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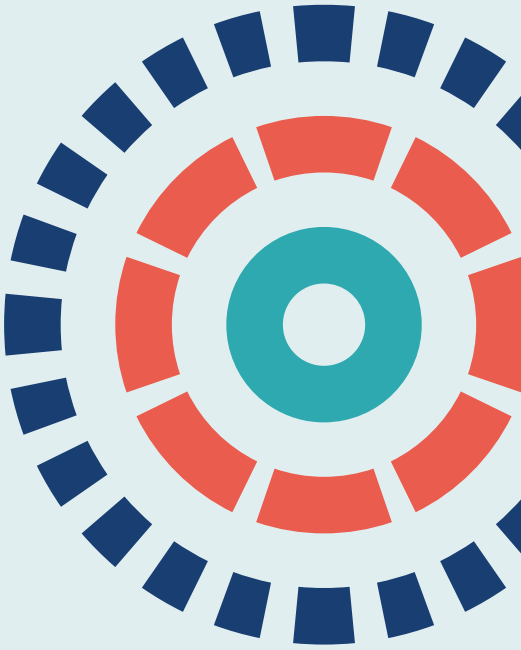

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Fluoxetine to improve functional outcomes in patients after acute stroke: the FOCUS RCT

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Abstract

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

Martin Dennis,[1*] John Forbes,[2] Catriona Graham,[3] Maree Hackett,[4] Graeme J Hankey,[5] Allan House,[6] Stephanie Lewis,[7] Erik Lundström,[8,9] Peter Sandercock[1] and Gillian Mead[1] on behalf of the FOCUS Trial Collaboration†

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Background: Our Cochrane review of selective serotonin inhibitors for stroke recovery indicated that fluoxetine may improve functional recovery, but the trials were small and most were at high risk of bias.

Objectives: The Fluoxetine Or Control Under Supervision (FOCUS) trial tested the hypothesis that fluoxetine improves recovery after stroke.

Design: The FOCUS trial was a pragmatic, multicentre, parallel-group, individually randomised, placebo-controlled trial.

Setting: This trial took place in 103 UK hospitals.

Participants: Patients were eligible if they were aged ≥ 18 years, had a clinical stroke diagnosis, with focal neurological deficits, between 2 and 15 days after onset.

Interventions: Patients were randomly allocated 20 mg of fluoxetine once per day or the matching placebo for 6 months via a web-based system using a minimisation algorithm.

Main outcome measures: The primary outcome was the modified Rankin Scale at 6 months. Patients, carers, health-care staff and the trial team were masked to treatment allocation. Outcome was assessed at 6 and 12 months after randomisation. Patients were analysed by their treatment allocation as specified in a published statistical analysis plan.

Results: Between 10 September 2012 and 31 March 2017, we recruited 3127 patients, 1564 of whom were allocated fluoxetine and 1563 of whom were allocated placebo. The modified Rankin Scale score at 6 months was available for 1553 out of 1564 (99.3%) of those allocated fluoxetine and 1553 out of 1563 (99.4%) of those allocated placebo. The distribution across modified Rankin Scale categories at

6 months was similar in the two groups (common odds ratio adjusted for minimisation variables 0.951, 95% confidence interval 0.839 to 1.079; $p = 0.439$). Compared with placebo, patients who were allocated fluoxetine were less likely to develop a new episode of depression by 6 months [210 (13.0%) vs. 269 (16.9%), difference −3.78%, 95% confidence interval −1.26% to −6.30%; $p = 0.003$], but had more bone fractures [45 (2.9%) vs. 23 (1.5%), difference 1.41%, 95% confidence interval 0.38% to 2.43%; $p = 0.007$]. There were no statistically significant differences in any other recorded events at 6 or 12 months. Health economic analyses showed no differences between groups in health-related quality of life, hospital bed usage or health-care costs.

Limitations: Some non-adherence to trial medication, lack of face-to-face assessment of neurological status at follow-up and lack of formal psychiatric diagnosis during follow-up.

Conclusions: 20 mg of fluoxetine daily for 6 months after acute stroke did not improve patients' functional outcome but decreased the occurrence of depression and increased the risk of fractures. These data inform decisions about using fluoxetine after stroke to improve functional outcome or to prevent or treat mood disorders. The Assessment oF FluoxetINe In sTroke recoverY (AFFINITY) (Australasia/Vietnam) and Efficacy oF Fluoxetine – a randomisEd Controlled Trial in Stroke (EFFECTS) (Sweden) trials recruited an additional 2780 patients and will report their results in 2020. These three trials have an almost identical protocol, which was collaboratively developed. Our planned individual patient data meta-analysis will provide more precise estimates of the effects of fluoxetine after stroke and indicate whether or not effects vary depending on patients' characteristics and health-care setting.

Trial registration: Current Controlled Trials ISRCTN83290762.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 22. See the NIHR Journals Library website for further project information. The Stroke Association (reference TSA 2011101) funded the start-up phase.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/hta24220).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AFFINITY	Assessment oF FluoxetINe In sTroke recoverY
CI	confidence interval
COR	common odds ratio
DMC	Data Monitoring Committee
eDRIS	eData Research and Innovation Service
EFFECTS	Efficacy oF Fluoxetine – a randomisEd Controlled Trial in Stroke
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
FLAME	FLuoxetine for motor recovery After acute ischaeMic strokE
FOCUS	Fluoxetine Or Control Under Supervision
GP	general practitioner
HPA	hypothalamic pituitary axis
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
ICF	informed consent form
IMP	investigational medicinal product
IQR	interquartile range
MD	doctor of medicine
MHI-5	Mental Health Inventory – 5 questions
mRS	modified Rankin Scale
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIHSS	National Institutes of Health Stroke Scale
o.d.	once per day
OR	odds ratio
PhD	Doctor of Philosophy
PHQ2	Patient Health Questionnaire 2
PI	principal investigator
PIB	participant information booklet
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	risk ratio
SD	standard deviation
SF-36	Short Form questionnaire-36 items
SIS	Stroke Impact Scale
SMD	standardised mean difference
SmPC	summary of product characteristics
smRSq	simplified modified Rankin Scale questionnaire
SRN	Stroke Research Network
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TIA	transient ischaemic attack
TSC	Trial Steering Committee

Plain English summary

Fluoxetine, sometimes referred to by the drug company name Prozac, has been used for many years to treat people who are depressed, including after a stroke. However, studies have suggested that treatment with fluoxetine started soon after a stroke might improve patients' physical recovery. The Fluoxetine Or Control Under Supervision (FOCUS) trial recruited 3127 volunteers who had had a stroke within the previous 2 weeks from 103 UK hospitals between 2012 and 2017. Participants were randomly allocated to take a 6-month course of fluoxetine or an identical placebo capsule containing no fluoxetine. They were followed up at 6 months and 12 months after recruitment. Patients completed questionnaires that indicated how much they had recovered, and also measured their mood, fatigue and quality of life. The results of the trial showed that the physical recovery of patients was very similar in both groups. This indicates that fluoxetine does not improve physical outcomes of stroke patients. However, participants receiving fluoxetine were less likely to develop depression after the stroke but once the fluoxetine was stopped these effects on mood disappeared. Unfortunately, patients on fluoxetine were slightly more likely to fall and fracture a bone than those on placebo. The FOCUS trial is the first of three large randomised controlled trials testing fluoxetine in stroke patients to be completed. The FOCUS trial results suggest that patients with stroke should not routinely be treated with fluoxetine.

The other two trials will give us further information about the effects of fluoxetine after stroke and whether or not its effects differ between countries or ethnic groups.

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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This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 22. See the NIHR Journals Library website for further project information. The Stroke Association (reference TSA 2011101) funded the start-up phase.

Chapter 1 Introduction

The burden of stroke

Approximately 130,000 people have a stroke each year in the UK and, even with acute treatments, about 50% of survivors will have long-term residual disability.[1] This places a huge burden on health and social services and informal carers. Although more can be done to implement treatments that we know are effective (e.g. the more widespread provision of thrombolysis and thrombectomy and more rapid access to stroke units), there is still an urgent need to identify new treatments that might reduce neurological impairments, disability and dependency after stroke. One promising intervention that needs to be tested is a widely used antidepressant drug, fluoxetine, which is a selective serotonin reuptake inhibitor (SSRI).

Serotonin reuptake inhibitors in animal models

In animals, SSRIs have several potentially beneficial effects on both normal and diseased brains. First, they have a neurotrophic effect. Neurotrophins are involved in embryogenesis and organogenesis, control neural plasticity in adults, regulate synaptic activity and neurotransmitter synthesis and are essential for the regeneration of nerves.[2] Adult neurogenesis is generally restricted to the subependymal cells of the ventricular system and the subgranular zone of the dentate gyrus in the hippocampus.[3] SSRI antidepressants increase neurogenesis and expression of neurotrophic/growth factors in the adult hippocampus,[4] which is likely to account for the behavioural benefits of antidepressants in animals.[5] Importantly, several studies have shown that migration of new neurones to damaged areas of brain may occur,[6] and that neurogenesis may also occur in areas of damaged brain in patients who have had ischaemic stroke.[7] Second, fluoxetine may have a neuroprotective effect associated with its anti-inflammatory effect (e.g. repression of microglia activation)[8] and enhancement of specific protein expression (e.g. hypoxia-inducible factor-1 alpha and heme oxygenase-1).[9] Third, SSRIs can indirectly affect the adrenergic system through the upregulation of beta-1 receptors.[10]

Selective serotonin reuptake inhibitors and motor function in humans

In healthy humans, functional magnetic resonance imaging studies have demonstrated that fluoxetine can modulate cerebral motor activity.[11] In eight patients who had a pure motor stroke who were given fluoxetine, there was hyperactivation in the ipsilesional primary motor cortex during a motor task; moreover, fluoxetine significantly improved motor skills in the affected side.[12] In a small-scale randomised trial of patients who had a unilateral stroke, the administration of citalopram, another SSRI, was associated with a significant improvement in neurological status, as measured with the National Institutes of Health Stroke Scale (NIHSS),[13] and a decrease of motor excitability over the unaffected hemisphere, as measured by transmagnetic stimulation.[14] Zittel *et al.*[15] investigated the effects of a single dose of 40 mg of citalopram in eight chronic stroke patients; dexterity was significantly improved. In a trial of 52 hemiplegic patients who were randomly allocated to receive one of three treatments (20 mg/day of fluoxetine vs. 150 mg/day of maprotiline vs. placebo) for 3 months against a background of physical therapy, those allocated to receive fluoxetine demonstrated the greatest recovery from disability.[16]

The FLuoxetine for motor recovery After acute ischaeMic strokE (FLAME) trial[17] evaluated the effects of SSRIs on motor recovery after stroke. This double-blind, placebo-controlled, multicentre trial randomised 118 patients who had an ischaemic stroke and unilateral motor weakness to receive either 20 mg of fluoxetine daily or placebo for 3 months. At day 90, the improvement in the Fugl-Meyer Assessment

Motor Score from baseline was significantly greater in the fluoxetine group [57 patients, adjusted mean 34.0, 95% confidence interval (CI) 29.7 to 38.4] than in the placebo group (56 patients, adjusted mean 24.3, 95% CI 19.9 to 28.7) ($p = 0.003$). In a post hoc analysis, the frequency of independent patients [modified Rankin Scale (mRS) of 0–2][18] was significantly higher in the fluoxetine group than in the placebo group (26.3% vs. 8.9%; $p = 0.015$), although there were no significant differences at other cut-off points. The small sample size limits the study's generalisability. All patients also received physiotherapy (of unknown intensity), so we do not know whether or not fluoxetine on its own, or with less intense physiotherapy, would also be effective. Importantly, we also do not know whether or not any benefits of fluoxetine persist beyond the treatment period and whether or not fluoxetine might improve outcome in stroke patients without motor deficits. Nevertheless, these promising but inconclusive results clearly justify further larger trials in patients who have motor deficits.

Might selective serotonin reuptake inhibitors be of benefit in recovery of non-motor aspects of stroke?

Several small studies have suggested that fluoxetine might have other neurological benefits (e.g. increased activation of agonist and antagonist muscles in paretic arms after stroke,[19] and improvements in executive function after stroke[20]). We do not know whether or not these beneficial effects of antidepressants are independent of their antidepressant effect.[21]

In people with depression, SSRIs modulate the hyperactivity of the hypothalamic pituitary axis (HPA).[22] After stroke, activation of the HPA occurs, resulting in hypercortisolism. Hypercortisolism is associated with the development of delirium after stroke and also predicts worse long-term outcome.[23] Thus, SSRIs might, by attenuating the hypercortisolism that is present after stroke, improve outcomes, including cognition.

Systematic review of effects of fluoxetine on post-stroke outcomes

In 2011, when the Fluoxetine Or Control Under Supervision (FOCUS) trial was being planned, a recent systematic review of randomised controlled trials (RCTs) testing whether or not a course of treatment with fluoxetine started shortly after stroke onset might improve function and prevent post stroke depression identified six RCTs published before December 2009, which together randomised 385 patients.[24] Meta-analysis demonstrated that fluoxetine helped recovery in neurological function (weighted mean difference −4.72, 95% CI −8.31 to −1.13), improved independence in activities of daily living (weighted mean difference −8.04, 95% CI −13.40 to −2.68) and reduced the incidence of post-stroke depression [odds ratio (OR) 0.25, 95% CI 0.11 to 0.56]. A Cochrane review of selective serotonin receptor antagonists in stroke[25] subsequently identified 56 trials comparing SSRIs with a control intervention (e.g. usual care or placebo), which were given in the first year after stroke. Fifty-two trials (4059 participants) reported data that could be included in the meta-analyses. Of these 52 trials, 28 used fluoxetine and 31 recruited patients within 3 months of stroke onset. The meta-analyses demonstrated beneficial effects of SSRIs on dependency, disability, neurological deficit, depression and anxiety at the end of treatment. There were benefits even in patients without depression at recruitment. However, there was substantial heterogeneity in the estimates of effect sizes; sensitivity analyses suggested that methodological limitations of many of the included trials may have led to overestimation of effect sizes and there was an excess of gastrointestinal side effects in patients receiving a SSRI.[25] Furthermore, most trials excluded people with cognitive impairment and aphasia, and only eight trials followed patients up after treatment had been discontinued.

Why choose fluoxetine?

There are many SSRI antidepressant medications available. We chose to evaluate fluoxetine because it is one of the most widely studied. Its safety profile is very well established, and the drug is well tolerated in long-term use, even in older patients. There was more evidence for its effectiveness in stroke than for that of alternatives, such as citalopram.[25] A number of manufacturers produce the drug and the price was low, which makes it particularly attractive to health services that are under severe cost pressures. Finally, of all the SSRIs, it has the longest half-life; therefore, gradual reduction in dose is not required when withdrawing the drug (which is inevitable in a trial), which is typically carried out to avoid the possibility of a SSRI-withdrawal syndrome.[26]

Potential concerns of using fluoxetine in stroke patients

There are potential risks associated with giving fluoxetine to a wide range of stroke patients. Its reported interaction with antiplatelet and anticoagulant medication might increase bleeding risk, although this is usually minor and limited to bruising. Like other antidepressants, fluoxetine may lower the seizure threshold and, therefore, could increase the frequency of post-stroke seizures. In our Cochrane review, there was a non-significant excess of seizures in patients who were allocated SSRIs.[25] Therefore, we excluded from the FOCUS trial patients who had a history of epileptic seizures. An adverse effect on glycaemic control in diabetic patients has been recorded. Hyponatraemia is a recognised adverse effect and may prove to be more common among stroke patients who may be taking concomitant angiotensin-converting enzyme (ACE) inhibitors, diuretics and proton pump inhibitors. Observational studies have suggested that bone fractures are more common in those taking SSRIs, and this has variably been attributed to an increased risk of fractures in depression, increased risk of falling while taking SSRIs (possibly owing to drowsiness, increased activity or motor effects) and direct effects of SSRIs on bone strength.[27,28] Furthermore, there are already concerns that stroke patients have a greater risk of falls owing to their neurological and functional deficits or concurrent medications (e.g. antihypertensive medication), and greater risk of fractures owing to osteoporosis affecting hemiplegic limbs.[29,30]

Nevertheless, fluoxetine has been very commonly prescribed for several years for selected patients who have had a stroke to treat depression and emotionalism without major problems emerging.

Patients who are commenced on psychotropic drugs, including fluoxetine, are encouraged to monitor the effects on their psychomotor function before resuming driving. However, stroke patients in the UK are advised not to drive for at least 1 month after a stroke, which should provide ample time in the trial for any potentially important adverse effects that would affect their driving ability to become apparent.

Rationale for the study

The need for large randomised trials of fluoxetine in stroke

Given these encouraging data, which suggested that fluoxetine might have substantial benefits for a wide range of stroke patients, there was an urgent need to carry out RCTs with adequate power to reliably detect clinically important benefits. Given that fluoxetine is inexpensive (approximately £2.50 per patient per month in the UK), simple to administer and generally well tolerated, if it had an effect that was a fraction of that seen in the FLAME trial[17] it would be a very worthwhile treatment option for patients, their carers and health and social services.

The need to identify the patients who might particularly benefit from treatment

Although fluoxetine might improve outcome for a range of stroke patients, it is also plausible, given its diverse pharmacological effects, that the balance of risk and benefit may vary in patients who have had different types of stroke. For instance, pre-clinical work had suggested that motor recovery may be specifically enhanced. In addition, fluoxetine influences bleeding risk, particularly in those taking antithrombotic medication, so there could be differences in effectiveness between patients who have had an ischaemic stroke (who are taking antithrombotics) and patients who have had a haemorrhagic stroke. Patients who have had a severe stroke associated with cognitive and communication problems may be at greater risk of adverse effects because they are unable to report early problems, but they might also have more to gain from a treatment that enhances recovery. In addition, patients who have had a severe stroke are normally at greater risk of post-stroke depression (which may be associated with stroke severity); however, as a consequence of their deficits, these patients are at greater risk that their post-stroke depression is not recognised and, thus, not treated.

The FOCUS trial collaboration (see *Appendix 1* for membership) aimed to robustly address several research questions.

Primary research question:

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

Secondary research questions:

2. If fluoxetine improves functional outcome, does any functional improvement persist after treatment is stopped?
3. Among patients who have had an 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 (HRQoL) 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?

Chapter 2 Methods

The full trial protocol is available at www.journalslibrary.nihr.ac.uk/programmes/hta/130430/#.

Design overview

The FOCUS trial was a pragmatic, investigator-led, multicentre, parallel-group, double-blind, placebo-controlled trial with broad entry criteria and follow-up to ascertain the primary and secondary outcomes at 6 and 12 months.

Setting

The FOCUS trial was carried out in hospital-based stroke services in the UK.

Participant inclusion/exclusion criteria

Inclusion criteria

- Aged ≥ 18 years.
- Brain imaging was compatible with intracerebral haemorrhage or ischaemic stroke.
- Randomisation could be undertaken between 2 and 15 days after stroke onset.
- Persisting focal neurological deficit was present at the time of randomisation. This needed to be severe enough to warrant 6 months' treatment with the FOCUS trial medication 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 next 12 months (e.g. had no fixed home address).
- Unable to speak English and had no close family member available to help with follow-up forms.
- Other life-threatening illness (e.g. advanced cancer) that would have made 12-month survival unlikely.
- History of epileptic seizures.
- History of allergy to fluoxetine.
- Contraindications to fluoxetine, including:
    - hepatic impairment (alanine aminotransferase level more than 3 times the upper normal limit).
    - renal impairment (creatinine level of > 180 µmol/l).
- Pregnancy or breastfeeding, and women of childbearing age not taking contraception. Minimum contraception was an oral contraceptive.
- Previous drug overdose or attempted suicide.
- Already enrolled into a clinical trial of an investigational medicinal product (IMP).
- Current or recent (within the previous month) depression requiring treatment with a SSRI antidepressant.

- Current medications that have a serious interaction with fluoxetine, including:
  - Use of a monoamine oxidase inhibitor during the previous 5 weeks [e.g. phenelzine (Nardil®, Kyowa Kirin Ltd, Tokyo, Japan), isocarboxacid, tranylcypromine, moclobemide (Manerix®, Mylan, Canonsburg, PA, USA), selegiline (Eldepryl®, Orion Pharma UK, Newbury, UK) and rasagiline (Azilect®, Teva UK Ltd, Castleford, UK)].
  - Pimozide (Orap®, Eumedica Pharmaceuticals, Basel, Switzerland).
  - Metoprolol for heart failure [introduced late in 2016 after a change to the summary of product characteristics (SmPC)] (see *Report Supplementary Material 1*).

Consent

The investigator was responsible for ensuring that informed consent was obtained and the consent form was completed, signed and dated by all parties before any protocol-specific procedures were carried out.

Participant information booklets (PIBs) and informed consent forms (ICFs) were provided (see the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/130430/#; accessed 7 May 2020). Separate versions were available for patients with capacity; proxies were used for patients without capacity. We developed easy-access versions for patients or proxies with cognitive or communication difficulties (see *Appendix 2*). The verbal explanation to the participant was provided by the investigator or designated person, and aimed to cover all the elements specified in the PIB/ICF. The participants were given every opportunity to clarify any points that they did not understand and, if necessary, ask for more information. Participants could withdraw their consent to participate at any time without loss of benefits to which they would otherwise be entitled.

The participants consented to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) and agreed that the information held and maintained by NHS Digital and other central UK NHS bodies could be shared with us and may be used to help contact them or provide information about their health status.

Written informed consent from the patient was always sought where possible. If this was not possible because the patient could not write, the randomising clinician or nurse could gain witnessed verbal consent. Laws governing consent procedures, and in particular those governing incapacitated adults and their involvement in research, were followed.

The patient or personal legal representative received a folder including a copy of the relevant version of the PIB, a copy of the completed ICF and a patient diary that contained contact details for the trial co-ordinating centre and prompted the recording and reporting of safety outcomes and adverse events, etc. The original ICF and PIB were filed in the site file with the randomisation form (see the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/130430/#; accessed 7 May 2020). The completed ICF was also scanned and uploaded onto the secure trial website or e-mailed, or faxed, to the trial office, before randomisation. The trial management system prompted the research team to do so via e-mail and/or fax until the consent form had been received.

Randomisation

Having obtained consent, the randomising person collected the baseline data necessary to complete a randomisation form (see the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/130430/#; accessed 7 May 2020) and entered the patient's baseline data into our computerised central randomisation service by means of a secure 24 hours per day/7 days per week (24/7) web interface. After the computer program checked these baseline data for completeness and consistency, it allocated that patient a unique study identification number and a treatment pack number that corresponded to

either fluoxetine or placebo. The system applied a minimisation program to achieve balance between the treatment groups for four factors:

1. delay since stroke onset (2–8 vs. 9–15 days)
2. predicted 6-month outcome (based on the six simple variable model)[31]
3. presence of a motor deficit (based on NIHSS)[13]
4. presence of aphasia (based on NIHSS).

The six simple variable model is a statistical model that predicts survival and functional outcome after stroke.[31] The variables are (1) the patient's age, (2) whether or not the patient was independent prior to the stroke, (3) whether or not they lived alone, (4) whether or not after the stroke the patient could lift both arms off the bed, (5) walking without help of another person and (6) talking without being confused (i.e. normal on the verbal component of the Glasgow Coma Scale[32]).

The minimisation algorithm randomly allocated the first patient to a treatment, but allocated each subsequent patient to the treatment that minimised the imbalance between the treatment groups with respect to the prognostic factors.[33] It was designed to allocate equal numbers to each of the two treatment groups (i.e. a 1 : 1 ratio). To ensure that we retained a random element to treatment allocation, patients were allocated to the group that minimised differences between groups with a probability of 0.8. The system contained a list of treatment codes for each centre and that matched the stocks held at that centre. At the end of the session, each patient was allocated a treatment code that corresponded to an active (20 mg of fluoxetine o.d.) or placebo treatment pack that contained a 6-month supply of capsules held at that centre.

The randomisation system took account of the drug stocks that were held locally to (1) ensure that the allocated treatment was available and (2) minimise wastage. The randomisation system automatically generated an e-mail/fax to the centre co-ordinator and the local research pharmacist to ensure that the allocated treatment was prescribed. The pharmacist or co-ordinator could access treatment codes to replace lost study medication through a secure website by entering the patient's study ID number and date of birth.

To facilitate drug reconciliation and stock control, the pharmacist or local co-ordinator removed an adhesive treatment number label (flag) from the medication bottle, stuck it onto the confirmation of allocation fax and faxed it back to the trial co-ordinating centre. The trial management system prompted them to do so via e-mail and/or fax until the fax was received.

Following randomisation, the trial co-ordinating centre sent a letter to inform the general practitioner (GP) of the patient's enrolment in the trial, including a copy of the consent form and the follow-up schedule (see the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/130430/#; accessed 7 May 2020).

The interventions

The interventions were 20 mg of fluoxetine o.d. or placebo for 6 months. The study medication (active and placebo) was manufactured by Unichem (Mumbai, India), imported by Niche Generics Ltd (Hitchin, UK), purchased from Discovery Pharmaceuticals Ltd (Castle Donington, UK) and quality assured, packaged, labelled and distributed by Sharp Clinical Services (Tredegar, UK). Patients were supplied with 186 capsules and were prescribed the study medication (20-mg capsules of fluoxetine or placebo) to be taken daily. If the patient was unable to swallow capsules and had an enteral feeding tube in place, the capsules were broken open and the contents put down the tube.

We measured adherence to the study medication in several ways: recording the date of first and last dose taken, number of missed doses while in hospital, capsule counts when unused capsules were

returned and estimated adherence at 6-month follow-up. We recorded the reasons for stopping the study medication early. 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. Therefore, for a particular participant, a capsule count might lead us to modify the estimate of the timing of the last dose (see *Chapter 3* for more detail).

Blinding

The patient, their families, the health-care team including the pharmacist, the staff in the co-ordinating centre and anyone involved in outcome assessments were blinded to the treatment allocation by using a placebo capsule that was visually identical to the fluoxetine capsules, even when broken open to allow the administration of the trial medication down an enteral feeding tube.

An emergency unblinding system was available. If a clinician thought that they needed to know the allocated treatment for a patient, they were asked to telephone a 24/7 helpline that was manned by staff from a co-ordinating centre, and provided access, directly or indirectly, to one of our chief investigators. The case for unblinding was discussed and, if agreed, the clinician was given a unique code (based on a simple arithmetic manipulation of the date) to unlock the web-based unblinding system. The clinician could then enter the patient's details, along with the reason(s) for unblinding, and they were provided with the treatment allocation. This was designed so that those in the co-ordinating centre and those conducting follow-up remained blind to the treatment allocation. Our information technology system logged any attempts to unblind.

Primary outcome

The primary outcome was the mRS (based on ordinal analysis to maximise power and to avoid the problem of including patients with a mRS of > 2 prior to their stroke) at 6 months after randomisation.[18,34] We also collected data on mRS at 12 months (one of our secondary objectives). Patients who died were attributed a score of 6 for this analysis.

The mRS is a simple, time-efficient measure with well-studied reliability that is used to categorise levels of functional outcome (see *Table 10*). It has been used extensively in large, multicentre stroke trials.

Any misclassification of patients into an inappropriate mRS category may reduce the power of the trial. To minimise misclassification and intermodality differences, we used the simplified modified Rankin Scale questionnaire (smRSq) described by Bruno *et al.*[18,35,36] This can be delivered via telephone and postal questionnaires and has been completed by patients and proxies.[36,37]

Secondary outcomes

To answer our secondary objectives, we collected the following outcome measures:

- Deaths from all causes by 6 and 12 months.
- The EuroQol-5 Dimensions, five-level version (EQ-5D-5L) to provide an overall measure of HRQoL and to allow a health economic analysis based on quality-adjusted life-years (QALYs).[38]
- The Mental Health Inventory – 5 questions (MHI-5), which is derived from the Short Form questionnaire-36 items (SF-36) and provided a measure of depression and anxiety symptoms. This brief measure performs well, compared with longer questionnaires (e.g. Mental Health Inventory – 18 questions, General Health Questionnaire –12 questions and General Health Questionnaire –30 questions), in the detection of depression and anxiety symptoms.[39–41]

- The vitality subscale of the SF-36 was used to assess patients' levels of fatigue.[42,43]
- The Stroke Impact Scale (SIS) provided 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. The SIS is a stroke-specific, comprehensive health status measure. The scale was developed with input from patients and caregivers and comprises eight domains (strength, hand function, activities of daily living/instrumental activities of daily living, mobility, communication, emotion, memory and thinking, and participation) from across the full impairment–participation continuum.[44–46] It also provided an overall assessment of recovery with a visual analogue scale. The scale has been validated for use by proxy respondents and has been delivered via telephone and postal questionnaires.[45,47,48]

Safety outcomes

- New diagnosis of depression since randomisation. This was collected at 6- and 12-month follow-up with GPs and participants. We recorded who had made the diagnosis, whether or not any treatment, and specifically any treatment with antidepressant medication, was initiated and whether or not there was any attempt at suicide or self-harm. Sometimes patients were started on an antidepressant without a clear prior diagnosis; in these cases, we made an individual judgement based on all available information and whether the antidepressant had been started for new depression (or low mood) or for another indication, such as neuropathic pain, anxiety or emotionalism without depression.
- Other adverse events, including further strokes (ischaemic or haemorrhagic), acute coronary events, upper gastrointestinal haemorrhage, falls resulting in injury, new bone fractures, epileptic seizures, symptomatic hypoglycaemia (< 3 mmol/l), hyperglycaemia (> 22 mmol/l) and hyponatraemia (Na^+ < 125 mmol/l). Retrospectively, we also categorised patients with other serious bleeds (e.g. lower gastrointestinal, renal tract and subdural) and thrombotic events (deep-vein thrombosis, pulmonary embolism, mesenteric thrombosis, ischaemic limbs) that led to hospital admission. Information on these events were collected via centres, GPs and participants at discharge and 6 months, although we became aware of some events occurring later because they led to hospital admissions that we recorded at the 12-month follow-up.

Follow-up

The principal investigator (PI) and researchers at each site collected the local data listed in the schedule of study assessments below. The chief investigators and the research team in the central co-ordinating office collected the central data (*Table 1*).

TABLE 1 Study assessment schedule

	Days	Weeks							
Assessment	**2–15**	**4–6**	**12**	**24**	**26**	**30**	**50**	**52**	**54**
Local									
Screen of eligibility	✓								
Check results of post-stroke bloods	✓								
Give PIB to patient and/or carer	✓								
Consent	✓								
Collect baseline data	✓								
Randomise	✓								

continued

TABLE 1 Study assessment schedule (*continued*)

	Days	Weeks						
Assessment	**2–15**	**4–6**	**12**	**24**	**26**	**30**	**50**	**52**	**54**
Record treatment code/study number	✓								
Prescribe study medication	✓								
Dispense 6 months' worth of treatment	✓								
Fax treatment code	✓								
Complete discharge form, including:		+							
Adverse events		+							
All medications		+							
Adherence		+							
Updated contact details		+							
Central (postal or telephone)									
E-mail/fax notification of allocation	✓								
Letter informing GP of participation	✓								
1-month follow-up for outpatients		o							
Send fax alert following discharge to GP of patient participation		✓							
Courtesy call to participant		✓							
3-month prompt to patients			✓						
GP questionnaire							✓		
New depression				✓			✓		
Other adverse events		o		✓					
Follow-up on previous adverse events				✓			✓		
All medications		o		✓			✓		
Adherence		o		✓					
Resource use				✓			✓		
Patient follow-up									
Safety outcomes and adverse events		o			✓				
Follow-up on previous adverse events					✓			✓	
Adherence		o			✓				
mRS					✓			✓	
SIS					✓			✓	
MHI-5					✓			✓	
EQ-5D-5L (HRQoL)					✓			✓	
SF-36 vitality subscale					✓			✓	
Resource use					✓			✓	
Retrieve residual capsules (pill count, reconciliation and destruction)					✓				

+, Only for patients enrolled as inpatients; o, only for patients enrolled as outpatients.

Study safety assessments

Our monitoring system was primarily aimed at identifying suspected unexpected serious adverse reactions (SUSARs), but also at identifying whether or not the frequency of serious adverse reactions was greater than in other populations given fluoxetine and sufficiently common to offset any benefits. We did not aim to detect the occurrence of the very many adverse events that occur in stroke patients and that were very unlikely to be related to participation in the trial or the medication.

The trial materials given to the patient and/or their carer contained details of the known adverse reactions to fluoxetine (based on the SmPC) and the adverse events that commonly occur after stroke. They received a diary in which they were encouraged to record the date and nature of any adverse events.

Patients who were enrolled while they were an inpatient had a hospital discharge form completed by the local co-ordinator at the time of discharge from the recruiting centre or shortly after. The data collected were entered on a secure web-based form or faxed to the co-ordinating centre to ensure that we were alerted to any important adverse reactions. We regularly prompted centres to complete discharge forms for patients with incomplete data.

Patients who were enrolled while they were an outpatient had a central follow-up at 1 month after recruitment to detect safety outcomes and adverse reactions.

At 12 weeks after randomisation, the trial co-ordinating centre staff posted a reminder to the patients to report any adverse events or difficulties with the trial medication, but this was not followed up unless a response was received.

All surviving patients who had not withdrawn consent or indicated that they did not want to be contacted directly were followed up at 6 and 12 months after randomisation, whether or not they adhered to their allocated treatment. At each follow-up, the GP was asked about safety outcomes and other adverse events. In order to detect adverse reactions between the scheduled follow-ups, patients, their carers or their GPs could report any adverse reactions to us via:

- post – a Freepost envelope and adverse events form to return to us with details of any adverse reactions that the patient had experienced
- a helpline – a telephone number that allowed the patients or their doctors to leave a message (if non-urgent) or to access a trial doctor (if urgent).

About 2 weeks before any central follow-up was due, the trial co-ordinating centre staff contacted the GPs (or hospital co-ordinators if no discharge form had been received) to check that the patient was alive and that they may be approached for follow-up. The GP was asked (and paid a fee of £56.00) to provide a list of non-IMPs and to complete a questionnaire including information regarding the patient's adherence to the IMP, details of any safety outcomes or adverse events, hospital admissions and up-to-date contact details for the patient.

If appropriate, the trial co-ordinating centre then posted a questionnaire to the patient at 4 weeks (only for those recruited as outpatients), 26 weeks and 52 weeks. If the patient did not respond to the postal questionnaire, they were telephoned by the co-chief investigators at 6 months and by a trained member of the team at 12 months. The questionnaire at 26 and 52 weeks aimed to capture the primary and secondary outcomes and included the outcome of any adverse events that have been reported earlier in the follow-up. If the patient had incapacity, the next of kin (proxy) was asked to complete and return the forms. If the patient was unable to speak English, we asked that their carer supported them in filling out the forms. If the follow-up information could not be obtained by the

postal or telephone questionnaire, we asked the local research team to arrange a face-to-face follow-up at a clinic or home visit.

Data linkage and extract to determine outcome and long-term survival

We collected data from our participating hospitals, the patients and their GPs about hospital admissions during the first 12 months. However, we also planned to obtain information about the health status and resource use of participants to determine outcomes beyond the end of the trial from the Health and Social Care Information Centre. This function has been devolved to NHS Digital in England and Wales and the eData Research and Innovation Service (eDRIS) in Scotland. No centrally held data are available for Northern Ireland.

Management of depression in the trial

Our hypothesis was that new episodes of depression would be less commonly diagnosed and treated in the group allocated to fluoxetine. We ascertained cases of depression by:

- asking about a diagnosis or initiation of an antidepressant during hospital admission or during the first month – this was recorded on the locally completed discharge form or the 1-month central follow-up form
- asking the GP at 6 months and 12 months
- asking the patient (or their proxy) at 6 months and 12 months.

Because the primary question addressed by the FOCUS trial was whether or not a SSRI (20 mg of fluoxetine o.d.) enhanced recovery from stroke, it would be an advantage if the control group were kept free from any SSRIs, including fluoxetine. However, it would be unethical to deny patients in the trial access to effective antidepressant treatment. We therefore asked collaborating clinicians and the patients' GPs to adhere to the following treatment guideline.

If a patient in the FOCUS trial was diagnosed as having depression (or pathological emotionalism) that the responsible clinician judged to be severe enough to justify treatment with antidepressant drugs, we recommended that, if possible, they should avoid any SSRIs and prescribe either mirtazapine or trazodone. Both drugs are compatible with fluoxetine (there are no common or important interactions), although because mirtazapine has some serotonergic activity there is likely to be a slightly greater risk of precipitating a serotonergic syndrome. Both drugs were recommended by the National Institute for Health and Care Excellence (NICE) for treatment of depression in patients with physical illness.[26] The clinician might alternatively use a tricyclic antidepressant of their choice. We advised that patients taking the trial drug and another antidepressant should be monitored carefully (e.g. check plasma sodium levels to exclude hyponatraemia) to identify any potential interactions.

Sample size

We planned to enrol at least 3000 patients in the main phase of the FOCUS trial. This aimed to provide 90% power with a two-sided 5% level of significance to detect a 5.6% absolute increase in percentage with mRS 0–2 from 27.0% to 32.6% based on an ordinal analysis, which is statistically more efficient than an analysis that dichotomises the mRS.[34]

In arriving at this sample size, we took account of the effect sizes seen in the FLAME trial[17] alongside the effects that we judged clinicians and their patients would find interesting. Because fluoxetine is safe and inexpensive, the FOCUS trial sought to reliably detect a moderate, but nonetheless clinically

important, benefit that might be associated with widespread use of fluoxetine in this population. However, we also took account of the feasibility of enrolling large numbers of patients into the FOCUS trial.

We based our expected outcomes for our placebo group on the distribution of the mRS score measured at 6 months after randomisation in the CLOTS trials,[49,50] which evaluated graduated compression stockings.

We used the ordered categorical data method described by Machin *et al.*[51]

The Trial Steering Committee (TSC) reviewed the target sample size and could adjust this based on:

- advice from the Data Monitoring Committee (DMC)
- accruing data on –
    - the enrolment into specific prespecified subgroups
    - completeness of follow-up
    - distribution of mRS categories in the population of enrolled subjects (i.e. both treatment groups combined), overall and in specific patient categories (e.g. those with motor deficits or aphasia).

For example, if the distribution of mRS was different from that anticipated, then the sample size could be increased. This approach had the advantage that such sample size adjustments could be made without reference to the accumulating unblinded data, and avoided the need for conditional power calculations, which could be unreliable.

Statistical analyses

Our statistical analysis plan was published prior to completion of data collection.[52] We summarise the plan here but, rather than reproduce the whole plan in detail, we have indicated in *Chapters 3–7* which analyses were not specified in the published plan. For all analyses, unless otherwise specified, we retained participants in the treatment group to which they were originally assigned, irrespective of the treatment they actually received (i.e. an intention-to-treat analysis). A statistical significance level of $p < 0.05$ (two tailed) was applied to all analyses. The final prespecified analyses were performed on the data set after any 'cleaning' that was required had been completed and the database was locked. The treatment allocation was only then unblinded. Certain post hoc analyses presented in this report included data that had been further cleaned after the main analyses had been carried out and published to correct minor anomalies detected during the analyses.

Primary analysis

This aimed to address our primary research question: does the routine early administration of fluoxetine (20 mg o.d.) for 6 months after an acute stroke improve patients' functional status at 6 months? To minimise missing data, our analyses of the primary outcome included a mRS score obtained between 90 days and 1 year after randomisation, taking the value measured closest to the 6-month time point.

The primary analysis used an ordinal logistic regression adjusted for factors in the baseline minimisation but also reported in an unadjusted manner. This approach is recommended by the Medicines and Healthcare products Regulatory Agency (UK). The ordinal analysis of mRS was conducted by treatment allocation, under the assumption of proportional odds in the model. This assumption was tested using the score test for proportional odds assumption.

All of the analyses were programmed by our trial statistician (CG), but the primary analysis was also independently programmed by a second statistician and the results were compared; any inconsistencies were identified and resolved by discussion.

Secondary analyses

Analyses of secondary outcomes and analysis of our primary outcome (ordinal mRS) in predefined subgroups were carried out to address the other research questions. Where the outcome of interest was binary, comparison by treatment group was examined using a binary logistic regression and adjusted for factors used in the minimisation algorithm.

Where the outcome of interest was continuous, descriptive statistics are presented [*n*, mean, standard deviation (SD), minimum, maximum, median, Q1, Q3] and were categorised by allocated treatment. Owing to the nature of the distribution of these measures in this population, a simple unadjusted analysis was performed comparing the two treatment groups using a Mann–Whitney *U*-test (i.e. not adjusted for variables in the minimisation algorithm).

These analyses were conducted for the following outcomes at 6 and 12 months:

- fatigue measured by the vitality subscale of the SF-36
- individual SIS domain scores, a 'motor score' derived from averaging scores across three domains (arm, hand, leg and foot strength; hand function; and mobility), a 'physical function score' derived by averaging across four domains (arm, hand, leg and foot strength; hand function; mobility; and daily activities) and recovery based on the visual analogue scale
- quality of life as measured by the EQ-5D-5L.

Our analyses aimed to answer the following questions:

1. If fluoxetine improves functional status (mRS) at 6 months, does any improvement in functional status persist after treatment is stopped? To answer this question, we used ordinal logistic regression to compare functional status (mRS scores) at the 12-month follow-up, as for our primary analysis.
2. Does fluoxetine influence the secondary outcome measures (living circumstances, quality of life, fatigue, stroke impact and mood) at 6 months and/or 12 months? The binary outcomes are living at home or with relative versus care home, hospital or long-term care; mRS at 6 months and 12 months (mRS 0–2 vs. mRS 3–6); and new diagnosis of depression corroborated by the GP or hospital after randomisation by 6 months and 12 months. The continuous outcomes are EQ-5D-5L, vitality subscale of SF-36, SIS and MHI-5.
3. Does fluoxetine increase the risk of serious adverse events? We compared the proportion of patients having any of the following adverse events (all binary outcomes) between randomisation and cessation of the trial medication (i.e. IMP), based on treatment received rather than intention to treat:

    (a) any recurrent stroke
    (b) ischaemic stroke [not transient ischaemic attacks (TIAs)]
    (c) haemorrhagic stroke
    (d) acute coronary syndromes
    (e) epileptic seizure
    (f) episode of hyponatraemia ($Na^+ < 125$ mmol/l)
    (g) upper gastrointestinal bleeding
    (h) other major bleeds (lower gastrointestinal, extracranial, urinary or intracranial but extracerebral)
    (i) poorly controlled diabetes including hyperglycaemia (> 22 mmol/l) or symptomatic hypoglycaemia

(j) falls resulting in injury
(k) new bone fractures
(l) attempted suicide/self-harm.

4. If fluoxetine is clinically effective, is it also cost-effective? We carried out a within-trial economic analysis of direct resource costs and health outcomes on an intention-to-treat basis. A health service perspective was adopted for measuring and valuing health service use over a 12-month time horizon. The methods are described in *Chapter 6*.
5. Is fluoxetine associated with longer survival? Functional outcome at 6 months post stroke is strongly associated with long-term survival; therefore, we wished to determine whether or not any benefits to functional outcome would translate into longer-term survival.[53] We used Cox proportional hazards regression to analyse the effect of treatment on survival to 12 months. We adjusted for the variables included in our minimisation algorithm. We present this analysis graphically [cumulative hazard of death (%) vs. time], providing a hazard ratio (HR) with 95% CIs and a *p*-value. This analysis will be repeated if survival data for a more prolonged period become available and sufficient resources are available to perform and report the analyses.
6. Does the presence or absence of any of the following factors materially alter the effect of fluoxetine on our primary outcome?

   (a) Stroke pathology (ischaemic vs. haemorrhagic vs. uncertain pathological type).
   (b) Age (≤ 70 or > 70 years).
   (c) Stroke severity [i.e. baseline probability of a good outcome on mRS calculated with the six simple variable model[31] to see if effects remain constant across the range of stroke severities (≤ 0.15 vs. > 0.15–1)].
   (d) Patients who were unable to consent for themselves, as this subgroup will allow us to address the question of whether or not routine use of fluoxetine is likely to benefit patients in whom a formal assessment of mood is impossible because of communication and cognitive problems.
   (e) Inability to assess mood because of communication or cognitive problems [NIHSS Q1b > 0 or Q1c > 0 or Q9 > 1 or unable to answer Patient Health Questionnaire 2 (PHQ2)[54] at randomisation]. Defining the patients' ability to have their baseline mood assessed based on NIHSS and PHQ2 is likely to be more meaningful than based on patient or proxy consent (see d above), especially because no proxy consent is allowed in Efficacy oF Fluoxetine – a randomisEd Controlled Trial in Stroke (EFFECTS) (Sweden).
   (f) Patients with and without depression at baseline because our systematic review suggested that the effects of SSRIs were greater in those who were depressed.[25] Depression at baseline was defined as an affirmative response to our baseline question of whether or not the patient has current depression or to both questions in the PHQ2 at baseline.
   (g) The functional status (mRS) at 6 months was compared with ordinal logistic regression in these mutually exclusive subgroups by entering a treatment-by-subgroup interaction into the regression model.

7. In patients with motor deficits at randomisation, does fluoxetine improve motor function? Patients with motor deficits were defined as those with a motor deficit affecting the face/arm or leg (based on NIHSS Q5–9 of > 0). For this subgroup analysis, in addition to comparing their overall functional outcome based on the ordinal analysis of mRS, we compared the motor score with the physical function scores based on the SIS domains described above.
8. In patients with aphasia at randomisation, does fluoxetine improve communication? Patients with aphasia were defined as those with an NIHSS Q9 of > 0. For this subgroup analysis, in addition to comparing their overall functional outcome based on mRS based on ordinal analysis, we compared with the SIS communication subscale.

9. For questions 7 and 8, because patients may have a combination of neurological deficits, individual patients may appear in more than one subgroup.
10. Is there a relationship between functional status at 6 months and mood and is this relationship affected by fluoxetine? We performed exploratory analyses of potential mediating factors (e.g. the role of depression).

Missing data

Our randomisation systems did not allow investigators to proceed to treatment allocation without entering complete baseline data. The mRS, our primary outcome, includes death; therefore, the number of participants with missing mRS at follow-up was small. Anyone with a missing mRS was not included in any analysis requiring mRS (complete-case analysis).

For secondary outcomes [e.g. SIS, MHI-5, vitality subscale of the SF-36 and EQ-5D-5L] for which missing data were expected because data were not available for patients who did not survive, we presented results for those who were alive at follow-up and any discrepancies in death rates between groups were taken into account in the interpretation. Missing data for single questions within scores were handled as detailed by each scoring method. Where responses to all questions within a scale or subscale were missing, that patient was not included in that part of the analysis.

Protocol deviations, adherence and blinding

Inclusion/exclusion violations: we reported the number and percentage of participants randomised who did not meet the entry criteria (e.g. non-strokes), with exclusion criteria. However, they were included in the primary analysis. A secondary analysis excluded ineligible patients (see below).

Unblinding: we reported the number of patients who required unbinding of study medication during the trial by treatment group and, where available, present the reasons for unblinding.

Adherence: each participant was issued with a 6-month supply of trial medication (186 capsules). At 6 months, they were asked if they had completed the course and taken all of the capsules and how often they took capsules on average. They were asked the reasons for stopping, as well as the date of stopping. Where possible, we retrieved and counted the unused trial medication. Before unblinding, we derived an estimated date on which the patient was thought to have taken their last dose of trial medication and used the interval (days) from first dose to that date as our main measure of adherence. This was based on all of the available information. We used a combination of the following to define several types of non-adherence to the protocol (see 1–8 below):

- inclusion/exclusion violations
- the answers to the adherence questions (see above)
- number, percentage and duration of any open-label SSRI intake before the 6-month follow-up
- the reasons for stopping trial medication.

A so-called intention-to-treat analysis, in which patients' outcomes are analysed in the groups that they were randomised to regardless of treatment received, provides the least biased and most robust evidence of the effect of treatment. However, the observed treatment effect may be reduced if a large number of patients are included who are unlikely to benefit because they did not have a stroke or more likely where a large proportion of patients do not receive the allocated treatment or actually received the alternative treatment (i.e. cross-overs).

Where the primary analysis does not demonstrate an improvement of functional outcome (mRS) at the 6-month follow-up, the question arises of whether or not this is this likely to be a result of poor adherence to the protocol and/or trial medication? This is important because we would not wish to abandon a potentially useful treatment simply because of poor adherence to trial protocols or trial medication. These might be improved in any future trials. We undertook further per-protocol analyses to reassure the clinical community that the trials have not underestimated any treatment effect to an extent that would alter future clinical practice, or more likely the need for further randomised trials of SSRI in stroke.

Inevitably, analyses that try to take account of adherence introduce a degree of patient selection and, thus, are likely to introduce bias.

These prespecified exploratory sensitivity analyses to account for non-adherence included all of the analyses of the primary outcome and selected secondary outcomes:

- living at home or with relative versus care home, hospital or long-term hospital care
- mRS at 6 months and 12 months (mRS 0–2 vs. mRS 3–6)
- new diagnosis of depression between randomisation and 6 months and 12 months
- SIS domain scores
- averaged score over all SIS domains
- SF-36 vitality subscale score
- utility based on EQ-5D-5L and population preferences.

These analyses do not include any analysis of subgroups defined on the basis of baseline variables. The following groups were sequentially added to the group excluded from the analyses:

1. Patients who did not meet the entry criteria for the trial.
2. Patients who did not receive any trial medication.
3. Patients who received < 90 days of trial medication because of failures in trial procedures, for example failures to transfer trial medication with patients during moves between hospitals, care homes and home. The 90-day cut-off point was chosen because previous trials have tested this duration of treatment with apparent benefit.[17,25]
4. Patients who received < 90 days of trial medication because of patient or relative concerns but not because of suspected adverse reactions.
5. Patients who received < 90 days of trial medication because they experienced symptoms that were attributed to the trial medication.
6. Patients who had been allocated to placebo who received a SSRI (fluoxetine or other) within the first 90 days and the SSRI was not known to have been stopped within 10 days of starting.
7. Patients who had been allocated to fluoxetine who received a SSRI (fluoxetine or other) within the first 90 days and the SSRI was not known to have been stopped within 10 days of starting.
8. Patients who did not complete at least 150 days of treatment. We chose this cut-off point because patients sometimes received the questionnaires shortly before 6 months, and some stopped the trial medication at that point, whereas others finished the 186 capsules. We regarded both as fully adherent.

Research governance

The trial was co-ordinated by a Project Management Group: Professor Martin Dennis, Professor Gillian Mead (the joint chief investigators and PIs for two participating sites), Karen Innes (trial manager) and Catriona Graham (trial statistician).

Trial co-ordinating centre

The trial co-ordinating centre was responsible for all aspects of the management of the FOCUS trial and was based at the Centre for Clinical Brain Sciences at the University of Edinburgh. Responsibilities included regulatory submissions and compliance; financial management; monitoring of sites; training; patient information and communication; end-point assessment; data collection systems and data management; IMP management; statistical analysis; reports and publications; and archiving of the trial master file in accordance with funder and sponsor requirements.

Trial Steering Committee

A TSC was established, including a stroke survivor and a carer, to oversee the conduct and progress of the trial. The terms of reference of the TSC, the draft template for reporting and the names and contact details were agreed at its first meeting (see *Report Supplementary Material 1*).

Data Monitoring Committee

An independent DMC was established to oversee the safety of participants in the trial. During the period of recruitment into the study, interim analyses of the baseline and follow-up data were supplied, in strict confidence, to the chairperson of the DMC, along with any other analyses that the committee requested. In the light of these analyses, the DMC could advise the chairperson of the TSC if, in their view, the randomised comparisons had provided (1) 'proof beyond reasonable doubt' that for all, or some, the treatment is clearly indicated or clearly contraindicated and (2) evidence that might reasonably be expected to materially influence future patient management. Appropriate criteria of proof beyond reasonable doubt were not specified precisely, but the DMC worked on the principle that a difference of at least three standard errors in an interim analysis of a major outcome event (e.g. death from all causes or independent survival at 6 months) would be needed to justify halting, or modifying, the study before the planned completed recruitment. This criterion has the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule was proposed. Following a report from the DMC, the TSC decided whether to modify entry to the study (or seek extra data).

The terms of reference of the DMC, the DMC charter and the names and contact details were agreed at the first meeting of the DMC (see *Report Supplementary Material 2*).

Patient and public involvement

In December 2010, service users overseeing a study of post-stroke fatigue commented on our plans for the FOCUS trial. We met with the group in May 2011. We included their suggestions about patient information booklets (i.e. explaining the rationale for using fluoxetine in people without depression, listing all side effects), and agreed that all trial participants would be sent a summary of the trial results if they wished. A group of stroke survivors with aphasia developed the easy-access version of the patient information booklet, guided by Professor Marian Brady (see *Appendix 2*). A stroke survivor, Judith Williamson, from the National Institute for Health Research (NIHR) Stroke Research Network (SRN), and Zena Jones (manager of the NIHR SRN patient and public involvement group) attended our first investigator meeting (in June 2011). In March 2013, the SRN patient and public involvement group advised us how to enhance the proportion of eligible patients consenting, and how to facilitate follow-up. This advice featured in our Autumn 2013 newsletter to sites. In November 2013, Ms Jones and Ms Williamson endorsed our plans to telephone patients immediately after hospital discharge. They edited the script that would guide the telephone call. They commented on a draft of the funding application to NIHR. Ms Williamson and a carer were on our TSC, offering advice and comments

throughout the trial. They were particularly influential in discussion of how we would disseminate the results of the trial to participants and their families. They commented on the final newsletter, which was sent out on the day the results were presented at conference, and published in *The Lancet*.[55] They have also had input into the drafting of this report, specifically the *Plain English summary*.

Chapter 3 Results 1: conduct

The main results of the FOCUS trial have been published.[55] In this chapter, and following chapters, we present the main results and additional information.

Recruitment

Between 10 September 2012 and 31 March 2017, 103 UK hospitals consented 3152 patients and enrolled 3127 patients. Recruitment was stopped after we had exceeded our minimum target of 3000 patients to account for recruitment of ineligible patients and withdrawals (*Figure 1*).

The network of centres was built on the networks that we had established to carry out previous trials, including the CLOTS[49,50] and IST3[43] trials. We enrolled new centres throughout the trial period. The trial co-ordinating centre worked closely with the research teams at prospective centres, and the majority of site initiation visits were carried out remotely using telephone and video conferencing. The trial was facilitated by the NIHR-funded research networks, which provided funding for local research nurses. Centres also received a £300 pharmacy start-up fee, and approximately £46 per patient recruited.

Thirty-one patients were identified as ineligible between obtaining consent and randomisation; in other cases, the patients, their proxy or their treating clinician changed their mind about participation in the trial. Of the 3127 patients who were enrolled, 1564 were allocated to the fluoxetine group and 1563 were allocated to the placebo group. Eleven of these patients did not meet our eligibility criteria: two in each group had a final diagnosis other than stroke and seven others were identified as meeting exclusion criteria after randomisation (e.g. a history of epilepsy, self-harm or some other contraindication to fluoxetine). The ineligible patients were retained in our intention-to-treat analyses. The patients' progress through the trial is shown in *Figure 2*.

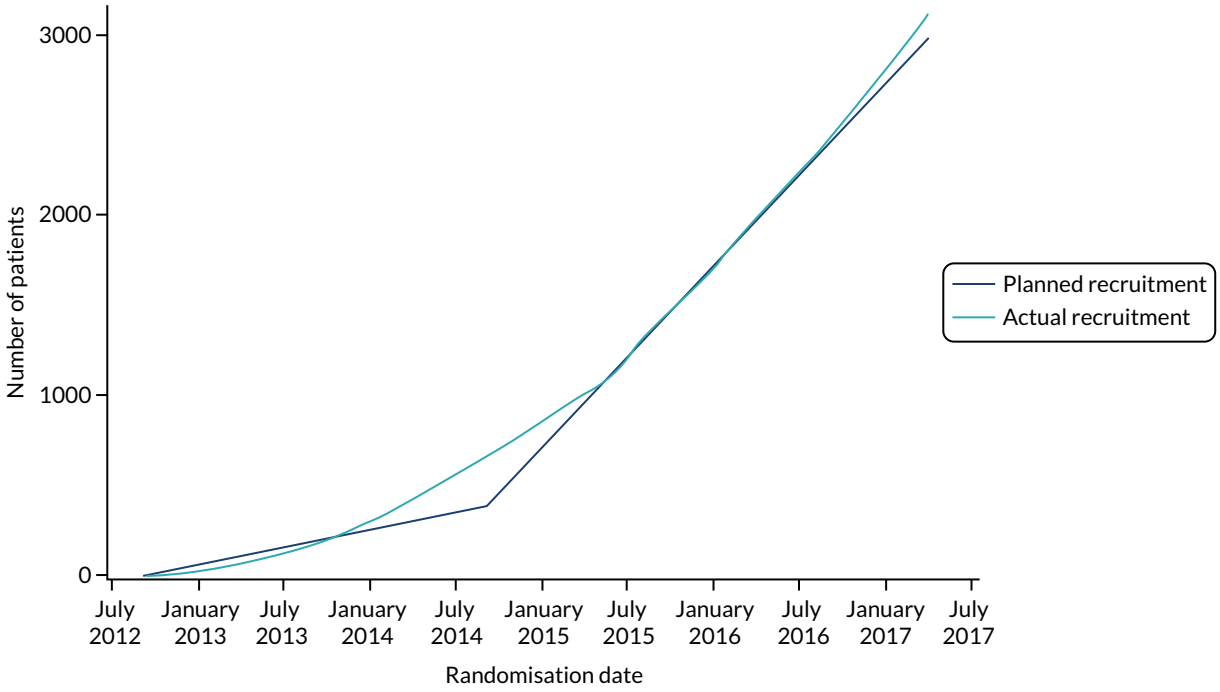

FIGURE 1 Recruitment graph showing planned vs. actual recruitment.

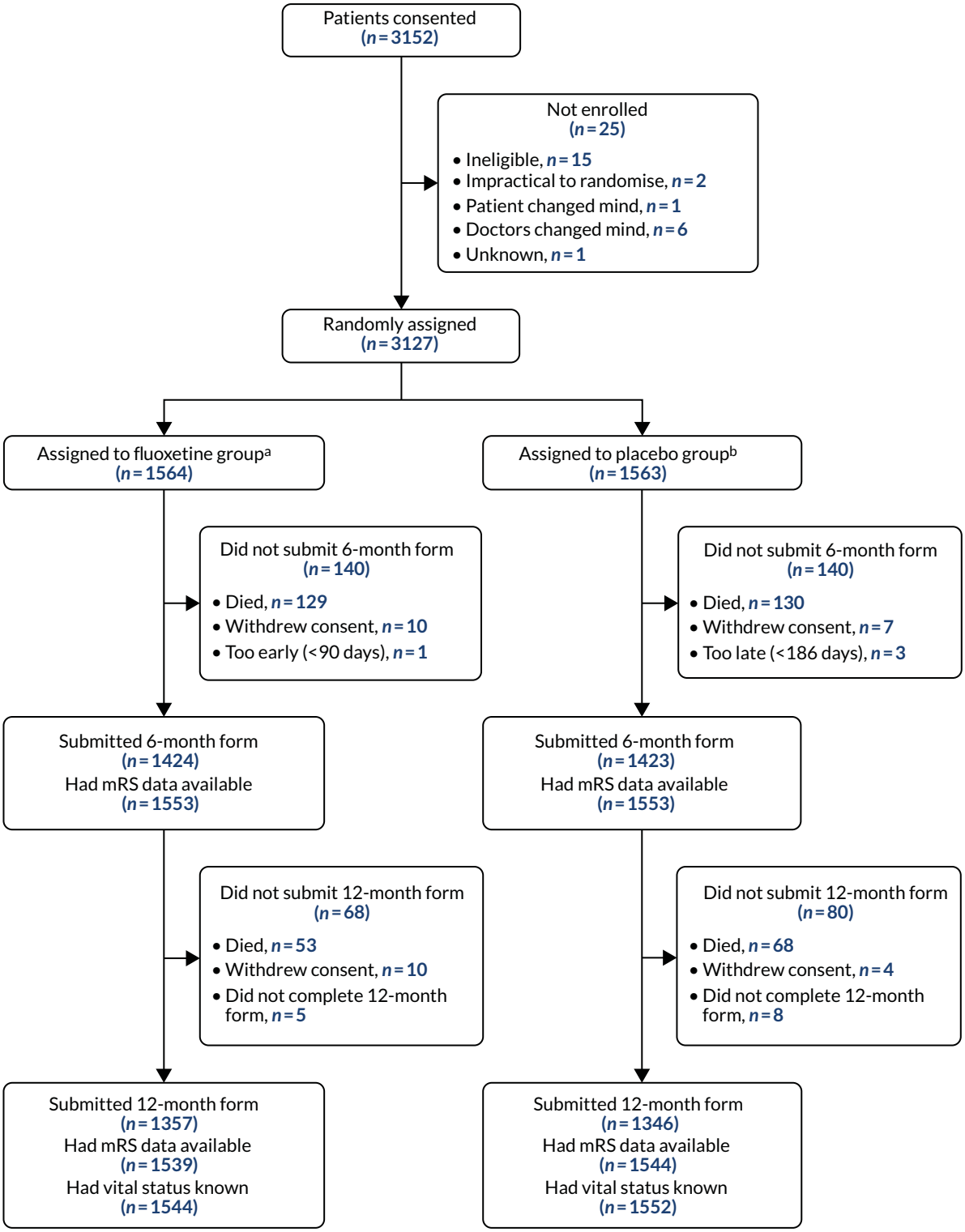

FIGURE 2 Participant flow. a, 1544 inpatients with discharge form; 20 recruited as outpatients; b, 1536 inpatients with discharge form; 27 recruited as outpatients. Reproduced from the FOCUS trial collaboration.[55] © 2018 The Author(s). Published by Elsevier Ltd. This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) license. See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

Baseline characteristics of recruited patients

The baseline characteristics of the two treatment groups were well balanced with respect to all measured variables (*Tables 2–6*).[55]

TABLE 2 Baseline characteristics: demographic and social

Characteristics of patients randomised	Allocated treatment	
	Fluoxetine (*N* = 1564)	Placebo (*N* = 1563)
Sex, *n* (%)		
Female	589 (37.66)	616 (39.41)
Male	975 (62.34)	947 (60.59)
Age, *n* (%)		
≤ 70 years	666 (42.58)	664 (42.48)
> 70 years	898 (57.42)	899 (57.52)
Age (years), mean (SD)	71.24 (12.35)	71.48 (12.06)
Ethnicity, *n* (%)		
Asian	30 (1.92)	31 (1.98)
Black	35 (2.24)	29 (1.86)
Chinese	0 (0.00)	1 (0.06)
Other	4 (0.26)	9 (0.58)
White	1495 (95.59)	1493 (95.52)
Marital status, *n* (%)		
Married	879 (56.20)	846 (54.13)
Partner	93 (5.95)	91 (5.82)
Divorced/separated	109 (6.97)	100 (6.40)
Widowed	337 (21.55)	354 (22.65)
Single	124 (7.93)	150 (9.60)
Other	22 (1.41)	22 (1.41)
Living arrangement, *n* (%)		
Living with someone else	1057 (67.58)	1034 (66.15)
Living alone	485 (31.01)	516 (33.01)
Living in an institution	10 (0.64)	4 (0.26)
Other living arrangement	12 (0.77)	9 (0.58)
Employment, *n* (%)		
Full-time employment	287 (18.35)	258 (16.51)
Part-time employment	76 (4.86)	70 (4.48)
Retired	1122 (71.74)	1134 (72.55)
Unemployed/disabled	53 (3.39)	60 (3.84)
Other employment	26 (1.66)	41 (2.62)

TABLE 3 Baseline characteristics: medical history

Characteristics of patients randomised	Allocated treatment, *n* (%)	
	Fluoxetine (*N* = 1564)	Placebo (*N* = 1563)
Coronary heart disease	281 (17.97)	300 (19.19)
Ischaemic stroke/TIA	274 (17.52)	294 (18.81)
Diabetes	337 (21.55)	303 (19.39)
Hyponatraemia	19 (1.21)	26 (1.66)
Intracranial bleed	27 (1.73)	23 (1.47)
Upper gastrointestinal bleed	25 (1.60)	26 (1.66)
Bone fractures	241 (15.41)	256 (16.38)
Depression	130 (8.31)	123 (7.87)

TABLE 4 Baseline characteristics: stroke diagnosis and classifications

Characteristics of patients randomised	Allocated treatment, *n* (%)	
	Fluoxetine (*N* = 1564)	Placebo (*N* = 1563)
Stroke diagnosis		
Non-stroke (final diagnosis)	2 (0.13)	2 (0.13)
Ischaemic stroke	1410 (90.15)	1406 (89.96)
Intracerebral haemorrhage	154 (9.85)	157 (10.04)
OCSP classification of ischaemic strokes		
Total anterior circulation infarct	318 (20.33)	317 (20.28)
Partial anterior circulation infarct	561 (35.87)	553 (35.38)
Lacunar infarct	307 (19.63)	283 (18.11)
Posterior circulation infarct	191 (12.21)	230 (14.72)
Uncertain	33 (2.11)	23 (1.47)
Cause of stroke: modified TOAST classification		
Large artery disease	278 (17.77)	234 (14.97)
Small vessel disease	252 (16.11)	218 (13.95)
Embolism from heart	377 (24.10)	411 (26.30)
Another cause	38 (2.43)	35 (2.24)
Unknown/uncertain	465 (29.73)	508 (32.50)

OCSP, Oxfordshire Community Stroke Project;[56] TOAST, Trial of Org 10172 in Acute Stroke Treatment.[57]

TABLE 5 Baseline characteristics: stroke severity, prognostic variables and mood at baseline

Characteristics of patients randomised	Allocated treatment	
	Fluoxetine (*N* = 1564)	Placebo (*N* = 1563)
SSV		
Age (years), mean (SD)	71.24 (12.35)	71.48 (12.06)
Independent before stroke, *n* (%)	1431 (91.50)	1435 (91.81)
Living alone, *n* (%)	485 (31.01)	516 (33.01)
Able to lift both arms off bed, *n* (%)	924 (59.08)	935 (59.82)
Able to talk and not confused, *n* (%)	1166 (74.55)	1164 (74.47)
Able to walk without help from another person, *n* (%)	435 (27.81)	412 (26.36)
Probability that alive and independent, median (IQR) (derived from SSV)	0.28 (0.07–0.63)	0.26 (0.07–0.63)
0 to ≤ 0.15, *n* (%)	592 (37.85)	591 (37.81)
> 0.15 to 1, *n* (%)	972 (62.15)	972 (62.19)
NIHSS, median (IQR)	6 (3–11)	6 (3–11)
Presence of a motor deficit, *n* (%)	1361 (87.02)	1361 (87.08)
Presence of aphasia, *n* (%)	457 (29.22)	449 (28.73)
Current diagnosis of depression (patient/proxy reported), *n* (%)	26 (1.66)	18 (1.15)
Taking a non-SSRI antidepressant, *n* (%)	65 (4.16)	77 (4.93)
Current mood: PHQ2,[54] *n* (%)		
2 yes responses	81 (5.18)	60 (3.84)
1 yes response	136 (8.70)	130 (8.32)
0 yes responses	1347 (86.13)	1373 (87.84)

IQR, interquartile range; NIHSS, National Institute for Health Research Stroke Scale;[13] SSV, six simple variable model.[31]

TABLE 6 Baseline characteristics: timing, location and source of consent

Characteristics of patients randomised	Allocated treatment	
	Fluoxetine (*N* = 1564)	Placebo (*N* = 1563)
Delay (days) since stroke onset at randomisation		
Delay, mean (SD)	6.93 (3.64)	6.98 (3.64)
2–8, *n* (%)	1070 (68.41)	1072 (68.59)
9–15, *n* (%)	494 (31.59)	491 (31.41)
Enrolled as a hospital inpatient (not outpatient clinic), *n* (%)	1544 (98.72)	1536 (98.27)
Patient consented, *n* (%)	1136 (72.63)	1118 (71.53)
Proxy consented, *n* (%)	428 (27.37)	445 (28.47)

Withdrawal

The term withdrawal is used widely in RCTs but it is important to be precise about what is meant. In the FOCUS trial, we separately categorised patients into the following groups:

- patients who had stopped their trial medication, but were content to be followed up
- patients who may or may not have stopped their medication but no longer wanted to be contacted directly for follow-up information, but were content for us to obtain follow-up information from family, friends, GPs or routine data sources
- patients or their proxies who withdrew consent and wanted the patient and their data to be taken out of the study from that point on, so that we used data collected up to that point only.

When we were informed that the patients wished to withdraw, we clarified which of the above applied. Only 31 patients withdrew consent; the timing and treatment allocations are shown in the participant flow diagram (see *Figure 2*) and treatment allocations were fairly well balanced.

Discharge forms

A discharge form (see the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/130430/#) was completed for all 3040 patients enrolled as inpatients.

The 6- and 12-month follow-ups

We completed the 12-month follow-up in the trial in June 2018. The participant flow diagram (see *Figure 2*) shows the completeness of follow-up with respect to our primary outcome and vital status. *Table 7* shows the methods of follow-up to obtain these data. Forty-nine per cent of 6-month follow-up assessments were obtained by postal questionnaire (see the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/130430/#). The remainder required a telephone reminder or were completed by telephone interview. The telephone follow-ups for participants not returning postal 6-month

TABLE 7 Methods of follow-up

Method of follow-up	Allocated treatment, *n* (%)	
	Fluoxetine	Placebo
6 months		
Completed 6-month postal questionnaire without telephone prompting	693 (48.6)	700 (49.1)
Required prompting or clarification by telephone to complete 6-month questionnaire	312 (21.9)	276 (19.4)
Completed 6-month questionnaire by telephone	420 (29.5)	450 (31.6)
Total completing 6-month questionnaire	1425 (100.0)	1426 (100.0)
12 months		
Completed 12-month postal questionnaire without telephone prompting	745 (54.9)	743 (55.2)
Required prompting or clarification by telephone to complete 12-month questionnaire	195 (14.4)	179 (13.4)
Completed 12-month questionnaire by telephone	417 (30.7)	424 (31.5)
Total completing 12-month questionnaire	1357 (100.0)	1346 (100.0)

questionnaires were carried out by the two co-chief investigators (MD and GM) who were trained and certified in the use of the mRS and had conducted an independent validation of the smRSq.[18,35,36] Those conducting the 12-month telephone follow-ups had received training in their application.

Based on our previous trials, we had expected 80% of follow-up to be returned by postal questionnaire, rather than 50%. This placed a much greater burden on the central co-ordinating team than expected. In addition, in the FOCUS trial, patients were followed up at 6 and 12 months, doubling the number of follow-ups. Because missing outcome data would reduce the power of the trial, and can more importantly introduce bias because it is rarely missing randomly, the central team allocated far more time and resources to follow-up than had been planned.

Reasons for the low response rate

We did not formally assess the reasons for the low rate of response to the postal questionnaires, but the following issues contributed:

- Centres providing incomplete or inaccurate postal addresses for participants. Increasingly, stroke services admit patients acutely to one hospital and then transfer the patients to another hospital, or community rehabilitation centre, for ongoing care. We collected the discharge address on our discharge form, and this was often completed when patients moved from the centre in which they were recruited. Downstream facilities often did not inform us that the patient had then been discharged to an address other than their original home address. Our team spent a lot of time tracking down these patients to obtain their current address.
  Anecdotally, patients had often not opened our postal questionnaires because they believed them to be circulars. Any indication of the content of the letter on the outside of the envelope (e.g. contains FOCUS trial questionnaires) could have an impact on patient confidentiality and was, therefore, not used.
- Our 6- and 12-month follow-up questionnaires included the SIS. This is long, containing 59 items in several domains. In one domain, the Likert scaling for three of the nine items is reversed (i.e. good outcomes have low instead of high scores in the 1–5 range). Patients found this confusing, and they often entered internally inconsistent information, which we then queried by telephone.
- The burden of carrying out telephone follow-ups to clarify or complete information received by post, or to complete the whole follow-up by telephone, was considerable, and was increased as a result of several factors, including:
  - Patients changing telephones from landlines to mobiles, which meant that our co-ordinating team spent a lot of time communicating with centres, downstream health-care facilities, patients' GPs and proxies to obtain up-to-date contact information.
  - Patients and proxies increasingly not answering calls from unknown numbers, which are often assumed to be marketing calls or scams. In many cases, patients or their proxies were telephoned at different times of the day and week, often on multiple occasions, before contact was actually made. To overcome this barrier, we often texted the recipient in advance of a phone call to increase the likelihood that they would answer. In future trials, it would be useful at the time of recruitment to enter the trial co-ordinating centre's number into the patients' and/or proxies' mobile phones as a contact so they could make a more informed decision about whether or not to answer a telephone call from the trial centre.

- General practitioners and their staff varied greatly in the assistance they would provide in completing the GP questionnaires and in helping us contact patients. Most were very helpful but:
  - Some refused to provide information because they were unaware that the patient had provided written consent for them to do so. We had routinely sent GPs a copy of the patient information and the completed consent form with a covering letter at the time of recruitment. It appears that this was often filed and, therefore, it was not obvious to the staff when they received a request 6 or 12 months later. Some patients had moved house and changed GPs, which meant that the original trial documentation was not necessarily available to the new GP.
  - Some GPs reported that they were simply too busy to help.
  - Some felt that the fee of £54 negotiated with the primary care network was insufficient, and that they required a much larger sum to complete a follow-up questionnaire. We occasionally paid a little more, but usually we obtained the data via an alternative route.

Unblinding

The emergency unblinding procedure was carried out for only three patients. One was on the request of a coroner after the patient died, a second was on the request of the sponsor, for a suspected unexpected serious adverse reaction, and the third was because the responsible clinician felt that knowledge of the treatment would significantly alter their management of the patient. All of the patients had been allocated fluoxetine.

Adherence

The primary measure of adherence was the estimated duration of study medication (interval in days from first to last dose of study medication) based on all available data. Capsule counts were available in 398 (25.6%) of those allocated fluoxetine and 410 (26.4%) of those allocated placebo. The patients returned a median of 32 [interquartile range (IQR) 10–135] capsules in the fluoxetine group and 33 (IQR 11–139) capsules in the placebo group. Our primary measure of adherence was available in 1417 (91%) patients in each group. The median duration of treatment was 185 (IQR 149–186) days in the fluoxetine group and 183 (IQR 136–186) days in the placebo group. The median delay between randomisation and first dose was 0 (IQR 0–1) days in both treatment groups. A total of 1519 (97%) participants in the fluoxetine group and 1494 (96%) participants in the placebo group received their first dose by day 2 after randomisation (*Table 8*). *Table 9* shows the number and proportion of patients meeting our eligibility criteria and different levels of adherence to the study medication.

TABLE 8 Number of days from the date of randomisation to the date of starting trial medication

	Allocated treatment, *n* (%)		
Interval to first dose	Fluoxetine	Placebo	Total, *n* (%)
0 days	817 (52)	816 (52)	1633 (52)
1 day	658 (42)	619 (40)	1277 (41)
2 days	44 (3)	59 (4)	103 (3)
3 days	17 (1)	17 (1)	34 (1)
≥ 4 days	16 (1)	30 (2)	46 (1)
Missing	8 (1)	11 (1)	19 (1)
Total	1564 (100)	1563 (100)	3127 (100)

TABLE 9 Number of trial participants who were ineligible, who had different degrees of adherence and who remained in the trial after removing ineligible patients and those with poor adherence

Groups cumulatively excluded	Number meeting each exclusion criterion	Cumulative number removed from analysis	Number remaining in fluoxetine group	Number remaining in placebo group
None: as per intention-to-treat analysis	0	0	1553	1553
Ineligible: did not meet all inclusion criteria	11	11	1548	1547
Received no study medication after randomisation	17	26	1540	1540
Received < 90 days of study medication owing to failure to follow trial procedures	128	152	1480	1474
Received < 90 days of study medication owing to patient/carer/doctor choice	208	342	1405	1359
Received < 90 days of study medication owing to suspected adverse reaction	265	607	1262	1237
Allocated placebo but received SSRI for > 10 days within 90 days	84	628	1262	1216
Allocated fluoxetine and received SSRI for > 10 days within 90 days	52	651	1239	1216
Received < 150 days of study medication unless died earlier still taking study medication	847	892	1122	1092
Received < 150 days of study medication for any reason including death	975	1016	1051	1039

Patients stopping the trial medication because of perceived adverse effects within the first 90 days was only marginally more common in the fluoxetine group ($n = 143$, 9.1%) than in the placebo group ($n = 122$, 7.8%). About two-thirds of patients took the study medication for at least 150 days.

Problems with adherence

We identified some reasons for non-adherence to the trial medication. These included:

- Recruiters not checking that they had someone named on the delegation log who could sign the initial prescription. Usually this just led to a short delay in starting the medication, but was more complicated if the patient was discharged or moved hospital prior to receiving the first dose.
- Delays in obtaining the trial medication from pharmacies, especially when the patient was randomised later in the day.
- In discharge letters to GPs, it was sometimes unclear that patients were in a placebo-controlled trial and that patient had been given their trial medication. This sometimes led GPs to prescribe fluoxetine or nursing home staff to ask for fluoxetine to be prescribed on admission or when a patient's supply was running low.
- Patients, or their families or nursing home staff, often wanted the trial medication in a blister pack, in a dosette box provided by pharmacists or in liquid form and so they would then request that the GPs prescribe fluoxetine – GPs would comply with this. Patients and relatives could put their trial medication into a dosette box, but we were unable to identify any means of getting pharmacies to put the trial medication into dosette boxes or blister packs. Thus, some patients allocated to the placebo group were inadvertently given fluoxetine by their GP.

We introduced a safety alert letter (see www.journalslibrary.nihr.ac.uk/programmes/hta/130430/#) after patient 1000 was recruited. This was automatically generated when we received the discharge form (see www.journalslibrary.nihr.ac.uk/programmes/hta/130430/#). The introduction of the safety fax had no effect on the frequency of inappropriate prescribing of antidepressants, and fluoxetine in particular, in the randomised patients.

The 24/7 helpline was very helpful in reducing these problems; in many cases, patients, their families or health-care staff rang the helpline to clarify the situation and we were able to reduce the non-adherence by talking with all of these groups.

Confirmation of safety outcome events and data cleaning

This was carried out by the data manager and co-chief investigator (MD) prior to unblinding of the treatment code. We did not have an event or outcome adjudication committee because there is evidence that these do not significantly improve data quality.[58] We aimed to obtain information from patients, their relatives, GPs and hospitals (usually via the research co-ordinators) to confirm the event, its nature and its date. We established some rules that were applied so that assumptions were made consistently.

Monitoring

We monitored the quality and integrity of the accumulating clinical data in accordance with a protocol agreed with the study sponsors [the Academic and Clinical Central Office for Research and Development (ACCORD) representing the University of Edinburgh and NHS Lothian], which involved central statistical monitoring, supplemented by on-site monitoring and detailed source data verification in the co-ordinating centre and triggered visits when patterns in the data at a centre seemed anomalous. All baseline data and in-hospital and 6- and 12-month outcome data were subject to verification checks built into the randomisation and data management system. In practice, almost all monitoring visits to centres were triggered by the occurrence of protocol deviations and violations, rather than any concerns about data quality.

Closeout

All trial monitoring activities, including those for trial closure, were carried out in compliance with the agreed FOCUS monitoring plan and in accordance with the trial sponsor's standard operating procedures to ensure that all study-related activities were reconciled, recorded and reported at the end of the trial in accordance with the trial protocol and all applicable regulatory requirements and that they complied with good clinical practice.

Remote closeouts were conducted by the FOCUS central team, using a combination of sponsor-approved checklists (see the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/130430/#; accessed 7 May 2020) and trial-specific instructions and documents for reconciliation of the investigator site file for completeness. A completed closeout checklist was available for all centres. Bespoke per-site reports were provided to each site to reconcile all essential documentation required for the investigator site file in preparation for archiving. The site files included site delegation logs, documentation of staff qualifications and training (good clinical practice, curricula vitae), IMP management and reconciliation, consent confirmation, randomisation records, documentation of violations, deviations, serious adverse events and SUSARs. A final closeout visit to the co-ordinating centre and trial master file review was conducted by the trial sponsor in preparation for final closure and archiving of all essential trial master file documents.

Chapter 4 Results 2: patient outcomes and events

The main results of the trial have been published.[55]

The number and percentage of patients in each mRS category by treatment group is shown in *Table 10*.

The primary outcome at 6 months in the two treatment groups is compared in *Figure 3*. An ordinal comparison of the distribution of patients across the mRS at 6 months, adjusted for variables included in the minimisation algorithm, was similar in the two groups [common odds ratio (COR) 0.951, 95% CI 0.839 to 1.079; $p = 0.439$], where a COR in favour of placebo is < 1.0. The unadjusted analysis provided similar results (COR 0.961, 95% CI 0.848 to 1.089; $p = 0.531$). The ordinal analysis of mRS has been conducted

TABLE 10 Number and percentage of patients in each mRS category by treatment group

	Allocated treatment, *n* (%)	
Primary outcome	**Fluoxetine**	**Placebo**
Disability on the mRS at 6 months		
0: no symptoms	114 (7.34)	124 (7.98)
1: no clinically significant disability despite symptoms	302 (19.45)	309 (19.90)
2: slight disability – unable to do everything	156 (10.05)	155 (9.98)
3: moderate disability – unable to live independently but can walk	518 (33.35)	510 (32.84)
4: moderately severe disability and unable to walk without help from another person	121 (7.79)	122 (7.86)
5: severe disability – unable to sit up	213 (13.72)	203 (13.07)
6: dead	129 (8.31)	130 (8.37)
Total number of patients with mRS	1553 (100.00)	1553 (100.00)
Number of patients with missing mRS	11	10
Total number of patients randomised	1564	1563

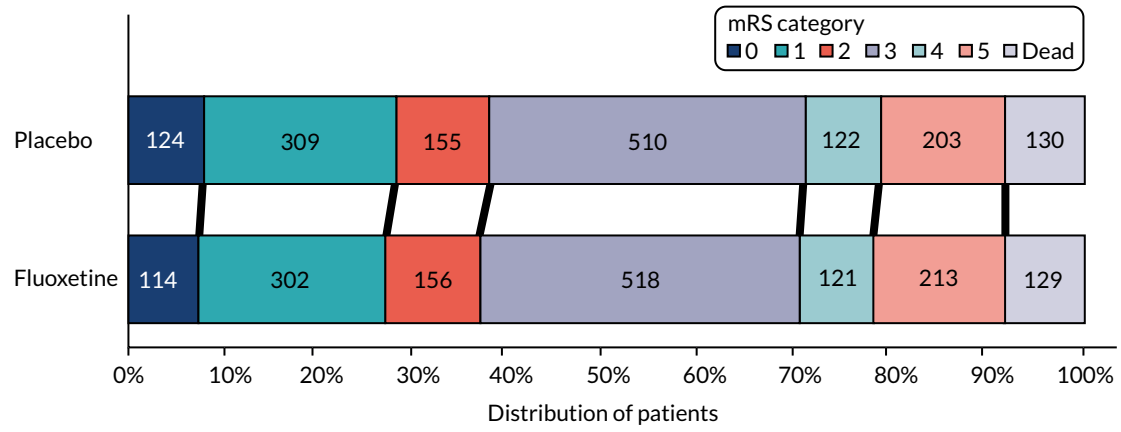

FIGURE 3 Comparison of the distribution of patients across the seven categories of the mRS in the two allocated treatments. Reproduced from the FOCUS trial collaboration.[55] © 2018 The Author(s). Published by Elsevier Ltd. This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) license. See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

by treatment allocation, under the assumption of proportional odds in the model. This assumption was found to hold using the score test for proportional odds assumption ($p = 0.9947$). Comparing the mRS dichotomised into 0–2 and 3–6, there was similarly little difference between the groups (adjusted OR 0.955, 95% CI 0.812 to 1.123; $p = 0.576$; unadjusted OR 0.957, 95% CI 0.827 to 1.107; $p = 0.352$).

The results of our prespecified subgroup analyses are shown in *Table 11*. There were no statistically significant interactions between the prespecified subgroups and the effect of treatment on the primary outcome.

TABLE 11 Primary outcome in prespecified subgroups

	Allocated treatment (*n*)				
6 months, adjusted analysis	**Fluoxetine**	**Placebo**	**COR**	**95% CI**	***p*-value**
Overall	1553	1553	0.952	0.840 to 1.079	0.439
Variables used in the minimisation					
Probability of being alive and independent at 6 months					
0 to ≤ 0.15	590	586	1.026	0.836 to 1.258	0.326
0.15 to 1	963	967	0.906	0.771 to 1.063	
Delay from onset to randomisation (days)					
2–8	1061	1067	0.957	0.822 to 1.114	0.951
9–15	492	486	0.940	0.750 to 1.178	
Motor deficit					
No	203	201	1.207	0.847 to 1.721	0.153
Yes	1350	1352	0.919	0.803 to 1.052	
Aphasia					
No	1099	1108	0.894	0.770 to 1.038	0.123
Yes	454	445	1.107	0.874 to 1.403	
Other prespecified subgroup analyses					
Stroke type					
Haemorrhagic	153	156	0.816	0.546 to 1.221	0.427
Ischaemic	1400	1397	0.969	0.848 to 1.107	
Age group (years)					
≤ 70	661	661	0.947	0.780 to 1.151	0.944
> 70	892	892	0.952	0.806 to 1.124	
Who gave consent					
Proxy	427	443	0.944	0.741 to 1.204	0.899
Patient	1126	1110	0.940	0.810 to 1.092	
Inability to assess mood					
No	1167	1165	0.891	0.770 to 1.031	0.089
Yes	386	388	1.125	0.871 to 1.452	
Baseline depression					
No	1457	1483	0.952	0.836 to 1.084	0.805
Yes	96	70	1.030	0.586 to 1.798	

Table 12 shows 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 (see *Table 9*). These are a series of prespecified per-protocol analyses that sequentially exclude subgroups of patients who either did not meet our eligibility criteria or had incomplete adherence to the study medication. There was no trend towards greater benefit in those with greater adherence.

Table 13 shows the safety outcomes at 6 months. Those allocated fluoxetine were less likely to be diagnosed with a new episode of depression [$n = 210$ (13.0%) vs. $n = 269$ (16.9%), difference in proportion −3.78%, 95% CI −1.26% to −6.30%; $p = 0.003$]. Those allocated fluoxetine had an increased risk of fractures [$n = 45$ (2.9%) vs. $n = 23$ (1.5%), difference in proportion 1.41%, 95% CI 0.38% to 2.43%; $p = 0.007$]. There were no statistically significant differences in other safety outcomes, although there were expected trends towards more events in the fluoxetine group for adverse effects listed in the SmPC for fluoxetine [epileptic seizures, falls, hyponatraemia ($Na^+ < 125$ mmol/l – reported by treating clinician) and markers of poor diabetic control] (see the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/130430/#; accessed 7 May 2020). There were only small differences in the rates of thrombotic and bleeding events (*Table 14*) despite concerns that fluoxetine might affect platelet function and interact with antithrombotic medications.

We also carried out a safety analysis, which analysed patients according to the treatment they received rather than the treatment they were allocated. These data are provided in *Report Supplementary Material 3*. The other secondary outcomes (fatigue, mood, HRQoL and SIS) are compared in *Tables 15* and *16*. Those treated with fluoxetine had better mood measured on the MHI-5 at the 6-month follow-up than those allocated placebo [median 76 (IQR 60–88) vs. 72 (IQR 56–88); $p = 0.010$]. This is consistent with the

TABLE 12 Effect of fluoxetine on the primary outcome in patients after exclusion of ineligible patients, and those with different degrees of non-adherence (see *Table 9*)

Groups cumulatively excluded	Number remaining in fluoxetine group	Number remaining in placebo group	COR for mRS	95% CI	*p*-value
None: as per intention-to-treat analysis	1553	1553	0.951	0.839 to 1.079	0.439
Ineligible: did not meet all inclusion criteria	1548	1547	0.949	0.837 to 1.077	0.418
Received no study medication after randomisation	1540	1540	0.948	0.835 to 1.076	0.406
Received < 90 days of study medication owing to failure to follow trial procedures	1480	1474	0.958	0.842 to 1.090	0.514
Received < 90 days of study medication owing to patient/carer/doctor choice	1405	1359	0.912	0.797 to 1.042	0.175
Received < 90 days of study medication owing to suspected adverse reaction	1262	1237	0.936	0.813 to 1.078	0.360
Allocated placebo but received SSRI for > 10 days within 90 days	1262	1216	0.923	0.801 to 1.064	0.268
Allocated fluoxetine and received SSRI for > 10 days within 90 days	1239	1216	0.927	0.804 to 1.068	0.294
Received < 150 days of study medication unless died earlier still taking study medication	1122	1092	0.888	0.765 to 1.032	0.121
Received < 150 days of study medication for any reason including death	1051	1039	0.921	0.788 to 1.075	0.296

TABLE 13 Safety outcomes at 6 months

Adverse events by 6 months	Allocated treatment, *n* (%)		Difference (%)	95% CI (%)	*p*-value
	Fluoxetine	Placebo			
Epileptic seizures	58 (3.71)	40 (2.56)	1.15	−0.07 to 2.37	0.065
Fall with injury	120 (7.67)	94 (6.01)	1.66	−0.11 to 3.43	0.066
Fractured bone	45 (2.88)	23 (1.47)	1.41	0.38 to 2.43	0.007
Hyponatraemia Na^+ < 125 mmol/l	22 (1.41)	14 (0.90)	0.51	−0.24 to 1.26	0.181
Hyperglycaemia	23 (1.47)	16 (1.02)	0.45	−0.33 to 1.22	0.260
Symptomatic hypoglycaemia	23 (1.47)	13 (0.83)	0.64	−0.11 to 1.39	0.094
New depression	210 (13.43)	269 (17.21)	−3.78	−6.30 to −1.26	0.003
New antidepressant prescription	280 (17.90)	357 (22.84)	−4.94	−7.76 to −2.12	0.001
Attempted/actual suicide	3 (0.19)	2 (0.13)	0.06	−0.02 to 0.34	0.655

TABLE 14 Recurrent strokes, thrombotic and haemorrhagic events by 6 months

Adverse events by 6 months	Allocated treatment, *n* (%)		Difference (%)	95% CI (%)	*p*-value
	Fluoxetine	Placebo			
Any stroke	56 (3.58)	64 (4.09)	−0.51	−1.86 to 0.83	0.454
All thrombotic events	78 (4.99)	92 (5.89)	−0.90	−2.49 to 0.69	0.268
Ischaemic stroke	43 (2.75)	45 (2.88)	−0.13	−1.29 to 1.03	0.826
Other thrombotic events	20 (1.28)	27 (1.73)	−0.45	−1.30 to 0.40	0.303
Acute coronary events	15 (0.96)	23 (1.47)	−0.51	−1.28 to 0.26	0.191
All bleeding events	41 (2.62)	38 (2.43)	0.19	−0.91 to 1.29	0.735
Haemorrhagic stroke	7 (0.45)	9 (0.58)	−0.13	−0.60 to 0.37	0.615
Upper gastrointestinal bleed	21 (1.34)	16 (1.02)	0.32	−0.44 to 1.08	0.409
Other major bleeds	13 (0.83)	14 (0.90)	−0.06	−0.71 to 0.58	0.845

TABLE 15 Secondary outcomes at 6 months: fatigue, mood and HRQoL

Outcome	Allocated treatment						*p*-value (Mann–Whitney *U*-test)
	Fluoxetine			Placebo			
	Missing (*n*)	Median	IQR	Missing (*n*)	Median	IQR	
Vitality subscale of SF-36	19	56.25	37.5–75.00	21	56.25	43.75–56.25	0.673
MHI-5	26	76.00	60.00–88.00	22	72.00	56.00–88.00	0.010
EQ-5D-5L	12	0.56	0.21–0.74	4	0.56	0.19–0.75	0.587

Patients who had died are excluded from the missing data. Higher values are associated with better outcome.

TABLE 16 Secondary outcomes at 6 months: SIS

	Allocated treatment						
	Fluoxetine			Placebo			*p*-value (Mann–Whitney *U*-test)
SIS domain	Missing (*n*)	Median	IQR	Missing (*n*)	Median	IQR	
Strength	13	56.25	31.25–81.25	14	62.50	37.50–81.25	0.701
Hand ability	14	45.00	0.00–90.0	18	50.00	0.00–90.00	0.482
Mobility	9	63.89	36.11–86.11	7	63.89	33.33–88.89	0.549
Motor	12	54.86	27.31–83.33	13	56.78	28.75–82.64	0.513
Daily activities	11	62.50	37.50–90.00	13	65.00	35.00–90.00	0.624
Physical function	11	56.77	30.38–84.31	12	58.82	30.56–84.10	0.515
Memory	23	82.14	57.14–96.43	18	82.14	57.14–96.43	0.307
Communication	12	89.29	67.86–100	11	92.86	71.43–100.0	0.192
Emotion	42	75.00	58.33–88.89	29	75.00	58.33–88.89	0.469
Participation	12	62.50	37.50–87.50	15	65.63	40.63–87.50	0.260
Recovery (VAS)	16	60.00	40.00–80.00	9	60.00	40.00–80.00	0.982

VAS, visual analogue scale.
Patients who had died are excluded from the missing data. Higher values are associated with better outcome.

lower rate of new episodes of depression that we observed. There were no statistically significant differences in any other secondary outcomes at 6 months, including any of the nine domains of the SIS, the vitality subscale of the SF-36 and the EQ-5D-5L.

The number and percentage of patients in each mRS category at the 12-month follow-up by treatment group is shown in *Table 17*. An ordinal comparison of the distribution of patients across the mRS at 12 months, adjusted for variables included in the minimisation algorithm, was similar in the two groups (COR 1.015, 95% CI 0.894 to 1.151; $p = 0.820$), where a COR in favour of placebo is < 1.0. The unadjusted analysis provided similar results (COR 1.011, 95% CI 0.892 to 1.145; $p = 0.866$). When

TABLE 17 Distribution of mRS categories at 12-month follow-up

	Allocated treatment, *n* (%)	
mRS at 12 months	Fluoxetine	Placebo
0	133 (8.64)	145 (9.39)
1	251 (16.31)	237 (15.35)
2	178 (11.57)	175 (11.33)
3	494 (32.10)	505 (32.71)
4	90 (5.85)	81 (5.25)
5	211 (13.71)	203 (13.15)
6 (dead)	182 (11.83)	198 (12.82)
Missing mRS	25	19
Total number of patients randomised	1564	1563

comparing the mRS dichotomised into 0–2 and 3–6, there was similarly little difference between the groups (adjusted OR 1.033, 95% CI 0.879 to 1.215; $p = 0.691$; unadjusted OR 1.019, 95% CI 0.880 to 1.181; $p = 0.799$).

The survival of patients in the two treatment groups is compared in *Figure 4*. Anyone who died after 1 year was considered to be alive and censored at 365 days and any participant who withdrew consent was considered to be alive and was censored at the time of withdrawal. There was no statistically significant difference in the hazards of death over the first 12 months after randomisation (HR 0.929, 95% CI 0.756 to 1.141; $p = 0.482$) adjusted for baseline variables.

Table 18 shows the number of patients with a new episode of depression or who had started an antidepressant between randomisation and 12 months. 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. More patients had been started on antidepressants in the placebo group than in the fluoxetine group, but some were started on antidepressants for indications other than depression.

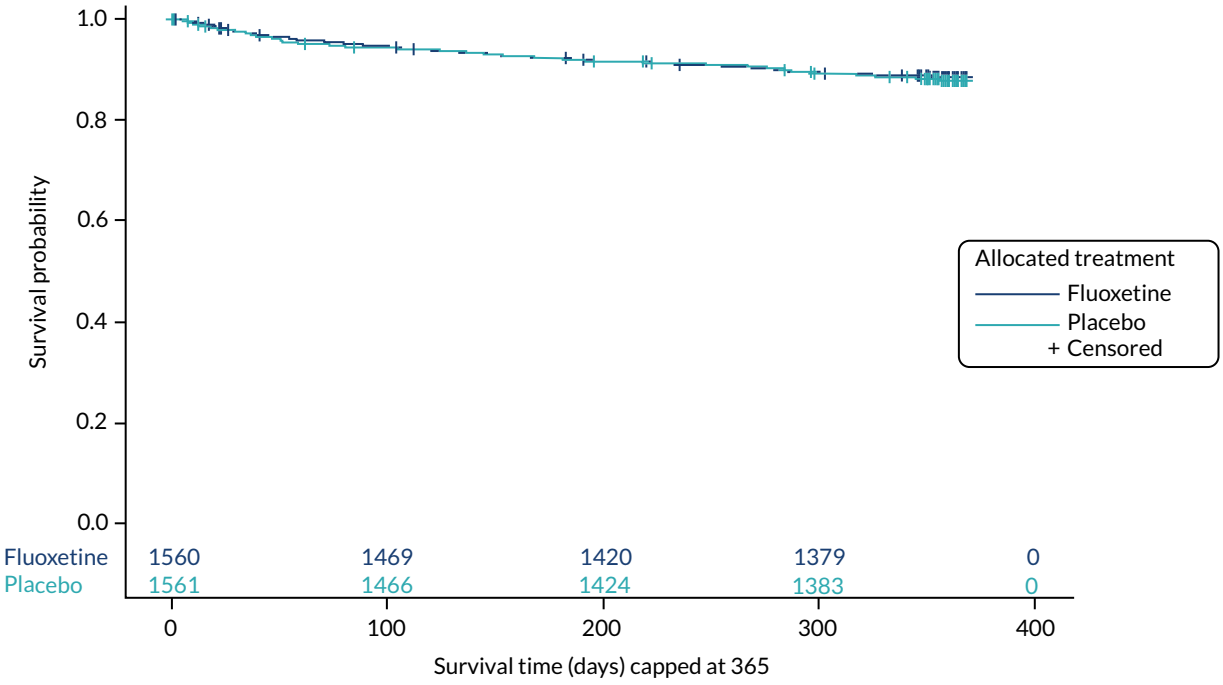

FIGURE 4 The Kaplan–Meier survival curves for the two allocated treatments with number of subjects at risk. Times have been capped at 365 days. Reproduced from the FOCUS trial collaboration.[55] © 2018 The Author(s). Published by Elsevier Ltd. This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) license. See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

TABLE 18 New depression and new antidepressant medication by 12 months

	Allocated treatment, *n* (%)				
Outcome by 12 months	**Fluoxetine**	**Placebo**	**Difference (%)**	**95% CI (%)**	***p*-value**
New depression	292 (18.67)	327 (20.92)	−2.25	−5.04 to 0.54	0.114
New antidepressant prescription	358 (22.89)	410 (26.23)	−3.34	−6.36 to −0.33	0.030

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The difference in MHI-5 scores between the groups at 6 months was not sustained at 12 months (*Table 19*), and there were no statistically significant differences between treatment groups in vitality or HRQoL at 12 months.

The SIS scored in the two treatment groups at 12 months is shown in *Table 20*. There was little difference between the treatment groups on any of the domains.

TABLE 19 Secondary outcomes at 12 months: fatigue, mood and HRQoL

	Allocated treatment						*p*-value (Mann–Whitney *U*-test)
	Fluoxetine			Placebo			
Outcome	Missing (*n*)	Median	IQR	Missing (*n*)	Median	IQR	
Vitality subscale of SF-36	31	50.00	37.50–75.00	35	50.00	37.50–75.00	0.904
MHI-5	34	72.00	56.00–88.00	36	76.00	56.00–88.00	0.711
EQ-5D-5L excluding dead patients	18	0.59	0.24–0.75	13	0.59	0.27–0.77	0.309

Higher values are associated with better outcome.

TABLE 20 Secondary outcomes at 12 months: SIS

	Allocated treatment						*p*-value (Mann–Whitney *U*-test)
	Fluoxetine			Placebo			
SIS domain	Missing (*n*)	Median	IQR	Missing (*n*)	Median	IQR	
Strength	35	56.25	31.25–75.00	31	56.25	37.50–75.00	0.384
Hand ability	34	50.00	0.00–90.00	33	50.00	5.00–90.00	0.281
Mobility	28	66.67	36.11–88.89	29	66.67	38.89–88.89	0.543
Motor	33	55.56	28.80–83.33	31	58.61	31.20–83.70	0.329
Daily activities	30	67.50	40.00–90.00	33	67.50	40.00–90.00	0.581
Physical function	30	57.81	32.81–84.24	31	60.10	33.54–85.28	0.372
Memory	33	78.57	60.71–96.43	32	82.14	57.14–96.43	0.425
Communication	32	89.29	67.86–100.0	29	89.29	71.43–100.0	0.314
Emotion	46	72.22	58.33–86.11	44	73.61	58.33–88.89	0.744
Participation	32	65.63	40.63–90.63	33	65.63	40.63–90.63	0.930
SIS recovery (VAS)	24	60.00	40.00–80.00	24	60.00	40.00–80.00	0.933

VAS, visual analogue scale.
Higher values are associated with better outcome.

We assessed the effect of treatment among the subgroup with motor deficit at baseline ($n = 2722$) and among those who had a mRS at 6 months ($n = 2702$) but found no evidence of an effect on the mRS ($p = 0.2172$). Of the 2722 participants who had a motor deficit at baseline, 2438 had a motor score outcome [fluoxetine median 48.43 (IQR 24.98–78.84) vs. placebo median 52.66 (IQR 25.28–77.22); $p = 0.471$]. In addition, in the 906 patients with aphasia at baseline, 899 had a mRS at 6 months and 794 had a SIS communication domain score at 6 months. There was little difference in the mRS (see *Table 11*) or SIS communication scores between the treatment groups [fluoxetine median 64.29 (IQR 32.14–89.29) vs. placebo 64.29 (IQR 35.71–89.29); $p = 0.497$].

Chapter 5 Results 3: post hoc analyses to better understand the observed effect of fluoxetine on the risk of bone fractures

Introduction

The statistically significant excess of bone fractures (see *Table 13*) that we observed is potentially important for several reasons. First, many observational studies have demonstrated an association between SSRI use and fractures.[27,28] However, the question of whether or not this association is causal has remained. RCTs provide stronger evidence of causality than any other research method. Second, if fractures affect patients' functional outcomes, then this excess might have offset some beneficial effects of fluoxetine on functional outcomes. Third, if SSRIs, and fluoxetine specifically, cause fractures, the following question arises: what are the mechanisms by which they have this effect? Is it owing to an increased risk of falling, which could be through several possible mechanisms, or the proposed effects of SSRIs on bone density, or both, or neither?

We have, therefore, carried out some post hoc analyses in an attempt to answer the following questions:

- What sort of fractures occurred after stroke and were they likely to have had an impact on patients' function?
- Might the increased risk of fractures, along with their associated loss of function, have offset the beneficial effects of fluoxetine on neurological recovery?
- What baseline factors were associated with fracture risk?
- Does the temporal pattern of fractures in the FOCUS trial provide any useful information about the relative importance of the potential mechanisms of SSRI-induced fractures?

Methods

We have published a brief account of further analyses and results that attempts to address these questions.[59] We extracted further information from our trial database while remaining blind to treatment allocation. Here we present the post hoc analyses in more detail. Having identified the excess risk of bone fractures in our prespecified analyses,[52] we also prespecified further analyses to address our additional research questions about fractures. We coded baseline medications to distinguish non-SSRI antidepressants, blood pressure lowering, bone density reducing (e.g. glucocorticoids) or bone density increasing (e.g. calcium, vitamin D and bisphosphonates) medications and those that might increase risk of falls (e.g. tranquillisers). In addition, we extracted available data on the fracture site and any associated falls or seizures. We had not systematically collected data that indicated the side of the body where fracture(s) occurred. We compared the number of fractures occurring in those with and without specific characteristics but formally tested each variable by plotting Kaplan–Meier survival curves in those with and without each characteristic and compared these with the log-rank statistic. We did not formally test differences in fracture risk where numbers were small (i.e. fewer than six). We included all variables with a p-value of < 0.1 into a Cox proportional hazards model to identify independent predictors of fracture risk. We repeated these analyses focusing on fractures only at sites typically associated with low bone density (i.e. neck of femur, wrist and vertebrae).

Results

Type of fractures

In our original published analysis of fractures,[55] we included 68 patients with at least one fracture each (see *Table 13*), where the fracture had been diagnosed on radiography after randomisation. However, in three patients, on reviewing all of the evidence, the fracture had probably occurred before randomisation. We excluded these patients (two from the fluoxetine group and one from the placebo group) from further analyses. Sixty-five of the 3127 (2.1%) patients who were enrolled had 67 definite new fractures (two patients sustained more than one fracture simultaneously) within 6 months of randomisation. The differences in fracture risk between the fluoxetine and the placebo group remained statistically significant (in a univariate analysis) having removed the three patients [43 (2.75%) vs. 22 (1.41%); difference 1.34%, 95% CI 0.34% to 2.34%; $p = 0.009$]. Among the 65 patients with fractures, 59 (90.8%) fractures resulted from a fall. The sites of the fractures are shown in *Table 21*; 26 patients (40%) had a neck of femur fracture, which was quite likely to have had an impact on patients' functional outcome.

Effect of removing the patients with fracture from estimates of effect on modified Rankin Scale

Removing the 65 patients with at least one fracture during follow-up from the primary analysis (ordinal imbalance) did not significantly alter the estimate of effect of fluoxetine on the mRS (COR including those with fractures 0.951, 95% CI 0.839 to 1.079; $p = 0.439$; COR for those without fractures 0.961, 95% CI 0.847 to 1.093; $p = 0.545$).[59]

Risk factors for fractures

Those who had a fracture within 6 months were older [mean age 76 (SD 12.2) vs. 71 (SD 11.6) years, difference 4.9 years, 95% CI for difference 2.0 to 7.9 years; $p = 0.001$] and had slightly more severe strokes [median NIHSS 7.0 (IQR 4–11) vs. 6.0 (IQR 3–11); $p = 0.407$]. The numbers (%) of patients with specific baseline characteristics divided into those with and without subsequent fractures are shown in *Table 22*, along with the *p*-value for the difference based on the log-rank analysis of the Kaplan–Meier curves. The differences were statistically significant only between those aged > 70 years and younger patients, between women and men and between those allocated to fluoxetine and those allocated to

TABLE 21 The site of fractures and associated events occurring between randomisation and 6-month follow-up

Fracture-related outcome	Number	%
Number of patients sustaining a fracture	65	
Number of fractures sustained	67	100.0
Site of fracture		
Neck of femur	26	40.0
Vertebral	10	15.4
Any long bone	10	15.4
Wrist	7	10.8
Rib	4	6.2
Pelvis	3	4.6
Clavicle	1	1.5
Other (e.g. skull and patella)	6	9.2
Site associated with osteoporosis	40	61.5
Associated with a fall	59	90.8
Associated with an epileptic seizure	1	1.5

TABLE 22 The number and percentage with each baseline characteristic in those patients with and without a fracture within 6 months of randomisation

Characteristic	Fracture by 6 months, *n* (%)		Log-rank statistic
	No	Yes	
Total number of patients randomised	3062 (100.0)	65 (100.0)	
Randomised treatment			
Fluoxetine	1521 (49.7)	43 (66.2)	0.008
Placebo	1541 (50.3)	22 (33.9)	
Sex			
Female	1167 (38.1)	38 (58.5)	0.001
Male	1895 (61.9)	27 (41.5)	
Age group (years)			
≤ 70	1313 (42.9)	17 (26.2)	0.003
> 70	1749 (57.1)	48 (73.9)	
Before the stroke			
Dependent in ADL	253 (8.3)	8 (12.3)	0.176
Ischaemic stroke/TIA	557 (18.2)	11 (16.9)	0.882
Diabetes	628 (20.5)	12 (18.5)	0.760
Bone fractures	486 (15.9)	11 (16.9)	0.829
Depression	244 (8.0)	9 (13.9)	0.091
Stroke type			
Intracerebral haemorrhage	301 (9.8)	10 (15.4)	0.132
Stroke deficits at baseline			
Unable to walk	2227 (72.7)	53 (81.5)	0.085
Unable to lift both arms	1243 (40.6)	25 (38.5)	0.870
Unable to talk	779 (25.4)	18 (27.7)	0.520
Motor deficit on NIHSS	2665 (87.0)	57 (87.7)	0.797
Visual field deficit on NIHSS	844 (27.6)	14 (21.5)	0.326
Limb ataxia on NIHSS	753 (24.6)	17 (26.2)	0.832
Baseline medications			
Non-SSRI antidepressant	137 (4.5)	5 (7.7)	
Treatments for osteoporosis	287 (9.4)	5 (7.7)	
Major or minor tranquillisers	121 (4.0)	3 (4.6)	
Parkinson's disease medication	14 (0.5)	2 (3.1)	
BP-lowering medication	2178 (71.1)	52 (80.0)	0.100
Treatments for vertigo	129 (4.2)	5 (7.7)	
Any of these drugs of interest	2349 (76.7)	55 (84.6)	0.116

ADL, activities of daily living; BP, blood pressure.

Notes

The log-rank statistic tests the statistical significance of the difference in Kaplan–Meier survival curves (measuring time to fracture) between those with and without these characteristics. No log-rank test was carried out where the characteristic was present in fewer than six patients.

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placebo. Medical history including prior fractures, stroke pathology, NIHSS, type of deficit and medications of different types had no statistically significant associations with fracture risk. Previous depression and being able to walk at the time of the stroke did not reach the 5% level of significance; however, they were included in our Cox proportional hazards model as they were approaching significance ($p < 0.1$).

The Cox proportional hazards model with all those variables reaching and approaching statistical significance is shown in *Table 23*.

When those variables that do not reach statistical significance at the 5% level are sequentially removed, the resulting Cox model (*Table 24*) contained just three variables: sex, age group and randomised treatment.

The Cox proportional hazards model (see *Table 23*) showed that only age of > 70 years (HR 1.97, 95% CI 1.13 to 3.45; $p = 0.017$), female sex (HR 2.131. 95% CI 1.294 to 3.511; $p = 0.003$) and fluoxetine treatment (HR 2.00, 95% CI 1.196 to 3.344; $p = 0.008$) were independent predictors of fracture. The model was almost identical when only those with fractures at sites likely to be affected by osteoporosis (i.e. neck of femur, vertebral and wrist) were included.

Temporal pattern of fractures

The Kaplan–Meier curve comparing fracture risk in the two treatment groups is shown in *Figure 5*. The risks appear to diverge early after randomisation, which might suggest that an increased risk of falling associated with taking fluoxetine contributed to the excess of fractures. A delayed divergence might have suggested that the excess was mainly owing to effects on bone density, which presumably would not have occurred immediately.

TABLE 23 Cox proportional hazards model with all variables reaching or approaching statistical significance in univariate analysis (see *Table 22*)

Parameter	Value	Probability > χ^2	HR	HR 95% CI
Sex	Female	0.008	1.978	1.193 to 3.280
Age group	> 70 years	0.018	1.973	1.123 to 3.467
Previous depression	No/unknown	0.135	0.581	0.285 to 1.184
Able to walk	No	0.240	1.462	0.776 to 2.755
Randomised treatment	Fluoxetine	0.009	1.992	1.191 to 3.330

TABLE 24 Final Cox proportional hazards model showing factors predictive of a fracture

Parameter	Value	Probability > χ^2	HR	HR 95% CI
Sex	Female	0.003	2.131	1.294 to 3.511
Age group	> 70 years	0.017	1.972	1.127 to 3.451
Randomised treatment	Fluoxetine	0.008	2.000	1.196 to 3.344

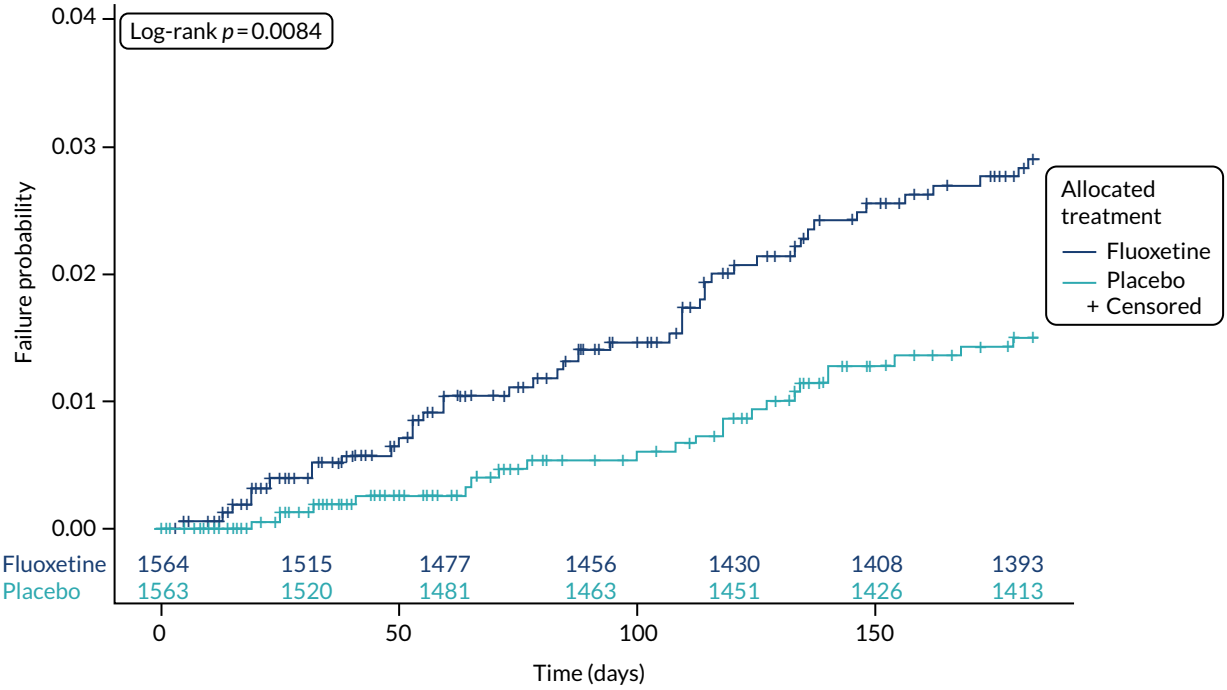

FIGURE 5 Kaplan–Meier curves to 6 months, with number of subjects at risk, comparing the risk of fracture in those allocated fluoxetine and placebo where patients dying or being lost to follow-up were censored. Reproduced from Dennis *et al.*[59] © American Heart Association, Inc.

Chapter 6 Results 4: health economic evaluation

Introduction

We undertook a within-trial economic analysis to estimate the cost-effectiveness of fluoxetine on an intention-to-treat basis. The primary treatment effect in the economic analysis was estimated using an individual-level regression model for average (mean) incremental costs and incremental survival times over 12 months after randomisation.

Methods

Resource use and costs

The number and duration of hospital stays and other secondary care contacts were recorded using information obtained from the case report form. We had planned to use data from NHS Digital in England and Wales, and from eDRIS for patients recruited in Scotland, but we were unable to obtain these data in time to produce analyses that could be included in this report.

Unit costs and analysis

We converted length-of-stay distributions into cost estimates based on a per-diem hospital cost. Resource use was valued from the perspective of the NHS using the 2017/18 and 2018/19 national tariffs with currencies and prices for 2018.[60] Per-diem hospital costs were derived using tariff information for Healthcare Resource Group codes AA22C to AA22G (Cerebrovascular Accident, Nervous System Infections or Encephalopathy) with varying levels of complexity and complications.[60] Our base case simulated unit costs using a gamma distribution around a mean of £515 per day with higher unit costs for the first 2 days to allow for conditional payments (best-practice tariffs) for acute stroke care (i.e. direct admissions to an acute stroke unit, initial brain imaging and thrombolysis assessment). We also considered other cost distributions, including the application of trim points for lengths of hospital stay beyond 63 days with lower unit costs of £240 per day. The results from the sensitivity analysis were quantitatively and qualitatively similar to those of the base-case analysis, so are not reported. Other secondary care contacts were costed using corresponding currencies and prices from the national tariff. The NHS indicative price for 20-mg capsules of fluoxetine was £2.27 for 30 capsules.[61] No discounting of resource costs was conducted as the time horizon was limited to 12 months for within-trial analysis.

Health outcomes

Survival times for the first 12 months after randomisation were measured in days, with anyone alive at 365 days being censored. Self-reported HRQoL at 6 and 12 months of follow-up was measured using the EQ-5D-5L preference-based scale. The EQ-5D-5L index values were calculated using English value sets. We also validated the EQ-5D-5L by checking the concordance with the mRS. We planned to use a standard multiplicative model to estimate quality-adjusted survival (QALYs) calculated by the area under linear interpolation of the EQ-5D-5L index value trajectory for each individual with survival times, the EQ-5D-5L utility index value at 6 and 12 months and a modelled baseline EQ-5D-5L utility index value. If no group differences in the EQ-5D-5L emerged, QALYs would not be estimated and the analysis would focus on any difference in survival days.

Cost-effectiveness model specification

The primary treatment effect in the economic analysis was estimated using an individual-level regression model for average (mean) incremental costs and incremental survival times over 12 months after randomisation. The model accounts for the joint distribution of costs and survival times using a general specification that allowed for different parametric and conditional distributions. Incremental cost-effectiveness ratios (ICERs) are reported for the difference in mean total costs between treatment groups divided by the difference in mean number of survival days between treatment groups. All analyses were based on cases with complete information on resource use and survival times.

Sensitivity analysis

Mean costs and survival times and differences between intervention treatment groups in costs and survival times were based on a bootstrapped analysis using 1000 (and 10,000) replicates. Uncertainty in the ICER was visually represented as a cost-effectiveness plane. Incremental net benefits and cost-effectiveness acceptability curves were not calculated if the ICER was centred on zero (i.e. no difference in mean costs and survival times). We conducted a companion analysis of cost-effectiveness in which we truncated the cumulative cost distribution at 6 months and estimated the incremental costs in relation to incremental differences in the primary outcome (mRS at 6 months).

Long-run economic analysis and assessment of treatment effect heterogeneity

Longer-run modelling, estimating the distribution of costs and quality-adjusted survival times calculated over the expected patient lifetimes, was planned if differences in the primary outcome emerged between treatment groups at 6 months. Our intention was to use a microsimulation model calibrated using information gained from the within-trial analysis of cost-effectiveness combined with additional data from (1) Assessment oF FluoxetINe In sTroke recoverY (AFFINITY) and EFFECTS,[62] (2) trials and observational studies reporting longer-term costs, survival and HRQoL following stroke, and (3) expert beliefs on the distributions of parameters where information was less readily available.

Secondary analyses are planned to address heterogeneous treatment effects using the pooled individual-level data from FOCUS, AFFINITY and EFFECTS.[62] Subpopulations with different average treatment effects will be identified using 'regression tree' or 'recursive partitioning' methods. These data-driven analyses complement prespecified subgroup analyses examining individual and group covariates of substantive interest, such as stroke severity (NIHSS) and the six simple variable model for prognosis.[31]

Results

Resource use and cost analysis

Hospital inpatient use and attendances and duration of fluoxetine therapy are reported in *Table 25*. At 12 months, the average number of inpatient hospital days was just over 30 days for both treatment groups, with little difference in the average number of hospital attendances. Fluoxetine therapy lasted 143 days on average, with a median of 6 months. The distributions of cumulative total costs (*Table 26*)

TABLE 25 Hospital resource use within 12 months of randomisation by allocated treatment

	Allocated treatment			
	Fluoxetine ($n = 1556$)		Placebo ($n = 1553$)	
Resource use	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Hospital inpatient days	32 (39)	16 (5–46)	31 (39)	15 (4–43)
Hospital attendances	0.343 (0.582)	0 (0–1)	0.338 (0.605)	0 (0–1)
Fluoxetine therapy (days)	143 (64)	182 (101–186)	0	0

TABLE 26 Cumulative health-care total costs within 12 months of randomisation by allocated treatment

	Allocated treatment			
	Fluoxetine ($n = 1548$)		Placebo ($n = 1553$)	
Cost (£)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Hospital inpatient days	18,561 (20,502)	10,870 (5113–26,195)	18,137 (20,214)	10,632 (4805–24,855)
Hospital attendances	162 (277)	0 (0–405)	159 (289)	0 (0–397)
Fluoxetine therapy	11 (5)	14 (8–14)	0	0
Total costs	18,784 (20,504)	11,150 (5231–26,400)	18,297 (20,201)	10,871 (5129–24,855)

were similar between the groups, with mean total costs of £18,784 (median £11,150) for patients allocated to fluoxetine and £18,297 (median £10,871) for patients allocated to placebo.

Health outcomes

Mean survival times up to 12 months were 334 days (11 months) for both treatment groups. The pattern and distribution of EQ-5D-5L dimensions and levels were similar at 6 months, with little change at 12 months (*Table 27*). The frequency of 'no problems' (i.e. level 1) and 'problems' (i.e. levels 2 to 5) across the five dimensions at 6 months revealed a slight advantage in mobility and usual activity for the placebo group and less anxiety and depression in the fluoxetine group. These differences diminished by 12 months. The 10 most frequent EQ-5D-5L profiles accounted for around one-fifth of profiles and there was a high degree of concordance between treatment groups at 6 and 12 months (*Table 28*). EQ-5D-5L index values averaged around 0.47 at 6 months with no significant difference between the treatment groups; at 12 months, there was a slight increase in the mean index value to 0.50 but no sign of difference between patients allocated to fluoxetine or placebo (*Table 29*). Given the similar survival trajectories and EQ-5D-5L index values up to 12 months, there is no evidence of a difference in quality-adjusted survival times.

Cost-effectiveness

Table 30 and *Figure 6* present the cost-effectiveness results at 12 months. Although there is a slight difference of around £500 in the mean total costs and a very small increase (< 1 day) in survival times for the fluoxetine group, neither of these differences are significant. The ICER of £2609 per day is not significantly different from zero, as illustrated in the cost-effectiveness plane (see *Figure 6*). The joint distribution of incremental costs and incremental survival days is essentially centred on zero.

Finally, given the statistically significant increase in fracture risk at 6 months in the fluoxetine group, exploratory analysis suggests that this is likely to account for around 37% of the difference in mean total costs reported above as patients who sustained a fracture reported a £13,330 (95% CI £8453 to £18,207) increase in mean total costs at 12 months.

TABLE 27 Distribution of EQ-5D-5L dimensions and levels at 6 and 12 months by allocated treatment

		6 months (%)			12 months (%)		
		Allocated treatment			Allocated treatment		
Dimension	Level	Fluoxetine ($n = 1413$)	Placebo ($n = 1422$)	Total ($N = 2835$)	Fluoxetine ($n = 1339$)	Placebo ($n = 1333$)	Total ($N = 2672$)
Mobility	No problems	17.8	21.4	19.6	19.5	21.5	20.5
	Slight problems	23.4	22.9	23.1	24.5	22.7	23.6
	Moderate problems	24.6	23.0	23.8	25.7	26.0	25.9
	Severe problems	17.5	17.5	17.5	16.1	15.8	15.9
	Unable to	16.8	15.2	16.0	14.3	13.9	14.1
Self-care	No problems	37.1	37.1	37.1	37.9	39.4	38.7
	Slight problems	19.4	19.8	19.6	21.4	20.5	20.9
	Moderate problems	19.3	18.0	18.7	18.8	16.1	17.4
	Severe problems	8.5	8.2	8.4	7.5	9.1	8.3
	Unable to	15.7	16.8	16.3	14.4	15.0	14.7
Usual activity	No problems	14.8	17.3	16.1	17.9	17.5	17.7
	Slight problems	22.1	21.6	21.8	21.1	25.2	23.2
	Moderate problems	20.2	18.5	19.4	22.8	19.7	21.3
	Severe problems	13.4	14.5	13.9	13.8	13.7	13.7
	Unable to	29.5	28.1	28.8	24.4	23.9	24.1
Pain/ discomfort	No pain	36.4	37.2	36.8	35.8	36.7	36.2
	Slight pain	29.3	28.3	28.8	30.8	33.3	32.1
	Moderate pain	24.6	24.1	24.3	23.1	21.5	22.3
	Severe pain	7.9	8.0	7.9	7.5	6.8	7.2
	Extreme pain	1.9	2.3	2.1	2.8	1.7	2.2
Anxiety/ depression	Not anxious	53.4	49.0	51.2	45.6	47.6	46.6
	Slightly anxious	25.3	26.9	26.1	34.6	31.7	33.1
	Moderately anxious	16.0	17.7	16.8	14.4	15.8	15.1
	Severely anxious	3.9	4.7	4.3	3.9	3.7	3.8
	Extremely anxious	1.4	1.8	1.6	1.6	1.4	1.5

TABLE 28 The 10 most frequent EQ-5D-5L profiles at 6 and 12 months by allocated treatment

	Allocated treatment							
	Fluoxetine				Placebo			
Rank	EQ-5D-5L profile	*n*	%	% (cumulative)	EQ-5D-5L profile	*n*	%	% (cumulative)
Analysis at 6 months								
1	1 1 1 1 1	90	6.3	6.3	1 1 1 1 1	105	7.4	7.4
2	2 1 2 1 1	34	2.4	8.7	1 1 2 1 1	33	2.3	9.7
3	2 1 2 2 1	30	2.1	10.8	2 1 2 1 1	31	2.2	11.9
4	5 5 5 1 1	29	2.0	12.8	1 1 1 2 1	27	1.9	13.7
5	1 1 2 1 1	27	1.9	14.7	2 1 2 2 1	23	1.6	15.4
6	2 1 1 1 1	25	1.8	16.5	5 5 5 1 1	21	1.5	16.8
7	1 1 1 2 1	17	1.2	17.7	2 2 2 1 1	19	1.3	18.2
8	5 5 5 2 1	16	1.1	18.8	5 5 5 2 1	18	1.3	19.4
9	5 5 5 2 2	16	1.1	19.9	1 1 1 1 2	16	1.1	20.6
10	2 2 2 2 1	14	1.0	20.9	2 1 1 1 1	16	1.1	21.7
Total		1425	100.0			1426	100.0	
Analysis at 12 months								
1	1 1 1 1 1	105	7.7	7.7	1 1 1 1 1	102	7.6	7.6
2	1 1 1 2 1	29	2.1	9.9	1 1 2 1 1	35	2.6	10.2
3	2 1 1 1 1	25	1.8	11.7	2 1 2 2 1	32	2.4	12.6
4	1 1 2 1 1	21	1.6	13.3	1 1 1 2 1	27	2.0	14.6
5	5 5 5 2 2	21	1.6	14.8	2 1 2 1 1	26	1.9	16.5
6	2 1 2 2 1	20	1.5	16.3	5 5 5 2 2	22	1.6	18.1
7	5 5 5 3 3	20	1.5	17.8	1 1 2 1 2	20	1.5	19.6
8	2 1 2 1 1	19	1.4	19.2	2 1 1 1 1	20	1.5	21.1
9	2 2 2 2 2	19	1.4	20.6	2 1 1 2 1	17	1.3	22.4
10	2 1 2 2 2	18	1.3	21.9	1 1 2 2 1	16	1.2	23.6
Total		1357	100.0			1346	100.0	

TABLE 29 The EQ-5D-5L index values at 6 and 12 months by allocated treatment

	Allocated treatment					
	Fluoxetine		Placebo			
EQ-5D-5L index	*n*	Mean (SD)	*n*	Mean (SD)	Mean difference (95% CI)	*p*-value
6 months	1413	0.470 (0.358)	1422	0.475 (0.360)	−0.005 (−0.031 to 0.022)	0.716
12 months	1339	0.491 (0.357)	1333	0.505 (0.352)	−0.013 (−0.040 to 0.014)	0.330

TABLE 30 Cost-effectiveness results

	Allocated treatment					
	Fluoxetine		Placebo			
Outcome	*n*	Mean (SD)	*n*	Mean (SD)	Mean difference (95% CI)	*p*-value
Total costs (£)	1548	18,784 (20,504)	1553	18,297 (20,201)	487 (−947 to 1920)	0.506
EQ-5D-5L index	1339	0.491 (0.357)	1333	0.505 (0.352)	−0.013 (−0.040 to 0.014)	0.330
Survival days	1560	334 (84)	1561	334 (85)	0.19 (−5.75 to 6.13)	0.951
ICER[a]					2609 (−11,931 to 17,149)	0.725

a Incremental total cost divided by incremental number of survival days.

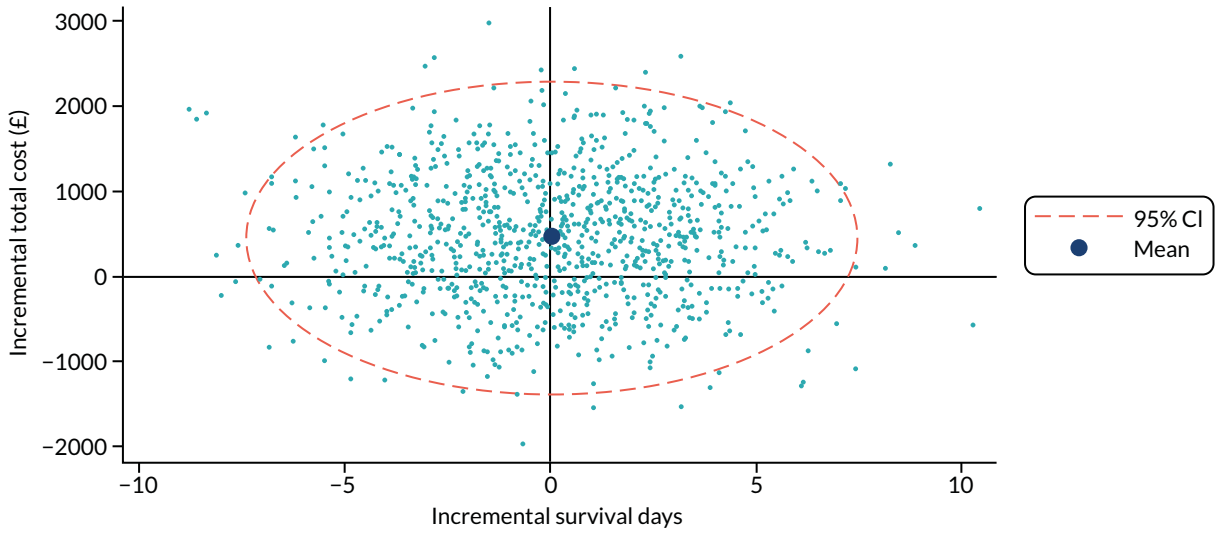

FIGURE 6 Cost-effectiveness plane with means centred.

Chapter 7 Results 5: an updated systematic review of randomised controlled trials of fluoxetine in stroke patients

Introduction

A 2012 Cochrane systematic review of SSRIs for stroke recovery[25] suggested that SSRIs, including fluoxetine, reduced disability in stroke patients even if they did not have depression, but poor methodological quality of the trials probably introduced bias. In general, systematic reviews and meta-analyses should be updated as soon as there are new studies that might change the conclusions of the review. Thus, we, in collaboration with many other individuals (see *Appendix 3*), conducted an updated meta-analysis focusing specifically on the role of fluoxetine for stroke recovery, rather than on all SSRIs. We have included the results of the FOCUS trial and any other RCTs completed since the earlier review.[25] We sought to determine whether or not fluoxetine, at any dose, given within the first year after stroke to patients who did not have to have mood disorders at randomisation, compared with usual care or placebo, reduced disability and dependency at the end of treatment, reduced neurological deficits and fatigue, and improved motor function, mood and cognition at the end of treatment and follow-up, with the same number of or fewer adverse effects. The methods and results of this updated systematic review have been published[63] and are included here to put the FOCUS trial results into context.

Methods

Protocol and registration

We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) to complete and report this study. We did not register the current review on PROSPERO as we used the same methods as the 2012 Cochrane review,[25] except for (1) including fluoxetine trials only, (2) excluding trials that require patients to have mood disorders at randomisation, (3) simplifying our sensitivity analyses by excluding trials at high or unclear risk of bias in at least one domain rather than considering each domain individually, (4) excluding trials comparing fluoxetine plus another 'active treatment' with the 'active treatment' and (5) defining incomplete outcome data reporting as systematic differences in withdrawals between groups rather than a total of > 5%. These five criteria were agreed prior to study selection and data extraction.

After study selection and data extraction, but prior to analyses, we decided to report the proportion of participants who were independent (mRS 0–2) rather than the proportion of participants who were dependent (mRS 3–5).

Random-effects models were used in the 2012 Cochrane review[25] because we assumed that the included studies would represent a random sample of the effect sizes that could be observed. Given that the large FOCUS trial[55] had systematically different results from the smaller trials, a random-effects model would have given disproportionate weight to smaller studies.[64] Therefore, we report fixed-effects models. We undertook sensitivity analyses using random-effects models and report any major differences between the two.

Eligibility criteria

- Participants: stroke in the previous year. Stroke was defined as sudden-onset focal neurological disturbance, assumed to be vascular in origin and lasting > 24 hours.[65] We excluded trials requiring patients to have a mood disorder at randomisation.

- Types of intervention: any dose of fluoxetine, any mode of delivery, given for any duration.
- Comparator group: usual care or a placebo. We excluded studies comparing fluoxetine plus another 'active treatment' with 'active treatment' alone, because of possible interactions.
- Outcomes: we prespecified two co-primary outcomes – independence or disability at the end of treatment (using any measure) – rather than the single primary outcome of independence because changes in disability (performance of activities of daily living) could be of importance to patients even without a change in overall dependence. Independence (or not) was defined as a dichotomous variable; we expected to find this commonly reported using the mRS. We anticipated disability being measured using a number of different continuous outcome measures, which we planned to combine using standardised mean differences (SMDs).
- Secondary outcomes: independence or disability at the end of follow-up. Neurological score, new depression during the trial but not based on standardised criteria, anxiety, cognition, quality of life, fatigue, health-care costs, death, motor scores, adverse events (at the end of treatment and/or at the end of follow-up), 'leaving the trial before scheduled follow-up', which included any reason other than death for missing outcome data.
- Report characteristics: we included all reports irrespective of year of publication, language and publication status. Where necessary, we sought unpublished data from authors.

Information sources

Our information sources and search strategy are described in *Appendix 2*. We screened reference lists from review articles and included papers. We contacted experts to identify additional studies.

Study selection

Duplicate references were removed using Covidence software (Melbourne, VIC, Australia; www.covidence.org). Titles and abstracts were scrutinised by two authors. Obviously irrelevant articles were excluded. Full texts of potentially relevant articles were retrieved and inclusion criteria applied by two authors. A third author was involved if there was disagreement. We included studies meeting our criteria.

Data collection process

Two reviewers independently extracted data from the new trials using Covidence. We contacted the authors if data were missing or required in a different format.

Data items

Continuous and dichotomous data were extracted. If trials reported the same number of patients at the beginning and the end, we assumed that there had been no deaths. If there was no description of how adverse events were recorded, we included any available data on adverse events, but did not assume the absence of serious adverse events unless the authors had explicitly reported this. If there was a different number of patients at the end of the trial, we extracted data on deaths and dropouts for other reasons. The denominator was the number of patients for whom a particular outcome was available.

Risk of bias of individual studies

Two authors applied the same criteria as previously.[25] We included allocation (selection bias), blinding (performance bias and detection bias), incomplete outcome data (systematic differences between groups in withdrawals from a study), selective reporting and other potential sources of bias.

Prespecified sensitivity analyses

Sensitivity analyses explored the influence of bias by excluding studies with unclear or high risk of bias across at least one key domain.[64]

Summary measures and synthesis of results

Risk ratios (RRs) were used for dichotomous data and for ordinal scales with an established cut-off point. SMDs were used for continuous data and ordinal scales with no standard cut-off point. We prespecified our interpretation of SMD: 0.2 represents a small effect, 0.5 represents a moderate effect

and 0.8 represents a large effect.[64] Unpublished data kindly provided by the authors of one trial[66] reported medians, IQRs and ranges (Dr Juan Marquez Romero, Mexican Institute of Social Security, Departmento de Neurologia Aguascalientes, Mexico, 20 September 2018, personal communication.). We estimated the mean and SD using the best available method.[67]

Risk of bias across studies

A funnel plot was used to investigate publication bias. When available, we scrutinised protocols to investigate selective reporting.

Subgroup analyses

Given that fluoxetine may be more effective when given earlier after stroke, we aimed to explore the influence of time since stroke at recruitment on our primary outcome by categorising studies as < 3 months, 3 to 6 months, 6 to 9 months and 9 to 12 months since the stroke.

Results

From the database searches, we identified 3412 references, removed 426 duplicates, screened 2988 references and assessed 499 full texts for eligibility (*Figure 7*). Three published papers had the same grant number,[68–70] very similar inclusion criteria and recruited patients from the same hospital during overlapping time periods; one appeared to be the 3-year follow-up data[70] from one of the earlier publications.[69] Thus, we included the publication with the largest number of patients reporting our prespecified outcomes[69] and categorised the other two[68,70] as 'awaiting assessment' pending further information. We identified three further new eligible trials from the database searches[66,71,72] and one by contact with experts.[73] We also included the FOCUS trial.[55]

These six new trials ($n = 3710$)[55,66,69,71–73] were added to seven eligible trials[12,16,17,74–78] ($n = 435$) identified in the 2012 Cochrane review[25] (total of 13 completed trials, $n = 4145$, *Table 31*). One further registered trial was withdrawn because it recruited no patients.[79]

Several ongoing RCTs together aim to recruit about 3775 patients.

Risk of bias

There were four high-quality trials ($n = 3283$) with a low risk of bias across important quality criteria[17,55,66,72] (*Figure 8*). One terminated early having recruited six patients, and reported no deaths.[72]

Results of studies and synthesis of results

Co-primary outcomes: independence (*Figure 9*) and disability at end of treatment (*Figure 10*)

Three trials ($n = 3249$) reported independence.[17,55,66] Fixed-effects meta-analysis found no difference in the proportion who were independent (36.6% fluoxetine vs. 36.7% control, RR 1.00, 95% CI 0.91 to 1.09; $p = 0.99$; $I^2 = 78\%$) and no difference in disability (seven trials, $n = 3404$, SMD 0.05, 95% CI −0.02 to 0.12; $p = 0.15$; $I^2 = 81\%$).

Two other trials[73,78] reported improvements in mRS in the fluoxetine group but the data were in a format that could not be used in the meta-analysis and the authors did not respond to our requests for clarification.

Random-effects models demonstrated a small but statistically significant benefit of fluoxetine for disability (SMD 0.34, 95% CI 0.04 to 0.64; $p = 0.03$; $I^2 = 81\%$), and a higher RR (RR 1.87, 95% CI 0.74

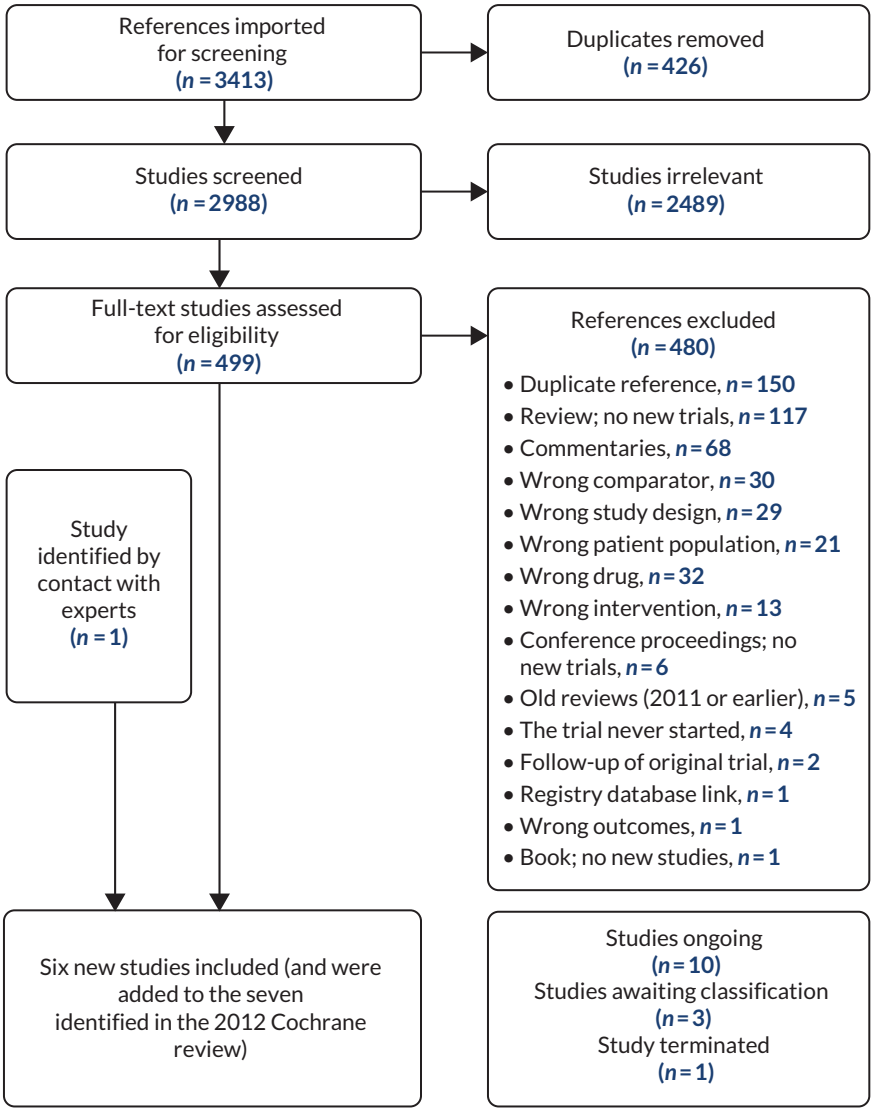

FIGURE 7 Flow diagram showing selection of studies. Reproduced from Mead *et al.*[63] *International Journal of Stroke*. Copyright © 2019 by SAGE Publications. Reprinted by permission of SAGE Publications, Ltd.

to 4.56; $p = 0.19$; $I^2 = 78\%$) of being independent than the fixed-effects models because of the greater weight given to smaller positive trials.

Secondary outcomes at the end of treatment: summary effect sizes (Table 32)

Fluoxetine was associated with better neurological scores (eight trials, $n = 803$, SMD −0.28, 95% CI −0.42 to −0.14; $p < 0.001$; $I^2 = 77\%$), lower (fewer depressive symptoms) depression scores (six trials, $n = 3113$, SMD −0.16, 95% CI −0.23 to −0.09; $p < 0.0001$; $I^2 = 92\%$), fewer diagnoses of depression (two trials, $n = 3194$, RR 0.77, 95% CI 0.65 to 0.90; $p = 0.001$; $I^2 = 53\%$) but more seizures (seven trials, $n = 3815$, 3.9% vs. 2.6%, RR 1.49, 95% CI 1.05 to 2.11; $p = 0.03$; $I^2 = 0$). Random-effects models gave broadly similar results. The FOCUS trial identified a small excess of bone fractures in the fluoxetine group, which was statistically significant (see *Table 13*). No other trial reported fractures.

End of follow-up

Two trials ($n = 2924$) reported disability at the end of follow-up (SMD 0.11, 95% CI −0.17 to 0.40; $p = 0.45$; $I^2 = 85\%$; fixed effects). Only one trial (FOCUS) reported independence at the end of follow-up; there was no difference between groups.[55]

TABLE 31 Characteristics of the RCTs that are included in this review

Study (first author and year)	Country	Participants (pathological type and time since stroke)	Number recruited	Number included at end of treatment	Dose and duration of fluoxetine	Control	Outcomes reported by the trial authors	Follow-up period
Birchenall 2019[72]	France	Stroke or brain haemorrhage, day 3 to day 15	6 (study terminated early)	6	20 mg daily for 3 months	Placebo	Several clinical and TMS measurements, death	End of treatment and at month 6
Chollet 2011[17]	France	Ischaemic stroke, 5–10 days	118	113	20 mg daily for 3 months	Matching placebo	Primary outcome: FMMS. Secondary endpoints: NIHSS, mRS and MADRS at 0, 30 and 90 days. AEs	End of treatment
Dam 1996[16]	Italy	Ischaemic stroke, 1–6 months	35	33	20 mg daily for 12 weeks	Matching placebo	HDRS, HSS (total, gait and motor scores), BI, death, AEs	End of treatment
FOCUS collaboration 2018[55]	UK	Any stroke, 2–15 days	3127	3106	20 mg daily for 6 months	Matching placebo	Primary: mRS Secondary: SIS, depression, MHI5, fatigue, EQ-5D-5L, health care costs	End of treatment and then 6 months later
He 2004[74]	China	First ever stroke, all pathological types; mean time 3.1 days in fluoxetine and 3.5 days in control	84	71	20 mg daily for 8 weeks	Usual stroke care	HAMD, SSS, AEs	End of treatment
He 2016[69]	China	Ischaemic stroke, within 1 week	374	350	20 mg daily for 90 days	Usual care	NIHSS, BI, AEs	End of treatment and at day 180
Kong 2007[75]	China	Any pathological type, within 7 days	90	73	20 mg daily for 8 weeks	Matching placebo	HAMD, BI, NIHSS Somatic side effects and hyponatraemia	End of treatment

continued

TABLE 31 Characteristics of the RCTs that are included in this review (*continued*)

Study (first author and year)	Country	Participants (pathological type and time since stroke)	Number recruited	Number included at end of treatment	Dose and duration of fluoxetine	Control	Outcomes reported by the trial authors	Follow-up period
Li 2004[76]	China	Any pathological type; mean time to recruitment was 2 days	67	67	20 mg daily for 4 weeks	Routine stroke care	HAMD, CSS; AEs in fluoxetine group	End of treatment
Marquez-Romero 2013[66]	Mexico	Intracerebral haemorrhage within 10 days	32	30	20 mg daily for 90 days	Matching placebo	Primary: FMMS, mRS Secondary: NIHSS, BI, AEs	End of treatment
Pariente 2001[12]	France	Lacunar ischaemic stroke	8	8	Single 20-mg dose	Placebo	Finger tapping and clinical scales presented only as graphs. fMRI activation location	Post treatment
Robinson 2000[77] (follow-up reported in Mikami 2011[78])	USA and Argentina	All pathological types, within 6 months	33	28	Dose increased over 3 weeks from 10 mg to 30 mg daily; total 12 weeks	Matching placebo	HDRS, mRS, FIM, MMSE, JHFI, death, AEs	End of treatment
Shah 2016[73]	India	Haemorrhagic stroke, 5–10 days after onset	89	84	10 mg for 1 week; increased to 20 mg after 1 week; total 3 months	Inert capsule 'similar' to fluoxetine	Primary outcome: FMMS mRS and AEs	End of treatment
Zhao 2011[71]	China	Stroke with aphasia, 'early treatment with fluoxetine', precise time not stated	82	71	20 mg daily for 12 weeks	Standard care	MESSS, ADL	End of treatment

ADL, activities of daily living; AE, adverse event; BI, Barthel Index; CSS, Chinese Stroke Scale; FIM, Functional Independence Measure; FMMS, Fugl-Meyer Motor Scale; fMRI, functional magnetic resonance imaging; HAMD/HDRS, Hamilton Depression Rating Scale; HSS, Hemispheric Stroke Scale; JHFI, Johns Hopkins Functioning Inventory; MADRS, Montgomery–Åsberg Depression Rating Scale; MMSE, Mini Mental State Examination; MESSS, Modified Edinburgh-Scandinavian Stroke Scale; SSS, Scandinavian Stroke Scale; TMS, transmagnetic stimulation.

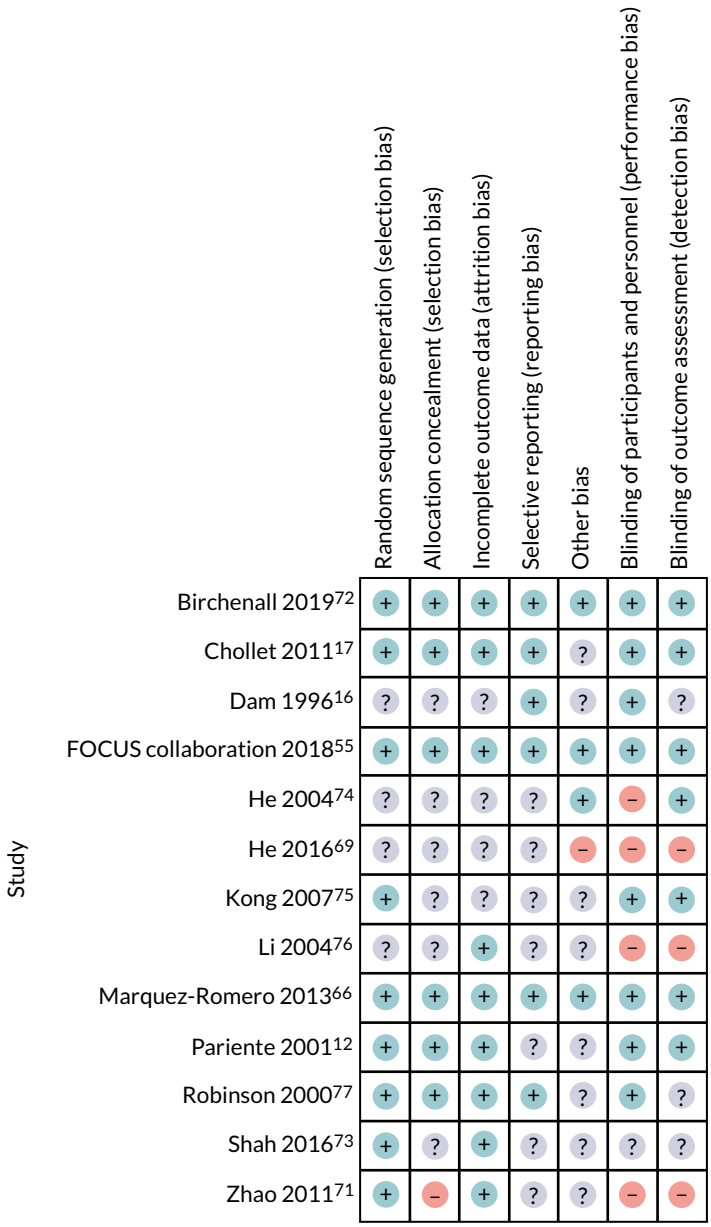

FIGURE 8 Risk of bias. +, low risk of bias; ?, unclear risk of bias; –, high risk of bias. Reproduced from Mead *et al.*[63] *International Journal of Stroke*. Copyright © 2019 by SAGE Publications. Reprinted by permission of SAGE Publications, Ltd.

Sensitivity analyses: high-quality trials at low risk of bias only (Table 33) *(fixed effects)*

The fixed-effects models found a small but statistically significant effect on depression scores at the end of treatment (two trials, $n = 2861$, SMD −0.11, 95% CI −0.19 to −0.04; $p = 0.002$; $I^2 = 69\%$). Random-effects models found a slightly larger effect size for depression, which was not statistically significant (SMD −0.23, 95% CI −0.56 to 0.10; $p = 0.07$; $I^2 = 61\%$).

Subgroup analyses

We did not conduct subgroup analyses because all trials except two ($n = 68$) recruited patients within 3 months of stroke onset.

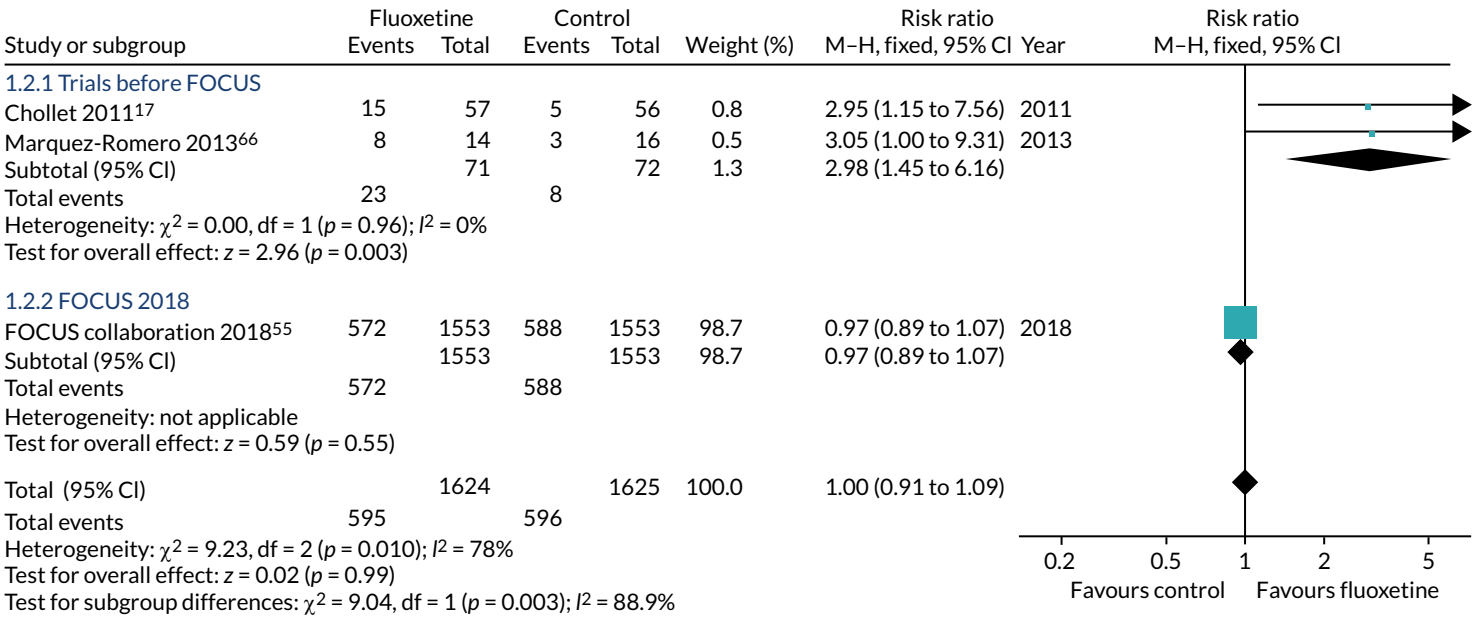

FIGURE 9 Forest plot: mRS (0–2) at the end of treatment. df, degrees of freedom; M–H, Mantel–Haenszel. Reproduced from Mead *et al.*[63] *International Journal of Stroke*. Copyright © 2019 by SAGE Publications. Reprinted by permission of SAGE Publications, Ltd.

Study or subgroup	Control Mean	Control SD	Control Total	Fluoxetine Mean	Fluoxetine SD	Fluoxetine Total	Weight (%)	Standard mean difference IV, fixed, 95% CI	Year
1.4.1 Trials before FOCUS									
Dam 1996[16]	61.9	13	16	54.1	21.1	16	0.9	0.43 (−0.27 to 1.14)	1996
Robinson 2000[77]	60.5	10.8	13	63.1	8.2	15	0.8	−0.27 (−1.01 to 0.48)	2000
Kong 2007[75]	60.4	12.5	37	52.3	13.5	36	2.1	0.62 (0.15 to 1.09)	2007
Zhao 2011[71]	−27.6	7.1	37	−34.6	5.2	34	1.8	1.11 (0.60 to 1.61)	2011
Marquez-Romero 2013[66]	65	21.42	14	45	73.15	16	0.9	0.35 (−0.37 to 1.07)	2013
He 2016[69]	88.81	14.69	177	84.74	18.85	170	10.2	0.24 (0.03 to 0.45)	2016
Subtotal (95% CI)			294			287	16.6	0.37 (0.21 to 0.54)	
Heterogeneity: $\chi^2 = 13.56$, df = 5 ($p = 0.02$); $I^2 = 63\%$									
Test for overall effect: $z = 4.42$ ($p < 0.00001$)									
1.4.2 FOCUS 2018									
FOCUS collaboration 2018[55]	59.66	31.16	1413	60.15	31.5	1410	83.4	−0.02 (−0.09 to 0.06)	2018
Subtotal (95% CI)			1413			1410	83.4	−0.02 (−0.09 to 0.06)	
Heterogeneity: not applicable									
Test for overall effect: $z = 0.42$ ($p = 0.68$)									
Total (95% CI)			1707			1697	100.0	0.05 (−0.02 to 0.12)	
Heterogeneity: $\chi^2 = 31.24$, df = 6 ($p < 0.0001$); $I^2 = 81\%$									
Test for overall effect: $z = 1.42$ ($p = 0.15$)									
Test for subgroup differences: $\chi^2 = 17.68$, df = 1 ($p < 0.0001$); $I^2 = 94.3\%$									

FIGURE 10 Forest plot: disability at the end of treatment. df, degrees of freedom. IV, inverse variance. Reproduced from Mead *et al.*[63] *International Journal of Stroke*. Copyright © 2019 by SAGE Publications. Reprinted by permission of SAGE Publications, Ltd.

TABLE 32 Effects sizes from meta-analysis of primary and secondary outcomes at the end of treatment, from all trials using fixed-effects models, where at least two trials provided data that could be included

Outcome	Number of trials (number of participants) contributing to the meta-analysis	Effect size (RR or SMD) and 95% CI	*p*-value	I^2
Independent (mRS 0–2)	3 ($n = 3249$)	RR 1.00 (0.91 to 1.09)	0.99	78%
Disability	7 ($n = 3404$)	SMD 0.05 (–0.02 to 0.12)	0.15	81%
Neurological deficit score	8 ($n = 803$)	SMD –0.28 (–0.42 to –0.14)	< 0.0001	77%
Depression-continuous data	6 ($n = 3113$)	SMD –0.16 (–0.23 to –0.09)	< 0.0001	92%
Depression-dichotomous	2 ($n = 3194$)	RR 0.77 (0.65 to 0.90)	0.001	53%
Motor score	5 ($n = 3079$)	SMD 0.06 (–0.02 to 0.13)	0.12	95%
Cognition	2 ($n = 2834$)	SMD –0.04 (–0.11 to 0.03)	0.32	0%
Death	11 ($n = 3824$)	RR 1.0 (0.79 to 1.26)	1.00	0%
Seizures	7 ($n = 3815$)	RR 1.49 (1.05 to 2.11)	0.03	0%
Gastrointestinal symptoms (nausea, diarrhoea, abdominal pain)	7 ($n = 688$)	RR 1.38 (0.99 to 1.94)	0.06	8%
Serious bleeding	2 ($n = 3477$)	RR 1.10 (0.72 to 1.62)	0.67	0%
Leaving before the end of first follow-up	11 ($n = 3972$)	RR 0.92 (0.61 to 1.40)	0.71	0%

RR if < 1.0 indicate fluoxetine better than control. SMD if negative indicates improvement with fluoxetine.
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TABLE 33 Summary effect sizes for trials at low risk of bias, at the end of treatment, where at least two trials reported the outcome of interest (fixed-effects models)

Outcome	Number of trials and participants contributing to the meta-analysis	Effect size (RR or SMD) and 95% CI	*p*-value	I^2
Independent (mRS 0–2)	3 ($n = 3269$)	RR 1.00 (0.91 to 1.09)	0.99	78%
Disability	2 ($n = 2853$)	SMD –0.01 (–0.09 to 0.06)	0.75	0%
Neurological deficit score	2 ($n = 142$)	SMD –0.30 (–0.63 to 0.04)	0.08	0%
Depression (continuous data)	2 ($n = 2861$)	SMD –0.11 (–0.19 to –0.04)	0.002	69%
Motor score	3 ($n = 2936$)	SMD 0.02 (–0.05 to 0.09)	0.58	88%
Death	4 ($n = 3260$)	RR 0.99 (0.79 to 1.25)	0.95	0%
Gastrointestinal symptoms	2 ($n = 148$)	RR 2.19 (1.0 to 4.76)	0.05	0%
Leaving the trial before first follow-up	4 ($n = 3283$)	RR 1.01 (0.48 to 2.10)	0.98	0%
Seizures	3 ($n = 3275$)	RR 1.47 (0.99 to 2.18)	0.06	0%

RR if < 1.0 indicate fluoxetine better than control. SMD if negative indicates improvement with fluoxetine.
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Chapter 8 Discussion

In this section, we first discuss the main results of the FOCUS trial,[55] and the possible explanations of why we did not confirm the very encouraging results of the earlier RCTs included in our 2012 systematic review.[25] We then discuss the results of our post hoc analyses relating to fractures and, finally, the results of our updated systematic review, which aims to put the FOCUS trial results into the context of all completed similar trials.

The FOCUS trial, along with its sister trials in Australasia/Vietnam (AFFINITY) and Sweden (EFFECTS),[62] which are ongoing at the time of this report, was established to answer several questions. Our discussion will first focus on whether or not we have addressed these questions.

Primary question: does the routine, early administration of fluoxetine (20 mg o.d.) for 6 months after an acute stroke improve patients' functional outcome?

Our results do not support the hypothesis that a course of fluoxetine improves patients' outcomes. We have considerable confidence that this is the correct conclusion because of the trial's methodological strengths.

The strengths of the study, supporting the internal validity of the results, are that bias was minimised by central randomisation without any prospect of foreknowledge; blinding of patients, carers and outcome assessment (with only three episodes of unblinding); very few losses to follow-up (< 1%); and published prespecified intention-to-treat analyses. The small difference in the number of patients stopping the trial medication for perceived adverse effects suggests that unblinding owing to adverse effects was unlikely to have had a significant effect on our results. In any case, expectation bias would normally be expected to bias the result in favour of the active treatment. Random error was also minimised by randomising a large number of patients and high rates of follow-up, providing much greater statistical power than previous similar trials.

However, it is important to consider whether or not methodological factors could have caused us to miss an improvement in outcome. Possible explanations might include:

- Inadequate power to detect a small but clinically significant improvement in functional outcome. Our sample size estimate indicated that we had 90% probability of detecting an effect equivalent to a COR of 1.23 at the 5% significance level. The planned total sample size for the FOCUS, AFFINITY and EFFECTS trials,[62] 6000 patients, provides 90% power to detect a smaller effect size equivalent to a COR of 1.16. Our estimate of effect in the FOCUS trial was a COR of 0.951 (95% CI 0.839 to 1.079; $p = 0.439$; these 95% CIs, which include neither 1.16 nor 1.23, make it very unlikely that we have overlooked a treatment effect of the size that we had considered likely or of clinical importance).
- Inclusion of the wrong type of stroke patients. For instance, those included in the FLAME trial,[17] on average, had more severe strokes and all had motor deficits. Our prespecified subgroup analyses (see *Table 11*) did not identify any interaction between our overall effect and any subgroup. We specifically explored whether or not there was a benefit for patients who had a motor deficit at baseline; there was not.

The external validity of the results, at least for the UK stroke population, is supported by the large number of participating hospitals throughout the UK. Compared with unselected stroke patients admitted to UK hospitals (*Table 34*), there were a few differences to the subjects enrolled in the trial.[80,81] The patients enrolled in the FOCUS trial had slightly more severe strokes (NIHSS 6 vs. 4),

TABLE 34 Baseline characteristics at randomisation and comparison with characteristics of unselected stroke admissions in UK national audits: Sentinel Stroke National Audit Programme 2013–14[80] and Scottish Stroke Care Audit 2017[81]

	Allocated treatment		Comparative data from UK national audits	
Characteristics of patients randomised	Fluoxetine	Placebo	Sentinel Stroke National Audit Programme (*N* = 74,307)	Scottish Stroke Care Audit (*N* = 9345)
All patients, *n* (%)	1564 (100.00)	1563 (100.00)		
Female, *n* (%)	589 (37.66)	616 (39.41)	50%	49%
Male, *n* (%)	975 (62.34)	947 (60.59)	50%	51%
Age (years), mean (SD)	71.24 (12.35)	71.48 (12.06)	77	73
Lives alone, *n* (%)	485 (31.01)	516 (33.01)		38%
Independent before stroke, *n* (%)	1431 (91.50)	1435 (91.81)	81%	82%
Past history, *n* (%)				
Prior ischaemic stroke/TIA	274 (17.52)	294 (18.81)	27%	
Known diabetes	337 (21.55)	303 (19.39)	19%	
Stroke type, *n* (%)				
Ischaemic stroke	1410 (90.15)	1406 (89.96)	88%	87%
Intracerebral haemorrhage	154 (9.85)	157 (10.04)	11%	13%
Stroke severity				
Able to walk at enrolment, *n* (%)	435 (27.81)	412 (26.36)		48%
Able to lift both arms off bed, *n* (%)	924 (59.08)	935 (59.82)		63%
Able to talk and not confused, *n* (%)	1166 (74.55)	1164 (74.47)		66%
NIHSS, median (IQR)	6 (3–11)	6 (3–11)	4 (2–10)	
Enrolled as a hospital inpatient, *n* (%)	1544 (98.72)	1536 (98.27)		100%

which probably reflected the inclusion criteria that required patients to have a neurological deficit persisting at the time of enrolment. Also, 60% were male, compared with a UK average of 50%: an unexplained but common observation in stroke trials.[82] Patients enrolled were slightly younger (mean 71.4 years) than unselected patients who were admitted to hospital with stroke in the UK, which might partly explain the male preponderance, with older women being under-represented. Many of the studies included in the previously published systematic review of RCTs of fluoxetine were from China; non-white patients made up < 5% of those recruited in the FOCUS trial. The ongoing AFFINITY trial is recruiting in Vietnam and will include a much larger proportion of Asian patients.[62]

The primary outcome measure, the modified Rankin Scale, was too insensitive

Some might criticise our use of the mRS, and specifically the smRSq, because it is too simple and not a directly observed assessment of function, but is patient or proxy reported. However, the smRSq is a valid, reliable measure of functional outcome, which is patient centred, thus ensuring that our results are relevant for patients and their families.[18,35–37] We cannot definitely exclude an effect of fluoxetine on a directly measured neurological deficit, such as the Fugl-Meyer Motor Score, which was measured in the FLAME trial.[17] A structured neurological examination during follow-up would have been impractical

to include in this large pragmatic multicentre trial. In addition, local face-to-face assessments of outcomes are likely to be more prone to unblinding owing to patients reporting adverse effects of trial medication to those assessing outcome, than would occur through postal and telephone follow-up. However, we have shown that even if fluoxetine improves neurological deficits, a resulting improvement in functional status measured with the mRS or SIS is unlikely.

Non-adherence might have diluted any benefit

The main limitation of the FOCUS trial was the degree of non-adherence to the trial medication, which might have led us to underestimate any treatment effect. However, adherence measured in the FOCUS trial was superior to that reported in routine clinical practice and not very different between the treatment groups in the trial.[83] Where reduced adherence resulted from patients experiencing possible adverse reactions or a perceived change (or lack of change) in their condition, then this might be more likely to differ between the fluoxetine and placebo groups. We repeated the analysis of our primary outcome, having sequentially excluded patients with different reasons for, and different degrees of, adherence. Such per-protocol analyses may increase the risk of bias, usually in favour of the active treatment. Our analyses (see *Table 12*) did not show any trend towards greater benefit from fluoxetine in those with greater adherence.

Excess of fractures may have offset the functional benefits

Removing the 65 patients with one or more fractures during follow-up from the primary analysis (ordinal analysis of the mRS) did not significantly alter the estimate of effect of fluoxetine on mRS (COR including those with fractures 0.951, 95% CI 0.839 to 1.079; $p = 0.439$; COR for those without fractures 0.961, 95% CI 0.847 to 1.093; $p = 0.545$).

Patients recruited received lower background rehabilitation intensity than in FLAME

The proponents of fluoxetine as a medication that helps functional recovery claim that it amplifies the effects of physical therapy by enhancing neuroplasticity.[17] We had no measure of the intensity of rehabilitation or delivery of physical therapies during follow-up. This is likely to have varied considerably between centres and patients. Our results are very likely to apply to the effects of fluoxetine in patients admitted to UK hospitals with a stroke. The EFFECTS trial is being carried out in Sweden where the impression is that patients receive higher doses of physiotherapy and other physical rehabilitation than in the UK. The EFFECTS trial is also estimating the intensity of physiotherapy treatment. The planned individual patient data meta-analysis will be able to determine if there are differences in the effect of fluoxetine on functional outcome between the UK and Sweden, and perhaps explore any interaction with intensity of physiotherapy.

Secondary questions

If fluoxetine improves functional outcome, does any improvement persist after treatment is stopped?

We demonstrated no effect at 6 months, and the data at 12 months do not suggest any improvement in any measure of functional outcome in the fluoxetine group compared with the placebo group.

Does the routine early administration of fluoxetine after acute stroke causing motor impairment improve patients' motor function and does any improvement persist after treatment is stopped?

There was no evidence of benefit from fluoxetine on motor outcomes (as defined by relevant domains of the SIS) at 6 or 12 months in those patients with motor dysfunction at baseline based on the NIHSS. Similarly, in those with communication difficulties at baseline, there was no evidence of benefit from fluoxetine on the communication domain of the SIS at 6 or 12 months in those patients with communication dysfunction at baseline based on the NIHSS.

In those patients with impairments that preclude the formal assessment of post-stroke mood, does fluoxetine improve outcomes?

A prespecified subgroup analysis did not indicate any interaction between the patients' ability or not to have their mood assessed at baseline and a treatment effect (see *Table 11*).

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?

The only improvement in patients' outcome at 6 months was a small improvement in mood, measured with the MHI-5 (see *Table 15*). This was consistent with our observation that new episodes of depression were less commonly diagnosed and thus treated within the first 6 months in the group allocated fluoxetine (see *Table 13*). The difference in MHI-5 between groups and the difference in rates of new depression by 12 months were no longer statistically significant (see *Tables 19* and *20*). No other secondary measure of outcome was significantly improved.

A previous systematic review included five RCTs, including FLAME,[17] in non-depressed stroke patients, which tested whether or not SSRIs (two fluoxetine, two sertraline and one escitalopram) prevented the development of post-stroke depression.[84] In a pooled analysis, 23 out of 248 (9.3%) patients treated with a SSRI developed post-stroke depression, compared with 59 out of 242 (24.4%) patients treated with a placebo; the authors reported an OR of 0.37 (95% CI 0.22 to 0.61; $p = 0.001$).[84] The rate of depression in the placebo arms of these trials was much higher than that in the FOCUS trial, which may have reflected the characteristics of the patients, who tended to have had more severe strokes than those in the FOCUS trial, or perhaps different methods of diagnosing depression. This is consistent with our findings in the direction, if not the magnitude, of the treatment effect.

Does fluoxetine reduce the cost of health care over the first year?

No; there was no evidence from our health economic analyses that fluoxetine was associated with a reduced cost of health care over the first year (see *Tables 25* and *26*).

Does fluoxetine increase the risk of serious adverse events?

Our data showed a statistically significant increase in the risk of bone fractures in the group allocated fluoxetine. The observed 1.4% absolute excess of bone fractures at 6 months with fluoxetine in the FOCUS trial is consistent with previous reports from large case–control and cohort studies.[28–30] The size of the increased risk in the previous observational studies tended to be greater than in the FOCUS trial, but this might be attributable to the inherent confounding by treatment indication in observational studies.

The rates of other serious adverse reactions referred to in the SmPC of fluoxetine, which we included as secondary outcomes in this trial (e.g. epileptic seizures, falls, hyponatraemia, uncontrolled diabetes and upper gastrointestinal bleeding), were higher in the fluoxetine group than in the placebo group, but the absolute differences were small and were not statistically significant (see *Table 13*). It seems likely that there is an excess of these recognised adverse effects, but we had an insufficient number of patients to confirm this reliably. Despite concerns about fluoxetine's effect on platelet function and interactions with antiplatelet and anticoagulant medications, we observed no effect on bleeding or thrombotic adverse events (see *Table 14*). The trial was not powered to detect increases in these recognised adverse effects of fluoxetine.

The AFFINITY and EFFECTS trials, which are of similar design to the FOCUS trial, but with smaller recruitment targets, are in progress.[62] These should allow us to confirm the effects on post-stroke depression and bone fractures and provide more precise estimates of the benefits and harms of early fluoxetine to guide its use in stroke patients and perhaps other elderly people with comorbidities.

Summary

In summary, the FOCUS trial has shown that 20 mg of fluoxetine started early and given daily for 6 months after an acute stroke did not influence patients' functional outcome, but did decrease the occurrence of depression and increase bone fractures. These results do not support the routine use of fluoxetine for the prevention of post-stroke depression or to promote recovery of function. Ongoing trials and a planned individual patient data meta-analysis are needed to confirm or refute a modest benefit of fluoxetine for functional outcome, either overall or in particular subgroups, and to provide more precise estimates of any harms.

Discussion of the post hoc analyses relating to fractures occurring during the 6-month treatment period

The most common site of fractures among patients with stroke enrolled in the FOCUS trial and assigned fluoxetine or placebo for 6 months was the neck of femur, and most fractures were in sites associated with osteoporosis; almost all resulted from a fall. Greater age, female sex and allocation to fluoxetine were independent predictors of subsequent fractures. An increased risk of falling is likely to explain much of the excess risk of fractures because most fractures were associated with a fall. Falls with injury were more common in the fluoxetine group than in the placebo group [$n = 120$ (7.67%) vs. $n = 94$ (6.01%); $p = 0.0663$], although the difference did not quite reach statistical significance and the risks in the two treatment groups diverged early after randomisation. No other baseline factors analysed had statistically significant associations with fracture risk.

These findings in an adequately powered prospective randomised trial confirm that the association between SSRI and fracture risk noted in observational studies is real and is not due to methodological biases, and that SSRI medication is likely to be causative. Our finding that greater age and female sex are associated with a greater fracture risk confirms the findings of previous observation studies in stroke.[28–30] The risk of fractures appears to increase soon after randomisation (see *Figure 5*) and most fractures were related to falls (see *Table 21*), suggesting that the predominant mechanism explaining the excess of fractures is likely to be the non-significant excess of falls seen in the FOCUS trial compared with the control group (see *Table 13*). This might be due to effects on cognition, co-ordination, balance or activity levels. However, we cannot exclude a contribution from fluoxetine's possible effect on bone density.

These predefined secondary analyses have several limitations. The number of fractures in the first 6 months was modest, which means that we were only able to identify powerful predictors of fracture risk. Our only baseline indicators of bone density were previous fractures and the use of medications to reduce bone density loss at baseline. We had no direct measures of bone density. In addition, the effect of fluoxetine, and other medications, may have been diluted by non-adherence or changes to medication after randomisation. We did not collect data on current medication at the time of the fracture. Also, we did not systematically collect fractures beyond 6 months so cannot determine whether or not the effect of fluoxetine on fracture risk persists, as it might if it causes osteoporosis, or whether or not the risk subsides after stopping if it caused falls by affecting balance, etc., or increased activity by reducing depression. We did not systematically collect data on the side of the fracture so we could not reliably confirm previous findings that fractures most often affect the side of any weakness.[30]

The cost-effectiveness of fluoxetine

There was no evidence that fluoxetine improves health outcomes, and it did not have a significant effect on the costs of health care, even though it reduced the frequency of new depression and increased the risk of fractures. Treatment with fluoxetine is cheap, but treatment is not justified by the clinical or economic outcomes.

The FOCUS results in the context of all similar randomised controlled trials

The updated systematic review of fluoxetine for stroke recovery identified 13 trials that recruited > 4000 patients, of which four trials ($n = 3283$) were of high methodological quality.

There were no differences between groups for the co-primary outcomes of dependency and disability. Fluoxetine was associated with better neurological scores at the end of treatment, lower depression scores (fewer symptoms of depression) and fewer diagnoses of depression, although the effect sizes were all small and there was substantial heterogeneity. There was a higher risk of seizures with fluoxetine. However, when only high-quality trials were considered, the only statistically significant difference between groups was lower depression scores (fewer symptoms) at the end of treatment.

We used fixed-effects models as these give appropriate weight to larger trials. The sensitivity analysis using random-effects models found a large benefit of fluoxetine on independence (RR 1.87) because of the disproportionate weight given to smaller trials. Fixed- and random-effects models produced only slightly different effect sizes for depression scores.

Previous meta-analyses suggested that fluoxetine might reduce dependency and disability if given early after stroke.[24,25,85] This meta-analysis, which includes many more patients than previous reviews, has not confirmed these promising effects. Although one of the reviews[85] strongly recommended fluoxetine to promote neurological recovery, this recommendation was based on the results of just four reports,[17,68,74,75] only one of which was high quality.[17]

Thus, these data do not support the routine prescription of fluoxetine early after stroke in order to reduce dependency and disability. Clinicians and patients may wish to consider the routine use of fluoxetine early after stroke for its small effects on reducing the incidence of new depression, but this would need to be weighed up against the excess of seizures and bone fractures. The most important depression-related outcome after stroke is suicide, which is about double what it is in the non-stroke population; however, it is rare, and for that reason the RCTs shed no light on whether or not antidepressant treatment reduces the risk.

There are some limitations at the study and outcome level: only four trials were of high methodological quality, and not all had been registered prospectively or they reported the same outcomes. Furthermore, different scales were used for the same outcome; although we used SMD to combine data, the interpretation of SMD is not intuitive, and clinicians prefer to know the effect size on a familiar scale (e.g. Functional Independence Measure). Two large ongoing trials (AFFINITY and EFFECTS[62]) are using the same measures as those used in the FOCUS trial. A future meta-analysis will report mean differences for continuous data.

We did not register the review in PROSPERO, but we used almost the same methods as the 2012 Cochrane review, which had a prospectively published protocol.[25] We used sensitive searches developed by Cochrane Stroke,[86] and there was complete retrieval of identified research, no language restrictions and inclusion of unpublished data.

About three-quarters of the patients were from the FOCUS trial. There was quite marked heterogeneity, even for the high-quality trials (see *Table 33*); this might be explained by the different types of patients and health-care settings. Five of the low-quality trials were from China; the three reporting disability all found favourable effects of fluoxetine. As the evidence base increases, it may be possible to undertake meta-regression analyses to determine the factors (e.g. country, health-care setting and trial quality) associated with good outcome.

Conclusions

The results of the FOCUS trial show that, in the context of the UK NHS, routine use of fluoxetine does not improve functional outcomes in patients with a recent stroke. There was evidence that its use reduces the risk of developing new episodes of depression after stroke, but that this is at the expense of an increased risk of adverse effects, including bone fractures.

Ongoing trials (AFFINITY and EFFECTS[62]), which used almost identical methods to those of the FOCUS trial, and the investigators with whom we have closely collaborated, will report in 2020. An individual patient data meta-analysis including data from FOCUS, AFFINITY and EFFECTS is planned. This will indicate whether or not the findings of the FOCUS trial are generalisable to other countries, ethnic groups and health-care systems. They will also help to provide more precise, and generalisable, estimates of the risks associated with several months of fluoxetine treatment in a predominantly elderly population. Such data are likely to be relevant to the use of fluoxetine, and perhaps other SSRIs, in similar populations (i.e. elderly patients with comorbidities). This knowledge could be of use when counselling patients about the pros and cons of starting treatment with fluoxetine.

Most previous RCTs of fluoxetine, and other SSRIs, have been carried out in patients with depression, who are often much younger than those recruited into stroke trials, and have only tested short courses with the purpose of demonstrating an improvement in mood.[87] There is a good case for studying the effects of prolonged courses of fluoxetine, not just those on mood, in older patients who are likely to be more susceptible to adverse effects. Such information would be useful in balancing the risks against the perceived benefits of using SSRIs for a variety of indications.

In advance of the FOCUS trial results becoming available, we carried out systematic reviews to determine whether or not SSRIs might be of benefit in conditions other than stroke through the same mechanisms that we thought might underpin the hypothesised benefit in stroke. All the reviews suggested promising effects of SSRIs.[88–90] However, before embarking on large trials in these other conditions, the relevance of the neutral results of the FOCUS trial needs to be considered carefully.

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Contributions of authors

Professor Martin Dennis (https://orcid.org/0000-0003-1148-8972) (Stroke Physician, University of Edinburgh, UK) was co-chief investigator; participated in the TSC; was involved in the design of the trial; collected, verified and analysed data; and drafted this report.

Professor John Forbes (https://orcid.org/0000-0002-8255-3762) (Health Economist, University of Limerick, Ireland) participated in the TSC, was involved in the design of the trial and analysed health economic data.

Ms Catriona Graham (https://orcid.org/0000-0003-1889-712X) (Unblinded Statistician, University of Edinburgh, UK) participated in the TSC, was involved in the design of the trial, wrote the first draft of the statistical analysis plan and verified and analysed data.

Professor Maree Hackett (https://orcid.org/0000-0003-1211-9087) (Psychologist, University of Sydney, Australia) was involved in the trial design and helped carry out relevant systematic reviews.

Professor Graeme J Hankey (https://orcid.org/0000-0002-6044-7328) (Neurologist, University of Western Australia, Australia) was involved in the trial design and helped carry out relevant systematic reviews.

Professor Allan House (https://orcid.org/0000-0001-8721-8026) (Psychiatrist, University of Leeds, UK) was involved in the trial design and advised on the management of depression within the trial.

Professor Stephanie Lewis (https://orcid.org/0000-0003-1210-2314) (Blinded Statistician, University of Edinburgh, UK) was involved in the trial design and advised on the statistical analysis plan.

Professor Erik Lundström (https://orcid.org/0000-0002-5313-9052) (Neurologist, Karolinska Institutet, and Uppsala University, Sweden) was involved in the design of the trial.

Professor Peter Sandercock (https://orcid.org/0000-0001-8484-0135) (Neurologist, University of Edinburgh, UK) chaired the TSC of the initial phase.

Professor Gillian Mead (https://orcid.org/0000-0001-7494-2023) (Stroke Physician/Geriatrician, University of Edinburgh, UK) was co-chief investigator, participated in the TSC, was involved in the design of the trial and data collection, and co-ordinated the systematic review of the RCTs.

All members of the writing committee listed here have commented on the analyses and drafts of this report and have seen and approved the final version of the report.

Publications

Mead G, Hackett ML, Lundstrom 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.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review and appropriate agreements being in place.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Membership of the FOCUS Trial Collaboration

Co-chief investigators

Martin Dennis and Gillian Mead.

Writing group

Martin Dennis (chairperson), John Forbes, Catriona Graham, Maree Hackett, Graeme J Hankey, Allan House, Stephanie Lewis, Erik Lundström, Peter Sandercock and Gillian Mead.

FOCUS Trial Co-ordinating Centre

Rosemary Anderson, David Buchanan, Ann Deary, Jonathan Drever, Ruth Fraser, Catriona Graham, Karen Innes, Connor McGill, Aileen McGrath, David Perry, Pauli Walker and Carol Williams.

Telephone 6- and 12-month follow-up (numbers conducted)

Martin Dennis (1394), Carol Williams (227), Gillian Mead (220), Rosemary Anderson (173), Yvonne Chun (60), Lynn Dinsmore (50), Emma Maschauer (46), Wellcome Trust Clinical Research Facility (Greig Fraser, Katherine Lawrence and Alison Shaw) (27), Amanda Barugh (15), Shadia Mikhail (8), Gordon Blair (6), Ingrid Hoeritzauer (6) and Maggie Scott (4).

Trial Steering Committee

Stroke Association funded phase: Peter Sandercock (chairperson), Steff Lewis (statistician), Judith Williamson (patient involvement), Martin Dennis (co-chief investigator), Gillian Mead (co-chief investigator), John Forbes (health economist), Graeme J Hankey (AFFINITY), Maree Hackett (AFFINITY), Veronica Murray (EFFECTS) (deceased), Karen Innes (trial manager) and Ray French (sponsor representative).

NIHR funded phase: David Stott (independent chairperson), David Burgess (lay member), Jonathan Emberson (independent statistician), Graham Ellis, Pippa Tyrrell, Judith Williamson (patient involvement), Martin Dennis (co-chief investigator), Gillian Mead (co-chief investigator), Karen Innes (trial manager) and Ray French (sponsor representative).

Co-applicants on funding applications

NIHR Stroke Research Network Portfolio Development Application

Gillian Mead (co-PI and convener of the group), Martin Dennis (co-PI), Marian Brady, John Forbes, Maree Hackett, Allan House, Steff Lewis, Malcolm MacLeod, Hazel Milligan, David Perry, Peter Sandercock, Frank Sullivan, Frederike van Wijck and Caroline Watkins.

Stroke Association
Gillian Mead, Martin Dennis, Peter Sandercock, Malcolm MacLeod, Stephanie Lewis, Frank Sullivan, Allan House, John Forbes, Maree Hackett, Craig Anderson and Graeme J Hankey.

NIHR Health Technology Assessment
Gillian Mead, Martin Dennis, Peter Sandercock, Malcolm MacLeod, Stephanie Lewis, D Morales, Allan House, John Forbes, Maree Hackett, Craig Anderson and Graeme J Hankey.

Independent Data Monitoring Committee

Peter Langhorne, Fiona Reid and Helen Rodgers.

Other activities

Marian Brady (Glasgow Caledonian University) helped produce aphasia-friendly versions of the patient information leaflet and consent form (see *Appendix 2*). Dan Morales reviewed information sent to GPs.

Investigational medicinal product

Manufactured by Unichem (Mumbai, India).

Sourced through Niche Generics Ltd (Hitchin, UK) and Discovery Pharmaceuticals Ltd (Castle Donington, UK).

Packaged and distributed by Bilcare Ltd (Pune, India), then Sharp Clinical Services (Tredegar, UK).

Participating centres

We have listed each hospital with the total number of patients recruited [*n*], followed by the names of the local PI(s) and other significant contributors in that centre. The hospitals are ordered depending on the numbers recruited.

Recruiting centres
Royal Infirmary Edinburgh, Edinburgh [141] [G Mead (PI), N Hunter, R Parakramawansha, A Fazal, P Taylor, W Rutherford, K McCormick, R Buchan, A MacRaild, Y Chun, R Paulton, S Burgess, D McGowan, J Skwarski, F Proudfoot, R Murphy, A Barugh, J Perry]; Leeds General Infirmary, Leeds [123] [J Bamford (PI), C Bedford, D Waugh, E Veraque, M Kambafwile, L Makawa, P Smalley, M Randall, L Idrovo, A Hassan, T Thirugnana-Chandran, R Vowden, J Jackson]; St Thomas' Hospital, London [115] [A Bhalla (PI), C Tam, Professor A Rudd, C Gibbs, J Birns, L Lee Carbon, E Cattermole, A Cape, L Hurley, K Marks, S Kullane]; Royal Hampshire County Hospital, Winchester [110] [N Smyth (PI), E Giallombardo, C Eglinton, J Wilson, D Dellafera, P Reidy, M Pitt, L Sykes, A Frith, V Croome, J Duffy, D Cooke, M Hancevic, L Kerwood, C Narh, C Merritt, J Willson]; Royal Hallamshire Hospital, Sheffield [107] [A Ali (PI), S Bell, T Jackson, H Bowler, C Kamara, A Naqvi, J Howe, K Stocks, G Dunn, K Endean, F Claydon, S Duty, C Doyle, K Harkness, E Richards, M Meegada, A Maatouk, L Barron, K Dakin, R Lindert, Professor A Majid]; Calderdale Royal Hospital, Halifax [81] [P Rana (PI), A Nair, C Brighouse-Johnson, J Greig, M Kyu, S Prasad, M Robinson, B Mclean, I Alam, L Greenhalgh, Z Ahmed]; University Hospitals of North Midlands NHS Trust, Stoke-on-Trent [80] [Professor C Roffe (PI), S Brammer, A Barry, C Beardmore, K Finney, H Maguire, P Hollinshead, J Grocott, I Natarajan, J Chembala, R Sanyal, S Lijko, N Abano, A Remegoso, P Ferdinand, S Stevens, C Stephen, P Whitmore,

A Butler, C Causley, R Varquez, G Muddegowda, R Carpio, J Hiden, H Denic]; Royal Devon and Exeter Hospital, Exeter [73] [J Sword (PI), F Hall, J Cageao, S Keenan, R Curwen, M James, P Mudd, C Roughan, H Kingwell, A Hemsley, C Lohan, S Davenport, T Chapter, A Bowring, M Hough, D Strain, K Gupwell, K Miller, A Goff, E Cusack, S Todd, R Partridge, G Jennings, K Thorpe, J Stephenson, K Littlewood]; Monklands Hospital, Airdrie [70] [M Barber (PI), F Brodie, S Marshall, D Esson, C McInnes, I Coburn, F Ross, V Withers, E Bowie, H Barcroft, L Miller]; York Hospital, York [69] [P Willcoxson (PI), M Keeling, M Donninson, R Evans, D Daniel, J Coyle, M Elliott, P Wanklyn, J Wightman, E Iveson, A Porteous, N Dyer, M Haritakis, M Ward, L Wright, J Bell, C Emms, P Wood, P Cottrell, L Doughty, L Carr, C Anazodo, M O Neill, J Westmoreland, R Rodriguez, R Mir, C Donne, E Bamford, P Clark Brown]; Pinderfields Hospital, Wakefield [67] [A Stanners (PI), I Ghouri, A Needle, M Eastwood, M Carpenter, P Datta, R Davey, F Razik, G Bateman, J Archer, V Balasubramanian, L Jackson, L Benton, J Ball, R Bowers, J Ellam, K Norton]; Southend University Hospital NHS Foundation Trust, Essex [64] [P Guyler (PI), S Tysoe, P Harman, A Kundu, T Dowling, S Chandler, O Omodunbi, T Loganathan, S Noor, S Kunhunny, D Sinha, A Siddiqui, A Siddiqui, M Sheppard, S Shah, S Kelavkar, K Ng, L Wilson, A Ropun, L Kamuriwo, R Orath Prabakaran, E France, S Rashmi]; Pilgrim Hospital, Boston [63] [D Mangion (PI), C Constantin, S Markova, A Hardwick, J Borley, L De Michele Hock, T Lawrence, J Fletcher, K Netherton, R Spencer, H Palmer]; Lincoln County Hospital, Lincoln [60] [M Soliman (PI), S Leach, Professor J Sharma, R Brown, C Taylor, I Wahishi, S Arif, S Bell, A Fields, S Butler, J Hindle, E Watson, J Borley, C Hewitt]; University Hospital Aintree, Liverpool [60] [C Cullen (PI), D Hamill, Z Mellor, T Fluskey, V Hankin, A Keeling, R Durairaj, D Wood, J Peters, D Shackcloth, R Tangney, T Hlaing, V Sutton, M Harrison, S Stevenson, J Ewing]; Bradford Royal Infirmary, Bradford [59] [C Patterson (PI), J Price, H Wilson, H Ramadan, S Maguire, S Khan, R Bellfield, U Hamid, M Hooley, R Ghulam, L Masters, W Gaba, O Quinn]; Luton and Dunstable University Hospital, Luton [56] [L Sekaran (PI), M Tate, N Mohammed, S Sethuraman, L Alwis, R Robinson, K Bharaj, R Pattni, F Justin, C Tam, M Chauhan, L Eldridge, S Mintias, J Palmones]; Bristol Royal Infirmary, Bristol [54] [C Holmes (PI), L Guthrie, P Murphy, N Devitt, J Leonard, M Osborn, L Ball, A Steele, E Dodd, A Holloway, P Baker, R Patel, I Penwarden, S Caine, S Clarke, L Dow, S Williams, R Wynn-Williams]; John Radcliffe Hospital, Oxford [51] [J Kennedy (PI), A DeVeciana, P Mathieson, I Reckless, R Teal, U Schulz, Professor G Ford, P Mccann]; St George's Healthcare NHS Trust, London [47] [G Cluckie (PI), G Howell, J Ayer, B Moynihan, R Ghatala, B Clarke, G Cloud, B Patel, U Khan, N Al-Samarrai, F Watson, T Adedoyin, S Trippier, N Chopra, L Zhang, L Choy, K Kennedy, R Williams, V Jones, N Clarke, A Dainty, A Blight]; South Glasgow University Hospital, Glasgow [45] [J Selvarajah (PI), W Smith, F Moreton, A Welch, D Kalladka, B Cheripelli, E Douglas, A Lush, X Huang, S El Tawil, N Day, K Montgomery, H Hamilton, D Ritchie, S Ramachandra, K McLeish]; Northwick Park Hospital, Harrow [44] [D Cohen (PI), B Badiani, M Abdul-Saheb, A Chamberlain, M Mpelembue, R Bathula, M Lang, J Devine, L Alwis, L Southworth, L Burgess, N Epie, A David, E Owoyele, F Guo, A Oshodi, V Sudkeo]; Royal Bournemouth Hospital, Bournemouth [44] [K Thavanesan (PI), D Tiwari, J Bell, C Ovington, E Rogers, R Bower, G Hann, B Longland, O David, A Hogan, S Loganathan, J Roberts, C Cox, S Orr, M Keltos]; Yeovil District Hospital, Yeovil [41] [K Rashed (PI), D Wood, B Williams-Yesson, J Board, S De Bruijn, C Buckley, C Vickers, S Board, J Allison, E Keeling, T Duckett, D Donaldson, C Barron, L Balian, A Edwards, J Wilson]; Royal Derby Hospital, Derby [40] [T England (PI), A Hedstrom, E Bedford, M Harper, E Melikyan, W Abbott, K Subramanian, M Goldsworthy]; The Princess Royal Hospital, Telford [40] [M Srinivasan (PI), I Mukherjee, U Ghani, A Yeomans, D Donaldson, F Hurford, R Chapman, S Shahzad, O David, N Motherwell, L Tonks, R Young]; Gloucestershire Royal Hospital, Gloucester [39] [D Dutta (PI), P Brown, F Davis, D Ward, J Turfrey, M Obaid, B Cartwright, B Topia, J Spurway, C Hughes, L Hill, S OConnell, K Collins, R Bakawala]; 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Appendix 2 Development of easy-access versions of patient information and consent forms by Professor Marian Brady, Research Group Lead for Living with Stroke, Glasgow Caledonian University

Aim

Development of accessible versions of participant information sheets and consent forms for the FOCUS trial.

Methods

Initial drafts of accessible versions of the standard FOCUS information sheets and consent forms were prepared for review by people with aphasia based on established methodologies[91,92] and sound ethical principles[93] by an experienced speech and language therapist and stroke rehabilitation researcher (Marian Brady).

Accessible versions of the standard materials were drafted:

- participant information sheets
- participant consent forms.

Two meetings were planned with Speakeasy (Bury, UK) members in Dundee on 28 October and again on 4 November 2011. Version 1 of the accessible materials were sent in advance of the first meeting to members of the Speakeasy group (peer support group for people with aphasia following stroke) based in Dundee. These were sent in advance to provide sufficient time for the Speakeasy members with language impairment to review and prepare in advance of the first meeting. The process of drafting and review with comments was scheduled to continue to contribute to the iterative development of accessible materials until the Speakeasy group felt that they were suitable to be used in the trial with people with aphasia.

Results

The members reviewed version 1 of the proposed accessible materials in advance of the meeting. Eight members attended. The materials were reviewed on a statement-by-statement basis with reference (where necessary) to the standard materials. In this way, we ensured that the essence of the statement contained in the standard format was retained in the accessible version, and made comments.

Version 2 of the accessible materials was prepared in response to the group's comments. Version 2 was reviewed by the FOCUS trial team at the University of Edinburgh, including the PIs, trial manager and other trial staff. They raised some feasibility issues regarding the version 2, which was in colour and on A4 sheets. They queried whether printing the accessible versions in black and white (considerably cheaper than the colour) would be acceptable to the group and to people with aphasia. They also highlighted that printing in black and white would allow sites to easily photocopy the

materials, which would support implementation of the trial at sites. They also asked whether or not the A4 size of the materials could be reduced to an A5 booklet, again to support implementation.

Version 3 of the materials was shared with the Speakeasy group (black and white and A5 version), with a specific response requested in relation to the above issues via the post to members who had participated in the first meeting. The Speakeasy members responded that although colour printing would be preferable, for cost reasons the black-and-white versions were acceptable. They also felt that although larger A4 was preferable, the A5 version would also be acceptable. All other changes were accepted, and no further changes were requested. A second scheduled face-to-face meeting was agreed to be unnecessary and was cancelled.

The ethics committee responded positively to the accessible versions of information sheets and consent forms and agreed that accessible versions could be made available to all potential trial participants as deemed required by trial staff. The ethics committee's response to the materials was fed back to the Speakeasy members.

Discussion and conclusions

In addition, and beyond the FOCUS trial, the accessible materials used in this trial contributed to the NIHR template materials supporting the involvement of people with aphasia in stroke research.[94]

Reflections/critical perspective

Involvement of people with aphasia supported the development of accessible materials to support the ethical inclusion of people with aphasia in the FOCUS trial. The perspective of people with a language impairment is vital to the development of such materials as it is not possible for people with intact language skills to perceive all the challenges experienced with a language impairment.

Preparation of accessible versions of materials in stroke research is increasingly standard practice (Big CACTUS[95] and ICONS II[96]). There is some suggestion that reliance on proxy consent may contribute to selection bias in the participant recruitment.[97]

Appendix 3 Contributors to the updated systematic review, search strategy and references

Contributors to updated systematic review

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Joshua Cheyne of Cochrane Stroke ran the literature searches.

Maureen Harding obtained articles for full-text review.

Dr Juan Marquez Romero provided unpublished data from the fluoxetine for motor recovery after acute intracerebral hemorrhage (FMRICH) trial.

Professor Chollet responded to requests for information about other new trials.

Dr Jan Bembenek and Professor Anna Czlonkowska provided further information about FOCUS-Poland.

Professor Peter Sandercock commented on the manuscript.

Contributions

Gillian Mead conceived the study, screened references, extracted data, assessed risk of bias, carried out the analyses and wrote the first draft.

Lynn Legg searched for selected studies for inclusion, collected data, assessed risk of bias, managed studies through the review process and contributed to the final version.

Russel Tilney, Cheng Fang Hsieh, Simiao Wu, Erik Lundström, Ann-Sofie Rudberg, Mansur Kutlubaev, Babak Soleimani and Amanda Barugh screened citations, retrieved potentially relevant papers and screened their eligibility for the systematic review, assisted with data extraction and drafted the manuscript for submission.

Maree Hackett extracted data and edited the final manuscript.

Graeme J Hankey and Martin Dennis conceived the study, provided expertise in relation to analysis methods and edited the draft paper.

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Search strategy for updated systematic review

The following searches were carried out (Cochrane Stroke Group Trials Register; date searched: 17 July 2018):

- Cochrane Central Register of Controlled Trials (CENTRAL) (via The Cochrane Library) (date range searched: 2018, issue 6).
- MEDLINE (via Ovid) (date range searched: 1948 to 17 July 2018).
- EMBASE (via Ovid) (date range searched: 1980 to 17 July 2018).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via EBSCO*host*) (date range searched: 1982 to 17 July 2018).
- Allied and Complementary Medicine (AMED) (via Ovid) (date range searched: 1985 to 17 July 2018)
- PsycINFO (via Ovid) (date range searched: 1967 to 17 July 2018).
- US National Institutes of Health Ongoing Trials Register [via ClinicalTrials.gov (www.clinicaltrials.gov)].
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch) (date searched: 26 June 2018).

Cochrane Central Register of Controlled Trials (CENTRAL) (via The Cochrane Library) (2018, issue 6) search strategy

#1. MeSH descriptor Cerebrovascular Disorders explode all trees
#2. (stroke in Title, Abstract or Keywords or poststroke in Title, Abstract or Keywords or post-stroke in Title, Abstract or Keywords or cerebrovasc* in Title, Abstract or Keywords or (brain in Title, Abstract or Keywords and vasc* in Title, Abstract or Keywords) or (cerebral in Title, Abstract or Keywords and vasc* in Title, Abstract or Keywords) or cva* in Title, Abstract or Keywords or apoplex* in Title, Abstract or Keywords or SAH in Title, Abstract or Keywords)
#3. ((brain* in Title, Abstract or Keywords or cerebr* in Title, Abstract or Keywords or cerebell* in Title, Abstract or Keywords or intracran* in Title, Abstract or Keywords or intracerebral in Title, Abstract or Keywords) and (ischemi* in Title, Abstract or Keywords or ischaemi* in Title, Abstract or Keywords or infarct* in Title, Abstract or Keywords or thrombo* in Title, Abstract or Keywords or emboli* in Title, Abstract or Keywords or occlus* in Title, Abstract or Keywords))
#4. ((brain* in Title, Abstract or Keywords or cerebr* in Title, Abstract or Keywords or cerebell* in Title, Abstract or Keywords or intracerebral in Title, Abstract or Keywords or intracranial in Title, Abstract or Keywords or subarachnoid in Title, Abstract or Keywords) and (haemorrhage* in Title, Abstract or Keywords or hemorrhage* in Title, Abstract or Keywords or haematoma* in Title, Abstract or Keywords or hematoma* in Title, Abstract or Keywords or bleed* in Title, Abstract or Keywords))
#5. MeSH descriptor hemiplegia this term only
#6. MeSH descriptor paresis explode all trees
#7. MeSH descriptor Gait Disorders, Neurologic explode all trees
#8. (hemipleg* in Title, Abstract or Keywords or hemipar* in Title, Abstract or Keywords or paresis in Title, Abstract or Keywords or paretic in Title, Abstract or Keywords)
#9. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)
#10. MeSH descriptor Serotonin Uptake Inhibitors explode all trees
#11. (serotonin in Title, Abstract or Keywords or 5-HT in Title, Abstract or Keywords or “5 HT” in Title, Abstract or Keywords or 5-hydroxytryptamine in Title, Abstract or Keywords or “5 hydroxytryptamine” in Title, Abstract or Keywords)
#12. (uptake in Title, Abstract or Keywords or reuptake in Title, Abstract or Keywords or re-uptake in Title, Abstract or Keywords)
#13. inhib* in Title, Abstract or Keywords
#14. (#11 and #12 and #13)
#15. SSRI* in Title, Abstract or Keywords
#16. (alaproclat* in Title, Abstract or Keywords or cericlamin* in Title, Abstract or Keywords or citalopram in Title, Abstract or Keywords or dapoxetin* in Title, Abstract or Keywords or escitalopram in Title, Abstract or Keywords or femoxetin* in Title, Abstract or Keywords or fluoxetin* in Title, Abstract or Keywords or fluvoxamin* in Title, Abstract or Keywords or paroxetin* in Title, Abstract or Keywords or sertralin* in Title, Abstract or Keywords or trazodone in Title, Abstract or Keywords or vilazodone in Title, Abstract or Keywords or zimelidine in Title, Abstract or Keywords)
#17. (Celexa in Title, Abstract or Keywords or Cipramil in Title, Abstract or Keywords or Cipram in Title, Abstract or Keywords or Recital in Title, Abstract or Keywords or Emocal in Title, Abstract or Keywords or Dalsan in Title, Abstract or Keywords or Sepram in Title, Abstract or Keywords or Seropram in Title, Abstract or Keywords or Citox in Title, Abstract or Keywords or Priligy in Title, Abstract or Keywords or Lexapro in Title, Abstract or Keywords or Cipralex in Title, Abstract or Keywords or Seroplex in Title, Abstract or Keywords or Esertia in Title, Abstract or Keywords or Prozac in Title, Abstract or Keywords or Fontex in Title, Abstract or Keywords or Seromex in Title, Abstract or Keywords or Seronil in Title, Abstract or Keywords or Sarafem in Title, Abstract or Keywords or Ladose in Title, Abstract or Keywords or Motivest in Title, Abstract or Keywords or Fluctin in Title, Abstract or Keywords or fluox in Title, Abstract or Keywords or Lovan in Title, Abstract or Keywords or Luvox in Title, Abstract or Keywords or Fevarin in Title, Abstract or

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#18. (#10 or #14 or #15 or #16 or #17)
#19. (#9 and #18).

MEDLINE (via Ovid) search strategy

1. cerebrovascular disorders/or exp basal ganglia cerebrovascular disease/or exp brain ischemia/or exp carotid artery diseases/or exp intracranial arterial diseases/or exp "intracranial embolism and thrombosis"/or exp intracranial hemorrhages/or stroke/or exp brain infarction/or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. hemiplegia/or exp paresis/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. exp Gait Disorders, Neurologic/
8. or/1-7
9. exp Serotonin Uptake Inhibitors/
10. ((serotonin or 5-HT or 5 HT or 5-hydroxytryptamine or 5 hydroxytryptamine) adj5 (uptake or reuptake or re-uptake) adj5 inhib$).tw.
11. SSRI$1.tw.
12. (alaproclat$ or cericlamin$ or citalopram or dapoxetin$ or escitalopram or femoxetin$ or fluoxetin $ or fluvoxamin$ or paroxetin$ or sertralin$ or trazodone or vilazodone or zimelidine).tw,nm.
13. (Celexa or Cipramil or Cipram or Recital or Emocal or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Esertia or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Fluctin or fluox or Lovan or Luvox or Fevarin or Faverin or Favoxil or Movox or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Zoloft or Lustral or Serlain or Asentra).tw,nm.
14. 9 or 10 or 11 or 12 or 13
15. 8 and 14
16. exp animals/not humans.sh.
17. 15 not 16
18. Randomized Controlled Trials as Topic/
19. random allocation/
20. Controlled Clinical Trials as Topic/
21. control groups/
22. clinical trials as topic/or clinical trials, phase i as topic/or clinical trials, phase ii as topic/or clinical trials, phase iii as topic/or clinical trials, phase iv as topic/
23. Clinical Trials Data Monitoring Committees/
24. double-blind method/
25. single-blind method/
26. Placebos/
27. placebo effect/

28. cross-over studies/
29. Multicenter Studies as Topic/
30. Therapies, Investigational/
31. Drug Evaluation/
32. Research Design/
33. Program Evaluation/
34. evaluation studies as topic/
35. randomized controlled trial.pt.
36. controlled clinical trial.pt.
37. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
38. multicenter study.pt.
39. (evaluation studies or comparative study).pt.
40. meta analysis.pt.
41. meta-analysis as topic/
42. random$.tw.
43. (controlled adj5 (trial$ or stud$)).tw.
44. (clinical$ adj5 trial$).tw.
45. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
46. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
47. ((multicenter or multicentre or therapeutic) adj5 (trial$ or stud$)).tw.
48. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
49. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
50. (coin adj5 (flip or flipped or toss$)).tw.
51. latin square.tw.
52. versus.tw.
53. (cross-over or cross over or crossover).tw.
54. placebo$.tw.
55. sham.tw.
56. (assign$ or alternate or allocat$ or counterbalance$ or multiple baseline).tw.
57. controls.tw.
58. (treatment$ adj6 order).tw.
59. (meta-analy$ or metaanaly$ or meta analy$ or systematic review or systematic overview).tw.
60. or/18-59
61. 17 and 60

EMBASE (via Ovid) search strategy

1. cerebrovascular disease/or basal ganglion hemorrhage/or exp brain hematoma/or exp brain hemorrhage/or exp brain infarction/or exp brain ischemia/or exp carotid artery disease/or cerebral artery disease/or cerebrovascular accident/or exp intracranial aneurysm/or exp occlusive cerebrovascular disease/or stroke/
2. stroke unit/or stroke patient/
3. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
5. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
6. hemiparesis/or hemiplegia/or paresis/
7. (hemipleg$ or hemipar$ or paresis or paretic).tw.
8. or/1-7
9. exp serotonin uptake inhibitor/

10. ((serotonin or 5-HT or 5 HT or 5-hydroxytryptamine or 5 hydroxytryptamine) adj5 (uptake or reuptake or re-uptake) adj5 inhib$).tw.
11. SSRI$1.tw.
12. (alaproclat$ or ericlamin$ or citalopram or dapoxetin$ or escitalopram or femoxetin$ or fluoxetin$ or fluvoxamin$ or paroxetin$ or sertralin$ or trazodone or vilazodone or zimelidine).tw.
13. (Celexa or Cipramil or Cipram or Recital or Emocal or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Esertia or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Fluctin or fluox or Lovan or Luvox or Fevarin or Faverin or Favoxil or Movox or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Zoloft or Lustral or Serlain or Asentra).tw,tn.
14. 9 or 10 or 11 or 12 or 13
15. 8 and 14
16. limit 15 to human
17. Randomized Controlled Trial/
18. Randomization/
19. Controlled Study/
20. control group/
21. clinical trial/or phase 1 clinical trial/or phase 2 clinical trial/or phase 3 clinical trial/or phase 4 clinical trial/or controlled clinical trial/
22. Double Blind Procedure/
23. Single Blind Procedure/or triple blind procedure/
24. placebo/
25. "types of study"/
26. research subject/
27. random$.tw.
28. (controlled adj5 (trial$ or stud$)).tw.
29. (clinical$ adj5 trial$).tw.
30. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
31. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
32. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
33. (coin adj5 (flip or flipped or toss$)).tw.
34. versus.tw.
35. placebo$.tw.
36. controls.tw.
37. or/17-36
38. 16 and 37

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via EBSCOhost) search strategy

S23. S12 and S22
S22. S13 or S17 or S18 or S19 or S20 or S21
S21. AB Celexa or Cipramil or Cipram or Recital or Emocal or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Esertia or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Fluctin or fluox or Lovan or Luvox or Fevarin or Faverin or Favoxil or Movox or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Zoloft or Lustral or Serlain or Asentra
S20. TI Celexa or Cipramil or Cipram or Recital or Emocal or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Esertia or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Fluctin or fluox or Lovan or Luvox or Fevarin or Faverin or Favoxil or Movox or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Zoloft or Lustral or Serlain or Asentra

S19. TI (alaproclat* or cericlamin* or citalopram or dapoxetin* or escitalopram or femoxetin* or fluoxetin* or fluvoxamin* or paroxetin* or sertralin* or trazodone or vilazodone or zimelidine) OR AB (alaproclat* or cericlamin* or citalopram or dapoxetin* or escitalopram or femoxetin* or fluoxetin* or fluvoxamin* or paroxetin* or sertralin* or trazodone or vilazodone or zimelidine)
S18. TI SSRI* OR AB SSRI*
S17. S14 and S15 and S16
S16. TI inhib* OR AB inhib*
S15. TI (uptake or reuptake or re-uptake) OR AB (uptake or reuptake or re-uptake)
S14. TI (serotonin or 5-HT or 5 HT or 5-hydroxytryptamine or 5 hydroxytryptamine) OR AB (serotonin or 5-HT or 5 HT or 5-hydroxytryptamine or 5 hydroxytryptamine)
S13. (MH "Serotonin Uptake Inhibitors+")
S12. S1 or S2 or S3 or S6 or S9 or S10 or S11
S11. TI (hemipleg* or hemipar* or paresis or paretic) or AB (hemipleg* or hemipar* or paresis or paretic)
S10. (MH "Hemiplegia")
S9. S7 and S8
S8. TI (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*) or AB (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)
S7. TI (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid) or AB (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid)
S6. S4 and S5
S5. TI (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*) or AB (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*)
S4. TI (brain* or cerebr* or cerebell* or intracran* or intracerebral) or AB (brain* or cerebr* or cerebell* or intracran* or intracerebral)
S3. TI (stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH) or AB (stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH)
S2. (MH "Stroke Patients") OR (MH "Stroke Units")
S1. (MH "Cerebrovascular Disorders") OR (MH "Basal Ganglia Cerebrovascular Disease+") OR (MH "Carotid Artery Diseases+") OR (MH "Cerebral Ischemia+") OR (MH "Cerebral Vasospasm") OR (MH "Intracranial Arterial Diseases+") OR (MH "Intracranial Embolism and Thrombosis") OR (MH "Intracranial Hemorrhage+") OR (MH "Stroke") OR (MH "Vertebral Artery Dissections")

Allied and Complementary Medicine (AMED) (via Ovid) search strategy

1. cerebrovascular disorders/or cerebral hemorrhage/or cerebral infarction/or cerebral ischemia/or cerebrovascular accident/or stroke/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. hemiplegia/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. or/1-6
8. antidepressive agents/
9. ((serotonin or 5-HT or 5 HT or 5-hydroxytryptamine or 5 hydroxytryptamine) adj5 (uptake or reuptake or re-uptake) adj5 inhib$).tw.
10. SSRI$1.tw.
11. (alaproclat$ or cericlamin$ or citalopram or dapoxetin$ or escitalopram or femoxetin$ or fluoxetin$ or fluvoxamin$ or paroxetin$ or sertralin$ or trazodone or vilazodone or zimelidine).tw.

12. (Celexa or Cipramil or Cipram or Recital or Emocal or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Esertia or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Fluctin or fluox or Lovan or Luvox or Fevarin or Faverin or Favoxil or Movox or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Zoloft or Lustral or Serlain or Asentra).tw.
13. 8 or 9 or 10 or 11 or 12
14. 7 and 13

PsycINFO (via Ovid) search strategy

1. cerebrovascular disorders/or cerebral hemorrhage/or exp cerebral ischemia/or cerebral small vessel disease/or cerebrovascular accidents/or subarachnoid hemorrhage/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. (hemipleg$ or hemipar$ or paresis or paretic).tw.
6. hemiparesis/or hemiplegia/
7. or/1-6
8. exp serotonin reuptake inhibitors/
9. ((serotonin or 5-HT or 5 HT or 5-hydroxytryptamine or 5 hydroxytryptamine) adj5 (uptake or reuptake or re-uptake) adj5 inhib$).tw.
10. SSRI$1.tw.
11. (alaproclat$ or cericlamin$ or citalopram or dapoxetin$ or escitalopram or femoxetin$ or fluoxetin$ or fluvoxamin$ or paroxetin$ or sertralin$ or trazodone or vilazodone or zimelidine).tw.
12. (Celexa or Cipramil or Cipram or Recital or Emocal or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Esertia or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Fluctin or fluox or Lovan or Luvox or Fevarin or Faverin or Favoxil or Movox or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Zoloft or Lustral or Serlain or Asentra).tw.
13. 8 or 9 or 10 or 11 or 12
14. 7 and 13

Search strategy for the trial registers

Patient: stroke.
Intervention: alaproclate OR cericlamineOR citalopram OR clomipramine OR dapoxetine OR etoperidone OR femoxetine OR fenfluramine OR fluoxetine OR fluvoxamine OR norfenfluramine OR paroxetine OR sertraline OR trazodone OR vilazodone OR zimelidine.
Comparison: placebo.
Trial status: ongoing OR Recruiting OR Not yet recruiting OR Active.
Age: adult OR older adult.
Methods: Randomised Controlled Study.

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PHR

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