Stroke

ORIGINAL CONTRIBUTION

Effects of Fluoxetine on Outcomes at 12 Months After Acute Stroke

Results From EFFECTS, a Randomized Controlled Trial

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BACKGROUND AND PURPOSE: The EFFECTS (Efficacy of Fluoxetine—a Randomised Controlled Trial in Stroke) recently reported that 20 mg fluoxetine once daily for 6 months after acute stroke did not improve functional outcome but reduced depression and increased fractures and hyponatremia at 6 months. The purpose of this predefined secondary analysis was to identify if any effects of fluoxetine were maintained or delayed over 12 months.

METHODS: EFFECTS was an investigator-led, randomized, placebo-controlled, double-blind, parallel group trial in Sweden that enrolled adult patients with stroke. Patients were randomized to 20 mg oral fluoxetine or matching placebo for 6 months and followed for another 6 months. The primary outcome was functional outcome (modified Rankin Scale), at 6 months. Predefined secondary outcomes for these analyses included the modified Rankin Scale, health status, quality of life, fatigue, mood, and depression at 12 months.

RESULTS: One thousand five hundred patients were recruited from 35 centers in Sweden between 2014 and 2019; 750 were allocated fluoxetine and 750 placebo. At 12 months, modified Rankin Scale data were available in 715 (95%) patients allocated fluoxetine and 712 (95%) placebo. The distribution of modified Rankin Scale categories was similar in the 2 groups (adjusted common odds ratio, 0.92 [95% CI, 0.76–1.10]). Patients allocated fluoxetine scored worse on memory with a median value of 89 (interquartile range, 75–100) versus 93 (interquartile range, 82–100); P=0.0021 and communication 93 (interquartile range, 82–100) versus 96 (interquartile range, 86–100); P=0.024 domains of the Stroke Impact Scale compared with placebo. There were no other differences in secondary outcomes.

CONCLUSIONS: Fluoxetine after acute stroke had no effect on functional outcome at 12 months. Patients allocated fluoxetine scored worse on memory and communication on the Stroke Impact Scale compared with placebo, but this is likely to be due to chance.

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Key Words: antidepressive agents ■ disability studies ■ fluoxetine ■ functional status ■ randomized controlled trial ■ serotonin uptake inhibitors ■ stroke

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In 2011, the FLAME trial (Fluoxetine for Motor Recovery After Acute Ischemic Stroke) reported that fluoxetine enhanced motor recovery after acute ischemic stroke.[1] A Cochrane systematic review of 4059 patients included in 52 randomized controlled trials of SSRIs (selective serotonin reuptake inhibitors) for stroke recovery concluded that SSRIs could reduce disability but in the light of the methodological limitations and

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Nonstandard Abbreviations and Acronyms

AFFINITY	Assessment of Fluoxetine in Stroke Recovery Trial
EFFECTS	Efficacy of Fluoxetine—a Randomised Controlled Trial in Stroke
FLAME	Fluoxetine for Motor Recovery After Acute Ischemic Stroke Trial
FOCUS	Fluoxetine or Control Under Supervision trial
mRS	modified Rankin Scale
SSRI	selective serotonin reuptake inhibitor

heterogeneity of the trials, more data were needed.[2] In 2020, the EFFECTS (Efficacy of Fluoxetine—a Randomised Controlled Trial in Stroke) authors reported that 20 mg of fluoxetine once daily for 6 months after acute stroke did not improve functional outcome at 6 months compared with placebo, although the occurrence of depression was reduced and fractures and hyponatremia increased.[3] EFFECTS included 1500 stroke patients from Sweden, and the results were similar to those of 2 other large randomized controlled trials with comparable design.[4,5]

As specified in the protocol[6,7] and statistical analysis plan,[8] we followed-up participants to 12 months, to examine whether any effects of fluoxetine identified at 6 months were sustained or delayed.

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METHODS

The anonymized data that support the findings of this trial are available to other researchers from the corresponding author (Dr Lundström) upon reasonable request following receipt of a written application and proposal for use of the data, approval by the EFFECTS trial Steering Committee, and establishment of a data sharing agreement.

The design, methods, and primary results of the EFFECTS trial have been published.[3,6–8] Briefly, EFFECTS was a randomized, double-blind, placebo-controlled clinical trial conducted in 35 hospital stroke units in Sweden. The trial was approved by a central medical ethics committee in Stockholm (reference 2013/1265-31/2) and by the Swedish Medical Agency (reference 5.1-2014-43006); all patients provided written informed consent. EFFECTS was registered in the EU Clinical Trials Register and ClinicalTrials.gov. We have followed the CONSORT statement (Consolidated Standards of Reporting Trials).[9]

Eligible patients were adults (aged ≥18 years) with a clinical diagnosis of acute stroke within the previous 2 to 15 days, brain imaging consistent with ischemic or hemorrhagic stroke, and a persisting neurological deficit at the time of randomization. Patients were excluded if they were depressed or taking antidepressants; had a contraindication to fluoxetine; were unlikely to be available for follow-up during the subsequent 12 months; had another life-threatening illness that would make 12-month survival unlikely; were enrolled in another clinical trial of an investigational medicinal product or device; and women were excluded if pregnant, breast-feeding, or of child-bearing age and not using contraception. Baseline characteristics and outcome at 6 months are available in Tables I through III in the Data Supplement.

Randomization was via a secure, centralized, web-based system which used a minimization algorithm[3] and assigned patients to fluoxetine or placebo in a 1:1 ratio. Placebo capsules were visually identical to the fluoxetine capsules even when broken open. Fluoxetine 20 mg capsules or matching placebo capsules were administered orally once daily for 6 months.

Patients were followed-up at 6 and 12 months by postal questionnaire or telephone by one research nurse (N. Greilert Norin) in the trial coordinating center at Danderyd Hospital. If the patient was unable to complete the questionnaire, assistance was sought from their next of kin or carer. In this article, we report the following predefined secondary outcomes at 12 months:

1. Functional status, measured with the modified Rankin Scale (mRS).[10] We used the simple mRS questionnaire[11–13] to derive the mRS score.
2. Health status using the Stroke Impact Scale version 3.0.[14] The Stroke Impact Scale is a 59-item self-reported questionnaire that includes 8 domains: arm, hand, leg, and foot strength; hand function; mobility; communication and understanding; memory and thinking; mood and emotions; daily activities; and participation in work, leisure, and social activities. Four of the subscales (strength, hand function, daily activities, and mobility) can be combined into a composite physical domain. Scores for each domain range from 0 to 100, and higher scores indicate better health. The Stroke Impact Scale also contains a question to assess the patient's global experience of recovery. The patient is asked to score their recovery on a visual analog scale ranging from 0 to 100, with 0 meaning no recovery and 100 meaning full recovery.
3. Depression, defined as taking an antidepressant medication (Anatomic Therapeutic Chemical code beginning with N06A) at 12 months.
4. Mood, using the Mental Health Inventory 5 scale.[15] The Mental Health Inventory 5 is a subscale of the 36-Item Short Form Health Survey[16] containing 5 questions, each with 6 possible answers, with a score of 1 to 6; possible sum of scores ranges from 5 to 30. The total score is transformed into a value between 0 and 100, where 100 represents optimal mental health. A value below 60 has been suggested as moderate-to-poor mental health.[17]
5. Fatigue, using the vitality subscale[18] of the 36-Item Short Form Health Survey. Four questions, each with 5 answers scored from 1 to 5 (sum ranges from 4–20). The sum score is transformed to a value between 0 and 100. Scores below 50 indicate fatigue.[19]
6. Health-related quality of life, measured with the EQ-5D-5L.[20] EQ-5D-5 L includes 5 dimensions: mobility; personal care; usual activities; pain/discomfort; and

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anxiety/depression. We calculated an EQ-5D index—where 1 indicates the best health imaginable, and 0 indicates the worst health imaginable—using the UK cross-walk value set, since it is the most commonly used.[21]

The participant, care provider, investigator, and outcomes assessor remained masked to the allocated trial treatment until the 12 month assessment.

Except death, we did not collect any adverse event or safety outcome data between 6 and 12 months. Long-term follow-up is planned to at least 3 years using central registries.

Statistical Analysis

We published the statistical analysis plan before recruitment was completed and without awareness of any unmasked data.[8]

The primary outcome for this report, the mRS scores at 12 months, were analyzed using ordinal logistic regression before and after adjusting for the baseline factors included in the minimization algorithm.[3] We used the following co-variables in the algorithm: days between stroke and randomization; probability of being alive and independent at 6 months; motor deficit; and aphasia. We presented the results as an adjusted and a nonadjusted common odds ratio where a number below 1.0 indicates that placebo is better than fluoxetine, with a 95% CI.

The secondary outcomes were compared (unadjusted) using Mann-Whitney *U* test. For continuous secondary outcomes, the mean or median in each group was calculated with SD or interquartile range (IQR), depending on the distribution. The probability that outcomes in the fluoxetine group were significantly different from the placebo group were calculated as *P* values (2-sided).

All analyses were by intention-to-treat, and were carried out in SAS for Windows, Software 9.4, SAS Institute Inc, Cary, NC.

RESULTS

EFFECTS recruitment started 20 October, 2014 and ended 28 June, 2019; 750 were assigned to fluoxetine and 750 to placebo. Last 12 months follow-up was 8 July, 2020. Baseline characteristics were well balanced, 87.4% had ischemic stroke, 12.3% had intracerebral hemorrhage, 0.2% had nonstroke. The mean age was 71 years (SD, 11), 38.3% were women, 96.3% were previously independent, and the median National Institutes of Health Stroke Scale score was 3.[3] For both groups, the median duration of treatment was 180 days (IQR,

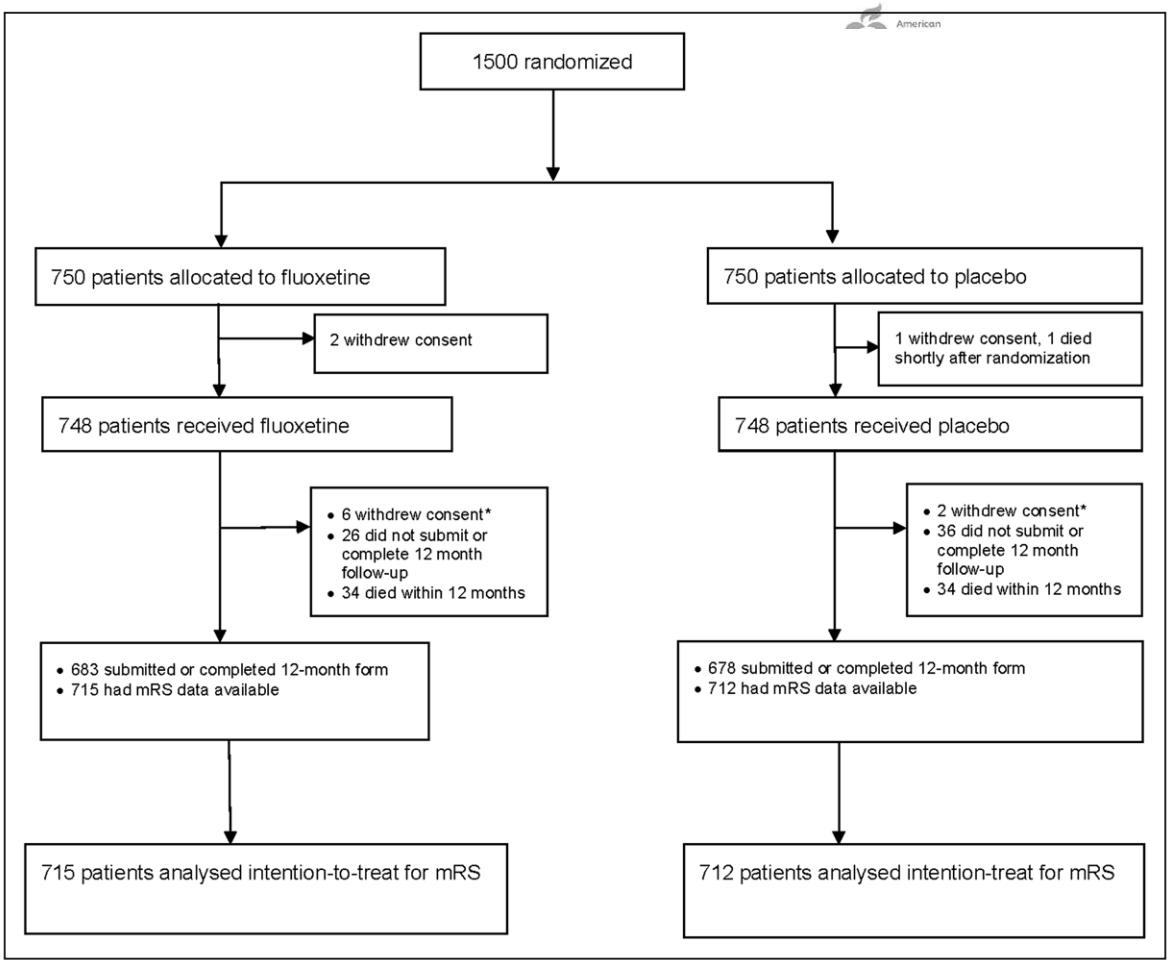

Figure. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.
*Two patients (one in each group) withdrew their consent regarding face-to-face follow-up, however, they both agreed to answer the questionnaire at 12 mo. mRS indicates modified Rankin Scale.

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180–180). Most patients (1338/1500, 89%) took the trial medication for at least 150 days.[3]

At 12 months, mRS data were available for 715 (95%) patients in the fluoxetine group and 712 (95%) patients in the placebo group (Figure 1). No patients withdrew consent for follow-up between 6 and 12 months; 4.1% (62/1500) were lost to follow-up at 12 months, and 4.5% (68/1500) died within 12 months (Table IV in the Data Supplement).

Table 1 shows the mRS[10] scores 12 months after randomization, that is, 6 months after cessation of trial medication. There was no difference in the distribution across mRS categories in the fluoxetine and placebo groups (adjusted common odds ratio, 0.92 [95% CI, 0.76–1.10]). The unadjusted analysis produced similar results (common odds ratio, 0.96 [95% CI, 0.80–1.15]; Table 1).

Table 2 shows the secondary outcomes in the fluoxetine and placebo groups. Patients randomized to fluoxetine had significantly worse values on the memory (median value of 89 [IQR, 75–100] versus 93 [IQR, 82–100]; *P*=0.0021] and communication (93 [IQR, 82–100] versus 96 [IQR, 86–100]; *P*=0.024) domains of the Stroke Impact Scale v3 compared with placebo. There were no other differences on the secondary outcomes (Table 2).

Six months after randomization, 5.8% (87/1500) of the patients reported that they were taking an open-label antidepressant; 4.8% (36/750) had been randomized to fluoxetine, and 6.8% (51/750) to placebo.[4]

At 12 months follow-up, 8.8% of the survivors from 6 months (129/1453) were taking an open-label antidepressant; 9.0% (65/725) randomized to fluoxetine, and 8.8% (64/728) to placebo (diff, 0.2% [95% CI, −3.1 to 3.8]; Tables V and VI in the Data Supplement). Of patients on an antidepressant at 6 months, 60% (51/87) patients continued to take antidepressant at 12 months follow-up; 41% (21/36) randomized to fluoxetine, and 59% (30/51) to placebo.

DISCUSSION

The results of the EFFECTS trial show that fluoxetine 20 mg daily for 6 months after acute stroke had no effect on functional outcome up to 1 year after stroke. Similar results have been found in the FOCUS (Fluoxetine or Control Under Supervision trial)[5] (n=3124, United Kingdom), and AFFINITY (Assessment of Fluoxetine in Stroke Recovery)[4] (n=1260, Australia, New Zealand and Vietnam) trials.

Although fluoxetine reduced depression by ≈4% (from 11% to 7%) at 6 months in EFFECTS, the proportion of patients on an antidepressant was similar for the 2 groups at 12 months (9%). Depression is an episodic disorder for most, and not being on antidepressant right at the 12 months assessment does not exclude they did not take one between 6 and 11 months; we cannot rule out that some patients were successfully treated already and drug not needed. Compared with our 6-month follow-up, no clinical evaluation of depression symptoms was performed at 12 months. In a meta-analysis of observational studies, the pooled frequency of depression 6 to 12 months poststroke was 31% and 33%, respectively,[22] >3× higher than the observed proportion in EFFECTS. One possible explanation might be that EFFECTS included patients with relatively mild stroke. Another explanation might be that patients showing symptoms of depression before study start were not included.

Our finding of better reported memory and communication for patients in the placebo group compared with those allocated to the fluoxetine group is unexpected and not supported by the results in FOCUS and AFFINITY. We view this result as a chance finding due to random error associated with multiple analyses.

Our study has several limitations. First, we did not routinely collect data on safety after 6 months, except death. Reassuringly, there was no difference between the groups in death, and we plan to follow the patients for at least 3 years via central registries in Sweden,

Table 1. Modified Rankin Scale[10] Score 6 and 12 Months After Randomization

modified Rankin Scale		6 months		12 months	
		Fluoxetine, n=737	Placebo, n=742	Fluoxetine, n=715	Placebo, n=712
0	No symptoms	156 (21)	170 (23)	160 (22)	178 (25)
1	No clinically significant disability despite symptoms	216 (29)	199 (27)	224 (31)	201 (28)
2	Slightly disability: unable to do everything	94 (13)	106 (14)	75 (11)	88 (12)
3	Moderately disability: unable to live independently but can walk	168 (23)	164 (22)	158 (22)	141 (20)
4	Moderately disability and unable to walk without help from another person	46 (6)	48 (7)	35 (5)	42 (6)
5	Severe disability: unable to sit up	32 (4)	33 (4)	29 (4)	28 (4)
6	Dead	25 (3)	22 (3)	34 (5)	34 (5)

Data at 6 mo have previously been published.[3] Data are n (%). Adjusted odds ratio at 6 mo: 0.94 (95% CI, 0.78–1.13). Common odds ratio at 6 mo: 0.97 (95% CI, 0.81–1.16). Adjusted odds ratio at 12 mo: 0.92 (95% CI, 0.76–1.10). Common odds ratio at 12 mo: 0.96 (95% CI, 0.80–1.15).

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Table 2. Secondary Outcomes at 6 and 12 Months by Allocated Treatment Group

	Fluoxetine (n=750) at 6 months			Placebo (n=750) at 6 months				Fluoxetine (n=642) at 12 months follow-up			Placebo (n=638) at 12 months follow-up			
	N*	Median	IQR	N*	Median	IQR	*P* value†	N*	Median	IQR	N*	Median	IQR	*P* value†
Stroke Impact Scale version 3.0[14] domains														
Strength	694	75	(50–94)	689	75	(50–94)	0.67	662	75	(50–94)	658	75	(50–94)	0.88
Hand ability	690	81	(50–100)	692	88	(50–100)	0.99	664	81	(56–100)	661	81	(50–100)	0.75
Mobility	696	89	(72–100)	698	89	(72–97)	1.00	665	89	(69–100)	662	89	(72–100)	0.84
Motor‡	697	80	(60–93)	695	81	(58–94)	0.95	665	79	(60–94)	661	80	(58–94)	0.88
Daily Activities	697	88	(69–98)	697	88	(68–98)	0.72	667	90	(70–98)	662	90	(68–98)	0.97
Physical function§	697	77	(56–90)	697	77	(56–91)	0.81	667	76	(57–91)	662	77	(55·–92)	0.98
Memory	696	89	(79–100)	698	93	(82–100)	0.0064	666	89	(75–100)	662	93	(82–100)	0.0021
Communication	695	96	(82–100)	697	92	(86–100)	0.83	664	93	(82–100)	661	96	(86–100)	0.024
Mood and emotional control	695	81	(67–92)	696	76	(64–89)	0.0002	665	78	(64–89)	658	78	(64–89)	0.63
Participation	690	66	(46–89)	682	69	(44–89)	0.55	663	69	(46–91)	656	71	(47–93)	0.79
Recovery (VAS)	695	70	(50–90)	695	70	(50–90)	0.79	666	75	(50–90)	662	80	(50–90)	0.58
Fatigue[18]	692	56	(44–69)	692	56	(44–69)	0.74	662	56	(44–75)	658	56	(44–75)	0.22
MHI-5 score[15]	697	76	(64–88)	695	72	(60–88)	0.0086	667	76	(60–88)	660	76	(60-88)	0.57
EQ-5D-5L[20]	687	0.73	(0.55–0.84)	684	0.71	(0.54–0.84)	0.83	664	0.74	(0.55–0.84)	658	0.74	(0.55-0.88)	0.86

Data on Stroke Impact Scale at 6 mo have previously been published.[3] Stroke Impact Scale v 3.0[14] is a patient-reported design to assess stroke outcome, where higher scores are better. Fatigue[18] was measured with the vitality sub-scale of the SF-36 questionnaire. Higher scores indicate more energy, less fatigue. The EQ-5D-5 L has 5 dimensions: mobility; personal care; usual activities; pain/discomfort; and anxiety/depression. We calculated an EQ-5D index using the UK cross-walk value, where 1 indicates the best health imaginable, and 0 indicates the worst health imaginable. EQ-5D-5L[20] indicates The 5-level EQ-5D version; MHI-5[15], mental health inventory-5; and VAS, Visual Analogue Scale.

*The number of patients with each of the secondary outcome scores. Data were only available for those who survived and who completed sufficient questions to derive a score.

†Mann-Whitney *U* test, between fluoxetine and placebo at 6 and 12 mo, respectively.

‡Mean of the strength, hand ability, and mobility domains.

§Mean of the strength, hand ability, mobility, and daily activities domains.

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to collect data on depression, fractures and epilepsy. Second, we did not monitor the level and intensity of rehabilitation between 6 and 12 months. Third, our definition of depression as a patient on an antidepressant drug is crude, probably underestimating the true occurrence, and it would have been better to evaluate depression face-to-face, as we did at 6 months. Nonetheless, defining depression—not the least in the context of brain damage, is difficult—which is reflected in the varied incidence in the literature.[22]

Our result is probably generalizable to high-income countries with a similar healthcare structure.

In conclusion, fluoxetine 20 mg once daily for six months after acute stroke had no effect on functional outcome at 12 months. Patients allocated fluoxetine scored worse on memory and communication on the Stroke Impact Scale compared with placebo, but this is likely to be due to chance. More precise estimates of any effects of fluoxetine will be available from our prospective meta-analysis of individual patient data from the FOCUS, AFFINITY, and EFFECTS trials.[23]

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Supplemental Materials

Online Tables I–VI

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