Safety and efficacy of fluoxetine on functional recovery after acute stroke (EFFECTS): a randomised, double-blind, placebo-controlled trial

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For the EFFECTS Trial Collaboration. Members of the writing committee are listed at the end of the Article; all members of the EFFECTS Trial Collaboration are listed in the appendix.

Summary	333 words
Manuscript	Approx 3700 words
Figures	2 (Titles and Legends text at page 20)
Tables	3 (Titles and Legends text at page 19-20)
References	28

Summary

BACKGROUND

Previous studies have suggested that fluoxetine could improve neurological recovery after stroke. The EFFECTS trial was designed to test the hypothesis that administration of fluoxetine for 6 months after acute stroke would improve functional outcome.

METHODS

EFFECTS was an investigator-led, parallel group, randomised, placebo-controlled trial that enrolled non-depressed stroke patients aged 18 years or older between two and 15 days after stroke onset in 35 hospitals in Sweden. The patients had a clinical diagnosis of ischemic or intracerebral haemorrhage with persisting focal neurological deficits at inclusion. A web-based randomisation system which incorporated a minimisation algorithm was used to allocate participants to fluoxetine 20 mg once daily or matching placebo capsules for 6 months with a ratio of 1:1. Patients, care providers, investigators, and outcomes assessors were masked to the allocation. The primary outcome was functional status, measured with the modified Rankin Scale (mRS) at 6 months. Patients were analysed according to their treatment allocation. EFFECTS is registered with ClinicalTrials.gov, number NCT02683213.

FINDINGS

Recruitment started 20 Oct 2014 and ended 28 June 2019, when the planned 1500 patients were included (750 to fluoxetine and 750 to placebo). mRS data were available for 737/750 (98%) in the fluoxetine group and 742/750 (99%) in the placebo group. The primary outcome - distribution across mRS categories– was neutral (common odds ratio adjusted for minimisation variables 0·94 [95% CI 0·78 to 1·13], p=0·42). Fluoxetine reduced depression (54 [7·2%] patients vs 81 [10·8%]; difference -3·6% [95% CI -0·065 to -0·0071]; p=0·015) but was associated with more bone fractures (28 [3·7%] vs 11 [1·5%]; difference 2·2% [95% CI 0·0066 to 0·039]; p=0·0058) and hyponatremia (11 [1·47%] patients vs 1 [0·13%];

difference 1·34% [95% CI 0·0043 to 0·022]; p=0·0038). There were no treatment-related deaths.

INTERPRETATION

Functional outcome after acute stroke did not improve with fluoxetine 20 mg once daily for 6 months. Fluoxetine reduced the occurrence of depression but increased the risk of bone fractures and hyponatraemia. Our results do not support the routine use of fluoxetine after acute stroke.

FUNDING

The Swedish Research Council, the Swedish Heart-Lung Foundation, the Swedish Brain Foundation, the Swedish Society of Medicine, King Gustav V and Queen Victoria's Foundation of Freemasons, and the Swedish Stroke Association (STROKE-Riksförbundet).

Key words

Stroke, fluoxetine, selective serotonin reuptake inhibitor, SSRI, stroke recovery, recovery of function, EFFECTS

Introduction

Worldwide, stroke affects 13·7 million people each year[1] and approximately half of all survivors are left with disability. [2] Whereas major advances have been made in acute treatment, there is a need for new treatments focused on long-term stroke recovery irrespective of eligibility for acute treatments. One possible drug is fluoxetine, a selective serotonin reuptake inhibitor (SSRI). SSRIs has been widely used for more than three decades to treat several hundred million people with mood disorders. A meta-analysis of animal stroke models has shown that fluoxetine improves neurobehavioral outcomes by 52%, probably by enhancing neuroplasticity. [3] In 2011, the FLAME trial (n=118) reported promising results for stroke recovery. [4] FLAME randomised ischaemic stroke patients to 20 mg fluoxetine daily or

placebo (ratio 1:1) for 3 months. The proportion of independent was 17 absolute percent higher in the fluoxetine group (26% versus 9%, p=0·015).

In a Cochrane review of SSRIs for stroke recovery from 2012, SSRIs appeared to reduce disability after ischaemic or intracerebral haemorrhage. [5] However, the review found heterogeneity between trials and methodological limitations in a sizable proportion of the studies; most were small and prone to systematic and random errors. The authors called for large, well-designed trials of SSRIs and stroke recovery. Three trial investigator teams collaboratively developed a core protocol but the trials were funded and run independently. [6,7] Minor variations were tailored to the national settings in the UK (Fluoxetine Or Control Under Supervision [FOCUS]), Australia, New Zealand, and Vietnam (Assessment oF FluoxetINe In sTroke recoverY [AFFINITY]), and Sweden (Efficacy of Fluoxetine–A Randomised Controlled Trial in Stroke [EFFECTS]). The AFFINITY trial results are reported in a parallel publication. [8]

In December 2018, FOCUS (n=3127) published its results. [9] The primary outcome – the distribution across mRS categories at 6 months – was neutral. Patients allocated fluoxetine were less likely than placebo to develop new depression by 6 months (13·4% versus 17·2%, *p*=0·0033), but they had more bone fractures (2·9% versus 1·5%]; *p*=0·007). The adherence to study medication was moderate. One in three took the trial medication for less than 150 of the prescribed 180 days, which might reduce the generalisability of the FOCUS results outside the UK.

EFFECTS hypothesised that administration of fluoxetine for 6 months after acute stroke in Sweden would improve functional outcome.

Methods

Study design and patients

EFFECTS was an investigator-led multicentre, randomised, placebo-controlled, parallel group trial of fluoxetine for stroke recovery. Eligible patients were identified from stroke and rehabilitation units in Sweden (appendix**,** p 12-15). The study protocol was approved by a central medical ethics committee in Stockholm (reference 2013/1265-31/2, date: 03/09/2013) and by the Swedish Medical Agency (reference 5.1-2014-43006, date 08/08/2014). All patients provided written informed consent before randomisation. Consent from relatives was not accepted. The protocol[6], statistical analysis plan[7], and an update on the amendment to the protocol[10] have been published. All inclusion and exclusion criteria are listed in the appendix p 3. Briefly, patients were eligible if brain imaging was compatible with intracerebral haemorrhage or ischaemic stroke, randomisation was possible between two and 15 days after stroke onset, and the patient had persisting focal neurological deficit(s) severe enough to warrant treatment with the investigational medicinal product for six months from the perspective of the randomising physician AND patient. Patients were excluded if they had a primary subarachnoid haemorrhage; were unlikely to be available for follow-up for the next 12 months; had a history of epileptic seizures; previous drug overdose or attempted suicide; or an ongoing depression. Patients on anti-depressant medication – regardless of indication – were also excluded. Other exclusion criteria were allergy or contraindication to fluoxetine; or medication(s) which could have a serious interaction with fluoxetine; hepatic impairment (alanine aminotransferase more than three times the upper normal limit) and renal impairment (creatinine > 180 μmol/L); pregnancy or breastfeeding.

Randomisation and masking

EFFECTS shared the randomisation system with the FOCUS trial. [9] After obtaining written informed consent, a medical doctor or nurse entered data into a secure web-based randomisation system. The system checked data for completeness and consistency and allocated the patient an ID and a treatment number. Patients were randomised in a 1:1 ratio to either fluoxetine 20 mg once daily or placebo for 6 months. We tested 20 mg daily which was the dose used in most previous trials of fluoxetine in stroke.

The system applied a minimisation program to achieve balance for four factors:

1) Delay since stroke onset (2–8 versus 9–15 days)
2) Predicted 6 months outcome based on the six simple variable (SSV) model [11]
3) Presence of a motor deficit based on National Institutes of Health Stroke Scale[12] (NIHSS) at inclusion
4) Presence of aphasia based on NIHSS at inclusion.

The SSV included six variables, four at the onset and two prior to the stroke. Onset variables were: age; ability to walk unassisted; ability to talk; and whether confusion is present or not. The two variables before stroke were whether the patient was independent and living alone. Details how to calculate the SSV is given in appendix page 4. The randomisation system was set up so that the investigator could not the next assignment in the sequence. The minimisation algorithm [13] randomly allocated the first patient to treatment, but each subsequent patient was allocated to the treatment that lead to the least difference between the treatment groups with respect to the prognostic factors. To ensure a random element to treatment allocation, patients were allocated to the group which minimised differences between groups with a probability of 0·8.

The placebo capsule was visually identical to the fluoxetine capsules, even when broken open. Patients, their families, health-care personnel, staff in the coordinating centre

(Karolinska Institutet, Department of Clinical Sciences Danderyd Hospital), and the pharmacy were masked to treatment allocation.

An emergency unblinding system was available but was designed so that the co-ordinating centre and those doing follow-up continued to be masked throughout the study.

Procedures

The intervention was initiated as soon as possible after the randomisation. We did not titrate the dose; we recommended the patient take it in the morning. The study medication (intervention and placebo) was made by Unichem (Goa, India), imported by Niche Generics Ltd (Hitchin, UK), bought from Discovery Pharmaceuticals Ltd (Castle Donington, UK), and quality assured, packaged, labelled, and distributed by Sharp Clinical Services to Apoteket AB in Sweden.

At the local centre, the trial medication was prescribed on the patient's medication chart as "EFFECTS trial medication (fluoxetine 20 mg/placebo), one capsule daily, orally (or enteral tube if unable to swallow) for 6 months". The study medication was dispensed for the first three months, 100 capsules, Bottle #1. The rationale for 100 capsules, was to have some in reserve, in case of delayed follow-up. When the patient was discharged, the trial medication was continued and documented on the discharge summary as well as on the patient's list of ongoing medication. After a little less than three months, the patient was given the last 100 capsules (Bottle #2) at a face-to-face follow-up at the local centre. Patients were instructed to bring Bottle #1 to this follow-up. When a patient could not attend a face-to-face meeting, the study medication was posted to them. The study drug was free of charge.

Patients who stopped taking the allocated treatment early were followed-up and their data were included in the primary analyses. The reason for stopping the treatment prematurely, for instance due to a Serious Adverse Event was recorded in the patient's electronic Case Report Form.

Each centre was reimbursed with 5000 SEK (≈375 GBP) per patient and supplied with medical record templates for inclusion as well as a template letter to inform Family Physicians about the trial.

If a patient was judged to have developed new clinical depression during follow up, we recommended that the patient stay on the study medication and add 15 mg mirtazapine, with the possibility of titrating up to 45 mg mirtazapine. If 45 mg mirtazapine did not work, we recommended adding 20 mg fluoxetine.

Outcomes

Details of the outcomes and definitions are described in the appendix. In summary, the primary outcome was functional status at 6 months (± 14 days), measured using the modified Rankin scale (mRS). [14] We used the simple modified Rankin scale questionnaire[15,16] (smRSq) delivered by postal questionnaire or via interview over the telephone to derive the mRS score.

Centrally (i.e. at the trial coordinating centre based at Danderyd Hospital), we collected the following secondary outcomes – also common to FOCUS and AFFINITY – by mail at 6 months: survival; the Stroke Impact Scale v. 3[17,18] (SIS), to provide an overall assessment of patient outcome as well as allowing us to assess the effect of treatment on specific outcomes of importance to the patients; and what medications – if any – the patient was on. All responses received were screened by the Trial Manager Assistant, an experienced research nurse. If there were missing data, inconsistent answers, or we did not receive a reply within two weeks, the Trial Manager Assistant called the patient or next of kin to complete the answers by telephone.

In addition, we collected the following secondary outcomes 3 and 6 month face-to-face follow-ups: National Institutes of Health Stroke Scale[12] (NIHSS) to assess stroke severity as

well as motor function and aphasia; Montreal Cognitive Assessment[19] (MoCA), to assess the patients' cognitive function; new diagnosis of depression since randomisation (Diagnostic and Statistical Manual of Mental Disorders[20] (DSM-IV) criteria, and Montgomery-Åsberg Depression Rating Scale[21] (MADRS)); adverse events; and safety outcomes (see appendix p 10 for definition). The psychiatric evaluation regarding depression was done by the local physician, a medical doctor. In case of uncertainty, a psychiatrist was consulted. Adherence was measured at 1 week (± 3 days), 1 month (± 7 days), 3 months (± 7 days), and 6 months (± 14 days), by asking the patient, carer or health personnel how often the patient took the study medication.

The research nurses counted the capsules returned and recorded this in the case report form. Adherence was defined as taking the study medication 5-7 days/week. Intermediate adherence was defined as taking the study medication 1-4 days/week or with some interruptions (Supplementary table h, appendix).

We have reported a majority of the prespecified secondary outcome in the present paper. Analysis of physical activities and health economics including quality of life is ongoing. Extensive information of depressive symptoms is to be reported later. The last 12 months follow-up is planned December 2020. In addition, we are going to follow-up all patients in national registries up to at least 3 years.

Statistical analysis

All outcomes were prespecified and described in detail in our published statistical analysis plan.[7] Enrolment of 1500 patients randomised 1:1 aimed to provide 90% power to detect a 5·6% absolute increase in the proportion with mRS 0–2 from, 27·0% to 32·6% based on an ordinal analysis. We hypothesised that an absolute difference of 5·6% would represent a clinically meaningful effects size for patient and society. For the primary analysis, we used

the common odds ratio with 95% confidence interval (CI), adjusted for factors in the baseline minimisation. We chose an ordinal analysis since it is considered more efficient than dichotomised analysis. [22] When secondary outcomes were binary, we used logistic regression, and presented the results as common odds ratio with 95% CIs, absolute and relative risk reduction. When variables were continuous, we used descriptive statistics, and when comparing the two groups, we used the Mann-Whitney test. We used intention-to-treat analysis. All analysis, except the primary outcome, are un-adjusted. Statistical analyses were done with SAS for Windows, version 9.4.

The unmasked trial statistician prepared analyses of the accumulating data for the Data Monitoring Committee according to a specific plan. No other person had access to these analyses. If we could not get any answer by mail, telephone, face-to-face follow-up, or registry the corresponding variable was set to missing. The steering committee did not do any interim analysis.

EFFECTS is registered with EudraCT, number 2011-006130-16; ISRCTN, number 13020412; and ClinicalTrials.gov, number NCT02683213.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All funders are non-commercial, with none from industry. The sponsor was Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, 182 88 Stockholm, Sweden. The sponsor's representative was EL.

Results

Recruitment in EFFECTS started 20 October 2014 and ended 28 June 2019 when the planned target was reached. A total of 1500 patients were included from 35 Swedish centres. The last 6 months follow-up was on 17 December 2019. Half of the enrolled patients were allocated fluoxetine (figure 1).

Of 3753 patients assessed for eligibility, 2253 were excluded (1547 did not meet inclusion criteria; 394 declined participation; and 312 were not recruited for other reasons). EFFECTS randomised 1500 patients (750 placebo and 750 placebo). After randomisation, 11 patients did not meet our eligibility criteria (protocol violators). Three had a final diagnosis other than stroke (two in fluoxetine and one in placebo), six patients had antidepressant at randomization (three in each group), and two patients randomised at day 16 (one in each group). In two cases (one in each group), the Family Physicians prescribed fluoxetine instead of just continuing on the study medication. The patient allocated placebo (crossover), were on fluoxetine approximately between 3 and 6 months. We unmasked one patient who developed symptoms of bipolar disorder. The psychiatrist responsible argued that knowledge of the allocation would substantially alter the management of the patient. The patient was allocated to placebo. Ineligible patients were retained in the intention-to-treat analyses. The number of patients assessed for the primary outcome, was 737 for fluoxetine and 742 for placebo.

Insert figure 1 here.

Baseline characteristics include: ischemic stroke 1312 (87·4%); intracerebral haemorrhage 185 (12·3%); non-stroke 3 (0·2%); mean age 70·8 (10·9) years; female 575 (38·3%); previously independent 1445 (96·3%); median NIHSS score 3·0 (2·0, 6·0) points; and presence of motor deficit 1046 (69·8%). The two treatment groups were well balanced (table

1) at baseline, and similar to a Swedish stroke population according to Riksstroke regarding age, risk factors, proportion ischemic vs intracerebral haemorrhage, and stroke severity, measured with NIHSS. [23] EFFECTS had a lower proportion of women and a slightly lower number of independent before stroke (appendix p 18), compared to Swedish stroke population. [23]

Insert table 1 here

Figure 2 shows the distribution of the mRS in the treatment and control group. The trial was neutral with respect to the primary outcome – functional status measured with mRS at 6 months (common odds ratio adjusted for minimisation variables 0·94 [95% CI 0·78 to 1·13]; p=0·42); figure 2.

Insert figure 2 here.

Patients allocated fluoxetine scored lower on memory and higher on emotion on the SIS (table 2). There was no difference in NIHSS and MoCA scores (table 2).

Insert table 2 here.

Fewer patients treated with fluoxetine had new depression (54 [7·2%] vs 81 [10·8%]; p=0·015); difference in proportions -3·6% [95% CI -0·065 to -0·0071]; p=0·015 (table 3) and uncontrolled diabetes. However, patients allocated fluoxetine had an increased risk of bone fractures (28 [3·7%] patients vs 11 [1·5%]; difference in proportions 2·2% [95% CI 0·0066 to

0·039]; p=0·0058), and hyponatraemia (11 [1·47%] patients vs 1 [0·13%]; difference 1·34% [95% CI 0·0043 to 0·022]; p=0·0038) (table 3). There were no treatment-related deaths.

Insert table 3 here.

The prespecified subgroup analyses are available in the appendix p 20. There was no significant interaction between the subgroups and the effect on the primary outcome.

Adherence to fluoxetine and placebo was very high. At 1 week, 1 month, 3 months, and 6 months the adherence to fluoxetine was 96% (703/730), 91% (658/721), 88% (630/722), and 89% (594/666), respectively. The adherence was almost identical for placebo: 94% (693/735), 93% (682/736), 86% (622/727), and 89% (595/673), respectively appendix p 21. Our monitors cross-checked the counting for 10% of the patients.[10] Our monitors cross-checked the counting for 10% of the patients.[10] The median duration of treatment was 180 days (IQR 180–180) for both groups. About 89% (1338/1500) took the study medication for at least 150 days.

The most common reason for stopping the study medication was perceived side effects; in the fluoxetine group 8·3% (62/750) stopped within the first 90 days compared with 8·8% (66/750) in the placebo group.

Discussion

EFFECTS is the second largest randomised controlled (RCT) of fluoxetine for stroke recovery. Fluoxetine 20 mg once daily after an acute stroke did not improve patients'

functional outcome at 6 months. However, depression was reduced and emotional scores on the SIS were improved with fluoxetine. Fluoxetine increased bone fractures.

EFFECTS has several strengths. Firstly, we reduced bias by central randomisation and masking of treatment for patients, care providers, investigators, and outcome assessors. Only one patient (0·067%) was unmasked. Secondly, we minimised random error with a large sample size and high follow-up (≥98% for the primary outcome). Thirdly, we had high adherence, 8**9**% at 6 months.

In comparison to FOCUS, EFFECTS added face-to-face follow-up at 6 months. This enabled us to include NIHSS, MoCA, and careful estimation of depression. The NIHSS scores were identical between the groups, a result that points in the same direction as a neutral mRS. The results on memory and cognition were conflicting. Patients allocated fluoxetine scored lower on the SIS domain for memory, but both groups had similar MoCA scores. Since MoCA is a more comprehensive test of memory, and the results in FOCUS were neutral on memory, fluoxetine probably does not affect cognition.

The occurrence of depression was lower in EFFECTS, compared to FOCUS, which could be attributed to another way of measuring depression or the fact that FOCUS included more severe strokes.

The external validity of our results is also supported by the fact that we included patients from 35 centres in Sweden with similar baseline characteristics as in Riksstroke[23] regarding stroke type, severity, and independency before stroke. Further confirmation of external validity is the fact that we observed similar results to FOCUS [9] and AFFINITY [8]; neutral

results for the primary outcome but reduction of depression. FOCUS had a population with more severe strokes (median NIHSS of 6) compared to the median NIHSS of 3 for EFFECTS.

Finally, our results are also in line with the updated version of the Cochrane review of SSRIs for stroke recovery from 2019.[24] When including only low bias RCTs, SSRIs do not improve recovery from stroke.

Safety outcome

The absolute excess risk of 2·2% of bone fractures in EFFECTS is consistent with FOCUS and previous reports from large case-control and cohort studies. [25] Serotonin receptors are found in all major types of bone cell, and the use of SSRIs has been linked to reduced bone mineral density.[26] This increased risk is highest after initiation, with a peak at 8 months for SSRI. [26]

Except for an increased risk of bone fractures and hyponatraemia, fluoxetine seems to be a reasonably safe drug in the stroke population. Gastrointestinal bleeding and thrombotic adverse events were similar between the groups, despite fluoxetine's known effect on platelet function and interaction between fluoxetine and antiplatelet and anti-coagulant medication. In EFFECTS, fluoxetine did not increase the number of epileptic seizures. Our finding of better diabetes control for patients allocated fluoxetine compared to placebo is unexpected. Rather, the reverse was expected due to the known side effects of fluoxetine We interpret the results as a chance finding due to random error associated with multiple analyses.

Limitations

EFFECTS has several limitations that affect its generalisability. Firstly, EFFECTS had a higher proportion of men enrolled (62%). This male predominance of men in stroke studies is

a known but unexplained observation. [27] Secondly, it was performed in only one country, Sweden. Healthcare systems vary between countries, and it is not certain that results from high-income countries are directly transferable to low and middle-income countries. Thirdly, in EFFECTS, we included patients with persisting focal neurological deficit present at the time of randomisation severe enough to warrant treatment from the physicians and the patient's perspective. In our power calculation we expected 27% of the control group to have mRS 0–2. It turned out that we had more than double the number (64%) of stroke with mRS 0–2 in the control group. Effectively, we ended up with a median NIHSS of three, and we cannot exclude that patients with a more severe stroke may benefit from fluoxetine. Fourthly, we could have included the Fugl-Meyer scale, a more sensitive motor scale used in the FLAME trial, since we did a face-do-face follow-up at 6 months (unlike FOCUS and AFFINITY trial). Although the scale is invented in Sweden, it is not used by all hospitals in our country, and we wanted to keep the study as simple as possible.

Finally, our use of the smRSq to calculate the mRS could be regarded as a limitation. The validity and reliability of the smRSq has been tested and found to be high.[15,16] Recently, a study of 3204 patients from the ENCHANTED trial showed good agreement between smRSq and mRS scores.[28] Reassuringly, the results for ENCHANTED were similar using smRSq compared to mRS face-to-face. In EFFECTS, it was important that data could be collected by mail or telephone. Also, it was important to use the same primary outcome as our sister trials FOCUS and AFFINITY to allow for the future pooling of individual patient data.

In summary, EFFECTS show that fluoxetine 20 mg given once daily for 6 months after an acute stroke did not improve patients' functional outcomes but did decrease depression. Our results do not support the routine use of fluoxetine to improve outcome or to prevent post-stroke depression. The results from the planned individual patient data meta-analysis are

required to confirm or refute a more modest benefit or harm. Until these results are published, we do not recommend further fluoxetine trials for stroke recovery.

Contributors

EL was the Chief Investigator, participated in the steering committee, was involved in the design of the trial, and collected, verified, and analysed data, and wrote first draft of the manuscript. EI was the Trial Manager, participated in the steering committee, was involved in the design of the trial, and collected, verified, analysed data. PN participated in the steering committee, was involved in the design of the trial, did the statistical analysis, and analysed data. BM participated in the steering committee, advised on the management of depression within the trial and was involved in the design of the trial. KSS was chair of the steering committee and was involved in the design of the trial.

PW, HW, JB, and BN participated in the steering committee and were involved in the design of the trial.

MD, GM, GJH, and MH were involved in the trial design, affiliated to the steering committee and analysed data. All members of the writing committee have refined the study protocol, commented on the analyses and drafts and seen and approved the final version of the manuscript.

Declaration of interest

Dr. Norrving has received honoraria for DMC work in the SOCRATES and THALES trials (Astra Zeneca) and the NAVIGATE-ESUS trial (Bayer).

Dr Wallén reports grants from the Swedish Medical Research Council (Vetenskapsrådet) during the conduct of the study; the grant was for the study which is presented in the submitted manuscript.

Prof Hankey reports grants from the National Health & Medical Research Council of Australia, Vetenskapsrådet (The Swedish Research Council), and United Kingdom National Institute for health Research Technology (NIHR), during the conduct of the study; and personal fees from American Heart Association, outside the submitted work.

Dr. Dennis reports that the University of Edinburgh received some funding from the grants for EFFECTS (Vetenskapsrådet) in relation to its provision of a randomisation system. The EFFECTS was planned and carried out in the collaboration with the FOCUS and AFFINITY trials which all addressed the same research questions and used similar methods.

Dr. Hackett report grants from National Health and Medical Research Council (Australia), outside the submitted work.

Dr. Lundström, RN Isaksson, Dr. Näsman, Dr. Mårtensson, Dr Borg, Dr Stibrant Sunnerhagen, Dr Mead and Dr Wester report nothing to disclosure.

Data sharing

The final cleaned data set will be saved in the Karolinska Institutet's electronic notebook, trial statistician (PN) and Chief Investigator (EL) will have access to data. All data will be stored anonymised, using the

EFFECTS trial ID. A limited number of variables will be shared with the FOCUS and AFFINITY trial enabling the planned individual patient data meta-analysis. The datasets used and/or analysed during the current study can be made available by the corresponding author on reasonable request. However, according to the Swedish Secrecy Act 24:8, an interested researcher first must apply and receive approval from the Swedish Ethical Review Authority. Written proposals will be assessed by the EFFECTS steering committee and a decision made about the appropriateness of the use of data. A data sharing agreement will be put in place before any data are shared.

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Titles and Legends for Tables

Table 1. Patient characteristics at randomisation.

Legend table 1: Data are n (%), mean (SD), or median (IQR). TIA=Transient Ischaemic Attack. OCSP=Oxfordshire Community Stroke Project. NIHSS=National Institutes of Health Stroke Scale. * One point or more on item 4 (Facial palsy) or, item 5 (Left or right arm motor drift) or, item 6 (Left or right leg motor drift) on NIHSS. † One point or more on NIHSS item 9 (Language/aphasia).

Non-strokes were in the fluoxetine group 1 primary subarachnoid haemorrhage, and 1 hydrocephalus; in the placebo group 1 cerebral tumour.

‡ The medical history was verified by the medical doctor using all available information at that time of randomisation. There was unknown prior medical history for 6 coronary artery diseases; 2 ischaemic stroke/TIAs; 2 diabetes; 19 hyponatraemias; 2 intracranial bleeds; 9 upper gastrointestinal bleeds; 14 bone fractures; 6 depressions respectively.

** There were 726 valid cases for the fluoxetine group, and 731 for placebo.

Table 2. Secondary outcomes at 6 months by allocated treatment.

Legend table 2: *N denotes 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. Data are median (IQR). Stroke Impact Scale v. 3.0 has a score between 0–100, where higher scores indicated better function. P-value=Mann-Whitney. †Mean of the Strength, Hand ability, and Mobility domains. ‡Mean of the Strength, Hand ability, Mobility, and Daily activities domains. NIHSS=National Institutes of Health Stroke Scale. MoCA=Montreal Cognitive Assessment.

Table 3. Safety outcomes within 6 months.

Legend table 3: Data are n (%), unless otherwise stated. All variables in this table are pre-specified safety outcomes. Antidepressant drug refers to treatment outside study medication. Other thrombotic events included 9 Transient Ischaemic Attacks, 1 central retinal artery occlusion, and 1 cerebral venous thrombosis. Other major bleed was defined as a bleeding that was reported by the local centre as a Serious Adverse Event. Details of the 11 major bleedings are given in Supplementary table i, and cause of death in Supplementary table j (appendix p 21-22).

Titles and Legends for Figures

Figure 1: Trial profile.

Legend figure 1: mRS=modified Rankin Scale.

Figure 2: Primary outcome, the modified Ranking Scale at 6 months.

Legend figure 2: Data are n above the bars and % inside the bars. There was 98% (737/750) modified Rankin Scale (mRS) data available in the fluoxetine, and 99% (742/750) in the placebo group. Patients in the fluoxetine group received one capsule of 20 mg fluoxetine per day in 6 months plus standard care. Patients in placebo group received a matching placebo capsule 6 months plus standard care. The mRS range from 0 to 6, with mRS 0 indicating no symptoms, mRS 1 no clinically significant disability, mRS 2 slight disability, mRS 3 moderate disability, mRS 4 moderately severe disability, mRS 5 severe disability, and mRS 6 death.