ORIGINAL ARTICLE

UDC: 616.858-085
DOI: 10.2298/VSP111114028K

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

Vladimir Kostić*, Eleonora Džoljić*, Zoran Todorović†, Milija Mijajlović*, Marina Svetel*, Elka Stefanova*, Nataša Dragašević*, Igor Petrović*, Milenko Milošević‡, Ivan Kovačević§, Branislava Miljković‖, Milena Pokrajac‖, Milica Prostran†

***Clinic of Neurology, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; †Department of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; ‡Department of Special Physical Education, Police Academy, Belgrade, Serbia; §National Pharmacovigilance Center, Medicines and Medical Devices Agency of Serbia, Belgrade, Serbia; ‖Department of Pharmacokinetics, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia**

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), 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 obolelih 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 kako pojedinačne, tako i ponovljene doze Flu od prvog do osamdesetog dana. Plazma koncentracije Flu i norfluoksetina (NORFlu) korelisane su sa rezultatima odeđenih testova za motorne funkcije: skala za procenu težine PB (UPDRS), test spretnosti kucanja (FTT) i Purdue pegboard Test PPT). Izraženost PD, depresije i demencije procenjivane su korišćenjem standardnih testova [(test dnevnih

Correspondence to: Eleonora Džoljić, Clinic of Neurology, Clinical Centre of Serbia, Faculty of Medicine University of Belgrade, Dr Subotica 6, 11000 Belgrade, Serbia. Phone: +381 11 30 64 222; E-mail: dr.elidz@gmail.com

aktivnosti (ADL), Hoehn.-Yahr. stadijumi (HJ), HDRS, MMSE)]. **Rezultati.** Ravnotežno stanje za Flu/NORFlu postignuto je 18. dana lečenja. Takav plato u koncentraciji Flu/NORFlu bio je praćen značajnim poboljšanjem rezultata, kako testova za depresiju, tako i za izraženost PB (HDRS, UPDRS i ADL, sledstveno). Dodatno, rezultati FTT-a i PPT-a bili su u porastu do 18. dana, sa blagim fluktuacijama oko platoa. Optimalna motorna postignuća zabeležena su pri koncentraciji Flu od oko 60–110 μg/L. **Zaključak.** Flu (20 mg/dan) značajno redukuje depresiju kod bolesnika sa PB i ne remeti motorne funkcije. S obzirom na mogući placebo efekat u istraživanjima sa PB i depresijom, neophodna su obimnija, prospektivna, randomizovana, placebo-kontrolisana klinička ispitivanja.

Ključne reči:
parkinsonova bolest; motorna aktivnost; depresioni poremećaji; fluoksetin; lečenje, ishod.

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 [1]. Such a depression is mostly persistent or recurrent. It may be accompanied with anxiety, cognitive impairment and may reduce effectiveness of antiparkinson's therapy [2–5]. Depression increases PD patients' disability and significantly reduces their quality of life. Consequently, approximately 50% of patients with PD receive antidepressant therapy [4–7].

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 [8]. 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 [1, 9, 10].

On the other hand, selective serotonin reuptake inhibitors (SSRIs) are used as a first line treatment of depression 51% of the time [1, 9, 10]**.** 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 [11–14], 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%) [15]. Imaging studies *in vivo* have also suggested depletion of 5-HT innervation to the striatum as measured *via* decreased 5-HT transporter binding [16–18]. 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 [19, 20], associated with cell loss [21, 22]. Tauscher et al. [23], 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. [24], 2004, showed that 80% 5-HT transporter occupancy was achievable with SSRI 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}I]-CIT and SPECT [25]. All these findings of SSRIs-5-HT transporter occupancy in PET/SPECT studies clearly reflect the pharmacologically induced changes in serotonergic transmission [5, 26].

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 [1, 10]. While epidemiological studies have not suggested increased risk of worsening PD using SSRIs for depression [27], almost one hundred detailed reports on extrapyramidal adverse effects linked to SSRIs antidepressants have been published [28, 29].

The influence of Flu on motor performances in PD patients still remains to be clarified. Extrapiramidal side effects of Flu seem to be related to the exacerbation of Parkinson's disability [30]. However, it was also reported that Flu did not increase Parkinson's disability either in retrospective [31] or in prospective studies [32]. Therefore, the authors argue for more systemic and controlled research examining the treatment of depression in patients with PD [1, 33, 34].

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), I and II [35, 36], accompanied with mild depression [(Hamilton Rating Scale for Depression (HDRS): $10 \leq \text{HDRS} \leq 23$)], without dementia [(Mini Mental State Examination (MMSE): ≥ 25)]. These 18 patients were either *de novo* PD patients (PD_0 group, N = 9), or PD patients who were on the stable antiparkinsonian treatment (PD_t group, N = 9), without selegiline, rasagiline and/or dopamine agonists for at least two months prior to Flu.

Patients with secondary parkinsonism, those with the MMSE score < 25 [36], 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-

tives, 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 than 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 T_{max} for Flu, ranging from 4 to 8 h after the single dose administration [37] (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 [38], ADL (Schwab and England Activities of Daily Living Score) and computerized version of the quantitative motor test Finger Tapping Test (FTT) [39] and the Purdue Pegboard Test (PPT) [40]. The current severity of depression was evaluated using the 17-item HDRS [41].

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, PD_0 and PD_t, 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 (PPTr) and PPT for the left hand (PPTl) scores (p = 0.66, and 0.89, respectively).

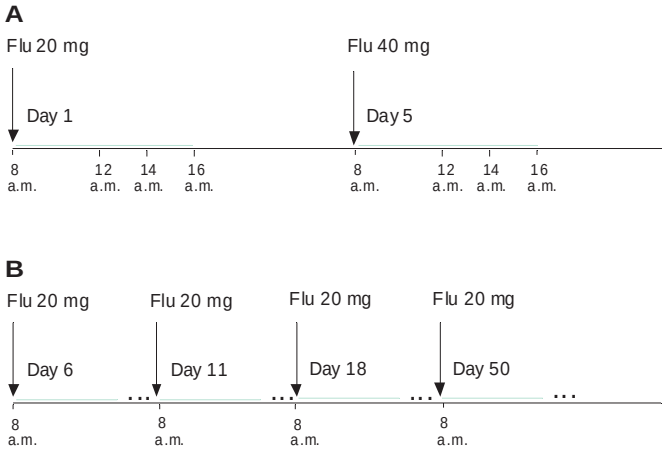

Fig. 1 – Design of the study: acute and chronic treatment of Parkinsonian patients with fluoxetine (Flu) (panel A – acute treatment with Flu, panel B – chronic treatment with Flu)

Among 6/18 patients with affected left side, FTTr was significantly better than FTTl ($p = 0.03$) and PPTr was significantly better than PPTl ($p = 0.02$). In addition, only PPTr 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 PD_0- and PD_t-patients are shown in Tables 1 and 2.

Chronic, treatment with Flu: plasma concentrations of Flu and NORFlu increased in a time-related manner (C_{Flu}, and C_{NORFlu}, respectively) (Figure 2).

Table 4 shows plasma concentrations of Flu and NORFlu, as well as motor performance scores for each group assessed during chronic treatment with Flu.

Different patterns of changes were observed in the PD_0 and PD_t patients. In the former case, a sustained increase in both C_{Flu}, and C_{NORFlu} was observed until day 18, i.e. the plateau was reached after 18 days of treatment. In the latter case, plasma concentrations continuously raised until the end of the observation period (day 50) (Table 4). C_{Flu} was significantly higher in PD_0 than in PD_t group after 18 days of treatment (Figure 2A, Table 4).

During chronic treatment with Flu, FTTr scores in the group PD_0 were continuously higher than in the group PD_t, reaching the significance on days 11 and 50 (P = 0.03 and 0.04, respectively) (Table 4). Such a difference was less pronounced regarding FTTl, PPTr and PPTl scores, never reaching statistical significance.

Table 1

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

Group of patients	Age (years)	Duration of PD (years)	Previous levodopa therapy		MMSE
			Duration (years)	Dose (mg/day)	
PD_0 (N = 9)	55.7 ± 3.0	2.7 ± 0.9	0	0	28.0 ± 0.6
PD_t (N = 9)	56.0 ± 2.7	3.6 ± 1.1	3.9 ± 0.9	458.3 ± 55.1	27.9 ± 0.9

MMSE – mini mental state examination; PD_0 – *de novo* PD patients; PD_t – 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), before (day 1) and on the 18th day of fluoxetine (Flu) medication (day 18 ≈ steady state for Flu) (mean ± S.E.M.)

Group of patients	HDRS		UPDRS		ADL	
	day 1	day 18	day 1	day 18	day 1	day 18
PD_0 (N = 9)	16.4 ± 2.1	10.4 ± 1.9*	26.7 ± 2.9	23.6 ± 3.4	81.7 ± 3.8	85.0 ± 3.4
PD_t (N = 9)	13.6 ± 0.9	8.2 ± 1.1*	29.0 ± 5.1	22.2 ± 4.6*	82.2 ± 3.3	85.6 ± 3.4*

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 PD_0 and PD_t patients (Table 2, HDRS scores, $p < 0.05$). At the same time, Parkinson's disability was remarkably improved, especially in PD_t 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 PD_0 and PD_t differ only in FTTr scores at 0 h and 8 h after the administration of 40 mg of Flu (day 5).

Table 3

Changes in fluoxetine (Flu) and norfluoxwtine (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.)

Day s of Flu treatment		Day 1 of the treatment				Day 5 of the treatment			
Parameter	Group	0 h	4 h	6 h	8 h	0 h	4 h	6 h	8 h
C_{Flu} (μg/L)	PD_0	0	9.58 ± 1.51	11.44 ± 1.31	14.80 ± 0.80	3.24 ± 1.51	19.98 ± 3.30	23.19 ± 1.89	27.40 ± 2.06
	PD_t	0	8.83 ± 1.02	14.76 ± 1.88	16.99 ± 2.28	5.87 ± 1.40	22.71 ± 3.39	25.60 ± 3.90	33.62 ± 2.87
C_{NORFlu} (μg/L)	PD_0	0	0	0	0	0	3.57 ± 1.78	7.48 ± 1.78*	10.48 ± 1.46
	PD_t	0	0	0	0	2.57 ± 1.71	7.72 ± 2.02	11.95 ± 0.48	12.87 ± 0.49
FTTr	PD_0	5.11 ± 0.40	4.91 ± 0.45	5.20 ± 0.35	5.01 ± 0.43	5.44 ± 0.24*	5.31 ± 0.28	5.19 ± 0.31	5.44 ± 0.30*
	PD_t	3.60 ± 0.53	3.55 ± 0.47	3.93 ± 0.43	4.14 ± 0.48	4.17 ± 0.44	4.16 ± 0.45	4.36 ± 0.43	4.16 ± 0.44
FTTl	PD_0	4.25 ± 0.41	4.34 ± 0.36	4.56 ± 0.36	4.57 ± 0.31	4.42 ± 0.24	4.46 ± 0.32	4.49 ± 0.32	4.83 ± 0.41
	PD_t	4.00 ± 0.49	4.05 ± 0.40	4.12 ± 0.46	4.10 ± 0.46	4.21 ± 0.45	4.24 ± 0.42	4.15 ± 0.42	4.38 ± 0.40
PPTr	PD_0	10.33 ± 0.93	11.56 ± 0.96	11.56 ± 1.07	11.22 ± 0.85	11.33 ± 0.94	12.22 ± 0.81	11.78 ± 0.98	11.89 ± 0.92
	PD_t	11.22 ± 1.10	11.56 ± 1.10	11.44 ± 1.09	11.78 ± 1.15	11.44 ± 1.08	11.67 ± 1.24	11.00 ± 1.27	10.89 ± 1.27
PPTl	PD_0	9.22 ± 0.66	9.89 ± 0.66	10.67 ± 0.67	10.44 ± 0.67	10.44 ± 0.75	10.67 ± 0.78	10.78 ± 0.88	10.33 ± 0.87
	PD_t	11.22 ± 0.91	11.89 ± 1.32	10.78 ± 1.28	12.00 ± 1.18	12.00 ± 1.12	12.00 ± 1.30	11.78 ± 1.27	11.44 ± 1.16

PD – Parkinson's disease; PD_0 – *de novo* PD patients; PD_t – PD patients with stable antiparkinson's therapy; C_{Flu}, C_{NORFlu} – 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; * – $p < 0.05$, PD_0 vs. PD_t.

Table 4

Changes in fluoxetine (Flu) and norfluoxetine (NORFlu) concentrations, and motor function scores (FTT, PPT) during chronic treatment with Flu (days 11–80: 20 mg/day) (mean ± S.E.M)

Parameter	Group	Days of Flu treatment		
		Day 11	Day 18	Day 50
C_{Flu} (μg/L)	PD_0	60.73 ± 7.31	112.21 ± 17.95*	87.99 ± 9.88
	PD_t	51.97 ± 6.52	62.34 ± 11.66	94.13 ± 20.54
C_{NorFlu} (μg/L)	PD_0	62.17 ± 12.29	129.17 ± 27.43	106.51 ± 28.73*
	PD_t	60.80 ± 9.45	82.84 ± 11.22	181.74 ± 18.00
FTTr	PD_0	5.51 ± 0.26*	5.56 ± 0.32	5.34 ± 0.45
	PD_t	4.36 ± 0.42	4.47 ± 0.43	3.73 ± 0.80
FTTl	PD_0	4.62 ± 0.35	4.71 ± 0.32	4.78 ± 0.60
	PD_t	4.27 ± 0.40	4.16 ± 0.43	4.11 ± 0.94
PPTr	PD_0	12.22 ± 1.06	12.89 ± 0.88	14.17 ± 0.53
	PD_t	11.61± 0.97	11.83 ± 1.08	14.67 ± 1.76
PPTl	PD_0	10.89 ± 0.83	11.44 ± 0.90	11.81 ± 1.25
	PD_t	12.06 ± 1.12	12.17 ± 1.19	14.50 ± 2.08

PD – Parkinson's disease; PD_0 – *de novo* PD patients; PD_t – PD patients with stable antiparkinson's therapy; C_{Flu}, C_{NORFlu} – 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; * – $p < 0.05$, PD_0 vs. PD_t

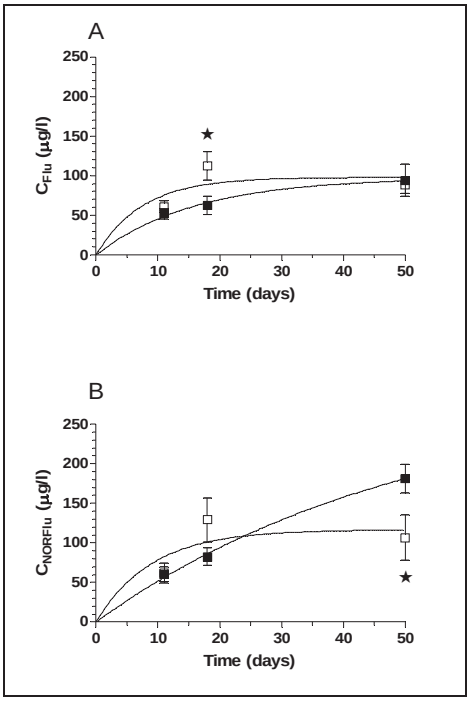

Fig. 2 – Changes in plasma concentrations of fluoxetine (C_{Flu}) and its active metabolite norfluoxetine (C_{NORFlu}) over time (panels A and B, respecively) in PD_0 (□) and PD_t patients (■), during chronic treatment with Flu (days 11–50, 20 mg/day). Each point represents the mean ± S.E.M. of plasma concentrations obtained from 9 separate PD_0 or PD_t patients. *$p < 0.05$, the PD_0 vs. the group PD_t

PD – Parkinson's disease; PD_0 – *de novo* PD patients; PD_t – PD patients with stable antiparkinson's therapy

Of note, the raise in C_{Flu} 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 (cummulative data from both PD_0 and PD_t 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 patiens 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 [40, 47]. Since all the patients were right-handed only among 6/18 patients with affected left side FTTr and PPTr were better than FTTl and PPTl, respectively, pointing to more efficient compensatory mechanisms in dominant hand [48, 49].

The pharmacological profile of fluoxetine is unique among the antidepressants used in PD patients. Fluoxetine is both SSRI agent and a $5HT_{2C}$ antagonist [50]. A recent investigation confirmed that $5HT_{1A}$ agonists and $5HT_{2C}$ antagonists could be important features in treatment of PD. In particular, $5HT_{2c}$ receptors seem to tonically inhibit dopamine release from all three major dopaminergic pathways. Accordingly, $5HT_{2c}$ antagonists could block such an inhibiton, especially in the terminal regions of the nigrostriatal and mesolimbic pathways [51].

Additionally, 5-HT_{2c} receptors are selectively located within substantia nigra pars reticulata (SNr) and medial globus pallidus (GPm) and 5-HT via 5-HT_{2c} receptors is excitatory in the SNr [52–55], which may contribute to the increased activity of these regions in PD. Systemic administration of selective 5-HT_{2c} antagonists to 6-hydroxydopamine-lesioned rodents potentates the antiparkinsonian action of dopamine D_1 and D_2 agonists [56, 57], which is an action mediated via 5-HT_{2c} receptors in the SNr [56]. Thus, 5-HT_{2c} receptor antagonists may improve parkinsonism and drugs with 5-HT_{2c} receptor antagonist action, such as fluoxetine, are unlikely to worsen PD [57].

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 [58, 59]. Moreover, transcranial ultrasound studies have suggested an association with reduced brainstem raphe echogenicity and nigral hyperechogenicity in patients with depression preceding PD onset compared with nondepressed patients with PD [60]. As the PD disease progresses, Lewy bodies occur with the rostral raphe, thalamus and limbic and cortical regions [15–22, 61], which may result in the mediating of mood disturbances in PD [23–26].

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 deneravtion *via* serotonergic cell loss in the raphe nucleus are also likely to be important [11–15, 22–26, 62]. Postmortem evidence showed lower density of neurons in the dorsal raphe nuclei in depressed versus nondepressed patients with PD [22] and cerebro-spinal fluid measurement *in vivo* showed reduced serotonin metabolite (5-HIAA) levels in depressed patients with PD [63, 64]. A [11C]-DASB PET study in seven patients with PD with untreated depression showed elevated serotonin transporter binding in the prefrontal cortex compared with non-PD-matched controls [65]. Recently, Politis et al. [66] have reported that the patients with PD with the highest scores for depressive symptoms showed significantly increased [11C]-DSAB binding in the amigdala, hypothalamus, caudal raphe nuclei and posterior cingytlate cortex compared with those patients with low depression scores, though not compared with healthy controls. The [11C]-DSAB binding values in other regions, including the anterior cingulate cortex, caudate, insula, prefrontal cortex, putamen rostral raphe nuclei, thalamus and ventral striatum, were similarly decreased in patients with PD, irrespective of their depressive symptoms scores, compared with the healthy controls. This study demonstrates that depressive symptoms in antidepressant-naïve patients with PD are associated with relatively higher serotonin binding in raphe nuclei and limbic structures. A relative increase in serotonin transporter binding in these regions could reflect either lower extracellular serotonin levels or a disease-related loss of presinaptic serotonergic neurotransmission in contributing to the pathophysiology of PD depression [62, 66].

The phenomenology of depression in PD is also different from that in patints with non-PD with less anhedonia and feeling of guilt [67]. While etiology of depression in Parkinson's disease is unclear (biochemical changes, psychosocial factors and situational stressors have all been implicated), it has an adverse effect on the quality of patients' lives and doctors should ensure that it is diagnosed and properly treated [1, 4, 5, 68].

Therefore, along with improvement on parkinsonian quality of life due to antidepressant activity of SSRI, symptoms such as bradikinesia, hypomima, hypophonia that overlap between depression and parkinsonism could ameliorate because an improvement of mood symptoms [1, 9, 10]. Evenmore, Suzuki et al [69], 2010, suggested that SSRIs such as fluoxetine potentially are therapeutic drugs for non-motor symptoms as well as motor symptoms in 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 PD_0 and PD_t patients' response to Flu treatment. The beneficial effects of Flu on motor symptoms of PD patients seem to be more pronounced in PD_t group (UPDRS and ADL scores). In addition, PPT scores were mostly higher in PD_t 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 PD_0 patients on days 11 and 50.

According to Taylor et al. [70], 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 [1, 71]. Our results support such an approach only partially: PD_0 and PD_t 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, successfull treatment of PD before the administration of antidepressants may diminish overlapping of depressive symptoms and core Parkinson's diasease symptoms [1].

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 dysability, bradykinesia and finger taps after one and four months of treatment, both in patients with and without depression [72, 73]. Also, Weintraub et al. [44], 2006, 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 [74, 75]. Additionaly, Ilic et al. [76] 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 nondemented depressed PD patients during 6 months, Ceravolo et al. [77], in 2000, 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%. Chung et al. [78] in 2005, reported that the short-term paroxetine treatment did not alter the motor response to levodopa in patients with PD.

On the other hand, in two retrospective studies worsening of motor symptoms was observed in only small number of PD patients treated with SSRIs [79, 80]. In a prospective study comprising 65 depressed PD out-patients treated with paroxetine (10–20 mg/day) for at least 3 months, two out of 52 patients who completed the study (3%) experienced worsening of parkinsonian symptoms [79]. However, van de Vijver et al. [80], in 2002, observed that the start of SSRI therapy in levodopa users was followed by a faster increase of antiparkinsonian drug treatment. Gony et al. [81], in 2003, failed to find any significant difference in the occurrence of serious extrapyramidal symptoms between different classes of SSRI antidepressant drugs in patients with PD treated with dopaminergic antiparkinsonian drugs. According to the results of several studies [82–84], including our results with Flu, it seems that the benefit of SSRIs outweigh the potential problems due to adverse effects and that they may be considered to be the rational choice in the treatment of depression in PD.

There are several limitations of the study: it was an open-label study without randomization including a small number of patients. As with all nonradomized, open-label trials at tertiary research centers, many non-specific factors**,** such as relatively long duration of symptoms in *de novo* PD patients, may have influenced the results. However, the quantitative evaluations of motor functions using FTT and PPT significantly improved objectivity and validity of our findings. The observed dropout rates (50% and 56% on days 50 and 80, respectively) are high but fit to the range observed in clinical trials to depression [83].

Conclusion

This pilot study suggests that Flu 20 mg is effective and well tolerated antidepressant in patients with Parkinson's disease. In addition, Flu improved motor function scores in PD patients and such improvement was observed in parallel with the increase in plasma Flu and NORFlu concentrations. Also, the effects of Flu were similar in *de novo* PD patients and in those already treated with antiparkinsonian medications.

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 SSRI antidepressants and allow the development of evidence-based guidelines.

Acknowledgment

This work was supported by the Ministry of Science, Republic of Serbia (Project No. 175090).

REFERENCES

1. *Veazey C, Aki SO, Cook KF, Lai EC, Kunik ME.* Prevalence and treatment of depression in Parkinson's disease. J Neuropsychiatry Clin Neurosci 2005; 17(3): 310−23.
2. *Kostíc VS, Filipović SR, Lecić D, Momcilović D, Sokić D, Sternić N.* Effect of age at onset on frequency of depression in Parkinson's disease. J Neurol Neurosurg Psychiatry 1994; 57(10): 1265−7.
3. *Kostić VS, Lečić D, Filipović S, Stojanović M.* Depression and Parkinsonęs disease. Psychiatriki 1995; 6: 125−35.
4. *Kostic VS, Stefanova E, Dragasevic N, Potrebic S.* Diagnosis and treatment of depression in Parkinson's disease. In: *Bedard MA, Agid Y, Chouinard S, Fahn S, Korczyn AD, Lesperance P,* editors. Mental and behavioral dysfunction in movement disorders. Totowa: Humana Press; 2003. p. 351−68.
5. *Hesse S, Barthel H, Schwarz J, Sabri O, Müller U.* Advances in in vivo imaging of serotonergic neurons in neuropsychiatric disorders. Neurosci Biobehav Rev 2004; 28(6): 547−63.
6. *Kuopio AM, Marttila RJ, Helenius H, Toivonen M, Rinne UK.* The quality of life in Parkinson's disease. Mov Disord 2000; 15(2): 216−23.
7. *Ritter JL, Alexander B.* Retrospective study of selegiline-antidepressant drug interactions and a review of the literature. Ann Clin Psychiatry 1997; 9(1): 7−13.

8. *Miyasaki JM, Shannon K, Voon V, Ravina B, Kleiner-Fisman G, Anderson K,* et al. Practice Parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006; 66(7): 996−1002.
9. *Richard IH, Kurlan R.* A survey of antidepressant drug use in Parkinson's disease. Parkinson Study Group. Neurology 1997; 49(4): 1168−70.
10. *Vajda FJ, Solinas C.* Current approaches to management of depression in Parkinson's Disease. J Clin Neurosci 2005; 12(7): 739−43.
11. *Fahn S, Libsch LR, Cutler RW.* Monoamines in the human neostriatum: topographic distribution in normals and in Parkinson's disease and their role in akinesia, rigidity, chorea, and tremor. J Neurol Sci 1971; 14(4): 427−55.
12. *Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F.* Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. J Neurol Sci 1973; 20(4): 415−55.
13. *Scatton B, Javoy-Agid F, Rouquier L, Dubois B, Agid Y.* Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Res 1983; 275(2): 321−8.
14. *Shannak K, Rajput A, Rozdilsky B, Kish S, Gilbert J, Hornykiewicz O.* Noradrenaline, dopamine and serotonin levels and metabolism in the human hypothalamus: observations in Parkinson's disease and normal subjects. Brain Res 1994; 639(1): 33−41.
15. *Kish SJ, Tong J, Hornykiewicz O, Rajput A, Chang LJ, Guttman M,* et al. Preferential loss of serotonin markers in caudate versus putamen in Parkinson's disease. Brain 2008; 131(Pt 1): 120−31.
16. *Kerenyi L, Ricaurte GA, Schretlen DJ, McCann U, Varga J,* et al. Positron emission tomography of striatal serotonin transporters in Parkinson disease. Arch Neurol 2003; 60(9): 1223−9.
17. *Guttman M, Boileau I, Warsh J, Saint-Cyr JA, Ginovart N, McCluskey T,* et al. Brain serotonin transporter binding in nondepressed patients with Parkinson's disease. Eur J Neurol 2007; 14(5): 523−8.
18. *Albin RL, Koeppe RA, Bohnen NI, Wernette K, Kilbourn MA, Frey KA.* Spared caudal brainstem SERT binding in early Parkinson's disease. J Cereb Blood Flow Metab 2008; 28(3): 441−4.
19. *D'Amato RJ, Zweig RM, Whitehouse PJ, Wenk GL, Singer HS, Mayeux R,* et al. Aminergic systems in Alzheimer's disease and Parkinson's disease. Ann Neurol 1987; 22(2): 229−36.
20. *Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E.* Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003; 24(2): 197−211.
21. *Halliday GM, Li YW, Blumbergs PC, Joh TH, Cotton RG, Howe PR,* et AL. Neuropathology of immunohistochemically identified brainstem neurons in Parkinson's disease. Ann Neurol 1990; 27(4): 373−85.
22. *Paulus W, Jellinger K.* The neuropathologic basis of different clinical subgroups of Parkinson's disease. J Neuropathol Exp Neurol 1991; 50(6): 743−55.
23. *Tauscher J, Pirker W, de Zwaan M, Asenbaum S, Brücke T, Kasper S.* In vivo visualization of serotonin transporters in the human brain during fluoxetine treatment. Eur Neuropsychopharmacol 1999; 9(1−2): 177−9.
24. *Meyer JH, Wilson AA, Sagrati S, Hussey D, Carella A, Potter WZ,* et al. Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [11C]DASB positron emission tomography study. Am J Psychiatry 2004; 161(5): 826−35.
25. *Laasonen-Balk T, Viinamäki H, Kuikka JT, Husso-Saastamoinen M, Lehtonen J, Tiihonen J.* 123I-beta-CIT binding and recovery from depression. A six-month follow-up study. Eur Arch Psychiatry Clin Neurosci 2004; 254(3): 152−5.
26. *Kostić VS, Djurić BM, Covicković-Sternić N, Bumbasirević L, Nikolić M, Mrsulja BB.* Depression and Parkinson's disease: possible role of serotonergic mechanisms. J Neurol 1987; 234(2): 94−6.
27. *Arbouw ME, Movig KL, Neef C, Guchelaar HJ, Egberts TC.* Influence of initial use of serotonergic antidepressants on antiparkinsonian drug use in levodopa-using patients. Eur J Clin Pharmacol 2007; 63(2): 181−7.
28. *Extrapyramidal effects of SSRI antidepressants.* Prescrire Int 2001; 10(54): 118−9.
29. *Richard IH, Maughn A, Kurlan R.* Do serotonin reuptake inhibitor antidepressants worsen Parkinson's disease? A retrospective case series. Mov Disord 1999; 14(1): 155−7.
30. *Leo RJ.* Movement disorders associated with the serotonin selective reuptake inhibitors. J Clin Psychiatry 1996; 57(10): 449−54.
31. *Caley CF, Friedman JH.* Does fluoxetine exacerbate Parkinson's disease? J Clin Psychiatry 1992; 53(8): 278−82.
32. *Dell'Agnello G, Ceravolo R, Nuti A, Bellini G, Piccinni A, D'Avino C,* et al. SSRIs do not worsen Parkinson's disease: evidence from an open-label, prospective study. Clin Neuropharmacol 2001; 24(4): 221−7.
33. *Oertel WH, Hoglinger GU, Caraceni T.* Depression in Parkinson's disease: an update. In: *Calne D, Calne S*, editors. Parkinson's Disease: Advances in Neurology: Parkinson's Disease. Philadelphia: Lippincott Wiliams and Wikins; 2001. p. 373.
34. *Jankovic J, Tolosa E.* Depression in Parkinson's Disease and Movement Disorders. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2007.
35. *Hoehn MM, Yahr MD.* Parkinsonism: onset, progression and mortality. Neurology 1967; 17(5): 427−42.
36. *Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C,* et al. Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord 2004; 19(9): 1020−8.
37. *Folstein MF, Folstein SE, McHugh PR.* "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12(3): 189−98.
38. *Altamura AC, Moro AR, Percudani M.* Clinical pharmacokinetics of fluoxetine. Clin Pharmacokinet 1994; 26(3): 201−14.
39. *Fahn S, Elton R.* Unified Parkinson's Disease Rating Scale. In: *Fahn S, Marsden CD, Calne DB, Goldstein M,* editors. Recent development in Parkinson's disease. Florham Park: MacMillan; 1987. p. 153−63.
40. *Shimoyama I, Ninchoji T, Uemura K.* The finger-tapping test. A quantitative analysis. Arch Neurol 1990; 47(6): 681−4.
41. *Lezak M.* Neuropsychological assessment. 2nd ed. New York, Oxford: University Press; 1983.
42. *Hamilton M* A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23: 56−62.
43. *Allain H, Schuck S, Mauduit N.* Depression in Parkinson's disease. BMJ 2000; 320(7245): 1287−8.
44. *Weintraub D, Taraborelli D, Morales KH, Duda JE, Katz IR, Stern MB.* Escitalopram for major depression in Parkinson's disease: an open-label, flexible-dosage study. J Neuropsychiatry Clin Neurosci 2006; 18(3): 377−83.
45. *Charlier C, Pinto E, Ansseau M, Plomteux G.* Relationship between clinical effects, serum drug concentration, and concurrent drug interactions in depressed patients treated with citalopram, fluoxetine, clomipramine, paroxetine or venlafaxine. Hum Psychopharmacol 2000; 15(6): 453−9.
46. *Nierenberg AA, Farabaugh AH, Alpert JE, Gordon J, Worthington JJ, Rosenbaum JF,* et al. Timing of onset of antidepressant response with fluoxetine treatment. Am J Psychiatry 2000; 157(9): 1423−8.
47. *Bolo NR, Hodé Y, Nédélec JF, Lainé E, Wagner G, Macher JP.* Brain pharmacokinetics and tissue distribution in vivo of fluvoxamine and fluoxetine by fluorine magnetic resonance spectroscopy. Neuropsychopharmacology 2000; 23(4): 428−38.

48. *Ringendahl H.* Factor structure, normative data and retest-reliability of a test of fine motor functions in patients with idiopathic Parkinson's disease. J Clin Exp Neuropsychol 2002; 24(4): 491−502.
49. *Helmich RC, de Lange FP, Bloem BR, Toni I.* Cerebral compensation during motor imagery in Parkinson's disease. Neuropsychologia 2007; 45(10): 2201−15.
50. *Helmich RC, Aarts E, de Lange F, Bloem B, Toni I.* Increased dependence of action selection on recent motor history in Parkinson's disease. J Neurosci 2009; 29(19): 6105−13.
51. *Ni YG, Miledi R.* Blockage of 5HT2C serotonin receptors by fluoxetine (Prozac). Proc Natl Acad Sci U S A 1997; 94(5): 2036−40.
52. *Alex KD, Pehek EA.* Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. Pharmacol Ther 2007; 113(2): 296−320.
53. *Di Matteo V, De Blasi A, Di Giulio C, Esposito E.* Role of 5-HT(2C) receptors in the control of central dopamine function. Trends Pharmacol Sci 2001; 22(5): 229−32.
54. *Hoyer D, Pazos A, Probst A, Palacios JM.* Serotonin receptors in the human brain. II. Characterization and autoradiographic localization of 5-HT1C and 5-HT2 recognition sites. Brain Res 1986; 376(1): 97−107.
55. *Invernizzi RW, Pierucci M, Calcagno E, Di Giovanni G, Di Matteo V, Benigno A,* et al. Selective activation of 5-HT(2C) receptors stimulates GABA-ergic function in the rat substantia nigra pars reticulata: a combined in vivo electrophysiological and neurochemical study. Neuroscience 2007; 144(4): 1523−35.
56. *Rick CE, Stanford IM, Lacey MG.* Excitation of rat substantia nigra pars reticulata neurons by 5-hydroxytryptamine in vitro: evidence for a direct action mediated by 5-hydroxytryptamine2C receptors. Neuroscience 199; 69(3): 903−13.
57. *Fox SH, Moser B, Brotchie JM.* Behavioral effects of 5-HT2C receptor antagonism in the substantia nigra zona reticulata of the 6-hydroxydopamine-lesioned rat model of Parkinson's disease. Exp Neurol 1998; 151(1): 35−49.
58. *Fox SH, Brotchie JM.* 5-HT(2C) receptor antagonists enhance the behavioural response to dopamine D(1) receptor agonists in the 6-hydroxydopamine-lesioned rat. Eur J Pharmacol 2000; 398(1): 59−64.
59. *Drevets WC, Thase ME, Moses-Kolko EL, Price J, Frank E, Kupfer DJ,* et al. Serotonin-1A receptor imaging in recurrent depression: replication and literature review. Nucl Med Biol 2007; 34(7): 865−77.
60. *Groenewegen HJ, Uylings HB.* The prefrontal cortex and the integration of sensory, limbic and autonomic information. Prog Brain Res 2000; 126: 3−28.
61. *Walter U, Hoeppner J, Prudente-Morrissey L, Horowski S, Herpertz SC, Benecke R.* Parkinson's disease-like midbrain sonography abnormalities are frequent in depressive disorders. Brain 2007; 130(Pt 7): 1799−807.
62. *Braak H, Del Tredici K.* Invited Article: Nervous system pathology in sporadic Parkinson disease. Neurology 2008; 70(20): 1916−25.
63. *Seppi K.* Abnormal serotonergic neurotransmission contributes to the pathopysiology of depression in PD. Mov Disord 2011; 26(3): 379.
64. *Mayeux R, Stern Y, Williams JB, Cote L, Frantz A, Dyrenfurth I.* Clinical and biochemical features of depression in Parkinson's disease. Am J Psychiatry 1986; 143(6): 756−9.
65. *Boileau I, Warsh JJ, Guttman M, Saint-Cyr JA, McCluskey T, Rusjan P,* et al. Elevated serotonin transporter binding in depressed patients with Parkinson's disease: a preliminary PET study with [11C]DASB. Mov Disord 2008; 23(12): 1776−80.
66. *Politis M, Wu K, Loane C, Turkheimer FE, Molloy S, Brooks DJ,* et al. Depressive symptoms in PD correlate with higher 5-HTT binding in raphe and limbic structures. Neurology 2010; 75(21): 1920−7.
67. *Ehrt U, Brønnick K, Leentjens AF, Larsen JP, Aarsland D.* Depressive symptom profile in Parkinson's disease: a comparison with depression in elderly patients without Parkinson's disease. Int J Geriatr Psychiatry 2006; 21(3): 252−8.
68. *Fox SH, Chuang R, Brotchie JM.* Serotonin and Parkinson's disease: On movement, mood, and madness. Mov Disord 2009; 24(9): 1255−66.
69. *Suzuki K, Okada K, Wakuda T, Shinmura C, Kameno Y, Iwata K,* et al. Destruction of dopaminergic neurons in the midbrain by 6-hydroxydopamine decreased hippocampal cell proliferation rate in rats: reversal by fluoxetine. PLoS One 2010; 5(2): e9260.
70. *Taylor AE, Saint-Cyr JA, Lang AE, Kenny FT.* Parkinson's disease and depression. A critical re-evaluation. Brain 1986; 109(Pt 2): 279−92.
71. *Okun MS, Watts RL.* Depression associated with Parkinson's disease: clinical features and treatment. Neurology 2002; 58(4 Suppl 1): S63−S70.
72. *Menza M, Marin H, Kaufman K, Mark M, Lauritano M.* Citalopram treatment of depression in Parkinson's disease: the impact on anxiety, disability, and cognition. J Neuropsychiatry Clin Neurosci 2004; 16(3): 315−9.
73. *Rampello L, Chiechio S, Raffaele R, Vecchio I, Nicoletti F.* The SSRI, citalopram, improves bradykinesia in patients with Parkinson's disease treated with L-dopa. Clin Neuropharmacol 2002; 25(1): 21−4.
74. *Meara RJ, Bhowmick BK, Hobson JP.* An open uncontrolled study of the use of sertraline in the treatment of depression in Parkinson's disease. J Serotonin Res 1996; 2(4): 243−9.
75. *Hauser RA, Zesiewicz TA.* Sertraline for the treatment of depression in Parkinson's disease. Mov Disord 1997; 12(5): 756−9.
76. *Ilic TV, Korchounov A, Ziemann U.* Complex modulation of human motor cortex excitability by the specific serotonin re-uptake inhibitor sertraline. Neurosci Lett 2002; 319(2): 116−20.
77. *Ceravolo R, Nuti A, Piccinni A, Dell'Agnello G, Bellini G, Gambaccini G,* et al. Paroxetine in Parkinson's disease: effects on motor and depressive symptoms. Neurology 2000; 55(8): 1216−8.
78. *Chung KA, Carlson NE, Nutt JG.* Short-term paroxetine treatment does not alter the motor response to levodopa in PD. Neurology 2005; 64(10): 1797−8.
79. *Tesei S, Antonini A, Canesi M, Zecchinalli A, Mariani CB, Pezzoli G.* Tolerability of paroxetine in Parkinson's disease: a prospective study. Mov Disord 2000; 15(5): 986-989.
80. *van de Vijver DA, Roos RA, Jansen PA, Porsius AJ, de Boer A.* Start of a selective serotonin reuptake inhibitor (SSRI) and increase of antiparkinsonian drug treatment in patients on levodopa. Br J Clin Pharmacol 2002; 54(2): 168−70.
81. *Gony M, Lapeyre-Mestre M, Montastruc JL.* Risk of serious extrapyramidal symptoms in patients with Parkinson's disease receiving antidepressant drugs: a pharmacoepidemiologic study comparing serotonin reuptake inhibitors and other antidepressant drugs. Clin Neuropharmacol 2003; 26(3): 142−5
82. *Tom T, Cummings JL.* Depression in Parkinson's disease: pharmacological characteristics and treatment. Drugs Aging 1998; 12(1): 55−74.
83. *Zesiewicz TA, Gold M, Chari G, Hauser RA.* Current issues in depression in Parkinson's disease. Am J Geriatr Psychiatry 1999; 7(2): 110−8.
84. *Machado M, Iskedjian M, Ruiz I, Einarson TR.* Remission, dropouts, and adverse drug reaction rates in major depressive disorder: a meta-analysis of head-to-head trials. Curr Med Res Opin 2006; 22(9): 1825–37.

Received on November 14, 2011.
Revised on March 1, 2012.
Accepted on May 8, 2012.
OnLine-first, August, 2012.