Fluoxetine Treatment in Poststroke Depression, Emotional Incontinence, and Anger Proneness

A Double-Blind, Placebo-Controlled Study

Smi Choi-Kwon, PhD, RN; Sung W. Han, RN; Sun U. Kwon, MD; Dong-Wha Kang, MD; Ji M. Choi, RN; Jong S. Kim, MD

Background and Purpose—The efficacy and safety of the selective serotonin reuptake inhibitor fluoxetine have rarely been studied in the treatment of poststroke emotional disturbances.

Methods—Stroke patients (152) who had poststroke depression (PSD), emotional incontinence (PSEI), or anger proneness (PSAP) were studied. PSD was evaluated by Beck Depression Inventory and *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, PSEI by Kim's criteria, and PSAP was assessed by Spielberger Trait Anger Scale. Subjects were randomly given either fluoxetine 20 mg/day (n=76) or placebo (n=76) for 3 months. Follow-up evaluations were done 1, 3, and 6 months after the beginning of the treatment. The primary outcome measurement was the scores of emotional disturbances at each follow-up assessment. The secondary outcome measurements were the percentage changes of the scores and the subjective responses of the patients.

Results—Although patients in the fluoxetine group more often dropped out because of adverse effects, fluoxetine administration was generally safe. Fluoxetine significantly improved PSEI and PSAP, whereas no definitive improvement of PSD was found. Improvement of PSAP was noted even at 3 months after the discontinuation of the treatment.

Conclusions—Fluoxetine is efficacious in the treatment of PSEI and PSAP. Its effect on PSD is not solidly confirmed. **(*Stroke*. 2006;37:156-161.)**

Key Words: depression ■ emotions ■ fluoxetine ■ serotonin ■ stroke

Emotional disturbances are common complications after stroke. Among them, poststroke depression (PSD) has been most often studied. However, recent studies have reported that poststroke emotional incontinence (PSEI)[1–4] or anger proneness (PSAP)[5] are also common. These emotional disturbances have been shown to be associated with a less successful outcome of rehabilitation therapy,[6] a decreased quality of life of patients,[7] and an increase in caregiver burden.[8] Therefore, proper management of the poststroke emotional disturbances is important.

Although previous studies have tried tricyclic antidepressants[9] and selective serotonin reuptake inhibitors (SSRIs)[10,11] in PSD, placebo-controlled studies have been rare, and the results have often been inconsistent.[12,13] SSRIs may also be effective in the treatment for PSEI and PSAP, because previous studies reported that these symptoms are related to serotonergic dysfunction in the brain.[5,14] Others have reported that SSRIs improved pathological crying[15] and irritable or impulsive behavior.[16] Few controlled studies, however, have been conducted so far using SSRIs in stroke patients exhibiting PSEI or PSAP. Therefore, in this double-blind, randomized placebo-controlled study, we examined the effect of fluoxetine in poststroke emotional disturbances including PSD, PSEI, and PSAP.

Methods

Patients

Between December 2003 and August 2004, consecutive stroke patients who attended outpatient clinics at the Asan Medical Center were interviewed for the presence of PSD, PSEI, and PSAP (for criteria, see below). Excluded were patients experienced the following: (1) did not undergo imaging (CT/MRI) studies; (2) had subarachnoid hemorrhage; (3) had transient ischemic attack without progression to stroke; (4) had communication problems (aphasia, dementia, or dysarthria) severe enough as not to undergo a reliable interview; (5) were scored ≤23 on Mini Mental State Examination;[17] (6) had a history of being diagnosed as having depression or other psychiatric illnesses before the onset of stroke; (7) had been already treated with psychiatric regimens including SSRI; and (8) lived alone so that information from the relatives was not available.

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From the College of Nursing (S.C.-K., J.M.C.), Seoul National University, and Department of Neurology (S.W.H., S.U.K., D.-W.K., J.S.K.), University of Ulsan, Asan Medical Center, Seoul, Korea.

Correspondence to Jong S. Kim, MD, Department of Neurology, Asan Medical Center, Song-Pa PO Box 145, Seoul 138-600, South Korea. E-mail jongskim@amc.seoul.kr

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Procedures

The interview was performed an average of 14 months after the onset of stroke by one of researchers. To increase the inter-rater reliability in the assessments, 3 formal training sessions were held, each session lasting ≈50 minutes. Training sessions were multifaceted, including didactic lectures of the study design, study procedures, and data collection methods. Psychometric scales, as well as a case study analysis, and qualitative interviewer skills were also reviewed. Then, the interview sessions were supervised initially at the data collection site by one of the authors (S.C.-K.), and any disagreements were resolved through discussion. Any questions that arose from the following interview were brought to the research team meeting to reach consensus on the appropriate answer. The majority of interviews were conducted in the presence of the relatives, who confirmed the patients' responses. When the relatives were not present during the interview (n=7; 3 in the placebo and 4 in the fluoxetine group), the patients' responses were confirmed by calling the relatives who lived with the patients.

PSD was considered to be present when either the Beck Depression Inventory (BDI) score was >13[18] or the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria were met.[2] PSEI was considered to be present if the patients exhibited excessive or inappropriate laughing (EIL), crying (EIC), or both, when compared with their premorbid state. When both the patient and relatives who lived with the patient agreed that EIL or EIC occurred on ≥2 occasions, we considered the patient as having PSEI.[2] When PSEI was present, the visual analogue scale (VAS) was used to assess the intensity of EIC or EIL. Baseline and follow-up assessments of EIL and EIC VAS reflect the summary of patients' EIL and EIC experiences during the follow-up interval. A 10-cm graduated vertical VAS, with delineated markings at 1-cm intervals, as well as delineated floor and ceiling end points, was used.

PSAP was defined to be present when the sum of the poststroke anger score measured by Spielberger Trait Anger Scale was higher than the prestroke one. Briefly, PSAP was assessed with the 10-item Spielberger Trait Anger Scale.[19] For each question, patients were asked to use a numerical scale (1=almost never, 2=sometimes, 3=often, and 4=almost always) to represent best their prestroke and current statuses. An overall anger score was obtained by the summation of individual scores.

The prestroke anger score was obtained retrospectively from the patients at the first interview. In addition, the patient and ≥1 of the relatives who lived with the patient should agree that the patient developed anger proneness after the stroke.[5] Higher VAS scores for EIC, EIL, and PSAP denote more intense EIC, EIL, and PSAP, respectively. The patients' modified Rankin scale (mRS), Barthel Index score, and neurological findings were recorded by 3 of the authors (J.S.K., S.U.K., D.W.K.). mRS was then categorized as severe (3–6) or mild (0–2) for statistical purpose.

This study was approved by the Institutional Review Board of the Asan Medical Center. All of the enrolled patients gave informed consent. The patients were randomly assigned to receive either fluoxetine 20 mg/day or placebo for 3 months. Treatment allocation was based on a computer-generated list of treatment numbers. Fluoxetine and placebo provided by Myung-In pharmaceutical company were given as a single morning dose in identical capsules in coded boxes. The patient, relatives, and the researchers were not aware of the drug being given. The assessments were performed 4 times: at enrollment, at 1 month, at 3 months, and at 6 months.

The primary end point of the study was the mean BDI score for PSD, mean VAS scores for EIC/EIL, and PSAP scores at all of the follow-up assessments. The secondary end points of the study were as follows: (1) the percentage changes in BDI scores for PSD and the percentage changes in VAS scores for EIC/EIL and PSAP scores; (2) the patients' subjective responses recorded as "aggravated," "no change," and "improved" in comparison with their original responses at the time of enrollment. The percentage changes in BDI, VAS scores for PSD, and EIC/EIL were calculated by subtracting the scores gained at follow-up meetings from the original scores and dividing that number by the enrollment score. The patients' subjective responses, such as "improved," corresponded with the percentage decrease in BDI scores, VAS for EIC/EIL, and PSAP.

Adverse effects reported by the patients were recorded at each follow-up assessment. Complete blood counts, transaminases, blood urea nitrogen, and creatinine were tested at 1 month after the beginning of the treatment to assess the laboratory adverse effects.

Analysis

The primary efficacy analysis was done using intention-to-treat analysis. Group differences were analyzed using descriptive statistics, Student t test, and χ^2 tests (SPSS version 11.5). Pearson correlation coefficients were used to explore relationships among emotional instability variables (between PSD versus PSEI, PSD versus PSAP, and PSEI versus PSAP). In addition, on-treatment analysis was performed to investigate the consistency of the primary results. Regarding safety evaluation, the analysis was based on the treated population (ie, all of the patients who were randomized and received ≥1 dose of study medication).

Results

As shown in Figure 1, of 190 patients who met the criteria, we excluded 38 patients; 37 patients declined to give us informed consent, and 1 was involved in another study. Therefore, 152 patients who had PSD, PSEI, or PSAP were enrolled in the study. Among 152 patients, 27 dropped out before completing the 3-month treatment protocol (15 received fluoxetine, and 12 received placebo), leaving 125 patients. Although there was no difference in the dropout rate between the 2 groups, the reasons for the dropouts were different ($P<0.05$); 4 in the fluoxetine group and 6 in the placebo made protocol violation; 10 in the fluoxetine and 2 in the placebo group wanted to discontinue the treatment because of adverse effects; and 1 in the fluoxetine and 2 in the placebo group were readmitted to the hospital because of other diseases. Two patients in the placebo group dropped out because they did not think it was effective.

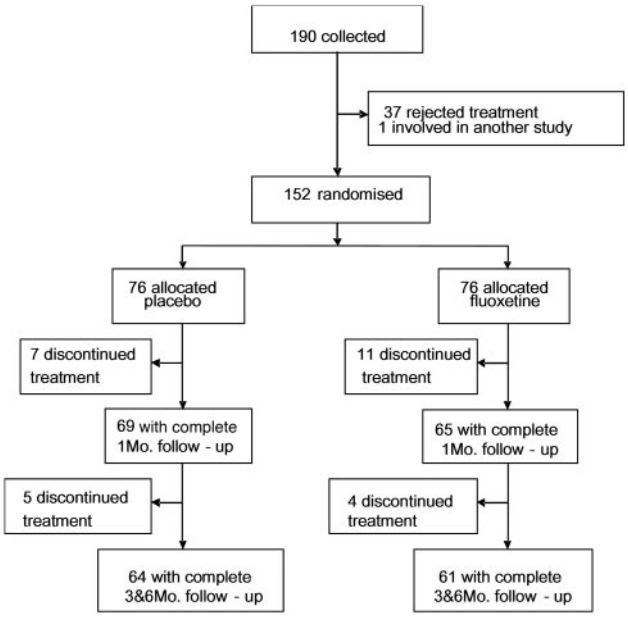

Figure 1. Flow diagram of the trial. Of 190 patients who met the inclusion criteria, 38 patients were excluded. Among 152 patients enrolled, 27 patients dropped out, finally leaving 125 patients.

As shown in Table 1, there were no significant differences between the 2 groups regarding demographics, stroke characteristics, the presence of risk factors, and mRS and Barthel Index scores, except the presence of hypertension. Among the 152 patients, 42 had PSD, 91 had PSEI, and 80 had PSAP. The presence of PSAP was closely related to EIC ($P=0.03$) but not to PSD. Among the patients either with EIC (n=106) or PSAP (n=95), 60 had both.

The EIC was not related with BDI, either. The frequency of PSD was different between the two groups ($P<0.05$) whereas the frequency of PSEI and PSAP was not. The patients who had both EIC and EIL were 13 in the placebo group, and 14 in the fluoxetine group.

Poststroke Depression

As shown in Figure 2A, there was a tendency for the BDI scores to decrease over time in both groups. Although the slope appears steeper in the fluoxetine group than in the control group, there was no significant difference in the mean BDI scores at any of the follow-up periods. The percentage changes in BDI scores at all of the follow-up assessments were not significantly different (Table 2). As shown in Table 3, there was no significant difference in the number of patients with subjective improvement, either.

TABLE 1. Characteristics of Patients

Characteristic	Placebo (n=76)	Fluoxetine (n=76)	*P* Value
Demography			
Age (y, SD)	58.18 (8.85)	58.41 (8.92)	
Education (y, SD)	10.70 (3.90)	11.00 (4.63)	
F/U after stroke onset (mo, SD)	14.37 (11.64)	12.43 (11.02)	
Male sex	60 (78.9)	57 (75.0)	
modified Rankin Scale			
0–2	66 (86.8)	69 (90.8)	
3–6	10 (13.2)	7 (9.2)	
Barthel index score (SD)	96.71 (10.20)	97.60 (6.92)	
Laterality			
Right	41 (53.9)	33 (43.4)	
Left	28 (36.8)	38 (50.0)	
Both	7 (9.2)	5 (6.6)	
Risk factors			
Hypertension	54 (71.1)	67 (88.2)	*
Diabetes mellitus	22 (28.9)	22 (28.9)	
Coronary artery disease	3 (3.9)	4 (5.3)	
Current smoker	11 (14.5)	15 (19.7)	
Hypercholesterolemia	16 (21.1)	21 (27.6)	
Pathogenic mechanism			
Large vessel disease	24 (31.6)	25 (32.9)	
Small vessel disease	30 (39.5)	32 (42.1)	
Cardiac embolism	10 (13.2)	8 (10.5)	
Undetermined	0 (0)	2 (2.6)	
Intracerebral hemorrhage	12 (15.8)	9 (11.8)	
Emotional instability			
Poststroke depression	32 (42.1)	19 (25.0)	*
Poststroke emotional incontinence	55 (71.1)	55 (72.4)	
Excessive/inappropriate crying	55 (72.4)	51 (67.1)	
Excessive/inappropriate laughing	13 (17.1)	18 (23.7)	
Poststroke anger proneness	53 (69.7)	42 (55.3)	

F/U indicates follow-up. *$P<0.05$.

Poststroke Emotional Incontinence

The effects of fluoxetine on EIC and EIL were examined separately. The mean VAS scores of EIC at enrollment between the fluoxetine and the placebo groups were different, but the mean VAS scores of EIL were not (Figure 2B and 2C). The VAS scores of EIC decreased at 1 month in both groups. At 3 months, the score remained stationary in the placebo group, whereas it remained decreased in the fluoxetine group. Thus, the mean EIC score in the fluoxetine group was significantly lower than in the placebo group at this time. There also were significant differences in the percentage changes of EIC scores at all of the follow-up assessments (Table 2). The mean EIL scores and the percentage changes between the 2 groups were not different at the follow-up assessments. However, the number of patients who reported improvement in both EIC and EIL was significantly higher in the fluoxetine group than in the placebo group at all of the follow-up assessments (Table 3).

Poststroke Anger Proneness

In patients with PSAP, the mean PSAP score at enrollment was not different between the fluoxetine and the placebo groups. There was a tendency for a decrease in the score in both groups, which was more marked in the fluoxetine group. In the fluoxetine group, the mean PSAP score tended to increase after 3 months. Nevertheless, the mean PSAP scores in the fluoxetine group were significantly lower than in the placebo group at 1, 3, and 6 months of follow-up (Figure 2D). The percentage changes of PSAP scores at each follow-up assessment were significantly different at 1 and 3 months but not at 6 months (Table 2). The number of patients with improvement in PSAP was also significantly higher in the fluoxetine group at all of the follow-up assessments than in the placebo group (Table 3).

The results regarding the efficacy of fluoxetine were not different from those described above when on-treatment analysis was performed. All of the patients who had completed the study had regularly taken the drugs, which were evaluated by the counting of returned tablets. There were no laboratory side effects except for an abnormal transaminase level noticed in 1 patient in the placebo group. As shown in Table 4, the frequency of adverse effects between the 2 groups was not different; it reached marginal significance ($P=0.08$) when we included all of the patients who dropped out because of side effects.

Discussion

Consistent with previous anecdotal reports,[15,20] PSEI improved with fluoxetine treatment. However, the effect was clearly shown in EIC but not in EIL, suggesting that there may be different pharmacological responses between EIC and

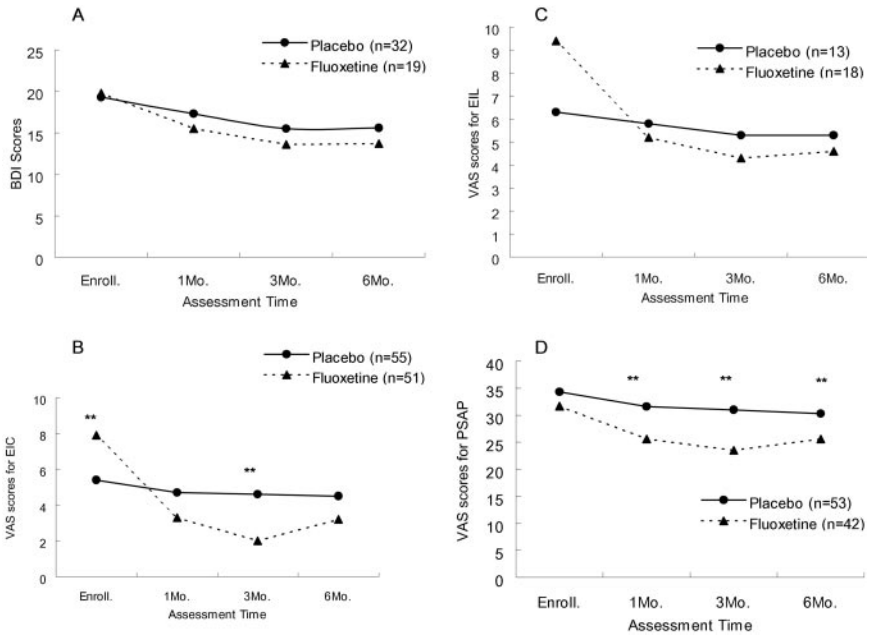

Figure 2. Mean BDI scores (A) and mean VAS scores for EIC (B), EIL (C), and PSAP (D) in the fluoxetine and placebo groups at each assessment. Mo., month. $^{**}P<0.01$.

EIL.[21] However, considering the presence of subjective improvement in patients with EIL and the relatively low initial VAS score in EIL, floor effects may have skewed our results.

The improvement of PSAP with fluoxetine medication is also in accordance with previous studies emphasizing serotonergic dysfunction as an etiology of aggression in patients with depression[22] or stroke.[5] Marked reduction in hostility after fluoxetine treatment has also been reported.[16] At 6 months of follow-up (3 months after the discontinuation of fluoxetine), the PSAP score but not the VAS score of EIC remained significantly lower that of the placebo group, suggesting that the effect of fluoxetine may be more prolonged in PSAP than in EIC.

On the other hand, PSD did not significantly improve after fluoxetine treatment. The efficacy of fluoxetine on PSD has been inconsistent.[12,13] The inconsistencies are not because of different dosages used, because all 3 of the studies used the same dosage (20 mg/day). Perhaps it may be related to different severities of depression. In our study, we included outpatients in the subacute or chronic stage and excluded patients who already had taken psychiatric medication. Therefore, the severity of PSD was generally mild (mean BDI score=19). On the other hand, the subjects of a previous study[12] were those who had major depression and hemiplegia ≤3 months after the stroke. Therefore, the possible therapeutic effect of fluoxetine may have been masked, because we used relatively mildly depressed patients.

TABLE 2. The % Changes at All Follow-Up Assessments

% Changes	Placebo	Fluoxetine	*P* Value
PSD (%, SD)	(n=32)	(n=19)	
At 1 mo	9.15 (19.9)	18.0 (26.8)	n.s.
At 3 mo	15.5 (21.8)	28.7 (27.0)	0.089
At 6 mo	14.7 (22.6)	27.1 (25.6)	n.s.
EIC (%, SD)	(n=55)	(n=51)	
At 1 mo	15.5 (31.8)	51.8 (44.7)	*
At 3 mo	21.0 (36.7)	68.9 (37.2)	*
At 6 mo	20.8 (36.8)	51.6 (42.4)	*
EIL (%, SD)	(n=13)	(n=18)	
At 1 mo	20.8 (33.4)	48.4 (42.8)	0.077
At 3 mo	29.2 (39.6)	53.8 (35.0)	n.s.
At 6 mo	29.2 (39.6)	48.2 (37.3)	n.s.
PSAP (%, SD)	(n=53)	(n=42)	
At 1 mo	7.4 (15.2)	17.6 (17.8)	*
At 3 mo	9.5 (25.7)	23.6 (21.3)	*
At 6 mo	10.6 (25.7)	20.1 (22.7)	n.s.

n.s. indicates not significant. $P<0.05$; $^{*}P<0.01$.

Nevertheless, another study using acute stroke patients also failed to show a beneficial effect of fluoxetine.[13] Moreover, a previous study reported that nortriptyline was more efficacious than fluoxetine in PSD.[9] Therefore, the less pronounced improvement after fluoxetine treatment in PSD rather than in PSEI or PSAP may be related to the relatively weak relationship of the former with serotonin system dysfunction as compared with the latter. In our study, the presence of PSAP was closely associated with EIC ($P=0.03$) but not with PSD, suggesting that PSAP and PSEI tend to cooccur and share a similar pathogenic mechanism, possibly serotonergic system dysfunction.[5] On the contrary, PSD seems to be associated with multiple neurotransmitter dysfunctions including the adrenergic system,[9] as well as the patient's psychogenic reaction related to their physical or social/environmental difficulties.[23]

Although patients in the fluoxetine group more often dropped out because of adverse effects, the frequency of side effects was not significantly different between the 2 groups, even when they were analyzed after the inclusion of those patients. Moreover, the adverse effects were never serious. Therefore, fluoxetine can be used in patients with poststroke emotional disturbances safely, although some are not tolerant with this medication.

Our study has several limitations. First, the number of patients with PSD was small, the severity of PSD was relatively mild,

TABLE 3. Subjective Responses in Fluoxetine and Placebo Group

Variable	Response	Placebo	Fluoxetine	*P* Value
Poststroke depression		(n=28)	(n=18)	
At 1 mo	Aggravated	0 (0)	0 (0)	
	No change	20 (71.4)	9 (50.0)	
	Improved	8 (28.6)	9 (50.0)	
At 3 mo	Aggravated	1 (4.0)	0 (0)	
	No change	12 (48.0)	5 (29.4)	
	Improved	12 (46.0)	12 (70.6)	
At 6 mo	Aggravated	2 (8.0)	0 (0)	
	No change	12 (48.0)	7 (41.2)	
	Improved	11 (44.0)	10 (58.8)	
Excessive/inappropriate crying		(n=48)	(n=44)	
At 1 mo	Aggravated	1 (2.1)	0 (0)	*
	No change	37 (77.1)	14 (31.8)	
	Improved	10 (20.8)	30 (68.2)	
At 3 mo	Aggravated	2 (4.3)	0 (0)	*
	No change	29 (64.4)	7 (15.9)	
	Improved	14 (30.4)	37 (84.1)	
At 6 mo	Aggravated	2 (4.3)	1 (2.3)	*
	No change	29 (64.4)	11 (25.0)	
	Improved	14 (30.4)	32 (72.7)	
Excessive/inappropriate laughing		(n=12)	(n=16)	
At 1 mo	Aggravated	1 (8.3)	0 (0)	*
	No change	10 (83.3)	3 (18.8)	
	Improved	1 (8.3)	13 (81.2)	
At 3 mo	Aggravated	1 (8.3)	0 (0)	*
	No change	9 (75.0)	1 (6.7)	
	Improved	2 (16.7)	14 (93.3)	
At 6 mo	Aggravated	1 (8.3)	1 (6.7)	†
	No change	9 (75.0)	4 (26.7)	
	Improved	2 (16.7)	10 (66.7)	
Post-stroke anger proneness		(n=48)	(n=40)	
At 1 mo	Aggravated	1 (2.1)	1 (2.5)	*
	No change	35 (72.9)	16 (40.0)	
	Improved	12 (25.0)	23 (57.5)	
At 3 mo	Aggravated	2 (4.4)	2 (5.1)	*
	No change	27 (60.0)	10 (25.6)	
	Improved	16 (35.6)	27 (69.3)	
At 6 mo	Aggravated	3 (6.7)	6 (15.3)	*
	No change	23 (51.1)	8 (20.5)	
	Improved	19 (42.2)	25 (64.1)	

Data are presented as no. (%). *$P<0.01$; †$P<0.05$.

and patients with PSD were not evenly randomized. Therefore, our data on PSD were inconclusive. Second, we excluded the patients who had communication problems and cognitive dysfunction. This may have influenced the results, because PSD attributable to left-sided stroke has been shown to be resistant to serotonin reuptake inhibitor treatment.[11] This is unlikely, however, because the numbers of patients with PSD, PSEI, and PSAP were not different in terms of lesion laterality between the fluoxetine and placebo groups. There also was no difference in the laterality of stroke in the PSD patients who responded to fluoxetine treatment.

Despite these limitations, our study clearly showed that fluoxetine is generally safe and improves PSEI and PSAP. Considering the fact that these emotional disturbances may affect the quality of life of the patients and caregivers,[7,8] future studies are needed to demonstrate whether fluoxetine treatment improves the quality of life of stroke patients, and decreases the caregivers' burden.

TABLE 4. Adverse Effects

Side Effects	Placebo (n=76)	Fluoxetine (n=76)
None	63 (82.9)	54 (71.1)
Nausea	2 (2.6)	6 (7.9)
Headache	3 (3.9)	2 (2.6)
Insomnia	3 (3.9)	2 (2.6)
Sexual dysfunction	1 (1.3)	2 (2.6)
Gastrointestinal discomfort	0 (0)	3 (4.0)
Decrease in appetite	1 (1.3)	3 (4.0)
Dizziness	1 (1.3)	2 (2.6)
Decreased concentration	0 (0)	1 (2.6)
General weakness	1 (1.3)	3 (4.0)
General edema	1 (1.3)	0 (0)

Data are presented as no. (%).

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