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

*EFFECTS Trial Collaboration**

Summary

Background Studies have suggested that fluoxetine could improve neurological recovery after stroke. The Efficacy oF Fluoxetine—a randomisEd Controlled Trial in Stroke (EFFECTS) trial aimed to assess whether administration of oral fluoxetine for 6 months after acute stroke improves functional outcome.

Methods EFFECTS was an investigator-led, multicentre, randomised, placebo-controlled, double-blind, parallel group trial that enrolled patients aged 18 years or older between 2 and 15 days after stroke onset in 35 stroke and rehabilitation centres in Sweden. Eligible patients had a clinical diagnosis of ischaemic or intracerebral haemorrhage, brain imaging that was consistent with intracerebral haemorrhage or ischaemic stroke, and had at least one persisting focal neurological deficit. A web-based randomisation system that incorporated a minimisation algorithm was used to randomly assign (1:1) participants to receive oral fluoxetine 20 mg once daily or matching placebo capsules for 6 months. 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, analysed in all patients with available mRS data at the 6-month follow-up; we did an ordinal analysis adjusted for the minimisation variables used in the randomisation. This trial is registered with EudraCT, 2011-006130-16; ISRCTN, 13020412; and ClinicalTrials.gov, NCT02683213.

Findings Between Oct 20, 2014, and June 28, 2019, 1500 patients were enrolled, of whom 750 were randomly assigned to fluoxetine and 750 were randomly assigned to placebo. At 6 months, mRS data were available for 737 (98%) patients in the fluoxetine group and 742 (99%) patients in the placebo group. There was no effect of fluoxetine on the primary outcome—distribution across mRS score categories—compared with placebo (adjusted common odds ratio 0·94 [95% CI 0·78 to 1·13]; p=0·42). The proportion of patients with a new diagnosis of depression was lower with fluoxetine than with placebo (54 [7%] patients *vs* 81 [11%] patients; difference –3·60% [–6·49 to –0·71]; p=0·015), but fluoxetine was associated with more bone fractures (28 [4%] *vs* 11 [2%]; difference 2·27% [0·66 to 3·87]; p=0·0058) and hyponatraemia (11 [1%] *vs* one [<1%]; difference 1·33% [0·43 to 2·23]; p=0·0038) at 6 months.

Interpretation Functional outcome after acute stroke did not improve with oral 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 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).

Lancet Neurol 2020; 19: 661–69

See **Comment** page 636

*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

Correspondence to:
Associate Prof Erik Lundström, Department of Neuroscience, Neurology, Uppsala University, Uppsala SE-751 85, Sweden
erik.lundstrom@neuro.uu.se

See **Online** for appendix

Introduction

Worldwide, stroke affects 13·7 million people each year,[1] and approximately half of all survivors are left with disability.[2] Although major advances have been made in acute treatment of stroke, there is still a need for new treatments that are focused on long-term stroke recovery irrespective of eligibility for acute treatments. One possible drug is fluoxetine, a selective serotonin-reuptake inhibitor (SSRI). SSRIs have been widely used for more than three decades to treat people with mood disorders. A meta-analysis of animal stroke models has shown that fluoxetine improves neurobehavioural outcomes by 52%, probably by enhancing neuroplasticity.[3]

In 2011, the FLuoxetine for motor recovery After acute ischaeMic strokE (FLAME) trial[4] reported promising results for stroke recovery. FLAME randomly assigned 118 patients with acute ischaemic stroke to 20 mg oral fluoxetine daily or placebo (ratio 1:1) for 3 months. The proportion of patients who were independent at 3 months was significantly higher in the fluoxetine group (26%) compared with in the placebo group (9%; p=0·015). A 2012 Cochrane systematic review of randomised controlled trials of SSRIs for stroke recovery showed that SSRIs could reduce disability after ischaemic or intracerebral haemorrhage;[5] however, it also highlighted heterogeneity between trials and methodological limitations in a large

Research in context

Evidence before this study

We did a Cochrane systematic review of selective serotonin-reuptake inhibitors (SSRIs) for stroke recovery, which included randomised controlled trials that recruited patients with stroke (ischaemic or haemorrhagic) at any time within the first year after stroke. The intervention was any SSRI, given at any dose, for any period. We searched Cochrane and clinical trial registers, MEDLINE, Embase, PubMed, and other biomedical databases from their inception to July 16, 2018, for randomised controlled trials using key words "stroke", "selective serotonin-reuptake inhibitor", and key words for individual SSRIs. There were no language restrictions. We identified 63 randomised controlled trials (recruiting 9168 participants), of which three trials (recruiting 3277 participants) were at low risk of bias. These three trials all used fluoxetine, and a meta-analysis found little or no effect of fluoxetine on disability score compared with placebo (standardised mean difference –0·01, 95% CI –0·09 to 0·06; p=0·75), although fewer patients had a new diagnosis of depression. The majority (93%) of the patients from these low bias trials was from the FOCUS trial (n=3127) done in the UK, which might reduce the generalisability of the meta-analysis.

Added value of this study

To the best of our knowledge, the EFFECTS trial is the second largest randomised controlled trial of fluoxetine for stroke recovery. This trial, which was at low risk of bias, has added a further 1500 patients to the three previous trials of fluoxetine that were of low risk of bias, and supports the conclusion of the Cochrane systematic review that fluoxetine does not improve functional recovery after acute stroke but that it reduces the proportion of patients with a new diagnosis of depression, compared with placebo.

Implications of all the available evidence

Although the median National Institutes of Health Stroke Scale score of 3 in the EFFECTS trial is similar to the general population of people with stroke in Sweden, we cannot rule out a benefit of fluoxetine in patients with more severe strokes. A further update of the Cochrane review of SSRI for stroke recovery, and a preplanned individual patient data meta-analysis of FOCUS, EFFECTS, and AFFINITY might identify a more modest effect in subgroups of patients. Until these results are known, we would not recommend further trials of fluoxetine for stroke recovery.

proportion of the studies (most of the studies were small and prone to systematic and random errors). Therefore, an international collaboration developed a core protocol for three trials of fluoxetine for recovery after stroke.[6,7] The trials were funded and run independently, and minor variations were tailored to the national settings in the UK (Fluoxetine Or Control Under Supervision [FOCUS]),[8] Australia, New Zealand, and Vietnam (Assessment oF FluoxetINe In sTroke recovery [AFFINITY]),[9] and Sweden (Efficacy oF Fluoxetine—a randomisEd Controlled Trial in Stroke [EFFECTS]).

The FOCUS trial[8] (n=3127) showed that oral fluoxetine 20 mg daily did not improve the distribution across modified Rankin Scale (mRS) score categories at 6 months, the primary outcome, compared with placebo. However, patients allocated to receive fluoxetine were less likely than those allocated to receive placebo to develop new depression by 6 months (13·4% *vs* 17·2%; p=0·0033), but had more bone fractures (2·9% *vs* 1·5%; p=0·007). The adherence to study medication was moderate; one in three patients 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. The AFFINITY trial[9] of oral fluoxetine 20 mg daily versus placebo in an ethnically diverse population with acute stroke reports similar results to FOCUS. AFFINITY and FOCUS have the same core protocol as EFFECTS.

The EFFECTS trial aimed to show whether administration of oral fluoxetine 20 mg 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, double-blind, parallel group trial that enrolled patients from 35 stroke and rehabilitation units in Sweden (appendix pp 12–15). Patients were eligible if they were aged 18 years or older with a clinical diagnosis of ischaemic or intracerebral haemorrhage in the previous 2–15 days; if brain imaging was compatible with intracerebral haemorrhage or ischaemic stroke; and the patient had at least one persisting focal neurological deficit severe enough (from the perspective of both the randomising physician and patient) to warrant treatment with fluoxetine for 6 months. 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; had previous drug overdose or attempted suicide; had an ongoing depression; were taking antidepressant medication, regardless of indication; were taking medications that could have a serious interaction with fluoxetine; had an allergy or contraindication to fluoxetine; had hepatic impairment (alanine aminotransferase more than 3 times the upper limit of normal) and renal impairment (creatinine >180 µmol/L); or were pregnant or breastfeeding. A full list of inclusion and exclusion criteria is shown in the appendix (p 3).

The study protocol 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; 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. The amendment to the protocol did not affect recruitment.

Randomisation and masking

The EFFECTS trial used the same randomisation system as the FOCUS trial.[8] A physician or nurse entered patients' baseline data into a secure web-based randomisation system. The system checked the data for completeness and consistency and allocated each patient an identification number and a treatment number. Patients were randomly assigned in a 1:1 ratio to either oral fluoxetine 20 mg once daily or placebo for 6 months. 20 mg daily was the dose used in most previous trials of fluoxetine in stroke.[5] The system applied a minimisation program to achieve balance between treatment groups for the following three factors: time after stroke onset (2–8 days *vs* 9–15 days); computer-generated predicted outcome at 6 months (probability of mRS 0–2 ≤0·15 *vs* >0·15 based on the six simple variable [SSV] model);[11] and presence of a motor deficit or aphasia at enrolment according to the National Institutes of Health Stroke Scale (NIHSS).[12] The SSV model includes six variables: whether the patient was independent and living alone before stroke onset; and patient age, ability to walk unassisted, ability to talk, and whether confusion is present or not, all at the onset of stroke. Details on how to calculate the SSV are shown in the appendix (p 4).

The randomisation system was set up so that the investigator could not see the next assignment in the sequence. The minimisation algorithm[13] randomly allocated the first patient to treatment, with each subsequent patient being allocated to the treatment that led 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 that minimised differences between groups with a probability of 0·8.

Patients, their families, health-care personnel, investigators, outcomes assessors, and staff in the coordinating centre (Karolinska Institutet, Department of Clinical Sciences Danderyd Hospital, Stockholm, Sweden), and the pharmacy were masked to treatment allocation. The placebo capsules were visually identical to the fluoxetine capsules, even when broken open. The success of the masking procedure was not assessed. An emergency unmasking system was available but was designed so that the coordinating centre and staff doing follow-up continued to be masked throughout the study.

Procedures

The intervention was initiated as soon as possible after randomisation. At the local stroke and rehabilitation centre, fluoxetine 20 mg or matching placebo was administered as one oral capsule daily (or via enteral tube if the patient was unable to swallow) for 6 months. We did not titrate the dose and we recommended the patient take it in the morning. At randomisation, study medication for the first 90 days was dispensed as a bottle of 100 capsules (bottle 1), which included 10 capsules as a 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 up to 7 days before 90 days, the patient was given the last 100 capsules (bottle 2) at a face-to-face follow-up at the same local centre. Patients were instructed to bring bottle 1 to this follow-up. The research nurses counted the capsules returned and recorded this in the case report form. When a patient could not attend a face-to-face meeting, the study medication was posted to them and the patient posted bottle 1 to the local centre. The study drug was free of charge. The study medication (intervention and placebo) was manufactured by Unichem (Goa, India), imported by Niche Generics (Hitchin, UK), bought from Discovery Pharmaceuticals (Castle Donington, UK), and quality assured, packaged, labelled, and distributed by Sharp Clinical Services (Tredegar, UK) to Apoteket (Stockholm, Sweden). 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—eg, a serious adverse event—was recorded in the patient's electronic case report form. Each study centre was reimbursed with 5000 SEK (approximately £375) per patient and supplied with medical record templates for inclusion as well as a template letter to inform family physicians about the trial.

At 6 months after randomisation, we assessed functional status using the mRS score. We used the simple mRS questionnaire (smRSq)[14,15] done by postal questionnaire or via interview over the telephone to derive the mRS score, which was centrally assessed. The following assessments took place by post at 6 months: survival; function in each domain of the Stroke Impact Scale (SIS) version 3[16,17] 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 the patient was taking. All responses received by mail 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 2 weeks, the trial manager assistant called the patient or next of kin to complete the answers by telephone.

Additionally, we did the following assessments at 3-month and 6-month face-to-face follow-up visits: NIHSS[12] for stroke severity, motor function, and aphasia; Montreal Cognitive Assessment (MoCA)[18] for cognitive function; new diagnosis of depression since randomisation (Diagnostic and Statistical Manual of Mental Disorders [DSM-IV][19] criteria, and Montgomery-Åsberg Depression Rating Scale [MADRS][20]); adverse events; and safety outcomes (appendix p 10).

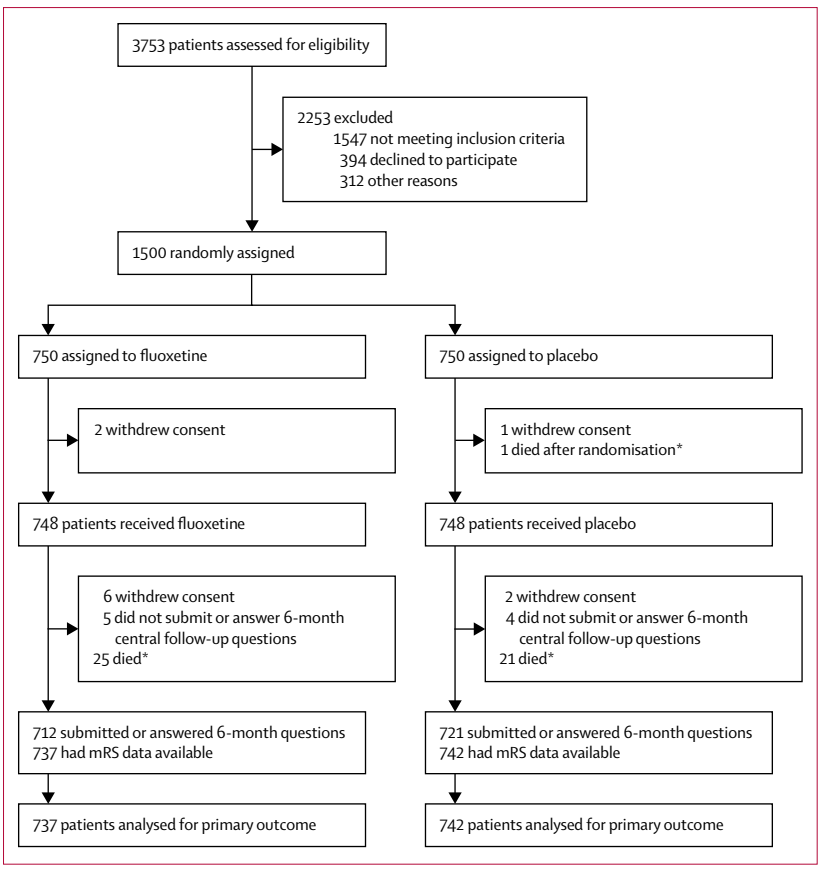

Figure 1: **Trial profile**
mRS=modified Rankin Scale. *Patients who died had mRS score 6 and were included in the primary analysis.

Information on specific depressive symptoms was also recorded at the 3-month and 6-month visits. The psychiatric evaluation regarding depression was done by the local physician. In case of uncertainty, a psychiatrist was consulted. 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 daily, with the possibility of titrating up to 45 mg mirtazapine. If 45 mg mirtazapine did not work, we recommended adding 20 mg fluoxetine once daily.

Adherence to the study medication was assessed by the team at the local centre at 1 week (plus or minus 3 days), 1 month (plus or minus 7 days), 3 months (plus or minus 7 days), and 6 months (plus or minus 14 days) by asking the patient, carer, or health personnel how often the patient took the study medication. Our monitors (Karolinska Trial Alliance, Stockholm, Sweden) cross-checked the counting of returned study medication for 10% of the patients.[10]

Outcomes

The primary outcome, which was centrally assessed, was functional status at 6 months (plus or minus 14 days) measured using the mRS.[21] The following secondary outcomes were centrally assessed at the trial coordinating centre at Danderyd Hospital at 6 months: survival and score in the assessed domains of the SIS version 3. The following secondary outcomes were assessed at face-to- face follow-up visits (not centrally assessed): NIHSS score; MoCA score; new diagnosis of depression; and adherence to trial medication (adherence was defined as taking the study medication 5–7 days per week, intermediate adherence was defined as taking the study medication 1–4 days per week or with some interruptions).

Safety outcomes assessed at the 3-month and 6-month face-to-face follow-ups by the local centre were relevant adverse events found in the 2012 Cochrane review[5] that would affect safety, especially in patients with stroke. These safety outcomes were new stroke (ischaemic or haemorrhagic), acute coronary events, upper gastrointestinal haemorrhage, new bone fractures, epileptic seizures, hyponatraemia (<130 mmol/L), and badly controlled diabetes (appendix p 10). Retrospectively, we also categorised patients with other serious bleeds (appendix p 11) and thrombotic events (pulmonary embolism, arterial embolism), which led to hospital admission. These were recorded at the local centres as serious adverse events.

In this Article we report the primary outcome, important secondary outcomes, and safety outcomes at 6 months. Analysis of physical activities and health economics, including quality of life, is ongoing and will be reported elsewhere. Extensive analysis of depressive symptoms is also ongoing and to be reported later. The last 12-month follow-up is planned for June 2020. Additionally, patients will be followed up in national registries for at least 3 years. A full list of secondary outcomes is in the appendix (pp 4–12).

Statistical analysis

All outcomes were prespecified and described in detail in our published statistical analysis plan.[7] Enrolment of 1500 patients randomly assigned 1:1 aimed to provide 90% power to detect a 5·6% absolute increase in the proportion of patients 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 effect size. The primary analysis was done in the modified intention-to-treat population (all randomly assigned patients who had mRS data available at 6 months), and we used the common odds ratio with 95% CI, adjusted for minimisation variables. We chose an ordinal analysis because it is considered to be more efficient than dichotomised analysis.[22] All secondary outcomes were analysed in the intention-to-treat population. For binary secondary outcomes, we used logistic regression and presented the results as common odds ratio with 95% CIs, absolute risk reduction, and relative risk reduction. For secondary outcomes with continuous variables, we used descriptive statistics and when comparing the two groups, we used the Mann-Whitney test. If any data could not be obtained by mail, telephone, face-to-face follow-up, or registry, the corresponding

	Fluoxetine (n=750)	Placebo (n=750)
Sex		
Women	287 (38%)	288 (38%)
Men	463 (62%)	462 (62%)
Age, years		
Mean	70·6 (11·3)	71·0 (10·5)
≤70	328 (44%)	316 (42%)
>70	422 (56%)	434 (58%)
Ethnicity		
Asian	1 (<1%)	6 (1%)
Black	4 (1%)	1 (<1%)
Chinese	0	0
White	743 (99%)	738 (98%)
Other	2 (<1%)	5 (1%)
Marital status		
Married	394 (53%)	363 (48%)
Partner	100 (13%)	96 (13%)
Divorced or separated	56 (8%)	58 (8%)
Widowed	87 (11%)	101 (14%)
Single	100 (13%)	120 (16%)
Other	13 (2%)	12 (2%)
Living arrangements before stroke		
Living with someone else	484 (65%)	467 (62%)
Living alone	266 (36%)	282 (38%)
Other	0	1 (<1%)
Employment status		
Full-time employment	158 (21%)	154 (21%)
Part-time employment	30 (4%)	38 (5%)
Retired	544 (73%)	538 (72%)
Unemployed	5 (1%)	10 (1%)
Other	13 (2%)	10 (1%)
Independent before stroke	717 (96%)	728 (97%)
Medical history*		
Coronary artery disease	123 (16%)	111 (15%)
Ischaemic stroke or transient ischaemic attack	126 (17%)	131 (18%)
Diabetes	140 (19%)	159 (21%)
Hyponatraemia	11 (2%)	8 (1%)
Intracranial bleed	18 (2%)	25 (3%)
Upper gastrointestinal bleed	23 (3%)	30 (4%)
Bone fractures	221 (30%)	189 (26%)
Depression	60 (8%)	50 (7%)
Stroke diagnosis		
Non-stroke (final diagnosis)†	2 (<1%)	1 (<1%)
Ischaemic stroke	662 (88%)	650 (87%)
Intracerebral haemorrhage	86 (12%)	99 (13%)
OCSP classification of ischaemic stroke		
Total anterior circulation infarct	179 (27%)	185 (29%)
Partial anterior circulation infarct	306 (46%)	288 (44%)
Lacunar infarct	100 (15%)	103 (16%)
Posterior circulation infarct	66 (10%)	60 (9%)
Uncertain	11 (2%)	14 (2%)

(Table 1 continues in next column)

(Continued from previous column)

	Fluoxetine (n=750)	Placebo (n=750)
Causes of ischaemic stroke (modified TOAST classification)		
Large artery disease	104 (16%)	88 (14%)
Small vessel disease	215 (33%)	205 (32%)
Embolism from the heart	141 (21%)	162 (25%)
Another cause	25 (4%)	16 (3%)
Unknown or uncertain cause	177 (27%)	179 (27%)
Predictive variables		
Able to walk at time of randomisation	392 (52%)	396 (53%)
Able to lift both arms off bed	597 (80%)	577 (77%)
Predicted 6-month outcome based on SSV model		
0·00–0·15	147 (20%)	149 (20%)
0·16–1·00	603 (80%)	601 (80%)
Neurological deficits at randomisation		
Median NIHSS score	3·0 (2·0–6·0)	3·0 (2·0–6·0)
Presence of a motor deficit‡	513 (68%)	533 (71%)
Presence of aphasia§	134 (18%)	134 (18%)
Ongoing depression at randomisation	0	0
Revascularisation treatment¶		
Intravenous thrombolysis	167 (23%)	158 (22%)
Thrombectomy only	10 (1%)	20 (3%)
Intravenous thrombolysis and thrombectomy	177 (24%)	178 (24%)
Days between stroke onset and randomisation		
Median	5·0 (4·0–8·0)	5·0 (3·0–8·0)
2–8 days	566 (75%)	570 (76%)
9–15 days	184 (25%)	180 (24%)

Data are n (%), mean (SD), or median (IQR). OCSP=Oxfordshire Community Stroke Project. NIHSS=National Institutes of Health Stroke Scale. SSV=six simple variables. TOAST=Trial of ORG 10172 in Acute Stroke Treatment criteria. *The medical history was verified by the physician using all available information at the time of randomisation. There was unknown medical history for six cases of coronary artery disease; two cases of ischaemic stroke or transient ischaemic attacks; two cases of diabetes; 19 cases of hyponatraemia; two intracranial bleeds; nine upper gastrointestinal bleeds; 14 bone fractures; and six cases of depression. †Non-strokes were one primary subarachnoid haemorrhage and one hydrocephalus in the fluoxetine group, and one cerebral tumour in the placebo group. ‡One point or more on item 4 (facial palsy), item 5 (left or right arm motor drift), or item 6 (left or right leg motor drift) on the NIHSS. §One point or more on NIHSS item 9 (language or aphasia). ¶There were 726 patients who were eligible for revascularisation treatment in the fluoxetine group, and 731 in the placebo group.

Table 1: **Baseline patient characteristics of all randomly assigned patients**

variable was set to missing. All analyses, except the primary outcome, were unadjusted.

Prespecified subgroup analyses were the effect of treatment allocation on the primary outcome subdivided by key baseline variables described in the published statistical analysis plan,[7] including the probability of being alive and independent (0·00 to ≤10·5 *vs* >0·15 to 1·00), time from stroke onset to randomisation (2–8 days *vs* 9–15 days), motor deficit (present or absent) or aphasia (present or absent), pathological type of stroke (ischaemic *vs* haemorrhagic), and age (≤70 years *vs* >70 years).

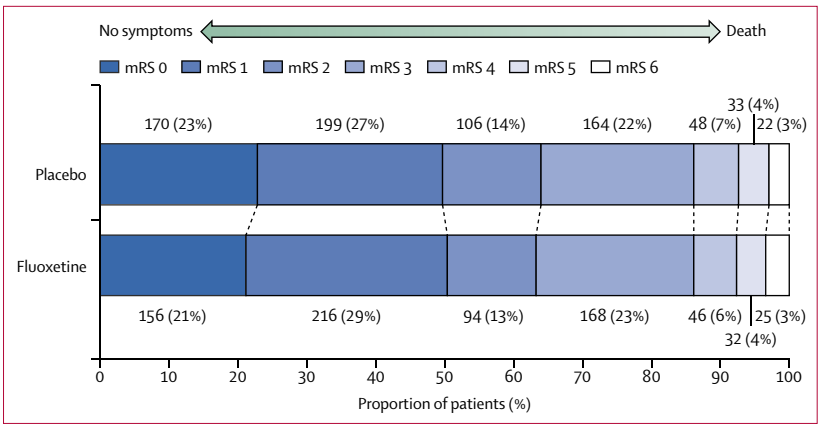

Figure 2: **Primary outcome of distribution of mRS scores at 6 months by treatment group (modified intention-to-treat population)**
mRS=modified Rankin Scale.

	Fluoxetine (n=750)		Placebo (n=750)		p value*
	n†	Median (IQR)	n†	Median (IQR)	
SIS domain scores					
Strength	694	75·0 (50·0–93·8)	689	75·0 (50·0–93·8)	0·67
Hand ability	690	81·3 (50·0–100·0)	692	87·5 (50·0–100·0)	0·99
Mobility	696	88·9 (72·2–100·0)	698	88·9 (72·2–97·2)	1·00
Motor‡	697	80·3 (60·4–92·8)	695	80·6 (58·1–93·8)	0·95
Daily activities	697	87·5 (69·4–97·5)	697	87·5 (67·5–97·5)	0·72
Physical function§	697	76·7 (56·3–90·2)	697	77·4 (55·5–91·0)	0·81
Memory	696	89·3 (78·6–100·0)	698	92·9 (82·1–100·0)	0·0064
Communication	695	96·4 (82·1–100·0)	697	92·1 (85·7–100·0)	0·83
Mood and emotional control	695	80·6 (66·7–91·7)	696	76·4 (63·9–88·9)	0·0002
Participation	690	65·6 (46·4–89·3)	682	68·8 (43·8–89·3)	0·55
Recovery	695	70·0 (50·0–90·0)	695	70·0 (50·0–90·0)	0·79
NIHSS	678	1·0 (0·0–2·0)	681	1·0 (0·0–2·0)	0·22
MoCA	632	26·0 (23·0–28·0)	630	26·0 (23·0–28·0)	0·82

NIHSS=National Institutes of Health Stroke Scale. MoCA=Montreal Cognitive Assessment. SIS=Stroke Impact Scale version 3. *p value=Mann-Whitney test. †The number of patients with scores available for each of the secondary outcomes, data were only available for those who survived and who completed sufficient questions to derive a score. ‡Mean of the strength, hand ability, and mobility domains. §Mean of the strength, hand ability, mobility, and daily activities domains.

Table 2: **Secondary outcomes at 6 months by treatment group (intention-to-treat population)**

Statistical analyses were done with SAS for Windows, version 9.4. The unmasked trial statistician (AJ) prepared analyses of the accumulating data for the independent data monitoring committee (appendix p 16). The trial steering committee did not do any interim analysis. This trial is registered with EudraCT, 2011-006130-16; ISRCTN, 13020412; and ClinicalTrials.gov, 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.

Results

Between Oct 20, 2014, and June 28, 2019, 3753 patients were assessed for eligibility, of whom 2253 were excluded (1547 did not meet inclusion criteria; 394 declined participation; and 312 were not recruited for other reasons [not recorded]). The remaining 1500 patients from 35 Swedish stroke and rehabilitation centres were randomly assigned to receive fluoxetine (750 patients) or placebo (750; figure 1).

After randomisation, 11 patients did not meet our eligibility criteria (protocol violators). Three had a final diagnosis other than stroke (two in the fluoxetine group and one in the placebo group), six patients were taking antidepressant medication at randomisation (three in each group), and two patients were randomly assigned at day 16 after stroke onset (one in each group). In two patients (one in each group), the physicians prescribed fluoxetine instead of continuing on the study medication. The patient assigned to the placebo group who crossed over was on fluoxetine for approximately 3–6 months. We unmasked one patient (assigned to the placebo group) who developed symptoms of bipolar disorder. The psychiatrist responsible for this decision argued that knowledge of the allocation would substantially alter the management of the patient. Ineligible patients were retained in the intention-to-treat analyses.

Baseline characteristics were well balanced between the two treatment groups (table 1). 1312 (87·4%) of 1500 patients had ischaemic stroke, 185 (12·3%) had intracerebral haemorrhage, and three (0·2%) had non-stroke. The mean age of patients at baseline was 70·8 years (SD 10·9), 575 (38·3%) patients were women, 1445 (96·3%) were previously independent, the median NIHSS score was 3·0 points (IQR 2·0–6·0), and 1046 (69·8%) had a motor deficit.

The mRS scores at 6 months were analysed in 737 (98%) of 750 patients in the fluoxetine group and 742 (99%) of 750 patients in the placebo group. A comparison of the distribution of patients across mRS categories at 6 months showed that there was no difference in the primary outcome between the fluoxetine group and the placebo group (common odds ratio adjusted for minimisation variables 0·94 [95% CI 0·78–1·13]; p=0·42); figure 2). There was no significant interaction between the prespecified subgroups and the effect on the primary outcome (appendix p 20).

Secondary outcomes at 6 months are shown in table 2. Patients assigned to the fluoxetine group scored significantly lower on the SIS domain of memory and significantly higher on the SIS domains of mood and emotional control at 6 months than did patients assigned to the placebo group. There was no difference between the two groups for the other domains of the SIS, or in NIHSS and MoCA scores (table 2).

The median duration of treatment was 180 days (IQR 180–180) for both groups. 1338 (89%) of 1500 patients 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, 62 (8%) of 750 patients stopped within the first 90 days compared with 66 (9%) of 750 in the placebo group. Adherence to study medication was high and almost identical in both groups at 1 week (703 [96%] of 730 fluoxetine *vs* 693 [94%] of 735 placebo), 1 month (658 [91%] of 721 *vs* 682 [93%] of 736), 3 months (630 [88%] of 722 *vs* 622 [86%] of 727), and 6 months (594 [89%] of 666 *vs* 595 [89%] of 673; appendix p 21). Denominators vary between follow-up times because valid data were not available for all patients at each follow-up.

Safety outcomes at 6 months are shown in table 3. Fewer patients treated with fluoxetine had a new diagnosis of depression (54 [7%] *vs* 81 [11%]; difference in proportions –3·60% [95% CI –6·49 to –0·71]; p=0·015) and uncontrolled diabetes compared with patients in the placebo group. However, compared with the placebo group, patients in the fluoxetine group had an increased risk of bone fractures (28 [4%] patients *vs* 11 [2%]; 2·27% [0·66 to 3·87]; p=0·0058), and hyponatraemia (11 [1%] patients *vs* one [<1%]; 1·33% [0·43 to 2·23]; p=0·0038; table 3). There were no treatment-related deaths; details of the causes of death are shown in the appendix (pp 21–22).

	Fluoxetine (n=750)	Placebo (n=750)	Difference (95% CI)	p value
Death*	25 (3%)	22 (3%)	0·40% (–1·36 to 2·16)	0·66
Attempted suicide	1 (<1%)	1 (<1%)	0·00% (–0·37 to 0·37)	1·00
New depression	54 (7%)	81 (11%)	–3·60% (–6·49 to –0·71)	0·015
Antidepressant drug†	36 (5%)	51 (7%)	–1·86% (–4·36 to 0·36)	0·098
Acute coronary events	5 (1%)	6 (1%)	–0·13% (–1·00 to 0·73)	0·76
Epileptic seizures	8 (1%)	11 (1%)	–0·40% (–1·53 to 0·73)	0·49
Uncontrolled diabetes	5 (1%)	15 (2%)	–1·33% (–2·49 to –0·17)	0·024
Hyponatraemia <130 mmol/L	11 (1%)	1 (<1%)	1·33% (0·43 to 2·23)	0·0038
Fractured bone	28 (4%)	11 (2%)	2·27% (0·66 to 3·87)	0·0058
Upper gastrointestinal bleeding	4 (1%)	3 (<1%)	0·13% (–0·56 to 0·82)	0·71
New stroke	36 (5%)	28 (4%)	1·07% (–0·98 to 3·11)	0·31
Ischaemic stroke	31 (4%)	26 (4%)	..	..
Intracerebral haemorrhage	5 (1%)	1 (<1%)	..	..
Subarachnoid haemorrhage	0	1 (<1%)	..	..
Thrombotic events				
Pulmonary embolism	3 (<1%)	6 (1%)	–0·40% (–1·18 to 0·38)	0·32
Other thrombotic events‡	5 (1%)	6 (1%)	–0·13% (–1·00 to 0·73)	0·76
Any bleeding events				
Subdural haematoma	1 (<1%)	1 (<1%)	0·00% (–0·37 to 0·37)	1·00
Traumatic subarachnoid haemorrhage	2 (<1%)	1 (<1%)	0·13% (–0·32 to 0·59)	0·56
Other major bleed§	7 (1%)	6 (1%)	0·13% (–0·80 to 1·07)	0·78

Data are n (%) unless otherwise stated. *Details of the causes of death are shown in the appendix (pp 21–22). †Treatment outside of the study medication. ‡Nine transient ischaemic attacks (four fluoxetine group, five placebo group), one central retinal artery occlusion (fluoxetine group), and one cerebral venous thrombosis (placebo group). §Defined as a bleeding that was reported by the local centre as a serious adverse event; details of the 13 major bleedings are shown in the appendix (p 21).

Table 3: **Safety outcomes at 6 months by treatment group (intention-to treat population)**

Discussion

To the best of our knowledge, EFFECTS is the second largest randomised controlled trial of fluoxetine for stroke recovery. Oral fluoxetine 20 mg once daily after an acute stroke did not improve patients' functional outcome at 6 months compared with placebo. However, there were fewer new diagnoses of depression, better emotional scores on the SIS, and increased bone fractures with fluoxetine compared with placebo.

Unlike the FOCUS[8] trial, the EFFECTS trial included face-to-face follow-up at 6 months, which enabled us to include NIHSS, MoCA, and a careful estimation of depression in our results. The NIHSS scores were identical between the two treatment groups in this study, a result that, along with the results for the primary outcome of mRS score, suggests that fluoxetine has no effect on functional outcome at 6 months after acute stroke. However, the results for memory and cognition were conflicting. Patients assigned to the fluoxetine group scored lower on the SIS domain for memory compared with patients in the placebo group, but both groups had similar MoCA scores. Because MoCA is a more comprehensive test of memory than the SIS, and the results from the FOCUS trial showed no effect of fluoxetine on memory, fluoxetine probably does not affect cognition. The overall proportion of patients with a new diagnosis of depression was lower in the EFFECTS trial compared with in the FOCUS trial, which could be attributed to the difference between the trials in how depression was measured or the inclusion in the FOCUS trial of patients with more severe strokes (median NIHSS of 6) compared with EFFECTS (median NIHSS of 3).

The external validity of our results is supported by the inclusion of patients from 35 centres in Sweden with similar baseline characteristics to the general population of patients with stroke in Sweden[23] regarding age, risk factors, proportion of patients with ischaemic versus intracerebral haemorrhage, and stroke severity measured with NIHSS. However, the population in the EFFECTS trial had a lower proportion of women and a slightly lower proportion of patients who were independent before stroke (appendix p 18), compared with the general Swedish population with stroke.[23]

Our main finding of no effect of fluoxetine on the primary outcome of mRS score, but a reduction of depression in the fluoxetine group compared with in the placebo group mirrors the results of the FOCUS trial[8] and the AFFINITY trial,[9] further supporting the external validity of our results. Our results are also in line with the 2019 Cochrane review of SSRIs for stroke recovery: when including only low bias randomised controlled trials, SSRIs do not improve recovery from stroke.[24]

The absolute excess risk of 2·27% for bone fractures in this trial is also consistent with the results from the FOCUS and AFFINITY trials and from 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 for patients with stroke. Gastrointestinal bleeding and thrombotic adverse events were similar between the groups in this study, despite fluoxetine's known effect on platelet function and interaction between fluoxetine and antiplatelet and anticoagulant medication.[5] Our finding of better diabetes control for patients in the fluoxetine group compared with those in the placebo group is unexpected. Rather, the reverse was expected because of the known side-effects of fluoxetine. We interpret this result as a chance finding due to random error associated with multiple analyses.

The EFFECTS trial has several strengths. First, we reduced bias by central randomisation and masking of treatment for patients, care providers, investigators, and outcome assessors. Only one patient (<1%) was unmasked. Second, we minimised random error with a large sample size and high follow-up (≥98% for the primary outcome). Finally, we had high adherence to study medication in both treatment groups: 89% at 6 months across both groups.

The EFFECTS trial has several limitations that affect the generalisability of our results. First, EFFECTS had a higher proportion of men enrolled (62%) than women. This predominance of men in stroke studies is a known but unexplained observation.[27] Second, the trial was done in only one country, Sweden. Health-care systems vary between countries, and it is not certain that results from high-income countries are directly transferable to low-income and middle-income countries. Third, in EFFECTS, we included patients with at least one persisting focal neurological deficit present at the time of randomisation severe enough from the physician's and the patient's perspective to warrant treatment. The proportion of patients in the placebo group with mRS 0–2 (64%) was more than double that expected in our power calculation (27%). At baseline, the median NIHSS was 3, and we cannot exclude that patients with more severe stroke could benefit from fluoxetine. Fourth, because we did a face-to-face follow-up at 6 months (unlike the FOCUS and AFFINITY trials), we could also have included the Fugl-Meyer Assessment scale, which was used in the FLAME[4] trial and is a more sensitive motor scale than the mRS. We did not use the Fugl-Meyer Assessment scale because, although it was invented in Sweden, it is not routinely used by all Swedish hospitals, 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. However, the validity and reliability of the smRSq has been tested and found to be high,[14,15] and a study of 3204 patients from the ENCHANTED trial showed good agreement between smRSq and mRS face-to-face scores.[28] In EFFECTS, it was important that data could be collected by mail or telephone because these methods were used in FOCUS and AFFINITY, and to use the same primary outcome as FOCUS and AFFINITY to allow future pooling of individual patient data.

In summary, the results from the EFFECTS trial show that oral fluoxetine 20 mg given once daily for 6 months after an acute stroke did not improve patients' functional outcomes; however, the proportion of patients with a new diagnosis of depression was lower compared with placebo. 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, collected, verified, and analysed data, and wrote the 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, and 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 MLH 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.

EFFECTS Writing Committee

Erik Lundström, Eva Isaksson, Per Näsman, Per Wester, Björn Mårtensson, Bo Norrving, Håkan Wallén, Jörgen Borg, Martin Dennis, Gillian Mead, Graeme J Hankey, Maree L Hackett, Katharina S Sunnerhagen.

Declaration of interests

BN has received honoraria for data monitoring committee work in the SOCRATES and THALES trials (AstraZeneca) and the NAVIGATE-ESUS trial (Bayer). HW has received grants from the Swedish Medical Research Council (Vetenskapsrådet) during the conduct of the study; the grant was for the study that is presented in the submitted manuscript. GJH has received grants from the National Health and Medical Research Council (NHMRC) of Australia, Vetenskapsrådet, and UK National Institute for Health Research Technology, during the conduct of the study; and personal fees from American Heart Association, outside of the submitted work. MD reports that the University of Edinburgh received some funding from the grants for EFFECTS (Vetenskapsrådet) in relation to its provision of a randomisation system. MLH has received grants from the NHMRC of Australia, outside of the submitted work. All other authors declare no competing interests.

Data sharing

The final cleaned data set will be saved in the Karolinska Institutet's electronic notebook, unmasked trial statistician (PN) and chief investigator (EL) will have access to the data. All data will be stored anonymised, using the EFFECTS trial identification. A limited number of variables will be shared with the FOCUS and AFFINITY trials enabling the planned individual patient data meta-analysis. The datasets used 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.

Acknowledgments

EFFECTS has received funding from the Swedish Research Council (registration number 2014-07072); the Swedish Heart-Lung Foundation (application number 2013-0496 and 2016-0245); the Swedish Brain Foundation (application number FO2017-0115); the Swedish Society of Medicine (ID 692921); King Gustav V and Queen Victoria's Foundation of Freemasons (year 2014); and the Swedish Stroke Association (STROKE-Riksförbundet; year 2012 and 2013). We thank all patients in the EFFECTS study, personnel in the EFFECTS Trial Collaboration, Trial Manager Assistant Nina Greilert Norin at EFFECTS, Chief Technical Officer Krister Kristianson at EDC Scandinavia, and our monitors Terése Brunsell, Maria Persson, and Ingalill Reinholdsson, at Karolinska Trial Alliance. The sponsor was Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, 182 88 Stockholm, Sweden. The sponsor's representative was EL.

References

1 Johnson CO, Nguyen M, Roth GA, et al. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019; **18:** 439–58.

2 Vos T, Allen C, Arora M, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388:** 1545–602.

3 McCann SK, Irvine C, Mead GE, et al. Efficacy of antidepressants in animal models of ischemic stroke: a systematic review and meta-analysis. *Stroke* 2014; **45:** 3055–63.

4 Chollet F, Tardy J, Albucher J-F, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. *Lancet Neurol* 2011; **10:** 123–30.

5 Mead GE, Hsieh C-F, Lee R, et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. *Cochrane Database Syst Rev* 2012; **11:** CD009286.

6 Mead G, Hackett ML, Lundström E, Murray V, Hankey GJ, Dennis M. The FOCUS, AFFINITY and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: a study protocol for three multicentre randomised controlled trials. *Trials* 2015; **16:** 369.

7 Graham C, Lewis S, Forbes J, et al. The FOCUS, AFFINITY and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: statistical and health economic analysis plan for the trials and for the individual patient data meta-analysis. *Trials* 2017; **18:** 627.

8 Dennis M, Mead G, Forbes J, et al. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. *Lancet* 2019; **393:** 265–74.

9 Affinity Trial Collaboration. Safety and efficacy of fluoxetine on functional outcome after acute stroke (AFFINITY): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2020; **19:** 651–60.

10 Lundström E, Isaksson E, Näsman P, et al. Update on the EFFECTS study of fluoxetine for stroke recovery: a randomised controlled trial in Sweden. *Trials* 2020; **21:** 233.

11 Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute and subacute stroke: development and validation of new prognostic models. *Stroke* 2002; **33:** 1041–47.

12 Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989; **20:** 864–70.

13 Altman DG, Bland JM. Treatment allocation by minimisation. *BMJ* 2005; **330:** 843.

14 Bruno A, Akinwuntan AE, Lin C, et al. Simplified modified Rankin scale questionnaire: reproducibility over the telephone and validation with quality of life. *Stroke* 2011; **42:** 2276–79.

15 Dennis M, Mead G, Doubal F, Graham C. Determining the modified Rankin score after stroke by postal and telephone questionnaires. *Stroke* 2012; **43:** 851–53.

16 Duncan PW, Reker DM, Horner RD, et al. Performance of a mail-administered version of a stroke-specific outcome measure, the Stroke Impact Scale. *Clin Rehabil* 2002; **16:** 493–505.

17 Duncan P, Reker D, Kwon S, et al. Measuring stroke impact with the stroke impact scale: telephone versus mail administration in veterans with stroke. *Med Care* 2005; **43:** 507–15.

18 Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; **53:** 695–99.

19 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders IV, 4th edn. Washington, DC: American Psychiatric Association, 1994.

20 Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979; **134:** 382–89.

21 van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; **19:** 604–07.

22 Bath PM, Gray LJ, Collier T, Pocock S, Carpenter J. Can we improve the statistical analysis of stroke trials? Statistical reanalysis of functional outcomes in stroke trials. *Stroke* 2007; **38:** 1911–15.

23 Riksstroke. Demography of stroke patients in Sweden (in Swedish). Riksstroke. http://www.riksstroke.org/wp-content/uploads/2019/09/Riksstroke_A%CC%8Arsrapport-2018_slutversionWEB.pdf (accessed Jan 3, 2020).

24 Legg LA, Tilney R, Hsieh C-F, et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. *Cochrane Database Syst Rev* 2019; **11:** CD009286.

25 Wadhwa R, Kumar M, Talegaonkar S, Vohora D. Serotonin reuptake inhibitors and bone health: a review of clinical studies and plausible mechanisms. *Osteoporos Sarcopenia* 2017; **3:** 75–81.

26 Rizzoli R, Cooper C, Reginster J-Y, et al. Antidepressant medications and osteoporosis. *Bone* 2012; **51:** 606–13.

27 Tsivgoulis G, Katsanos AH, Caso V. Under-representation of women in stroke randomized controlled trials: inadvertent selection bias leading to suboptimal conclusions. *Ther Adv Neurol Disord* 2017; **10:** 241–44.

28 Chen X, Li J, Anderson CS, et al. Validation of the simplified modified Rankin scale for stroke trials: experience from the ENCHANTED alteplase-dose arm. *Int J Stroke* 2020; published online Jan 22. DOI:10.1177/1747493019897858.