB. Metode. U ovom prospektivnom, kontrolisanom, otvorenom kliničkom ispitivanju, 18 bolesnika sa PB i blagom depresijom [10 ≤ Hamiltonova skala za depresiju (10 ≤ HDRS) ≤ 23], bez demencije [25 ≤ Mini mental test (MMSE)] lečeni su primenom Flu. Procenjivana su dejstva jako pojedinačne, tako i ponovljene doze Flu od prvog do osamdesetog dana. Plasma koncentracije Flu i norfluoksetina (NORFlu) koreliscane su sa rezultatima određenih testova za motorne funkcije: skala za procenu težine PB (UPDRS), test sprintnosti kucanja (FTT) i Purdue pegboard Test PPT. Izraženost PD, depresije i demencije procenjivane su korišćenjem standardnih testova [[test dnevnih...
Introduction

Depression is the most common and frequently disabling psychiatric condition in patients with Parkinson's disease (PD). Prevalence of depression in patients with PD varies from 7% to 76% depending on the assessment method. Such a depression is mostly persistent or recurrent. It may be accompanied with anxiety, cognitive impairment and may reduce effectiveness of antiparkinson's therapy. Depression increases PD patients' disability and significantly reduces their quality of life. Consequently, approximately 50% of patients with PD receive antidepressant therapy.

Optimal treatment for depression in PD patients has not been established. Several antidepressants were tested in randomized clinical trials without sufficient statistical power (e.g. citalopram, sertraline, fluoxetine, amitriptyline and nortriptyline). Amitriptyline seems to be more effective than fluoxetine in PD patients with severe depression. However, it is not necessarily the first choice for treatment of depression in PD patients, according to the recommendations of the American Academy of Neurology. In addition, the adverse effects of amitriptyline such as orthostatic hypotension, sedation, cognitive and anticholinergic effects might preclude its use and increase the dropout rate in parkinsonians.

On the other hand, selective serotonin reuptake inhibitors (SSRIs) are used as a first line treatment of depression 51% of the time. In postmortem studies of patients with PD, depletion of 5-hydroxytryptamine (5-HT) in the caudate as well as hypothalamus and frontal cortex was reported, with preferential loss of 5-HT in the caudate compared with the putamen, but with relatively less loss of 5-HT (66%) than dopamine (98%). Imaging studies in vivo have also suggested depletion of 5-HT innervation to the striatum as measured via decreased 5-HT transporter binding. The loss of striatal 5-HT in PD may be secondary to neurodegeneration within the raphe nuclei as Lewy bodies are seen in the raphe nuclei, associated with cell loss. Tauscher et al., 1999, were the first to demonstrate the pharmacodynamic action of the selective 5-HT transporter blocker fluoxetine in the human brain in vivo. Meyer et al., 2004, showed that 80% 5-HT transporter occupancy was achievable with SSRIs at therapeutic doses in a study on patients with mood and anxiety disorders. Apart from these drug-effects studies, it has been shown that recovery of central serotonergic system after SSRI therapy was associated with reduction of clinical symptoms in 18 depressive subjects using [123]CIT and SPECT. All these findings of SSRIs-5-HT transporter occupancy in PET/SPECT studies clearly reflect the pharmacologically induced changes in serotonergic transmission.

However, data on the efficacy and safety of SSRIs in PD are still lacking and sufficiently large scale randomised controlled trials are required. Although the introduction of SSRIs offers new opportunities for the treatment of depression in PD, these agents could produce extrapyramidal adverse reactions aggravating parkinsonism. While epidemiological studies have not suggested increased risk of worsening PD using SSRIs for depression, almost one hundred detailed reports on extrapyramidal adverse effects linked to SSRIs antidepressants have been published. The influence of Flu on motor performances in PD patients still remains to be clarified. Extrapyramidal side effects of Flu seem to be related to the exacerbation of Parkinson's disability. However, it was also reported that Flu did not increase Parkinson’s disability either in retrospective or in prospective studies. Therefore, the authors argue for more systemic and controlled research examining the treatment of depression in patients with PD.

The aim of this study was to determine motor performances of PD patients treated with antidepressant Flu and to assess a possible correlation between mood and motor performance scores with plasma concentrations of Flu and its active metabolite, norfluoxetine (NORFlu).

Methods

Efficacy and tolerability of Flu was assessed in the prospective, 80-day, controlled, open-label clinical trial, with blind assessment. Flu was administered to 18 patients with nonfluctuating PD in the early Hoehn and Yahr (HY) stages – as indicator of PD staging only), and II, accompanied with mild depression, without dementia, without history of stroke, neurological disorder other than PD, or any concomitant serious medical illness, and drug toxicity causing hallucinations, confusional episodes or delirium, were not included in the study. During the study, patients were not allowed to use neuroleptics, seda-
atives, hypnotics or other antidepressants, as well as drugs with potential extrapyramidal adverse effects.

The study was approved by the Ethical Committee of the Faculty of Medicine, University of Belgrade, Serbia. Before entering the study patients gave written informed consent.

All the tests were performed in 18 out of 18 patients on days 11 and 18. Afterwards, 9 out of 18 patients were tested on day 50, and 8 out of 18 patients on day 80 (dropout rates of 50% and 56%, respectively). Therefore results were showed only until day 50.

All the patients were treated with two consecutive dosing regimens.

First, acute treatment with Flu – first day, the patients received Flu, 20 mg per day, at 8 a.m. Evaluation of motor performances and blood sampling for Flu/NORFlu plasma concentration measurement were carried out immediately before the Flu treatment (day 1, 0 h), and 4 h, 6 h and 8 h after the administration of the drug. Flu was then withdrawn for three consecutive days. On the fifth day, patients received 40 mg of Flu at 8 a.m. and all the tests and blood sampling were repeated in the same order (day 5, 0–8 h after administration of the drug). The pattern of blood sampling depends on Tmax for Flu, ranging from 4 to 8 h after the single dose administration (Figure 1, panel A).

Second, chronic treatment with Flu – in the same patients, regular Flu treatment was initiated (20 mg per day, at 8 a.m.) on day 6 after the beginning of such a therapy, and the motor performances were evaluated on days 11, 18, 50 (steady state for Flu was reached after 18 days of Flu treatment) (Figure 1, panel B).

Two blinded refers evaluated severity of motor impairment using the Unified Parkinson's Disease Rating Scale (UPDRS) – motor score, ADL (Schwab and England Activities of Daily Living Score) and computerized version of the quantitative motor test Finger Tapping Test (FTT) and the Purdue Pegboard Test (PPT). The current severity of depression was evaluated using the 17-item HDRS.

Bioanalytical method used for determination of plasma Flu and NORFlu concentrations was high performance liquid chromatography (HPLC) coupled with mass spectrometry (MS). The method used a liquid chromatograph Therm Separation Products Spectra System (Autosampler AS3000, HPLC binary pump P 2000, Degasser SCM 1000), mass spectrometer with electro spray ionization source (Finnigan MAT SSQ 7000 LC/MS – ESI System), Computer Digital UNIX Alpha Station 255. Recovery was very high, not less than 90.8% for Flu and 80.2% for NORFlu. Limit of quantification was 2.5 μg/L for Flu and 10 μg/L for NORFlu, and limit of detection was 1 μg/L for Flu and 5 μg/L for NORFlu. Correlation coefficient was 0.9993 (concentration range of 2.5–250 μg/L), and 0.9989 (concentration range of 10–250 μg/L), for Flu and NORFlu, respectively. Coefficient of variation, calculated for precision, was not higher than 8.33% and 8.83% for Flu and NORFlu, respectively.

The results are expressed as the mean ± standard error of the mean (S.E.M.) of N observations (descriptive statistics). Comparisons between groups were analyzed using the Fisher's exact test, t-test, and one-way analysis of variance (ANOVA), when appropriate. In addition, correlation analysis, factor analysis, extraction method (principal component analysis), rotation method (Oblimin with Kaiser normalization) and trend analysis (fitting or least square method) were used.

Results

All the patients were right-handed. Both groups, PD₀ and PDₙ, had similar laterality of Parkinson’s symptoms (affected right side/affected left side = 6/3).

Among 12/18 patients with the affected right side, there was no significant difference between FFT for the right hand (FTTr) and FTT for the left hand (FTTl) scores, as well as between PPT for the right hand (PPT₉) and PPT for the left hand (PPTl) scores (p = 0.66, and 0.89, respectively).

Among 6/18 patients with affected left side, FTTl was significantly better than FTTr (p < 0.03) and PPTl was significantly better than PPTr (p < 0.02). In addition, only PPTl score was significantly higher in the left side-affected PD patients comparing to the right side-affected PD patients (p < 0.03).

Age, gender and main clinical scores of PD0- and PDt-patients are shown in Tables 1 and 2.

### Table 1

Baseline characteristics of patients with Parkinson's disease (PD): group of de novo patients without antiparkinson's medication (PD0) and the group with previous stable antiparkinson's therapy (PDt) (mean ± S.E.M.)

<table>
<thead>
<tr>
<th>Group of patients</th>
<th>Age (years)</th>
<th>Duration of PD (years)</th>
<th>Previous levodopa therapy</th>
<th>MMSE</th>
<th>Duration (years)</th>
<th>Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD0 (N = 9)</td>
<td>55.7 ± 3.0</td>
<td>2.7 ± 0.9</td>
<td>3.9 ± 0.9</td>
<td>458.3 ± 55.1</td>
<td>28.0 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>PDt (N = 9)</td>
<td>56.0 ± 2.7</td>
<td>3.6 ± 1.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MMSE – mini mental state examination; PD0 – de novo PD patients; PDt – PD patients with stable antiparkinsons therapy

### Table 2

Staging of Parkinson's disease (PD): the group of patients without antiparkinson's medication (PD0) and the group of patients with stable antiparkinson's therapy (PDt) (mean ± S.E.M.)

<table>
<thead>
<tr>
<th>Group of patients</th>
<th>Day 1</th>
<th>Day 18</th>
<th>Day 1</th>
<th>Day 18</th>
<th>Day 1</th>
<th>Day 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD0 (N = 9)</td>
<td>16.4 ± 2.1</td>
<td>10.4 ± 1.9*</td>
<td>26.7 ± 2.9</td>
<td>23.6 ± 3.4</td>
<td>81.7 ± 3.8</td>
<td>85.0 ± 3.4</td>
</tr>
<tr>
<td>PDt (N = 9)</td>
<td>13.6 ± 0.9</td>
<td>8.2 ± 1.1*</td>
<td>29.0 ± 5.1*</td>
<td>22.2 ± 4.6*</td>
<td>82.2 ± 3.3</td>
<td>85.6 ± 3.4*</td>
</tr>
</tbody>
</table>

HDRS – Hamilton Depression Motor Scale; UPDRS – Unified Parkinson’s Disease Rating Scale; ADL – Schwab and England Activities of Daily Living Score.* – p < 0.05, day 0 vs. day 18 (Student's t-test for paired data).

Depressive symptoms were similarly reduced after 18 days of Flu treatment in both PD0 and PDt patients (Table 2, HDRS scores, p < 0.05). At the same time, Parkinson's disability was remarkably improved, especially in PDt patients (Table 2, UPDRS and ADL, p < 0.05, both).

**Acute treatment with Flu:** there were no remarkable changes in motor function scores (FTT, PPT) after the administration of 20 mg of Flu (day 1), or 40 mg of Flu (day 5) (Table 3).

The groups PD0 and PDt differ only in FTTl scores at 0 h and 8 h after the administration of 40 mg of Flu (day 5).

### Table 3

Changes in fluoxetine (Flu) and norfluoxetine (NORFlu) concentrations, and motor function scores (FTT, PPT) during acute treatment with Flu (day 1: 20 mg; day 5: 40 mg) (mean ± S.E.M.)

<table>
<thead>
<tr>
<th>Day s of Flu treatment</th>
<th>Day 1 of the treatment</th>
<th>Day 5 of the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Group</td>
<td>Flu</td>
</tr>
<tr>
<td>PD0</td>
<td>0</td>
<td>9.58 ± 1.51</td>
</tr>
<tr>
<td>PDt</td>
<td>0</td>
<td>8.83 ± 1.02</td>
</tr>
<tr>
<td>CFlu (µg/L)</td>
<td>0</td>
<td>5.11 ± 0.40</td>
</tr>
<tr>
<td>CNORFlu (µg/L)</td>
<td>0</td>
<td>4.25 ± 0.41</td>
</tr>
<tr>
<td>FTTl</td>
<td>0</td>
<td>4.00 ± 0.49</td>
</tr>
<tr>
<td>PPTl</td>
<td>0</td>
<td>10.33 ± 0.93</td>
</tr>
<tr>
<td>PDI</td>
<td>9.22 ± 0.66</td>
<td>8.89 ± 0.66</td>
</tr>
<tr>
<td>PDI</td>
<td>11.22 ± 0.91</td>
<td>11.89 ± 1.32</td>
</tr>
</tbody>
</table>

PD – Parkinson’s disease; PD0 – de novo PD patients; PDt – PD patients with stable antiparkinson’s therapy; CFlu, CNORFlu – plasma concentrations of fluoxetine and norfluoxetine; FTTl, FTTr – Finger Tapping Test for right and left hand; PPTl, PPTr – *Purdue Pegboard Test for right (r) and left (l) hand; * – p < 0.05, PDs vs. PD0.


Figure 2 – Changes in plasma concentrations of fluoxetine (CFlu) and its active metabolite norfluoxetine (CNORFlu) over time (panels A and B, respectively) in PD0 (□) and PD patients (■), during chronic treatment with Flu (days 11–50, 20 mg/day). Each point represents the mean ± S.E.M. of plasma concentrations obtained from 9 separate PD0 or PD patients. *p < 0.05, the PD0 vs. the group PD.

PD – Parkinson’s disease; PD0 – de novo PD patients; PDt – PD patients with stable antiparkinson’s therapy; CFlu, CNORFlu – plasma concentrations of fluoxetine and norfluoxetine; FTTr, FTTL – finger tapping test for right and left hand; PPTr, PPTL – Purdue Pegboard Test for right (r) and left (l) hand; *p < 0.05, PD0 vs. PDt.

Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Days of Flu treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 11</td>
</tr>
<tr>
<td>CFlu (µg/L)</td>
<td>PD0</td>
<td>60.73 ± 7.31</td>
</tr>
<tr>
<td></td>
<td>PDt</td>
<td>51.97 ± 6.52</td>
</tr>
<tr>
<td>CNORFlu (µg/L)</td>
<td>PD0</td>
<td>62.17 ± 12.29</td>
</tr>
<tr>
<td></td>
<td>PDt</td>
<td>60.80 ± 9.45</td>
</tr>
<tr>
<td>FTTr</td>
<td>PD0</td>
<td>5.51 ± 0.26*</td>
</tr>
<tr>
<td></td>
<td>PDt</td>
<td>4.36 ± 0.42</td>
</tr>
<tr>
<td>FTTL</td>
<td>PD0</td>
<td>4.62 ± 0.35</td>
</tr>
<tr>
<td></td>
<td>PDt</td>
<td>4.27 ± 0.40</td>
</tr>
<tr>
<td>PPTr</td>
<td>PD0</td>
<td>12.22 ± 1.06</td>
</tr>
<tr>
<td></td>
<td>PDt</td>
<td>11.61 ± 0.97</td>
</tr>
<tr>
<td>PPTL</td>
<td>PD0</td>
<td>10.89 ± 0.83</td>
</tr>
<tr>
<td></td>
<td>PDt</td>
<td>12.06 ± 1.12</td>
</tr>
</tbody>
</table>

PD – Parkinson’s disease; PD0 – de novo PD patients; PDt – PD patients with stable antiparkinson’s therapy. CFlu, CNORFlu – plasma concentrations of fluoxetine and norfluoxetine; FTTr, FTTL – finger tapping test for right and left hand; PPTr, PPTL – Purdue Pegboard Test for right (r) and left (l) hand; *p < 0.05, PD0 vs. PDt.

Of note, the raise in CFlu between days 0 and 18 (the plateau) coincided with the increase in FTT and especially in PPT scores (Tables 3 and 4).

Factor analysis reveals that influence of Flu/NORFlu concentrations increased over time (cumulative data from both PD0 and PDt patients; plasma samples were taken on days 0, 5, 11, and 18, six hours after Flu administration). The variance explained by the concentrations of Flu and NORFlu permanently increased from 13.9% (day 5) to 29.9% (day 11) and 37.6% (day 18) of cumulative variance (values of 89.4%, 84.9% and 91.8%, respectively). At the same time, influence of motor function scores decreased over time: variance explained by PPT and FTT scores of 75.5%, 55%, and 54.1% (days 5, 11, and 18, respectively).

PPT and FTT scores significantly correlated on day 11 (r = 0.62; p < 0.01). In addition, an inverse correlation was found between Flu/NORFlu concentrations and PPT-, but not with FTT scores, on day 18 (r = -0.70 and 0.48, respectively).

Gastrointestinal, cardiovascular side effects and/or insomnia, somnolence and excessive daytime sleepness as adverse reactions to Flu were not reported in the PD patients considered in the study.

Discussion

The major results of our pilot study show that Flu treatment may alleviate depression in PD patients without deterioration of motor function scores. FTT, PPT and UPDRS-motor scores were even improved despite the parallel increase in plasma concentrations of Flu/NORFlu during the first 18 days of the study.

Depression in PD must be properly diagnosed and treated 42. However, rare reports on the use of various antidepressants in PD patients offer controversial data on their safety regarding motor adverse reactions. Controlled clinical studies confirming the efficacy of Flu in PD patients and assessing the risk-benefit ratio of such a therapy are still lacking 43. The broad therapeutic window for Flu is due to its highly variable pharmacokinetics 5, 44–46. Flu steady state is achieved approximately after 3 weeks (concentrations of approximately 110 µg/L). If plasma concentrations increase above 110 µg/L, the dosage should be adjusted accordingly. Factor analyses indicates that mean Flu concentrations of approximately 60–110 µg/L have the most powerful effect on both PPT and FTT scores, which were significantly improved within that concentration range.
The PPT and FTT are quantitative motor tests. While FTT more reflects motor speed, the PPT is a test for fine motor functions and coordination. Since all the patients were right-handed only among 6/18 patients with affected left side FTTr and PPTr were better than FTTi and PPTi, respectively, pointing to more efficient compensatory mechanisms in dominant hand.

The pharmacological profile of fluoxetine is unique among the antidepressants used in PD patients. Fluoxetine is both SSRI agent and a 5HT2c antagonist. A recent investigation confirmed that 5HT1A agonists and 5HT2c antagonists could be important features in treatment of PD. In particular, 5HT2c receptors seem to tonically inhibit dopamine release from all three major dopaminergic pathways. Accordingly, 5HT2c antagonists could block such an inhibition, especially in the terminal regions of the nigrostriatal and mesolimbic pathways.

Additionally, 5-HT2c receptors are selectively located within substantia nigra pars reticulata (SNr) and medial globus pallidus (GPM) and 5-HT via 5HT2c receptors is excitatory in the SNr, which may contribute to the increased activity of these regions in PD. Systemic administration of selective 5-HT2c antagonists to 6-hydroxydopamine-lesioned rodents potentiates the antiparkinsonian action of dopamine D1 and D2 agonists, which is an action mediated via 5HT2c receptors in the SNr. Thus, 5-HT2c receptor antagonists may improve parkinsonism and drugs with 5-HT2c receptor antagonist action, such as fluoxetine, are unlikely to worsen PD.

The pathophysiological mechanisms involved in mood disturbances in PD remain complex. Serotonergic dysfunction has been postulated as such systems are involved in mood disorders in non-PD and the raphe nuclei, as well as hippocampus and prefrontal cortex, appear to be the primary sites affected. Moreover, transcranial ultrasound studies have suggested an association with reduced brainstem raphe echogenicity and nigral hyperchogenicity in patients with depression preceding PD onset compared with nondepressed patients with PD. As the PD disease progresses, Lewy bodies occur with the rostral raphe, thalamus and limbic and cortical regions, which may result in the mediating of mood disturbances in PD.

In depression associated with PD, PD-specific pathology, with multiple transmitter deficiencies in mesocortical monoaminergic systems, plays a major role. This includes the mesocorticolimbic dopaminergic projection as well as mesocortical noradrenergic and serotonergic projections. Corticolimbic noradrenergic denervation through cell loss in the locus coeruleus and serotonergic denervation via serotonergic cell loss in the raphe nucleus are also likely to be important. Postmortem evidence showed lower density of neurons in the dorsal raphe nuclei in depressed versus nondepressed patients with PD and cerebro-spinal fluid measurement in vivo showed reduced serotonin metabolite (5-HIAA) levels in depressed patients with PD since fluoxetine can reverse the downregulation of cell proliferation in the subgranular zone by the unilateral 6-hydroxydopamine lesion.

All these various mechanisms could explain why the improvement in Parkinson's disability scores in our patients coincided with an increase in plasma Flu and NORFlu concentrations during the first 18 days of antidepressive treatment.

Another question is to assess the possible difference between PD0 and PD1 patients' response to Flu treatment. The beneficial effects of Flu on motor symptoms of PD patients seem to be more pronounced in PD group (UPDRS and ADL scores). In addition, PPT scores were mostly higher in PD patients during chronic treatment with Flu increasing continuously by the end of the study (day 50). However, the antidepressive efficacy of Flu was similar in both PD groups (HDRS). Also, the statistical significance was rarely observed between those groups regarding motor function scores; FTT values were even somewhat higher in PD0 patients on days 11 and 50.

According to Taylor et al., depressive symptoms precede those of motor dysfunction in 12–37% of patients with...
PD. On the other hand, algorithms for treating depression in PD suggest that optimal antiparkinsonian treatment should precede administration of antidepressants. Our results support such an approach only partially: PD0 and PD1 groups did not differ in their response to antidepressive therapy, while the influence of Flu on motor functions scores was not consistently related to the pretreatment with antiparkinsonian drugs. Nevertheless, successfully treated PD before the administration of antidepressants may diminish overlapping of depressive symptoms and core Parkinson’s disease symptoms.

In the present study, we failed to observe any deterioration in motor performance scores of patients with PD that was related to the increase in plasma Flu and NORFlu concentrations. A slight improvement was even observed in all the scores (UPDRS, ADL, FTT and PPT). Similar results were obtained with citalopram, which improved mood but did not decrease motor performance scores in PD treated with levodopa; at the same time, citalopram improved the parkinsonian dyskinesia, bradykinesia and finger taps after one and four months of treatment, both in patients with and without depression.

Also, Weintraub et al. reported that escitalopram was well tolerated, but produced only a partial response in the treatment of major depression in elderly PD patients (mean age of 72.1 years). Two open-label studies suggested that sertraline reduced depression in PD patients, with additional beneficial effect on anxiety, without influencing motor function. Additionally, Ilic et al. showed that the treatment with sertraline exerts complex modulatory effects on human motor cortex with potential behavioural usefulness. In another open-label study with paroxetine (20 mg/day) given to 33 non-demented depressed PD patients during 6 months, Ceravolo et al. reported a significant improvement of depression, as evaluated by HDRS, without influence on parkinsonian symptoms. In only one patient fully reversible worsening of tremor was observed. However, paroxetine frequently may induce tremor as an adverse effect, with a prevalence of 1% to 2%.

Therefore, our results would allow an optimal design for further large, prospective, randomized, placebo-controlled clinical trials that are necessary to evaluate the efficacy and safety of SSRIs antidepressants and allow the development of evidence-based guidelines.

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REFERENCES


