Fluoxetine to improve functional outcomes in patients after acute stroke: the FOCUS RCT

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Scientific summary

The FOCUS RCT

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Scientific summary

Background

Each year worldwide, stroke affects about 9 million people for the first time, and results in about 6.5 million people living with disability.

Fluoxetine, a selective serotonin reuptake inhibitor, is used to treat depression and emotional lability after stroke. Many clinical and pre-clinical studies have suggested that selective serotonin reuptake inhibitors might improve outcome after stroke through a range of mechanisms, which include enhancing neuroplasticity and promoting neurogenesis. In 2011, the FLuoxetine for motor recovery After acute ischaeMic strokE (FLAME) trial indicated that fluoxetine enhanced motor recovery [Chollet F, Tardy J, Albucher JF, Thalamas C, Berard E, Lamy C, *et al.* Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. *Lancet Neurol* 2011;**10**:123–30]. A subsequent Cochrane systematic review of selective serotonin reuptake inhibitors for stroke recovery identified 52 randomised controlled trials of selective serotonin reuptake inhibitors versus control in a total of 4060 patients [Mead GE, Hsieh CF, Lee R, Kutlubaev MA, Claxton A, Hankey GJ, Hackett ML. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. *Cochrane Database Syst Rev* 2012;**11:**CD009286]. This review suggested that selective serotonin reuptake inhibitors may reduce post-stroke disability, but greater effects were seen if studies with increased risk of bias were retained and patients with depression were included. Although promising, these data were not sufficiently compelling to alter stroke treatment guidelines or to alleviate concerns that any possible benefits of fluoxetine might be offset by serious adverse reactions.

Objectives

Primary question

1. Does the routine early administration of fluoxetine (20 mg once per day) for 6 months after an acute stroke improve patients' functional outcome?

Secondary questions

2. If fluoxetine improves functional outcome, does any improvement persist after treatment is stopped?
3. Among patients with acute stroke:

    i. If there is motor impairment, does fluoxetine improve patients' motor function and does any improvement persist after treatment is stopped?
    ii. If there is communication impairment, does fluoxetine improve patients' communication function and does any improvement persist after treatment is stopped?
    iii. If there are impairments that preclude the formal assessment of post-stroke mood, does fluoxetine improve patients' functional outcomes?
    iv. Does fluoxetine improve patients' outcome with respect to mood, fatigue, cognition, health-related quality of life or participation and does any improvement persist after treatment is stopped?
    v. Does fluoxetine reduce the cost of health care over the first year?
    vi. Does fluoxetine increase the risk of serious adverse events?

Methods

The Fluoxetine Or Control Under Supervision (FOCUS) trial was a pragmatic, multicentre, parallel-group, double-blind, placebo-controlled trial that was conducted in the UK with a centralised randomisation system to allocate individuals to treatment in a 1 : 1 ratio.

Patients

Inclusion criteria:

- Adults aged ≥ 18 years.
- A clinical diagnosis of acute stroke with brain imaging compatible with intracerebral haemorrhage or ischaemic stroke including a normal brain scan.
- Randomisation between 2 and 15 days after stroke onset.
- A persisting focal neurological deficit at the time of randomisation and severe enough to warrant 6 months of treatment from the patient's or carer's perspective.

Exclusion criteria:

- Subarachnoid haemorrhage except where secondary to a primary intracerebral haemorrhage.
- Unlikely to be available for follow-up for the following 12 months.
- Unable to speak English and no close family member available to help with follow-up.
- Other life-threatening illness (e.g. advanced cancer) that would make 12-month survival unlikely.
- History of epileptic seizures.
- History of allergy to fluoxetine.
- Contraindications to fluoxetine, including hepatic impairment (alanine aminotransferase > 3 × upper normal limit) and renal impairment (creatinine level of > 180 μmol/l).
- Pregnancy or breastfeeding, and women of childbearing age not taking contraception.
- Previous drug overdose or attempted suicide.
- Already enrolled into a controlled trial of an investigational medicinal product.
- Current or recent (within the last month) depression treated with a selective serotonin reuptake inhibitor, although patients were eligible if depressed or taking an antidepressant other than a selective serotonin reuptake inhibitor or a monoamine oxidase inhibitor.
- Current or recent use of medications that have a potentially serious interaction with fluoxetine.

Patients, or a proxy if patients had mental incapacity, provided written informed consent that covered accessing their medical records and routinely collected NHS data.

Randomisation and blinding

The clinician entered the patient's baseline data into a secure web-based randomisation system. After the data were checked for completeness and consistency, the system generated a unique study identification number and a treatment pack number that corresponded to fluoxetine or placebo. A minimisation algorithm was used to achieve optimum balance (ratio 1 : 1) between treatment groups for the following factors: delay since stroke onset (2–8 vs. 9–15 days), computer-generated prediction of 6-month outcome (probability of modified Rankin Scale of 0–2 was ≤ 0.15 vs. > 0.15 based on the six simple variable model) and presence of a motor deficit or aphasia (according to the National Institutes of Health Stroke Scale). The system also incorporated an element of randomisation over and above the minimisation algorithm, so that it allocated patients to the treatment group that minimised imbalance between the groups with a probability of 0.8 rather than 1.0.

The patients, their families, the health-care teams including the pharmacists, the staff in the co-ordinating centre and anyone involved in outcome assessments were blinded to the treatment allocation, as a placebo capsule was used.

Allocated treatments

The allocated treatments were 20 mg of fluoxetine once per day or placebo for 6 months. Patients were supplied with 186 capsules. We measured adherence to the study medication in several ways, but our primary measure of adherence was the best estimate of the interval between the first and the last dose based on all of the information available.

Primary outcome

The primary outcome was functional status, measured according to the modified Rankin Scale at the 6-month follow-up. We used the simplified modified Rankin Scale questionnaire delivered by postal questionnaire to determine modified Rankin Scale scores. Among those without a complete postal questionnaire, telephone interview was undertaken for any further clarification, completion of missing items or the whole questionnaire.

Secondary outcomes at 6 and 12 months

- Survival.
- Modified Rankin Scale score at 12 months.
- Health status measured using the Stroke Impact Scale for each of nine domains: arm, hand, leg and foot strength; hand function; mobility; communication and understanding; memory and thinking; mood and emotions; daily activities; participation in work, leisure and social activities; and overall rating of recovery on a visual analogue scale.
- Mood assessed with the Mental Health Inventory.
- Fatigue assessed with the vitality subscale of the Short Form questionnaire-36 items.
- Health-related quality of life measured with the EuroQol-5 Dimensions, five-level version, to generate utilities.

Safety outcomes

Safety outcomes were systematically recorded, including:

- recurrent stroke including ischaemic and haemorrhagic strokes
- acute coronary syndromes
- epileptic seizures
- hyponatraemia ($Na^+ < 125$ mmol/l)
- upper gastrointestinal bleeding
- other major bleeds (lower gastrointestinal, extracranial, subdural, extradural and subarachnoid)
- poorly controlled diabetes including hyperglycaemia (> 22 mmol/l) and symptomatic hypoglycaemia
- falls resulting in injury
- bone fractures
- new episode of depression during the trial (including a diagnosis made by the treating clinician and initiation of a new antidepressant prescription)
- attempted suicide or self-harm.

Follow-up

The recruiting hospital staff monitored early adherence, identified adverse events in hospital and completed the follow-up form at hospital discharge or death in hospital. The national co-ordinating centre staff followed up the patients at 6 and 12 months to measure the primary and secondary outcomes. Data on safety outcomes and medications were also collected from the patients' general practitioners at 6 and 12 months. Adherence to medication was measured by clinician and patient reports and returned capsule counts.

Sample size

We aimed to recruit at least 3000 patients to identify a treatment effect size of fluoxetine that we thought would be important to patients and health and social care services, and would justify a

6-month course of treatment. The FOCUS trial had 90% power to identify an increase in the proportion of patients with good outcomes (i.e. modified Rankin Scale of 0–2) from 39.6% to 44.7% (i.e. absolute difference 5.1%), based on an ordinal analysis expressed as a common odds ratio of 1.23.

Statistical analyses

For our primary outcome, we carried out an ordinal analysis expressing the result as a common odds ratio and 95% confidence interval adjusted using ordinal logistic regression for the variables in the minimisation algorithm. We performed Cox proportional hazards modelling to analyse the effect of treatment on survival to 12 months, also adjusting for the variables included in our minimisation algorithm. We compared the frequency of outcome events by calculating the differences in proportions between treatment groups with their 95% confidence intervals and *p*-values. We present the median scores on the Stroke Impact Scale, Mental Health Inventory – 5 questions, vitality subscale of the Short Form questionnaire-36 items and EuroQol-5 Dimensions, five-level version, with the interquartile ranges and *p*-value derived using non-parametric methods (Mann–Whitney *U*-test). For all of these scales, higher values represent better outcomes.

Prespecified subgroup analyses were the effect of treatment allocation on the primary outcome subdivided by key baseline variables described in our published statistical analysis plan, including probability of being alive and independent (0 to ≤ 0.15 vs. > 0.15 to 1); delay 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); ability to consent for themselves (yes or no); and whether or not mood was assessable at baseline and whether or not the patient was depressed at baseline. Subgroup analyses were undertaken by observing the change in log-likelihood when the interaction between the treatment and the subgroup was added into a logistic regression model. Statistical analyses were conducted using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) (SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in the USA and other countries. ® indicates USA registration).

The protocol was given ethics approved by the Scotland A Research Ethics Committee (reference 21/12/2011). The study was jointly sponsored by the University of Edinburgh and NHS Lothian. The full protocol is available online (see www.journalslibrary.nihr.ac.uk/programmes/hta/130430/#).

Results

Between 10 September 2012 and 31 March 2017, 103 UK hospitals enrolled 3127 patients; 1564 were allocated fluoxetine and 1563 were allocated placebo. The baseline characteristics of the two treatment groups were well balanced and were fairly similar to the characteristics of unselected stroke patients who were admitted to UK hospitals.

The primary measure of adherence was available in 1417 (91%) patients in each group. The median duration of treatment was 185 days (interquartile range 149–186 days) in the fluoxetine group and 183 days (interquartile range 136–186 days) in the placebo group. About two-thirds of patients took the study medication for at least 150 days.

Our primary outcome was available in 1553 out of 1564 (99.3%) patients allocated to fluoxetine and 1553 out of 1563 (99.4%) patients allocated to placebo at 6 months. An ordinal comparison of the distribution of patients across the modified Rankin Scale at 6 months, adjusted for variables included in the minimisation algorithm, was similar in the two groups (common odds ratio 0.951, 95% confidence interval 0.839 to 1.079; $p = 0.439$), where a common odds ratio in favour of placebo is < 1.0. The unadjusted analysis provided similar results (common odds ratio 0.961, 95% confidence interval 0.848 to 1.089; $p = 0.531$).

There were no statistically significant interactions between the prespecified subgroups and the effect of treatment on the primary outcome. We investigated the effect of fluoxetine on our primary outcome in subgroups defined by their meeting the eligibility criteria and being adherent to the study medication to different degrees. There is no trend towards greater benefit in those with greater adherence.

Those allocated fluoxetine were less likely than those allocated placebo to be diagnosed with a new episode of depression during the trial [$n = 210$ (13.0%) fluoxetine vs. $n = 269$ (16.9%) placebo, difference in proportion −3.78%, 95% confidence interval −1.26% to −6.30%; $p = 0.003$], and had better mood measured on Mental Health Inventory – 5 questions at 6-month follow-up (median score 76 fluoxetine vs. 72 placebo; $p = 0.010$). Those allocated fluoxetine had an increased risk of fractures compared with those allocated placebo [$n = 45$ (2.9%) fluoxetine vs. $n = 23$ (1.5%) placebo, difference in proportion 1.41%, 95% confidence interval 0.38% to 2.43%; $p = 0.007$]. There were no statistically significant differences in any other secondary outcomes at 6 months, including any of the nine domains of the Stroke Impact Scale, the vitality subscale of Short Form questionnaire-36 items and the EuroQol-5 Dimensions, five-level version, or other recorded safety outcomes.

The difference in the cumulative number of patients diagnosed with a new episode of depression over the 12 months between the two treatment groups was no longer statistically significant and the difference in Mental Health Inventory – 5 questions scores at 6 months was not sustained at 12 months. There were no statistically significant differences between treatment groups in any other secondary outcomes at 12 months, including survival (hazard ratio 0.929, 95% confidence interval 0.756 to 1.141; $p = 0.482$).

We assessed the effect of treatment among participants in the subgroup with motor deficit at baseline ($n = 2722$) who had a modified Rankin Scale score at 6 months ($n = 2702$), but found no evidence of an effect on the modified Rankin Scale ($p = 0.217$). Of the 2722 participants who had a motor deficit at baseline, 2438 had a motor score outcome [fluoxetine median 48.43 (interquartile range 24.98–78.84) vs. placebo median 52.66 (interquartile range 25.28–77.22); $p = 0.471$]. In addition, of the 906 patients with aphasia at baseline, 899 had a modified Rankin Scale score at 6 months and 794 had a Stroke Impact Scale communication domain score at 6 months. There was little difference in the modified Rankin Scale or Stroke Impact Scale communication scores [fluoxetine median 64.29 (interquartile range 32.14–89.29) vs. placebo median 64.29 (interquartile range 35.71–89.29); $p = 0.497$]. Our health economic analyses showed no difference between the treatment groups in health-related quality of life, use of health-care resources or health-care costs during the first year of follow-up.

Conclusions

The FOCUS trial provides reliable answers to our research questions:

1. Does the routine early administration of fluoxetine (20 mg once per day) for 6 months after an acute stroke improve patients' functional outcome? Answer: no.
2. Does any functional improvement persist after treatment is stopped? Answer: not relevant because no functional improvement was identified during treatment.
3. Among patients with acute stroke –

    i. If there is motor impairment, does fluoxetine improve patients' motor function and does any improvement persist after treatment is stopped? Answer: no, it does not appear to but the trial was not powered for this subgroup analysis.
    ii. If there is communication impairment, does fluoxetine improve patients' communication function and does any improvement persist after treatment is stopped? Answer: no, it does not appear to but the trial was not powered for this subgroup analysis.

iii. If there are impairments that preclude the formal assessment of post-stroke mood, does fluoxetine improve patients' functional outcomes? Answer: no, it does not appear to, but the trial was not powered for this subgroup analysis.
iv. Does fluoxetine improve patients' outcome with respect to mood, fatigue, cognition, health-related quality of life or participation and does any improvement persist after treatment is stopped? Answer: probably; it reduced the incidence of new episodes of depression in the first 6 months, and patients' mood at 6 months was better than for those taking placebo. However, similar results might be seen if fluoxetine simply stopped mood deteriorating. The differences in mood did not persist once the fluoxetine was stopped.
v. Does fluoxetine reduce the cost of health care over the first year? Answer: no, it does not appear to, but the trial was not powered for this outcome.
vi. Does fluoxetine increase the risk of serious adverse events? Answer: yes, it increased the risk of bone fractures.

These data will inform decision-making about the use of fluoxetine after stroke, whether aimed at improving functional outcome or preventing or treating mood disorders. Ongoing trials and a planned individual patient data meta-analysis are planned to confirm or refute a more modest benefit, either overall or in particular subgroups, and to provide more precise estimates of any harms.

Trial registration

This trial is registered as ISRCTN83290762.

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