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

*AFFINITY Trial Collaboration**

Summary

Background Trials of fluoxetine for recovery after stroke report conflicting results. The Assessment oF FluoxetINe In sTroke recoverY (AFFINITY) trial aimed to show if daily oral fluoxetine for 6 months after stroke improves functional outcome in an ethnically diverse population.

Methods AFFINITY was a randomised, parallel-group, double-blind, placebo-controlled trial done in 43 hospital stroke units in Australia (n=29), New Zealand (four), and Vietnam (ten). Eligible patients were adults (aged ≥18 years) with a clinical diagnosis of acute stroke in the previous 2–15 days, brain imaging consistent with ischaemic or haemorrhagic stroke, and a persisting neurological deficit that produced a modified Rankin Scale (mRS) score of 1 or more. Patients were randomly assigned 1:1 via a web-based system using a minimisation algorithm to once daily, oral fluoxetine 20 mg capsules or matching placebo for 6 months. Patients, carers, investigators, and outcome assessors were masked to the treatment allocation. The primary outcome was functional status, measured by the mRS, at 6 months. The primary analysis was an ordinal logistic regression of the mRS at 6 months, adjusted for minimisation variables. Primary and safety analyses were done according to the patient's treatment allocation. The trial is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12611000774921.

Findings Between Jan 11, 2013, and June 30, 2019, 1280 patients were recruited in Australia (n=532), New Zealand (n=42), and Vietnam (n=706), of whom 642 were randomly assigned to fluoxetine and 638 were randomly assigned to placebo. Mean duration of trial treatment was 167 days (SD 48·1). At 6 months, mRS data were available in 624 (97%) patients in the fluoxetine group and 632 (99%) in the placebo group. The distribution of mRS categories was similar in the fluoxetine and placebo groups (adjusted common odds ratio 0·94, 95% CI 0·76–1·15; p=0·53). Compared with patients in the placebo group, patients in the fluoxetine group had more falls (20 [3%] *vs* seven [1%]; p=0·018), bone fractures (19 [3%] *vs* six [1%]; p=0·014), and epileptic seizures (ten [2%] *vs* two [<1%]; p=0·038) at 6 months.

Interpretation Oral fluoxetine 20 mg daily for 6 months after acute stroke did not improve functional outcome and increased the risk of falls, bone fractures, and epileptic seizures. These results do not support the use of fluoxetine to improve functional outcome after stroke.

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*Members of the writing group are listed at the end of the Article; all members of the AFFINITY Trial Collaboration are listed in the appendix

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See **Online** for appendix

Introduction

Stroke is the second leading cause of disability-adjusted life-years worldwide.[1,2] Fluoxetine, a selective serotonin-reuptake inhibitor (SSRI), might improve neurological recovery and reduce disability after stroke. Fluoxetine exerts neuroprotective and neuroregenerative effects in preclinical models of acute brain ischaemia.[3,4] The FLuoxetine for motor recovery After acute ischaeMic strokE (FLAME) trial[5] found that in 118 patients with moderate to severe motor deficits, fluoxetine 20 mg once daily significantly improved motor recovery after 3 months. A Cochrane systematic review of 52 randomised controlled trials of SSRIs for stroke recovery in 4059 patients concluded that SSRIs might improve disability but, given methodological limitations and heterogeneity of the studies, more definitive trials were required.[6]

Our international collaboration therefore designed three trials of fluoxetine for recovery after stroke in the UK (Fluoxetine Or Control Under Supervision [FOCUS]), Sweden (Efficacy oF Fluoxetine—a randomisEd Controlled Trial in Stroke [EFFECTS]), and Australia, New Zealand, and Vietnam (Assessment oF FluoxetINe In sTroke recovery [AFFINITY]).[7,8] The FOCUS trial[9] (n=3127) reported that oral fluoxetine 20 mg daily for 6 months after stroke did not improve functional outcome as measured by the modified Rankin Scale (mRS),[10] but reduced depression and increased bone fractures compared with those in the placebo group. These results are consistent with the reported effectiveness of fluoxetine as an antidepressant,[11] and increased risk of fractures in people aged 65 years or older taking SSRIs.[12,13] However, because only two-thirds of the patients in the FOCUS trial[9] adhered to

Research in context

Evidence before this study

We did a Cochrane systematic review and searched Cochrane, clinical trial registers, MEDLINE, Embase, PubMed, and other biomedical databases for randomised controlled trials that recruited patients with stroke who had survived up to 1 year, and randomly allocated them to a selective serotonin reuptake inhibitor (SSRI), at any dose, for any period, and any indication, or to usual care or placebo from their inception to July 16, 2018. We identified 63 trials that compared any SSRI with control in 9168 patients with stroke. Approximately half of the trials required patients to have depression. Potential improvements in disability with fluoxetine were only present in trials at high risk of bias. A meta-analysis of the three trials at low risk of bias (n=3356 patients) found no effect of any SSRI compared with placebo on functional independence (risk ratio 1·00 95% CI 0·91 to 1·09; p=0·99) or disability score (standardised mean difference –0·01, 95% CI –0·09 to 0·06; p=0·75). The evidence suggests that SSRIs do not improve functional outcome after stroke, but doubt remains because this meta-analysis was dominated by one large trial, the FOCUS (Fluoxetine Or Control Under Supervision) trial in 3127 patients in the UK.

Added value of this study

The Assessment oF FluoxetINe In sTroke recoverY (AFFINITY) trial externally validates the FOCUS trial and Cochrane systematic review of randomised controlled trials of SSRIs for stroke recovery in an independent, ethnically diverse population with stroke, reinforcing the conclusion that fluoxetine does not improve functional outcome after stroke. The AFFINITY trial also provides data regarding the potential hazards of treating patients with acute stroke with fluoxetine 20 mg daily for 6 months, including increased risks of falls, fractures, and epileptic seizures.

Implications of all the available evidence

Based on the evidence, SSRIs should not be prescribed routinely to improve functional outcome after stroke because they are ineffective and increase serious adverse events. A pooled analysis of individual patient data from randomised controlled trials of SSRIs for stroke recovery is needed to examine the effects of SSRIs in specific patient subgroups, such as those with hemiparesis, severe stroke, and cognitive impairment; and on specific outcomes, such as the modified Rankin Scale, motor domains of the Stroke Impact Scale, falls, fractures, and epileptic seizures. Until these results are available, further trials of fluoxetine for stroke recovery are not recommended.

trial medication for at least 150 of the prescribed 180 days, a modest but important effect of fluoxetine on functional outcome might have been missed. Moreover, because 96% of the patients in FOCUS were white, the results might not be generalisable outside of the UK population.[9] Hence the AFFINITY and EFFECTS trials[14] continued to recruit patients in other countries.

The AFFINITY trial aimed to evaluate whether a 6-month course of oral fluoxetine is safe and effective, compared with placebo, for improving functional outcome after acute stroke in an ethnically diverse population.

Methods

Study design and participants

AFFINITY was a randomised, parallel group, double-blind, placebo-controlled trial done in 43 hospital stroke units in Australia (n=29), New Zealand (four), and Vietnam (ten). Eligible patients were adults (aged ≥18 years) with a clinical diagnosis of acute stroke within the previous 2–15 days, brain imaging consistent with ischaemic or haemorrhagic stroke, and a persisting neurological deficit that produced a mRS score of 1 or more. Patients were excluded if they had any definite indication for fluoxetine, or contraindication to fluoxetine (eg, history of epilepsy, bipolar disorder, drug overdose, fluoxetine allergy, or recent medication that could interact with fluoxetine; or biochemical evidence of hepatic impairment [serum alanine aminotransferase concentration >120 U/L], renal impairment [creatinine concentration >180 µmol/L, estimated glomerular filtration rate <30 mL/min per 1·73 m²], or hyponatraemia [sodium concentration <125 mmol/L]); if they were unlikely to be available for follow-up during the subsequent 12 months; if they had another life-threatening illness that would make 12-month survival unlikely (eg, terminal malignancy); if women were pregnant, breast-feeding, or of child-bearing age and not using contraception; or if patients were enrolled in another clinical trial of an investigational medicinal product or device.

The trial protocol was approved by the Royal Perth Hospital Ethics Committee on Feb 24, 2012 (approval number EC2011/131); subsequent amendments to the protocol were also approved. All participating sites received approval from their ethics committee and institutional review board. The trial protocol[7] and statistical analysis plan[8] were published before recruitment stopped, without awareness of any unblinded data. Written informed consent was obtained from each patient or, if the patients were unable to provide consent, from their legally approved surrogate.

Randomisation and masking

The patient's clinician entered the patient's baseline data into a secure, password-protected, centralised, web-based randomisation system that checked the data for completeness and consistency and generated a unique study identification number and treatment pack number

corresponding to fluoxetine or placebo in a 1:1 ratio. A minimisation algorithm[15] was used to achieve balance between the treatment groups in four predictors of mRS score: time after stroke onset (2–8 *vs* 9–15 days); presence of a motor deficit (National Institutes of Health Stroke Scale [NIHSS] questions 5 and 6); presence of aphasia (NIHSS question 9); and probability of survival free of dependency (mRS score 0–2) at 6 months (0·00–0·15 *vs* 0·16–1·00) calculated using a validated prognostic model comprising six baseline variables (age, living alone before the stroke, independent in activities of daily living before the stroke, and able to talk, lift both arms off the bed, and walk unassisted at the time of randomisation).[16]

All patients, carers, investigators, and outcome assessors were masked to the allocated treatment by use of placebo capsules that were visually identical to the fluoxetine capsules even when broken open. Success of masking was not assessed.

Procedures

Fluoxetine 20 mg capsules or matching placebo capsules were administered orally, once daily, for 6 months. If patients were unable to swallow, the capsules were broken open and contents administered via an enteral feeding tube.

Siegfried Malta (Hal Far, Malta) manufactured the capsules containing fluoxetine 20 mg according to good manufacturing practice (certificate MT/008HM/2017). Arena Pharmaceuticals (Zofingen, Switzerland) packed the capsules for Amneal Pharmaceuticals (South Yarra, VIC, Australia), which was the Therapeutic Goods Administration licence holder (sponsor) for the finished product in Australia. Pharmaceutical Packaging Professionals (Port Melbourne, VIC, Australia) purchased the fluoxetine capsules and manufactured the matching placebo capsules. Pharmaceutical Packaging Professionals packaged the trial medication in patient kits, labelled the bottles with trial-specific treatment codes (fluoxetine or placebo), and packaged, stored, and distributed the medication. The patient kits in Australia and New Zealand comprised two bottles, each containing 110 capsules, which were dispensed at randomisation and at day 90. An extra 20 capsules were a reserve in the event of any delay in attending the day 90 follow-up, or any loss or spillage of capsules. For patients in Vietnam, the kits comprised six bottles of trial medication, each containing 35 capsules. One bottle was dispensed at randomisation, two bottles at day 28, and three bottles at day 90. The Therapeutic Goods Administration of the Australian Government's Department of Health approved the export of trial medication to New Zealand and Vietnam (approval reference number EX17/336513).

Patients recruited in Australia and New Zealand were assessed by site investigators at 28 days (1 month) and 90 days (3 months) after randomisation in the hospital ward, outpatient clinic, via telephone or email, or by a study nurse at the patient's residence; follow-up at 180 days (6 months) was by postal questionnaire or telephone by trained staff in the trial coordinating centre (Stroke Trials Centre, University of Western Australia, Harry Perkins Research Institute, Queen Elizabeth II Medical Centre, Perth, WA, Australia). Patients recruited in Vietnam were assessed by the site investigator at 28, 90, and 180 days after randomisation in the hospital ward, outpatient clinic, via telephone or email, or at the patient's residence. If any patient was unable to complete the assessments, assistance was sought from their proxy (next of kin, close family member, or carer). Each assessment recorded mRS score, depression measured on the Patient Health Questionnaire 9 (PHQ-9),[17] cognition using the modified Telephone Interview for Cognitive Status (TICSm),[18] communication, motor function, and overall health status using the Stroke Impact Scale (SIS) version 3.0 (all domains assessed),[19] fatigue using the vitality subscale of the 36-Item Short Form Health Survey (SF-36),[20,21] and health-related quality of life using the European Quality of Life Five-Dimensional Five-Level (EQ-5D-5L) questionnaire.[22]

A new diagnosis of depression requiring treatment with antidepressants was also assessed at 1, 3, and 6 months by asking patients if they had been diagnosed with depression since their previous assessments and verifying the diagnosis and treatment with their clinician. If patients developed new depression requiring treatment during the trial treatment period, the protocol recommended continuation of trial medication and consideration of non-pharmacological (eg, psychological) interventions. If antidepressant medication was necessary, referral to a psychiatrist was recommended for consideration of potential interactions of any new medication with fluoxetine and risks of serotonin toxicity.

Safety and adverse events, all current medications, and adherence to trial medication were also recorded at each assessment. Serum sodium concentration, estimated glomerular filtration rate, and liver function were measured at the follow-up visit 28 days after randomisation if clinically appropriate. Adherence to trial medication was assessed by asking: "On average, since the last follow-up, how many times per week was the trial medication taken? 0, 1–2, 3–4, 5–6, or 7 times per week?" and by pill counts and collection of returned trial bottles. Bottle and pill counts were done by hospital trial pharmacists and entered on a drug accountability form. Any interruption to trial medication was recorded as temporary or permanent, together with the dates and reasons for stopping and restarting. All patients received organised, interdisciplinary care and rehabilitation in stroke units; organised stroke unit care is provided in hospital by nurses, doctors, and therapists who specialise in looking after patients with stroke and work as a coordinated team.

Outcomes

The primary outcome was functional status, as measured by the mRS, at 6 months after randomisation. In Australia and New Zealand, the primary outcome was centrally

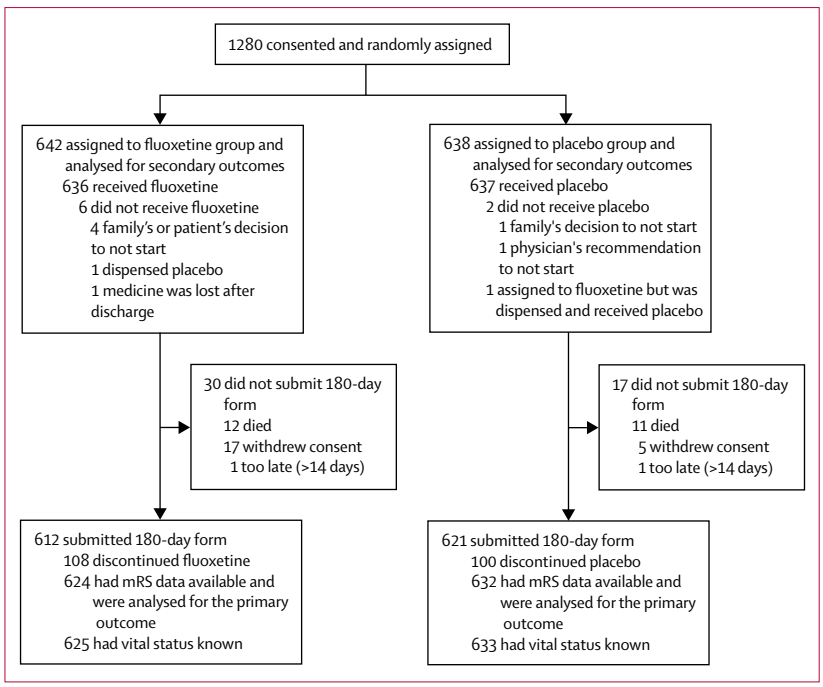

Figure 1: **Trial profile**
A 180-day follow-up form was submitted for seven patients who had died during follow-up (three fluoxetine, four placebo). mRS=modified Rankin Scale.

assessed; in Vietnam, it was assessed by the site investigator (appendix p 8). Secondary outcomes at 6 months were survival, depression (change in PHQ-9 score from baseline and PHQ-9 score ≥15), cognition (TICSm score), communication, motor function, and overall health status (SIS score), fatigue (vitality subscale of the SF-36), health-related quality of life (EQ-5D-5L), new diagnosis of depression requiring treatment with antidepressants, and trial medication adherence and cessation.

Adverse events assessed during follow-up were also included as secondary outcomes. These adverse events were any recurrent stroke (ischaemic or haemorrhagic), acute coronary syndromes, upper gastrointestinal bleeding requiring blood transfusion or endoscopy, other major bleeding (subdural, extradural, ocular, or lower gastrointestinal) requiring blood transfusion or procedural intervention, falls with injury, new bone fractures, epileptic seizures, symptomatic hypoglycaemia (blood glucose <3 mmol/L), symptomatic hyperglycaemia (blood glucose >22 mmol/L), new hyponatraemia (blood sodium <125 mmol/L), attempted suicide or self-harm, and death.

Statistical analysis

We estimated from two previous studies of patients with acute stroke that 42·2% of patients assigned to placebo would be functionally independent (mRS 0–2) at 6 months after randomisation.[23,24] We calculated the odds ratio (OR) of functional independence with fluoxetine versus placebo in the FLAME study[5] to be 3·57 (95% CI 1·2–10·6). We considered a conservative estimate of the effect of fluoxetine to be toward the lower 95% CI of the OR estimate reported in FLAME (eg, OR 1·34). If fluoxetine increased the proportion of patients who were functionally independent at 6 months by an OR of 1·34 from 42·2% (placebo) to 49·4% (fluoxetine), this would be clinically important and consistent with our Cochrane review.[6] Assuming a common OR of 1·34 for each cut-point across the mRS (eg, 0 *vs* 1–6, 0–1 *vs* 2–6) in the proportional odds logistic model, we estimated that the trial would require enrolment of 1600 patients to have 90% power, if up to 10% of patients dropped out before final follow-up (ie, 1440 patients with primary outcome data).[8,25]

Primary analysis was in the modified intention-to-treat population, which included all randomly assigned patients who had mRS data available at the 6-month follow-up. Analyses of secondary outcomes and adverse events were in the intention-to-treat population. A secondary safety analysis was done in all patients who received at least one dose of study medication. We also did prespecified per-protocol analyses for the primary outcome, which sequentially excluded subgroups of patients who did not meet our eligibility criteria or had incomplete adherence to the trial medication.

The primary analysis was of the mRS scores at 6 months in each treatment group using ordinal logistic regression after adjusting for the baseline factors included in the minimisation algorithm.[8] The ordinal analysis of mRS was done by treatment allocation under the assumption of proportional odds in the model. The result was expressed as a common OR (OR <1·0 favoured placebo) and its 95% CI. We also did six binary unadjusted logistic regressions corresponding to the six possible dichotomisations of scores on the mRS.

For secondary outcomes, the frequencies of categorical outcome events in each group were compared using Fisher's exact test. For continuous outcomes, the mean or median in each group, depending on the distribution, were calculated with measures of dispersion (SD or IQR). The probability that outcomes in the fluoxetine group were significantly different from the placebo group were calculated as p values ($p<0·05$ being considered statistically significant).

Prespecified subgroup analyses of the effect of fluoxetine versus placebo on the primary outcome were done for country of randomisation (Australia and New Zealand *vs* Vietnam), age (≤70 *vs* >70 years), time from stroke onset to randomisation (2–8 *vs* 9–15 days), stroke pathology (ischaemic *vs* haemorrhagic), stroke severity (median NIHSS scores 0–5 *vs* >5), motor deficit (present *vs* absent), aphasia (present *vs* absent), probability of survival free of dependency (0·00–0·15 *vs* 0·16–1·00), self-reported depression at baseline, and source of informed consent.

Post-hoc sensitivity analyses of the primary outcome were done to evaluate the possible effect of including patients who were lost to follow-up. We tested the robustness of the results by assuming two extreme imputation scenarios: one favouring fluoxetine in which all patients

	Fluoxetine (n=642)	Placebo (n=638)
Sex		
Women	231 (36%)	245 (38%)
Men	411 (64%)	393 (62%)
Age, years		
Mean	63·5 (12·5)	64·6 (12·2)
≤70	450 (70%)	432 (68%)
>70	192 (30%)	206 (32%)
Ethnicity		
Asian	356 (55%)	371 (58%)
White	267 (42%)	255 (40%)
Other	19 (3%)	12 (2%)
Marital status		
Married	463 (72%)	463 (73%)
Partner	29 (4%)	19 (3%)
Divorced or separated	37 (6%)	46 (7%)
Widowed	61 (9%)	70 (11%)
Single	52 (8%)	38 (6%)
Other	0 (0%)	2 (<1%)
Living arrangements		
Living with someone else	564 (88%)	556 (87%)
Living alone	78 (12%)	78 (12%)
Living in an institution	0	2 (<1%)
Other	0	2 (<1%)
Employment status		
Full-time employment	206 (32%)	180 (28%)
Part-time employment	77 (12%)	68 (11%)
Retired	315 (49%)	363 (57%)
Unemployed or disabled	24 (4%)	14 (2%)
Other	20 (3%)	13 (2%)
Independent before stroke	634 (99%)	630 (99%)
Previous medical history		
Coronary heart disease	58 (9%)	57 (9%)
Ischaemic stroke or transient ischaemic attack	77 (12%)	84 (13%)
Diabetes	143 (23%)	147 (23%)
Hyponatraemia	1 (<1%)	3 (<1%)
Intracranial bleed	11 (2%)	8 (1%)
Upper gastrointestinal bleed	11 (2%)	15 (2%)
Bone fractures	71 (11%)	74 (12%)
Depression	30 (5%)	20 (3%)
Stroke diagnosis		
Non-stroke (final diagnosis)	3 (<1%)	1 (<1%)
Ischaemic stroke	549 (86%)	542 (85%)
Intracerebral haemorrhage	90 (14%)	95 (15%)
OCSP classification of ischaemic stroke		
Total anterior circulation infarct	47 (9%)	50 (9%)
Partial anterior circulation infarct	271 (49%)	283 (52%)
Lacunar infarct	115 (21%)	105 (19%)
Posterior circulation infarct	114 (21%)	103 (19%)
Uncertain	2 (<1%)	1 (<1%)

(Table 1 continues in next column)

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	Fluoxetine (n=642)	Placebo (n=638)
Causes of ischaemic stroke (modified TOAST classification)		
Large artery disease	123 (22%)	134 (25%)
Small vessel disease	261 (47%)	250 (46%)
Embolism from the heart	95 (17%)	93 (17%)
Another cause	9 (2%)	8 (1%)
Unknown or uncertain cause	61 (11%)	57 (10%)
Predictive variables		
Able to walk at time of randomisation	282 (44%)	279 (44%)
Able to lift both arms off bed	443 (69%)	431 (68%)
Able to talk and not confused	554 (86%)	557 (87%)
Predicted 6-month outcome based on SSV		
Median probability of survival free of dependency	0·57 (0·26–0·87)	0·55 (0·24–0·87)
0·00–0·15	100 (15%)	103 (16%)
0·16–1·00	542 (84%)	535 (84%)
Neurological deficits		
Median NIHSS	6 (3–9)	6 (3–9)
Presence of a motor deficit	557 (87%)	548 (86%)
Presence of aphasia	129 (20%)	121 (19%)
Depression		
Diagnosis of depression (patient or proxy reported)	15 (2%)	17 (3%)
Taking a non-SSRI antidepressant drug	5 (1%)	5 (1%)
Mood measured by PHQ-9		
Median score	4 (1–7)	4 (2–7)
Score 0–14	601 (98%)	596 (98%)
Score ≥15	12 (2%)	11 (2%)
Delay since stroke onset at randomisation, days		
Mean delay	6·1 (3)	6·3 (3)
2–8	486 (76%)	479 (75%)
9–15	156 (24%)	159 (25%)
Consent		
Patient consented	345 (54%)	328 (51%)
Person responsible consented	284 (44%)	295 (46%)
Proxy consented	3 (<1%)	1 (<1%)
Waiver acknowledgment	10 (2%)	14 (2%)

Data are n (%), mean (SD), or median (IQR). NIHSS=National Institutes of Health Research Stroke Scale. OCSP=Oxfordshire Community Stroke Project. PHQ-9=Patient Health Questionnaire 9 (higher scores indicate more depressive symptoms).[17] SSRI=selective serotonin-reuptake inhibitor. SSV=six baseline variables that predict functional status, as measured by the modified Rankin Scale, after stroke (age, living alone before the stroke, independent in activities of daily living before the stroke, and able to talk, lift both arms off the bed, and walk unassisted at the time of randomisation).[16] TOAST=Trial of ORG 10172 in acute stroke treatment criteria.

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

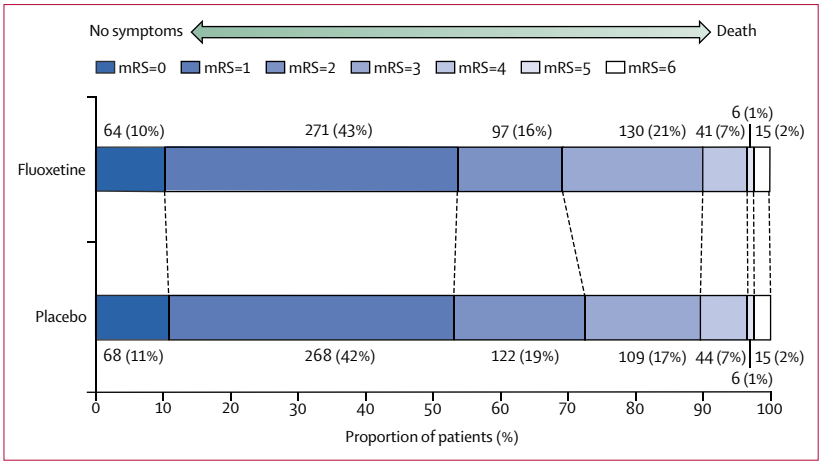

Figure 2: **Primary outcome of the distribution of the mRS scores at 6 months by treatment group (modified intention-to-treat population)**
mRS=modified Rankin Scale.

	Fluoxetine (n=642)	Placebo (n=638)	p value
New depression	33 (5%)	46 (7%)	0·13
New antidepressant	30 (5%)	43 (7%)	0·12
Mood (PHQ-9 score)	2·0 (1·0–5·0)	2·0 (1·0–5·0)	0·42
PHQ-9 score ≥15	4 (<1%)	6 (1%)	0·75
Cognition (TICSm score)	24·0 (20·0–27·0)	24·0 (19·0–27·0)	0·62
SIS domain scores			
Strength	75·0 (56·3–93·8)	75·0 (56·3–93·8)	0·26
Hand ability	85·0 (55·0–100·0)	85·0 (55·0–100·0)	0·39
Mobility	91·7 (69·4–100·0)	88·9 (66·7–97·2)	0·08
Motor*	83·5 (63·5–94·2)	82·4 (60·4–93·2)	0·28
Daily activities	90·0 (72·5–100·0)	90·0 (70·0–97·5)	0·25
Physical function†	85·5 (66·2–94·9)	83·8 (63·4–93·8)	0·24
Memory	89·3 (78·6–100·0)	89·3 (75·0–100·0)	0·28
Communication	98·2 (89·3–100·0)	96·4 (85·7–100·0)	0·61
Mood and emotional control‡	80·6 (66·7–88·9)	77·8 (66·7–86·1)	0·0028
Participation	81·3 (59·4–96·9)	75·0 (56·3–96·9)	0·48
Recovery (VAS)	80·0 (60·0–90·0)	80·0 (60·0–90·0)	0·90
Fatigue (vitality subscale of the SF-36)	70·0 (55·0–80·0)	70·0 (55·0–80·0)	0·36
Health-related quality of life (EQ-5D-5L)	0·81 (0·63–1·00)	0·78 (0·58–0·93)	0·083

Data are n (%) or median (IQR). Data were only available for patients who survived and who completed sufficient questions to derive a score. The numbers of patients with missing scores were similar in the two treatment groups. EQ-5D-5L=European Quality of Life Five-Dimensional Five-Level questionnaire (where 1 indicates the best health imaginable and −0·676 indicates the worst health imaginable). PHQ-9=Patient Health Questionnaire 9 (higher score indicates more depressive symptoms). SF-36=36-Item Short Form Health Survey (higher scores indicate less disability). SIS=Stroke Impact Scale (where higher scores are better). TICSm=modified Telephone Interview for Cognitive Status. VAS=visual analogue scale. *Mean of the strength, hand ability, and mobility domains. †Mean of the strength, hand ability, mobility, and daily activities domains. ‡Mood and emotional control domain of the SIS: nine questions about "how you feel, changes in your mood, and your ability to control your emotions, since your stroke" (where higher scores are better).

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

with missing mRS data were imputed a score of 0 in the fluoxetine group and a score of 6 in the placebo group, and another scenario favouring placebo in which the imputation was reversed.

Risk differences and their 95% CIs for adverse events were calculated using the FREQ procedure. The confidence intervals around the risk differences were calculated as Wald intervals based on the normal approximation.

Statistical analyses were done with SAS, version 9.4. An independent data monitoring committee (appendix p 2) oversaw the study. The unmasked trial statistician (QY) prepared analyses of the accumulating data, which the data monitoring committee reviewed in confidence at least annually. The trial is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12611000774921.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 11, 2013, and June 30, 2019, 1280 patients were recruited from 43 hospital stroke units in Australia (n=532), New Zealand (n=42), and Vietnam (n=706). Recruitment was terminated before the target of 1600 patients was reached because funding expired on Dec 31, 2019. Of the 1280 patients, 642 patients were randomly allocated to receive fluoxetine and 638 to receive placebo (figure 1). Baseline characteristics in the two groups were balanced (table 1).

Trial medication was started in 1273 patients (636 in the fluoxetine group, 636 in the placebo group, and one in the fluoxetine group who was dispensed placebo). There were 57 protocol violations in 57 (4·5%) of 1280 patients: one (0·1%) patient (fluoxetine group) did not meet our eligibility criteria after discovery of participation in another trial of an investigational medicinal product; in four (0·3%) patients (three in the fluoxetine group, one in the placebo group), the diagnosis was later revised to be non-stroke and these patients were excluded from the final analyses (table 1); one patient (0·1%) was assigned a treatment pack containing fluoxetine but was mistakenly dispensed a different treatment pack number, which contained placebo; 20 (1·6%) patients (ten fluoxetine, ten placebo) were prescribed open-label fluoxetine; nine (0·7%) patients (five fluoxetine, four placebo) were prescribed another SSRI; 11 (0·9%) patients (four fluoxetine, seven placebo) lost their trial medication or did not take it as prescribed; four (0·3%) patients (two fluoxetine, two placebo) took medications that could interact with fluoxetine (eg, antipsychotic medications, tramadol); and seven (0·5%) patients (four fluoxetine, three placebo) were more than 14 days late for scheduled follow-up. Emergency unmasking was not necessary for any patient.

By the 6-month follow-up visit, 22 (1·7%) of 1280 patients had withdrawn consent for follow-up (17 [3%] of 642 in the fluoxetine group, five [1%] of 638 in the placebo group), two (0·2%; one [<1%] from each group) were lost

to follow-up, and 23 (1·8%; 12 [2%] in the fluoxetine group, 11 [2%] in the placebo group) had died and not had a 180-day follow-up form submitted (for seven patients who died close to the 6-month follow-up, the site investigators submitted follow-up forms; figure 1). There was no difference in the methods of follow-up between groups (appendix p 8).

The mRS at 6 months was analysed in 624 (97%) of 642 patients allocated to receive fluoxetine and in 632 (99%) of 638 patients allocated to receive placebo. An ordinal comparison of the distribution of patients across mRS categories at 6 months, adjusted for variables in the minimisation algorithm, was similar in both groups (common OR 0·94, 95% CI 0·76–1·15; p=0·53; figure 2). The unadjusted analysis produced similar results (common OR 0·97, 95% CI 0·79–1·18; p=0·74; appendix p 11). The assumption of proportional odds in the model of mRS by treatment was upheld in the score test for proportional odds assumption (p=0·44 unadjusted). Dichotomised mRS scores were also not significantly different between groups for mRS 0–2 versus mRS 3–6 (unadjusted OR 0·86, 95% CI 0·67–1·09; p=0·21; post-hoc adjusted OR 0·82, 0·63–1·08; p=0·16), or other dichotomies of the mRS (appendix p 11). Analysis of the primary outcome showed no significant interactions or modification of the effect of fluoxetine across several prespecified subgroups (appendix p 15).

Secondary outcomes at 6 months are shown in table 2. Patients allocated to receive fluoxetine had higher scores in the SIS domain of mood and emotional control than those allocated to receive placebo (p=0·0028), but there were no significant differences between treatment groups in the other domains of the SIS (including measures of motor function [strength, hand ability, mobility] and daily activities), other assessment scales, or death (table 3).

The mean duration of trial treatment was 167 days (SD 48·1). Trial medication was temporarily stopped in 158 patients (87 fluoxetine, 71 placebo; appendix p 9), and permanently stopped in 105 (16%) patients in the fluoxetine group and 100 (16%) in the placebo group (appendix pp 9, 14). There was no significant difference between groups in temporary or permanent discontinuation of trial medication (appendix p 9) or time to permanent discontinuation (appendix p 14). There were also no differences between groups in compliance with trial medication (appendix p 10).

Adverse events at 6 months are shown in table 3. Compared with patients in the placebo group, patients in the fluoxetine group had more falls causing injury (20 [3%] of 642 *vs* seven [1%] of 638; difference 2·02% [95% CI 0·45–3·59]; p=0·018), bone fractures (19 [3%] *vs* six [1%]; difference 2·02% [0·51–3·53]; p=0·014), and epileptic seizures (ten [2%] *vs* two [<1%]; difference 1·24% [0·19–2·30]; p=0·038). There were no significant differences between groups in other events, including survival (appendix p 16). Trial medication was stopped by 68 patients (27 in the fluoxetine group, 41 in the placebo group) due to a suspected adverse reaction to the medication. No patients required a reduction in dose of trial medication (eg, alternate daily) and there were no treatment-related deaths.

	Fluoxetine (n=642)	Placebo (n=638)	Difference (95% CI)	p value
Death	15 (2%)	15 (2%)	–0·01% (–1·64 to 1·67)	1·00
Any recurrent stroke	18 (3%)	26 (4%)	–1·27% (–3·27 to 0·72)	0·22
All thrombotic events				
Ischaemic stroke	11 (2%)	21 (3%)	–1·58% (–3·29 to 0·13)	0·076
Acute coronary events	1 (<1%)	2 (<1%)	–0·16% (–0·69 to 0·37)	0·62
All bleeding events				
Haemorrhagic stroke	3 (<1%)	1 (<1%)	0·31% (–0·30 to 0·92)	0·62
Upper gastrointestinal bleed	1 (<1%)	1 (<1%)	0·00% (–0·43 to 0·43)	1·00
Epileptic seizures	10 (2%)	2 (<1%)	1·24% (0·19 to 2·30)	0·038
Fall with injury	20 (3%)	7 (1%)	2·02% (0·45 to 3·59)	0·018
New bone fracture	19 (3%)	6 (1%)	2·02% (0·51 to 3·53)	0·014
New hyponatraemia (blood sodium <125 mmol/L)	3 (<1%)	2 (<1%)	0·15% (–0·53 to 0·84)	1·00
Symptomatic hyperglycaemia (blood glucose >22 mmol/L)	0	0	..	..
Symptomatic hypoglycaemia (blood glucose <3 mmol/L)	0	0	..	..
Attempted or actual suicide	0	2 (<1%)	–0·16% (–0·75 to 0·12)	0·25
Other adverse event	62 (10%)	68 (11%)	–1·00% (–4·31 to 2·31)	0·56

Data are n (%), unless otherwise stated.

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

The primary results were not altered by post-hoc sensitivity analyses confined to patients who adhered to the trial protocol and allocated treatment (appendix p 12). A post-hoc analysis, imputing missing mRS data under two extreme scenarios, also produced non-significant results for the most extreme scenarios in favour of fluoxetine (unadjusted OR 1·08, 95% CI 0·89–1·32; p=0·44; adjusted OR 1·05, 0·86–1·29; p=0·61), and in favour of placebo (unadjusted OR 0·86, 0·71–1·05; p=0·14; adjusted OR 0·83, 0·68–1·02; p=0·077).

Discussion

The main finding of the AFFINITY trial was that adding fluoxetine 20 mg daily for 6 months after acute stroke to organised, interdisciplinary stroke unit care did not improve functional outcome at 6 months in an ethnically diverse population. Other major findings were that fluoxetine increased falls, fractures, and epileptic seizures at 6 months, compared with placebo.

The AFFINITY trial had a smaller sample size than the FOCUS trial[9] but both trials recruited patients of similar sex (women 37%), stroke severity (median NIHSS=6), and at a similar time (mean 1 week) after stroke onset. The AFFINITY trial population was a mix of Asian (n=727 [57%]) and white (n=522 [41%]) patients, whereas the FOCUS trial population was predominantly white (n=2988 [96%]). Patients in AFFINITY were also younger (mean

age 64 years in AFFINITY *vs* 71 years in FOCUS), and more likely to be married (n=926 [72%] *vs* n=1725 [55%]), living with someone else (n=1120 [87%] *vs* n=2091 [67%]), employed (n=531 [41%] *vs* n=691 [22%]), and independent before their stroke (n=1264 [99%] *vs* n=2866 [92%]) compared with the patients in FOCUS. Adherence to trial medication was lower in AFFINITY than in FOCUS; in AFFINITY, 78 (12%) patients assigned to fluoxetine and 76 (12%) patients assigned to placebo stopped trial medication within the first 90 days (appendix pp 9, 14), whereas in FOCUS, 143 (9%) patients assigned to fluoxetine and 122 (8%) patients assigned to placebo stopped trial medication within the first 90 days. Despite these differences, the results of the AFFINITY trial almost replicate those of the FOCUS trial,[9] supporting the internal and external validity of both trials. The EFFECTS trial[14] of fluoxetine versus placebo in 1500 patients with stroke in Sweden also reports similar results to FOCUS and AFFINITY. Moreover, the results of the FOCUS, AFFINITY, and EFFECTS trials are consistent with a Cochrane review of randomised controlled trials of SSRIs for stroke recovery,[26] and trials that specifically tested fluoxetine.[27] Collectively, these trials provide compelling evidence that fluoxetine does not improve functional outcome after stroke.

The predominant inconsistency among the evidence from randomised controlled trials is the FLAME trial,[5] which did report a significant benefit of fluoxetine on motor recovery after stroke. The FLAME trial differed from AFFINITY, FOCUS, and EFFECTS in that it was a phase 2 trial of oral fluoxetine 20 mg daily versus placebo in a selected population of 118 patients with recent (5–10 days) ischaemic stroke and a moderate to severe hemiparesis or hemiplegia, defined by a Fugl-Meyer Motor Scale (FMMS) score of 55 or less.[5] The FMMS ranges from 0 (hemiplegia) to 100 points (normal motor performance), with 66 points for the upper extremity and 34 points for the lower extremity. Patients enrolled in FLAME had more severe strokes (mean baseline NIHSS 13 *vs* median NIHSS 6 in AFFINITY).[5] Somatosensory and other neurological deficits that might influence recovery were not reported in FLAME. The primary outcome in FLAME, the mean change in FMMS scores between randomisation and day 90, was greater with fluoxetine than placebo (34·0 points fluoxetine *vs* 24·3 points placebo; difference 9·8 points, 95% CI 3·4–16·1; p=0·003). The proportion of functionally independent patients (mRS scores 0–2) at day 90 was also higher with fluoxetine than placebo (n=15 [26%] *vs* n=5 [9%]; p=0·02), but there were no differences between fluoxetine and placebo for other mRS categories. The FLAME trial[5] result might be a false-positive due to random error, because only 57 patients were treated with fluoxetine and followed up to 90 days, and there is large variation in spontaneous motor recovery after acute stroke.[28] Alternatively, the FLAME trial result might be a true-positive, and fluoxetine might indeed improve motor recovery in patients with severe motor impairment. The AFFINITY trial did not include a large number of patients with severe hemiparesis and did not measure motor recovery by the FMMS, but did measure motor functions as domains within the SIS and found no effect of fluoxetine compared with placebo. Our planned individual patient data meta-analysis of the FOCUS, AFFINITY, and EFFECTS trials[8] will constitute a larger number of patients with stroke with severe motor impairments and should enable a more reliable analysis of the effect of fluoxetine compared with placebo on the mRS and motor domains of the SIS at 6 months in this subgroup.

The AFFINITY trial also confirms the FOCUS trial[9] finding that long-term fluoxetine in patients with stroke has hazards, increasing the risk of bone fractures. We also found that fluoxetine significantly increased the risk of falls with injury and epileptic seizures in patients with stroke. The FOCUS trial[9] reported increases in falls with injury and seizures in patients who were allocated to receive fluoxetine that were similar to in AFFINITY, but not significant. The AFFINITY and FOCUS trials collectively provide robust evidence about the effect of an SSRI on the incidence of fractures and falls causing injury, increasing the absolute risk of each by about 2% over 6 months among patients with recent stroke.

Although fluoxetine is more effective than placebo in treating major depressive disorders,[11] and reduced the rate of new depression in the FOCUS trial[9] and other trials,[27,29] we only observed improved mood and emotional control, as measured by the SIS, at 6 months with fluoxetine; the lower rate of depression after stroke with fluoxetine versus with placebo was not statistically significant. We believe our trial did not have statistical power to show a significant effect of fluoxetine on depression after stroke because the absolute rates of depression in both groups in AFFINITY were substantially lower (less than half) than in FOCUS, possibly because of under-reporting, particularly in Vietnam where the reporting of changes in mood might be affected by the cultural setting.[30]

A key strength of the trial is that it was done in stroke units throughout Australia, New Zealand, and Vietnam where the AFFINITY trial medication was added to best-practice, organised interdisciplinary stroke care and rehabilitation. The inclusion of different ethnic groups being managed in different health-care systems, and a comprehensive array of secondary outcome measures, including cognition, mood, and motor scales, support the external validity and generalisability of the trial results. Adherence to trial medication was high and similar between treatment groups, which also minimised possible performance bias. Follow-up for the primary outcome was high and there was no difference between groups in withdrawals from treatment, minimising the possibility of attrition bias.

Potential limitations of the trial include our failure to recruit the target sample size of 1600 patients because of funding constraints (1280 patients recruited; 1256 with primary outcome data *vs* 1440 planned to have primary

outcome data). We also failed to recruit a large proportion of patients with severe, disabling stroke. Hence, the proportion of patients assigned placebo who recovered functional independence (mRS 0–2) at 6 months was higher (458 [72%] of 638) than estimated in our sample size calculations (42%). The dose of fluoxetine was 20 mg once daily because this was the dose reported to be effective in the FLAME trial[5] and used in other fluoxetine trials for stroke recovery,[6] and is less likely to cause adverse effects than higher doses. However, we did not test higher doses of fluoxetine. Our measures of adherence to trial medication by self-report and capsule-counting were prone to error (eg, the absence of tablets in the bottles returned to investigators might not necessarily mean adherence to taking the tablets) and, therefore, our estimates of adherence and compliance might be inflated. However, there was no difference between groups in reported adherence to, and discontinuation of, trial medication. The nature and degree of adjunctive rehabilitation was not documented because that would have added complexity and potential measurement error to this pragmatic trial. However, all patients were admitted to stroke units in which organised, interdisciplinary assessment (and rehabilitation as required) was provided as standard practice. There was a slight difference in ascertainment of mRS status at 6 months between groups (fluoxetine n=624 [97%] *vs* placebo n=632 [99%]), but sensitivity analyses using imputations did not alter the results. Our primary measure of efficacy was a broad measure of functional outcome, which might not be sensitive to changes in measures of specific neurological functions. However, we also measured eight domains of the SIS, including measures of motor function (strength, hand ability, mobility), physical function, and daily activities, and found no effect of fluoxetine on any of these measures. The mRS might be less sensitive to change in patients with less severe stroke, but there was no evidence of an effect of fluoxetine on the mRS in patients with more severe stroke (NIHSS >5; appendix p 15), and no effect of fluoxetine on any secondary outcome except for the SIS domain mood and emotional control .

In summary, the AFFINITY trial reinforces the conclusion of the latest Cochrane review[26] that SSRIs are not effective at improving functional outcome after stroke. It also shows that fluoxetine might improve mood but has important adverse effects, particularly bone fractures. A planned individual patient data meta-analysis of the AFFINITY, FOCUS, and EFFECTS trials will produce greater precision in the estimates of the effects of fluoxetine on functional outcome in important patient subgroups such as those with hemiparesis, severe stroke, and cognitive impairment.[8]

Contributors

GJH was Chief Investigator A of the National Health and Medical Research Council (NHMRC) of Australia Project Grant 1059094, co-Chair of the steering committee, Chair of the trial coordinating committee, involved in the design of the trial, recruited and followed up patients enrolled at his hospital site, adjudicated all adverse and serious adverse events in the trial (blind to treatment allocation), and wrote the first and final versions of the manuscript. MLH was Chief Investigator B of the NHMRC Project Grant 1059094, co-Chair of the steering committee, involved in the trial design, and advised on management of the trial. OPA was Chief Investigator C of the NHMRC Project Grant 1059094, participated in the steering committee, involved in the trial design, and advised on the management of depression within the trial. LF was Chief Investigator D of the NHMRC Project Grant 1059094, participated in the steering committee, and was involved in the trial design. GEM was Chief Investigator E of the NHMRC Project Grant 1059094, participated in the steering committee as co-Chief Investigator of the FOCUS trial, and was involved in the trial design. MSD was Chief Investigator F of the NHMRC Project Grant 1059094, participated in the steering committee as co-Chief Investigator of the FOCUS trial, was involved in the trial design, and advised regularly about trial management. CE-B was Chief Investigator G of the NHMRC Project Grant 1059094 and participated in the steering committee. AHF was Chief Investigator H of the NHMRC Project Grant 1059094, participated in the steering committee, and advised on the management of depression in the trial. LB was Chief Investigator I of the NHMRC Project Grant 1059094, participated in the steering committee, was involved in the trial design, advised on the statistical analysis plan and independently analysed the trial data and verified the final analysis. SJ was Chief Investigator E of the NHMRC Project Grant 1059094 from 2014 to 2018, and participated in the steering committee. TL was Chief Investigator E of the NHMRC Project Grant 1059094 in 2019. VM (deceased December, 2014) was an Associate Investigator of the NHMRC Project Grant 1059094, participated in the steering committee as Chief Investigator of the EFFECTS trial, and was involved in the trial design. EL participated in the steering committee as Chief Investigator of the EFFECTS trial and was involved in the trial design. CSA was an Associate Investigator of the NHMRC Project Grant 1059094, participated in the steering committee, was involved in the trial design, and provided trial strategic advice. HT-N was national coordinator for Vietnam, and the Principal Investigator responsible for recruitment and follow-up of patients enrolled at his hospital site. JG was national coordinator for New Zealand, the Principal Investigator responsible for recruitment and follow-up of patients enrolled at his hospital site, and commented on the draft manuscript. QY undertook the statistical analysis of the trial data for the Data Monitoring Committee meetings and for the final results. The contributions other members of the AFFINITY trial collaboration are listed in the appendix (pp 1–7).

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Declaration of interests

GJH has received grants from the NHMRC of Australia, Vetenskapsrådet (The Swedish Research Council), and UK National Institute for Health Research Technology, during the conduct of the study; and personal fees from the American Heart Association, outside of the submitted work. MLH, CE-B, LB, and TL have received grants from the NHMRC of Australia during the conduct of the study. CSA has received grants from the NHMRC of Australia, and grants and personal fees from Takeda, outside of the submitted work. All other members of the writing group declare no competing interests.

Data sharing

The trial protocol and statistical analysis plan have been published elsewhere.[7,8] A fully anonymised trial dataset with individual patient data and a data dictionary will be available to other researchers after the publication of the full trial results from the final follow-up at 12 months. Written proposals and requests are to be directed to GH (co-Chief Investigator). Proposals will be assessed by the AFFINITY trial Steering Committee and a data sharing agreement established if, and before, any data are to be shared.

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References

1 Hankey GJ. Stroke. *Lancet* 2017; **389:** 641–54.
2 GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019; **18:** 439–58.
3 Lim CM, Kim SW, Park JY, Kim C, Yoon SH, Lee JK. Fluoxetine affords robust neuroprotection in the postischemic brain via its anti-inflammatory effect. *J Neurosci Res* 2009; **87:** 1037–45.
4 Wang JW, David DJ, Monckton JE, Battaglia F, Hen R. Chronic fluoxetine stimulates maturation and synaptic plasticity of adult-born hippocampal granule cells. *J Neurosci* 2008; **28:** 1374–84.
5 Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. *Lancet Neurol* 2011; **10:** 123–30.
6 Mead GE, Hsieh CF, Lee R, et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. *Cochrane Database Syst Rev* 2012; **11:** CD009286.
7 Mead G, Hackett ML, Lundström E, Murray V, Hankey GJ, Dennis M. The FOCUS, AFFINITY and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: a study protocol for three multicentre randomised controlled trials. *Trials* 2015; **16:** 369.
8 Graham C, Lewis S, Forbes J, et al. The FOCUS, AFFINITY and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: statistical and health economic analysis plan for the trials and for the individual patient data meta-analysis. *Trials* 2017; **18:** 627.
9 Dennis M, Mead G, Forbes J, et al. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. *Lancet* 2019; **393:** 265–74.
10 Bruno A, Shah N, Lin C, et al. Improving modified Rankin Scale assessment with a simplified questionnaire. *Stroke* 2010; **41:** 1048–50.
11 Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018; **391:** 1357–66.
12 Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ* 2011; **343:** d4551.
13 Brännström J, Lövheim H, Gustafson Y, Nordström P. Association between antidepressant drug use and hip fracture in older people before and after treatment initiation. *JAMA Psychiatry* 2019; **76:** 172–79.
14 EFFECTS Trial Collaboration. Safety and efficacy of fluoxetine on functional recovery after acute stroke (EFFECTS): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2020; **19:** 661–69.
15 Altman DG, Bland JM. Treatment allocation by minimisation. *BMJ* 2005; **330:** 843.
16 Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute and subacute stroke: development and validation of new prognostic models. *Stroke* 2002; **33:** 1041–47.
17 Williams LS, Brizendine EJ, Plue L, et al. Performance of the PHQ-9 as a screening tool for depression after stroke. *Stroke* 2005; **36:** 635–38.
18 de Jager CA, Budge MM, Clarke R. Utility of TICS-M for the assessment of cognitive function in older adults. *Int J Geriatr Psychiatry* 2003; **18:** 318–24.
19 Duncan PW, Bode RK, Min Lai S, Perera S. Rasch analysis of a new stroke-specific outcome scale: the Stroke Impact Scale. *Arch Phys Med Rehabil* 2003; **84:** 950–63.
20 Mead G, Lynch J, Greig C, Young A, Lewis S, Sharpe M. Evaluation of fatigue scales in stroke patients. *Stroke* 2007; **38:** 2090–95.
21 Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 health survey: manual and interpretation guide. Boston, MA: New England Medical Center, Health Institute, 1993.
22 Norman R, Cronin P, Viney R. A pilot discrete choice experiment to explore preferences for EQ-5D-5L health states. *Appl Health Econ Health Policy* 2013; **11:** 287–98.
23 CLOTS Trials Collaboration. Thigh-length versus below-knee stockings for deep vein thrombosis prophylaxis after stroke: a randomized trial. *Ann Intern Med* 2010; **153:** 553–62.
24 Sandercock P, Wardlaw JM, Lindley RI, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet* 2012; **379:** 2352–63.
25 Howard G, Waller JL, Voeks JH, et al. A simple, assumption-free, and clinically interpretable approach for analysis of modified Rankin outcomes. *Stroke* 2012; **43:** 664–69.
26 Legg LA, Tilney R, Hsieh C-F, et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. *Cochrane Database Syst Rev* 2019; **11:** CD009286.
27 Mead GE, Legg L, Tilney R, et al. Fluoxetine for stroke recovery: meta-analysis of randomized controlled trials. *Int J Stroke* 2019; published online Oct 17. DOI:10.1177/1747493019879655.
28 van der Vliet R, Selles RW, Andrinopoulou ER, et al. Predicting upper limb motor impairment recovery after stroke: a mixture model. *Ann Neurol* 2020; **87:** 383–93.
29 Kraglund KL, Mortensen JK, Damsbo AG, et al. Neuroregeneration and vascular protection by citalopram in acute ischemic stroke (TALOS). *Stroke* 2018; **49:** 2568–76.
30 Steel Z, Silove D, Giao NM, et al. International and indigenous diagnoses of mental disorder among Vietnamese living in Vietnam and Australia. *Br J Psychiatry* 2009; **194:** 326–33.