



## Article

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

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

3

4 Version 5

5 Date 8 May 2020

6

7

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

10

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12

Summary	333 words
Manuscript	Approx 3700 words
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13

## 14 Summary

### 15 BACKGROUND

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

### 19 METHODS

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

### 30 FINDINGS

31 Recruitment started 20 Oct 2014 and ended 28 June 2019, when the planned 1500 patients  
32 were included (750 to fluoxetine and 750 to placebo). mRS data were available for 737/750  
33 (98%) in the fluoxetine group and 742/750 (99%) in the placebo group. The primary outcome  
34 - distribution across mRS categories— was neutral (common odds ratio adjusted for  
35 minimisation variables 0·94 [95% CI 0·78 to 1·13],  $p=0\cdot42$ ). Fluoxetine reduced depression  
36 (54 [7·2%] patients vs 81 [10·8%]; difference -3·6% [95% CI -0·065 to -0·0071];  $p=0\cdot015$ )  
37 but was associated with more bone fractures (28 [3·7%] vs 11 [1·5%]; difference 2·2% [95%  
38 CI 0·0066 to 0·039];  $p=0\cdot0058$ ) and hyponatremia (11 [1·47%] patients vs 1 [0·13%];

39 difference 1.34% [95% CI 0.0043 to 0.022]; p=0.0038). There were no treatment-related  
40 deaths.

#### 41 INTERPRETATION

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

#### 46 FUNDING

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

#### 50 *Key words*

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

## 53 Introduction

54 Worldwide, stroke affects 13.7 million people each year<sup>1</sup> and approximately half of all  
55 survivors are left with disability.<sup>2</sup> Whereas major advances have been made in acute  
56 treatment, there is a need for new treatments focused on long-term stroke recovery  
57 irrespective of eligibility for acute treatments. One possible drug is fluoxetine, a selective  
58 serotonin reuptake inhibitor (SSRI). SSRIs has been widely used for more than three decades  
59 to treat several hundred million people with mood disorders. A meta-analysis of animal stroke  
60 models has shown that fluoxetine improves neurobehavioral outcomes by 52%, probably by  
61 enhancing neuroplasticity.<sup>3</sup> In 2011, the FLAME trial (n=118) reported promising results for  
62 stroke recovery.<sup>4</sup> FLAME randomised ischaemic stroke patients to 20 mg fluoxetine daily or

63 placebo (ratio 1:1) for 3 months. The proportion of independent was 17 absolute percent  
64 higher in the fluoxetine group (26% versus 9%,  $p=0.015$ ).

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

76

77 In December 2018, FOCUS ( $n=3127$ ) published its results.<sup>9</sup> The primary outcome – the  
78 distribution across mRS categories at 6 months – was neutral. Patients allocated fluoxetine  
79 were less likely than placebo to develop new depression by 6 months (13.4% versus 17.2%,  
80  $p=0.0033$ ), but they had more bone fractures (2.9% versus 1.5%);  $p=0.007$ ). The adherence to  
81 study medication was moderate. One in three took the trial medication for less than 150 of the  
82 prescribed 180 days, which might reduce the generalisability of the FOCUS results outside  
83 the UK.

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

## 86 Methods

### 87 Study design and patients

88 EFFECTS was an investigator-led multicentre, randomised, placebo-controlled, parallel  
89 group trial of fluoxetine for stroke recovery. Eligible patients were identified from stroke and  
90 rehabilitation units in Sweden (appendix, p 12-15). The study protocol was approved by a  
91 central medical ethics committee in Stockholm (reference 2013/1265-31/2, date: 03/09/2013)  
92 and by the Swedish Medical Agency (reference 5.1-2014-43006, date 08/08/2014). All  
93 patients provided written informed consent before randomisation. Consent from relatives was  
94 not accepted. The protocol<sup>6</sup>, statistical analysis plan<sup>7</sup>, and an update on the amendment to the  
95 protocol<sup>10</sup> have been published. All inclusion and exclusion criteria are listed in the appendix  
96 p 3. Briefly, patients were eligible if brain imaging was compatible with intracerebral  
97 haemorrhage or ischaemic stroke, randomisation was possible between two and 15 days after  
98 stroke onset, and the patient had persisting focal neurological deficit(s) severe enough to  
99 warrant treatment with the investigational medicinal product for six months from the  
100 perspective of the randomising physician AND patient. Patients were excluded if they had a  
101 primary subarachnoid haemorrhage; were unlikely to be available for follow-up for the next  
102 12 months; had a history of epileptic seizures; previous drug overdose or attempted suicide;  
103 or an ongoing depression. Patients on anti-depressant medication – regardless of indication –  
104 were also excluded. Other exclusion criteria were allergy or contraindication to fluoxetine; or  
105 medication(s) which could have a serious interaction with fluoxetine; hepatic impairment  
106 (alanine aminotransferase more than three times the upper normal limit) and renal impairment  
107 (creatinine > 180 µmol/L); pregnancy or breastfeeding.

108 Randomisation and masking

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

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

- 116 1) Delay since stroke onset (2–8 versus 9–15 days)
- 117 2) Predicted 6 months outcome based on the six simple variable (SSV) model<sup>11</sup>
- 118 3) Presence of a motor deficit based on National Institutes of Health Stroke Scale<sup>12</sup>  
119 (NIHSS) at inclusion
- 120 4) Presence of aphasia based on NIHSS at inclusion.

121 The SSV included six variables, four at the onset and two prior to the stroke. Onset variables  
122 were: age; ability to walk unassisted; ability to talk; and whether confusion is present or not.

123 The two variables before stroke were whether the patient was independent and living alone.

124 Details how to calculate the SSV is given in appendix page 4. The randomisation system was

125 set up so that the investigator could not see the next assignment in the sequence. The

126 minimisation algorithm<sup>13</sup> randomly allocated the first patient to treatment, but each

127 subsequent patient was allocated to the treatment that lead to the least difference between the

128 treatment groups with respect to the prognostic factors. To ensure a random element to

129 treatment allocation, patients were allocated to the group which minimised differences

130 between groups with a probability of 0.8.

131 The placebo capsule was visually identical to the fluoxetine capsules, even when broken

132 open. Patients, their families, health-care personnel, staff in the coordinating centre

133 (Karolinska Institutet, Department of Clinical Sciences Danderyd Hospital), and the  
134 pharmacy were masked to treatment allocation.  
135 An emergency unblinding system was available but was designed so that the co-ordinating  
136 centre and those doing follow-up continued to be masked throughout the study.

## 137 Procedures

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

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

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



158

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

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

## 166 Outcomes

167 Details of the outcomes and definitions are described in the appendix. In summary, the  
168 primary outcome was functional status at 6 months ( $\pm$  14 days), measured using the modified  
169 Rankin scale (mRS).<sup>14</sup> We used the simple modified Rankin scale questionnaire<sup>15,16</sup> (smRSq)  
170 delivered by postal questionnaire or via interview over the telephone to derive the mRS score.

171

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

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

183 well as motor function and aphasia; Montreal Cognitive Assessment<sup>19</sup> (MoCA), to assess the  
184 patients' cognitive function; new diagnosis of depression since randomisation (Diagnostic  
185 and Statistical Manual of Mental Disorders<sup>20</sup> (DSM-IV) criteria, and Montgomery-Åsberg  
186 Depression Rating Scale<sup>21</sup> (MADRS) ); adverse events; and safety outcomes (see appendix  
187 p 10 for definition). The psychiatric evaluation regarding depression was done by the local  
188 physician, a medical doctor. In case of uncertainty, a psychiatrist was consulted. Adherence  
189 was measured at 1 week ( $\pm$  3 days), 1 month ( $\pm$  7 days), 3 months ( $\pm$  7 days), and 6 months ( $\pm$   
190 14 days), by asking the patient, carer or health personnel how often the patient took the study  
191 medication.

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

196

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

## 202 Statistical analysis

203 All outcomes were prespecified and described in detail in our published statistical analysis  
204 plan.<sup>7</sup> Enrolment of 1500 patients randomised 1:1 aimed to provide 90% power to detect a  
205 5.6% absolute increase in the proportion with mRS 0–2 from, 27.0% to 32.6% based on an  
206 ordinal analysis. We hypothesised that an absolute difference of 5.6% would represent a  
207 clinically meaningful effects size for patient and society. For the primary analysis, we used

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

216

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

222

223 EFFECTS is registered with EudraCT, number 2011-006130-16; ISRCTN, number  
224 13020412; and ClinicalTrials.gov, number NCT02683213.

## 225 Role of the funding source

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

## 232 Results

233 Recruitment in EFFECTS started 20 October 2014 and ended 28 June 2019 when the planned  
234 target was reached. A total of 1500 patients were included from 35 Swedish centres. The last  
235 6 months follow-up was on 17 December 2019. Half of the enrolled patients were allocated  
236 fluoxetine (figure 1).

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

250

251 *Insert figure 1 here.*

252

253 Baseline characteristics include: ischemic stroke 1312 (87.4%); intracerebral haemorrhage  
254 185 (12.3%); non-stroke 3 (0.2%); mean age 70.8 (10.9) years; female 575 (38.3%);  
255 previously independent 1445 (96.3%); median NIHSS score 3.0 (2.0, 6.0) points; and  
256 presence of motor deficit 1046 (69.8%). The two treatment groups were well balanced (table

257 1) at baseline, and similar to a Swedish stroke population according to Riksstroke regarding  
258 age, risk factors, proportion ischemic vs intracerebral haemorrhage, and stroke severity,  
259 measured with NIHSS. <sup>23</sup> EFFECTS had a lower proportion of women and a slightly lower  
260 number of independent before stroke (appendix p 18), compared to Swedish stroke  
261 population. <sup>23</sup>

262

263 *Insert table 1 here*

264

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

269

270 *Insert figure 2 here.*

271

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

274

275 *Insert table 2 here.*

276

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

281 0·039]; p=0·0058), and hyponatraemia (11 [1·47%] patients vs 1 [0·13%]; difference 1·34%  
282 [95% CI 0·0043 to 0·022]; p=0·0038) (table 3). There were no treatment-related deaths.

283

284 *Insert table 3 here.*

285

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

288

289 Adherence to fluoxetine and placebo was very high. At 1 week, 1 month, 3 months, and 6  
290 months the adherence to fluoxetine was 96% (703/730), 91% (658/721), 88% (630/722), and  
291 89% (594/666), respectively. The adherence was almost identical for placebo: 94%  
292 (693/735), 93% (682/736), 86% (622/727), and 89% (595/673), respectively appendix p 21.

293 Our monitors cross-checked the counting for 10% of the patients.<sup>10</sup> Our monitors cross-  
294 checked the counting for 10% of the patients.<sup>10</sup> The median duration of treatment was 180  
295 days (IQR 180–180) for both groups. About 89% (1338/1500) took the study medication for  
296 at least 150 days.

297 The most common reason for stopping the study medication was perceived side effects; in the  
298 fluoxetine group 8·3% (62/750) stopped within the first 90 days compared with 8·8%  
299 (66/750) in the placebo group.

300

## 301 Discussion

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

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

306

307 EFFECTS has several strengths. Firstly, we reduced bias by central randomisation and  
308 masking of treatment for patients, care providers, investigators, and outcome assessors. Only  
309 one patient (0·067%) was unmasked. Secondly, we minimised random error with a large  
310 sample size and high follow-up ( $\geq 98\%$  for the primary outcome). Thirdly, we had high  
311 adherence, 89% at 6 months.

312

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

320

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

324

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

329 results for the primary outcome but reduction of depression. FOCUS had a population with  
330 more severe strokes (median NIHSS of 6) compared to the median NIHSS of 3 for  
331 EFFECTS.  
332 Finally, our results are also in line with the updated version of the Cochrane review of SSRIs  
333 for stroke recovery from 2019.<sup>24</sup> When including only low bias RCTs, SSRIs do not improve  
334 recovery from stroke.

335

### 336 *Safety outcome*

337 The absolute excess risk of 2.2% of bone fractures in EFFECTS is consistent with FOCUS  
338 and previous reports from large case-control and cohort studies.<sup>25</sup> Serotonin receptors are  
339 found in all major types of bone cell, and the use of SSRIs has been linked to reduced bone  
340 mineral density.<sup>26</sup> This increased risk is highest after initiation, with a peak at 8 months for  
341 SSRI.<sup>26</sup>  
342 Except for an increased risk of bone fractures and hyponatraemia, fluoxetine seems to be a  
343 reasonably safe drug in the stroke population. Gastrointestinal bleeding and thrombotic  
344 adverse events were similar between the groups, despite fluoxetine's known effect on platelet  
345 function and interaction between fluoxetine and antiplatelet and anti-coagulant medication. In  
346 EFFECTS, fluoxetine did not increase the number of epileptic seizures. Our finding of better  
347 diabetes control for patients allocated fluoxetine compared to placebo is unexpected. Rather,  
348 the reverse was expected due to the known side effects of fluoxetine We interpret the results  
349 as a chance finding due to random error associated with multiple analyses.

### 350 *Limitations*

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



353 a known but unexplained observation.<sup>27</sup> Secondly, it was performed in only one country,  
354 Sweden. Healthcare systems vary between countries, and it is not certain that results from  
355 high-income countries are directly transferable to low and middle-income countries. Thirdly,  
356 in EFFECTS, we included patients with persisting focal neurological deficit present at the  
357 time of randomisation severe enough to warrant treatment from the physicians and the  
358 patient's perspective. In our power calculation we expected 27% of the control group to have  
359 mRS 0–2. It turned out that we had more than double the number (64%) of stroke with mRS  
360 0–2 in the control group. Effectively, we ended up with a median NIHSS of three, and we  
361 cannot exclude that patients with a more severe stroke may benefit from fluoxetine. Fourthly,  
362 we could have included the Fugl-Meyer scale, a more sensitive motor scale used in the  
363 FLAME trial, since we did a face-to-face follow-up at 6 months (unlike FOCUS and  
364 AFFINITY trial). Although the scale is invented in Sweden, it is not used by all hospitals in  
365 our country, and we wanted to keep the study as simple as possible.

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

373

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

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

#### 380 Contributors

381 EL was the Chief Investigator, participated in the steering committee, was involved in the design of the  
382 trial, and collected, verified, and analysed data, and wrote first draft of the manuscript. EI was the Trial  
383 Manager, participated in the steering committee, was involved in the design of the trial, and collected,  
384 verified, analysed data. PN participated in the steering committee, was involved in the design of the trial,  
385 did the statistical analysis, and analysed data. BM participated in the steering committee, advised on the  
386 management of depression within the trial and was involved in the design of the trial. KSS was chair of the  
387 steering committee and was involved in the design of the trial.  
388 PW, HW, JB, and BN participated in the steering committee and were involved in the design of the trial.  
389 MD, GM, GJH, and MH were involved in the trial design, affiliated to the steering committee and analysed  
390 data. All members of the writing committee have refined the study protocol, commented on the analyses  
391 and drafts and seen and approved the final version of the manuscript.

#### 392 Declaration of interest

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

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

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

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

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

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

#### 409 Data sharing

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

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

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## 429 References

- 430 1 Johnson CO, Nguyen M, Roth GA, *et al.* Global, regional, and national burden of stroke, 1990–2016: a  
431 systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology* 2019; **18**: 439–  
432 58.
- 433 2 GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national  
434 incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a  
435 systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**: 1545–602.
- 436 3 McCann SK, Irvine C, Mead GE, *et al.* Efficacy of antidepressants in animal models of ischemic stroke: a  
437 systematic review and meta-analysis. *Stroke* 2014; **45**: 3055–63.
- 438 4 Chollet F, Tardy J, Albucher J-F, *et al.* Fluoxetine for motor recovery after acute ischaemic stroke  
439 (FLAME): a randomised placebo-controlled trial. *The Lancet Neurology* 2011; **10**: 123–30.
- 440 5 Mead GE, Hsieh C-F, Lee R, *et al.* Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery.  
441 In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd, 2012.  
442 <http://onlinelibrary.wiley.com.proxy.kib.ki.se/doi/10.1002/14651858.CD009286.pub2/abstract> (accessed  
443 Sept 27, 2015).
- 444 6 Mead G, Hackett ML, Lundström E, Murray V, Hankey GJ, Dennis M. The FOCUS, AFFINITY and  
445 EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: a study protocol for  
446 three multicentre randomised controlled trials. *Trials* 2015; **16**: 369.
- 447 7 Graham C, Lewis S, Forbes J, *et al.* The FOCUS, AFFINITY and EFFECTS trials studying the effect(s)  
448 of fluoxetine in patients with a recent stroke: statistical and health economic analysis plan for the trials  
449 and for the individual patient data meta-analysis. *Trials* 2017; **18**: 627.
- 450 8 Hankey GJ. Safety and efficacy of fluoxetine on functional outcome after acute stroke (AFFINITY): a  
451 randomised, double-blind, placebo-controlled trial. .
- 452 9 Dennis M, Mead G, Forbes J, *et al.* Effects of fluoxetine on functional outcomes after acute stroke  
453 (FOCUS): a pragmatic, double-blind, randomised, controlled trial. *The Lancet* 2019; **393**: 265–74.
- 454 10 Lundström E, Isaksson E, Näsman P, *et al.* Update on the EFFECTS study of fluoxetine for stroke  
455 recovery: a randomised controlled trial in Sweden. *Trials* 2020; **21**: 233.
- 456 11 Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute and subacute stroke:

457 development and validation of new prognostic models. *Stroke* 2002; **33**: 1041–7.  
458 12 Brott T, Adams HP, Olinger CP, *et al.* Measurements of acute cerebral infarction: a clinical examination  
459 scale. *Stroke* 1989; **20**: 864–70.  
460 13 Altman DG, Bland JM. Treatment allocation by minimisation. *BMJ* 2005; **330**: 843.  
461 14 Swieten JC van, Koudstaal PJ, Visser MC, Schouten HJ, Gijn J van. Interobserver agreement for the  
462 assessment of handicap in stroke patients. *Stroke* 1988; **19**: 604–7.  
463 15 Bruno A, Akinwuntan AE, Lin C, *et al.* Simplified modified rankin scale questionnaire: reproducibility  
464 over the telephone and validation with quality of life. *Stroke* 2011; **42**: 2276–9.  
465 16 Dennis M, Mead G, Doubal F, Graham C. Determining the modified Rankin score after stroke by postal  
466 and telephone questionnaires. *Stroke* 2012; **43**: 851–3.  
467 17 Duncan PW, Reker DM, Horner RD, *et al.* Performance of a mail-administered version of a stroke-  
468 specific outcome measure, the Stroke Impact Scale. *Clin Rehabil* 2002; **16**: 493–505.  
469 18 Duncan P, Reker D, Kwon S, *et al.* Measuring stroke impact with the stroke impact scale: telephone  
470 versus mail administration in veterans with stroke. *Med Care* 2005; **43**: 507–15.  
471 19 Nasreddine ZS, Phillips NA, Bédirian V, *et al.* The Montreal Cognitive Assessment, MoCA: a brief  
472 screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; **53**: 695–9.  
473 20 American Psychiatric Association. DSM-IV, 4th edn. American Psychiatric Association, 1994.  
474 21 Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*  
475 1979; **134**: 382–9.  
476 22 Optimising Analysis of Stroke Trials (OAST) Collaboration, Bath PMW, Gray LJ, Collier T, Pocock S,  
477 Carpenter J. Can we improve the statistical analysis of stroke trials? Statistical reanalysis of functional  
478 outcomes in stroke trials. *Stroke* 2007; **38**: 1911–5.  
479 23 Riksstroke. Demography of stroke patients in Sweden. Riksstroke. [http://www.riksstroke.org/wp-](http://www.riksstroke.org/wp-content/uploads/2019/09/Riksstroke_A%CC%8Arsrapport-2018_slutversionWEB.pdf)  
480 [content/uploads/2019/09/Riksstroke\\_A%CC%8Arsrapport-2018\\_slutversionWEB.pdf](http://www.riksstroke.org/wp-content/uploads/2019/09/Riksstroke_A%CC%8Arsrapport-2018_slutversionWEB.pdf) (accessed Jan 3,  
481 2020).  
482 24 Legg LA, Tilney R, Hsieh C-F, *et al.* Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery.  
483 *Cochrane Database Syst Rev* 2019; **2019**. DOI:10.1002/14651858.CD009286.pub3.  
484 25 Wadhwa R, Kumar M, Talegaonkar S, Vohora D. Serotonin reuptake inhibitors and bone health: A  
485 review of clinical studies and plausible mechanisms. *Osteoporos Sarcopenia* 2017; **3**: 75–81.  
486 26 Rizzoli R, Cooper C, Reginster J-Y, *et al.* Antidepressant medications and osteoporosis. *Bone* 2012; **51**:  
487 606–13.  
488 27 Tsivgoulis G, Katsanos AH, Caso V. Under-representation of women in stroke randomized controlled  
489 trials: inadvertent selection bias leading to suboptimal conclusions. *Ther Adv Neurol Disord* 2017; **10**:  
490 241–4.  
491 28 Chen X, Li J, Anderson CS, *et al.* Validation of the simplified modified Rankin scale for stroke trials:  
492 Experience from the ENCHANTED alteplase-dose arm. *Int J Stroke* 2020; : 1747493019897858.  
493

494 **Titles and Legends for Tables**

495 Table 1. Patient characteristics at randomisation.

496 Legend table 1: Data are n (%), mean (SD), or median (IQR). TIA=Transient Ischaemic

497 Attack. OCSF=Oxfordshire Community Stroke Project. NIHSS=National Institutes of Health

498 Stroke Scale. \* One point or more on item 4 (Facial palsy) or, item 5 (Left or right arm motor

499 drift) or, item 6 (Left or right leg motor drift) on NIHSS. † One point or more on NIHSS item

500 9 (Language/aphasia).

501 Non-strokes were in the fluoxetine group 1 primary subarachnoid haemorrhage, and 1

502 hydrocephalus; in the placebo group 1 cerebral tumour.

503 ‡ The medical history was verified by the medical doctor using all available information at

504 that time of randomisation. There was unknown prior medical history for 6 coronary artery

505 diseases; 2 ischaemic stroke/TIAs; 2 diabetes; 19 hyponatraemias; 2 intracranial bleeds; 9

506 upper gastrointestinal bleeds; 14 bone fractures; 6 depressions respectively.

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

508

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

510 Legend table 2: \*N denotes the number of patients with each of the secondary outcome

511 scores. Data were only available for those who survived and who completed sufficient

512 questions to derive a score. Data are median (IQR). Stroke Impact Scale v. 3.0 has a score

513 between 0–100, where higher scores indicated better function. P-value=Mann-Whitney.

514 †Mean of the Strength, Hand ability, and Mobility domains. ‡Mean of the Strength, Hand

515 ability, Mobility, and Daily activities domains. NIHSS=National Institutes of Health Stroke

516 Scale. MoCA=Montreal Cognitive Assessment.

517

518 Table 3. Safety outcomes within 6 months.

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

## 526 Titles and Legends for Figures

527 Figure 1: Trial profile.

528 Legend figure 1: mRS=modified Rankin Scale.

529

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

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

539