Fluoxetine for reducing disability after stroke: meta-analysis of randomised controlled trials

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<td>Mead, Gillian; University of Edinburgh, Geriatric Medicine</td>
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</table>
| Legg, Lynn; University of Strathclyde,  
Tilney, Russel; Mater Dei Hospital, Department of Medicine  
Hsieh, Cheng Fang; Kaohsiung Medical University Hospital, Division of  
Geriatrics and Gerontology, Department of Internal Medicine and  
Department of Neurology  
Wu, Simiao; University of Edinburgh, Centre for Clinical Brain Sciences;  
Sichuan University, West China Hospital, Department of Neurology  
Lundström, Erik; Karolinska Institutet, Department of Clinical  
Neuroscience, Department of Neurology  
Rudberg, Ann-Sofie; Karolinska Institutet, Department of Clinical  
Neurosciences  
Kutlubaev, Mansur; Bashkir State Medical University  
Dennis, Martin; Western General Hospital, 8Dept. of Clinical  
Neurosciences;  
Soleimani, Babak; NHS Lothian  
Barugh, Amanda; NHS Lothian  
Hankey, Graeme; University of Western Australia Faculty of Medicine  
Dentistry and Health Sciences |

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Fluoxetine for reducing disability after stroke: meta-analysis of randomised controlled trials

Authors: Gillian E Mead, MD, FRCP; Lynn Legg, PhD; Russel Tilney, MD; Cheng Fang Hsieh, MD; Simiao Wu, MD, PhD; Erik Lundström, MD, PhD; Ann-Sofie Rudberg MD; Mansur Kutlubaev MD, PhD; Martin S Dennis MD; Babak Soleimani MB ChB; Amanda Barugh PhD; Maree L. Hackett PhD; Graeme J Hankey MD, FRACP

Gillian E Mead, Geriatric Medicine, University of Edinburgh

Lynn Legg, Department of Medicine for the Elderly, Royal Alexandra Hospital, Paisley

Russel Tilney, Department of Medicine, Mater Dei Hospital, Malta

Cheng Fang Hsieh, Division of Geriatrics and Gerontology, Department of Internal Medicine and Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

Simiao Wu, Department of Neurology, West China Hospital, Sichuan University, Chengdu, China 610041

Erik Lundström, Karolinska Institutet, Department of Clinical Neuroscience, and adjunct senior lecturer at Department of Neuroscience, Neurology, Uppsala University, Sweden

Ann Sofie Rudberg, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Mansur Kutlubaev, Department of Neurology, G.G. Kuvatov Republican Clinical Hospital; Department of Neurology, Bashkir State Medical University, Ufa, Russia

Martin S Dennis, Centre for Clinical Brain Sciences, University of Edinburgh

Babak Soleimani, NHS Lothian

Amanda Barugh, NHS Lothian

Maree L. Hackett, Faculty of Medicine, UNSW Sydney; The George Institute for Global Health, Australia; The University of Central Lancashire

Graeme J Hankey, Medical School, The University of Western Australia

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Corresponding Author:
Gillian E Mead
Geriatric Medicine
University of Edinburgh
Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh EH16 4SA
Gillian.E.Mead@ed.ac.uk
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Figure 4. Forest plot, disability at end of treatment
Objective: To determine whether fluoxetine, at any dose, given within the first year after stroke to patients who did not have to have mood disorders at randomisation led to a reduction in disability, dependency, neurological deficits and fatigue; improved motor function, mood, and cognition at the end of treatment and follow-up, with the same number or fewer adverse effects.

Methods: Searches in July 2018 included several databases, trials registers, reference lists, contact with experts. We excluded RCTs requiring patients to have mood disorder at randomisation. Co-primary outcomes were dependence and disability. Dichotomous data were synthesised using risk ratios (RR) and continuous data using standardised mean differences (SMD). Quality was appraised using Cochrane risk of bias methods. Sensitivity analyses explored influence of study quality.

Results: The searches identified 3412 references of which 491 full texts were assessed for eligibility. Six new completed RCTs (n=3710) were eligible, making a total of 13 trials (n=4145). There was no difference in the proportion independent at the end of treatment (3 trials, n=3249, 36·6% fluoxetine vs 36·7% control; RR 1·00, 95% confidence interval 0·91 to 1.09, p=0·99, I² 78%) and no difference in disability (7 trials n=3404, SMD 0·05, -0·02 to 0·12 p=0·15, I²=81%). Fluoxetine was associated with better neurological scores and less depression but more seizures. Among the four (n=3283) high quality RCTs, the only difference between groups was lower depression scores with fluoxetine.

Conclusion: Fluoxetine does not reduce disability and dependency after stroke. It improves depression scores but increases seizures. Ongoing RCTs will determine its effects in stroke vary depending on ethnicity, background treatment and other factors.

Classification of evidence: meta-analysis
Background and purpose

Worldwide, stroke is the second leading cause of death, the third leading cause of disability [1], and results in 6.5 million years being lived with disability [2]. Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) which has been used for many years to treat mood disorders, including post-stroke depression. A 2010 systematic review suggested that fluoxetine might improve recovery in stroke patients without depression [3]. In 2011, a randomised controlled trial (RCT) recruiting 118 patients with hemiparesis due to recent (5-10 days previously) ischaemic stroke reported better motor recovery and reduced dependency with 3 months treatment with fluoxetine [4], possibly by promotion of neurogenesis [5], neuroprotection [6], modulation of cerebral motor activity [7] and prevention of depression. A 2012 Cochrane systematic review of SSRIs for stroke recovery suggested that fluoxetine reduced disability after stroke even in patients without depression, but poor methodological trial quality probably introduced bias [8]. Since then one large (n=3127) trial of fluoxetine for stroke recovery has been published [9]. Meta-analyses should be updated as soon as there are new studies that might change the conclusions of the review.

Objective

We sought to determine whether fluoxetine, at any dose, given within the first year after stroke to patients who did not have to have mood disorders at randomisation, reduced disability, dependency, neurological deficits and fatigue, and improved motor function, mood, and cognition at the end of treatment and follow-up, with the same number or fewer adverse effects.

Methods

Protocol and registration
We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). Data supporting this review are available from the corresponding author.

We did not register the current review on PROSPERO as we used the same methods as the 2012 Cochrane review, except for a) including only fluoxetine trials b) excluding trials requiring patients to have mood disorders at randomisation, c) 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, d) excluding trials comparing fluoxetine plus another ‘active treatment’ versus the ‘active treatment’ and e) defining incomplete outcome data reporting as systematic differences in withdrawals between groups rather than a total of >5%. These five criteria (a-e) 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 independent (modified Rankin score, mRS 0-2) rather than the proportion dependent (mRS 3-5).

Random effects models were used in the 2012 Cochrane review because we assumed that the included studies would represent a random sample of the effect sizes that could be observed. As the large Fluoxetine or Control Under Supervision (FOCUS) trial had systematically different results from the smaller trials, a random effects model would have given disproportionate weight to smaller studies [10]. Therefore we report fixed effects models. We performed 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 more than 24 hours [11]. 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 arm was usual care or a placebo. We excluded studies comparing fluoxetine plus another 'active treatment' versus ‘active treatment' alone, because of possible interactions.

Outcomes: We pre-specified two co-primary outcomes: independence or disability at the end of treatment (using any measure). Improvements in disability (performance of activities of daily living) could be important to patients even without a change in overall dependence.

Secondary outcomes: independence and disability at the end of follow-up. Neurological score, depression, anxiety, cognition, quality of life, fatigue, healthcare 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

Searches were performed:

Cochrane Stroke Group Trials Register (17 July 2018);

* Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2018, Issue 6);

* MEDLINE Ovid (from 1948 to 17 July 2018);
* Embase Ovid (from 1980 to 17 July 2018);

* CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; from 1982 to 17 July 2018);

* AMED (Allied and Complementary Medicine; from 1985 to 17 July 2018);

* PsycINFO Ovid (from 1967 to 17 July 2018).

* US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov); and * World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch) on 26th June 2018.

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 (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 beginning and end, we assumed 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 drop-outs 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 using the same criteria as previously [8]. 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.

Pre-specified sensitivity analyses

Sensitivity analyses explored the influence of bias by excluding studies with unclear or high risk of bias across one or more key domains [10].

Summary measures and synthesis of results

Risk ratios (RRs) were used for dichotomous data and for ordinal scales with an established cut-point. Standardised mean differences (SMD) were used for continuous data and ordinal scales with no standard cut-point. We pre-specified our interpretation of SMD: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect [10].

One trial [12] reported medians, interquartile ranges and ranges. We estimated the mean and standard deviation (SD) using the best available method [13].

Risk of bias across studies
Funnel plot was used to investigate publication bias. When available, we scrutinised protocols to investigate selective reporting.

**Subgroup analyses**

Because 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 less than three months, three to six months, six to nine months, nine to 12 months.
Results

From the database searches, we identified 3412 references, removed 426 duplicates, screened 2988 references, and assessed 500 full texts for eligibility (figure 1). Three published papers had the same grant number [14-16], very similar inclusion criteria and recruited patients from the same hospital during overlapping time periods; one appeared to be the three year follow-up data [16] from one of the earlier publications [15]. Thus we included the publication with the largest number of patients reporting our pre-specified outcomes [15] and categorised the other two [14,16] as ‘awaiting assessment’ pending further information. We identified three further new eligible trials from the database searches [12, 17, 18] and one by contact with experts [19]. We also included FOCUS [9].

These six new trials (n=3710) [9, 12, 15, 17-19] were added to seven eligible trials [4, 20-25] (n=435) identified in the 2012 Cochrane review (total 13 completed trials, n=4145, table 1). One further registered trial was withdrawn because it recruited no patients [27].

Several ongoing RCTs together aim to recruit about 3775 patients (appendix).

Risk of Bias

There were four high quality trials (n=3283) with a low risk of bias across important quality criteria [4, 9,12,18] (figure 2). One terminated early having recruited 6 patients, and reported no deaths [18]. The Funnel plot for disability showed no clear evidence of publication bias (available on request).

Results of studies and synthesis of results

Co-primary outcomes: independence and disability at end of treatment (figures 3 and 4).
Three trials (n=3249) reported independence. Fixed effects meta-analysis found no difference in the proportion independent (36.6% in fluoxetine vs 36.7% control; RR 1.00, 95% confidence interval 0.91 to 1.09, p=0.99, I² 78%) and no difference in disability (7 trials n=3404, SMD 0.05 (-0.02 to 0.12) p=0.15, I²=81%).

Two other trials [19, 26] 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 on disability (SMD 0.34, 0.04 to 0.64, p=0.03, I²=81%); and a higher RR (RR 1.87 (0.74 to 4.56; p=0.19, I²=78%) of being independent than the fixed effects models because of the greater weight given to smaller positive trials.

**Secondary outcomes at end of treatment: summary effect sizes (table 2)**

Fluoxetine was associated with better neurological scores (8 trials, n=803, SMD -0.28 (-0.42 to -0.14) p=<0.001, I² 77%), better depression scores (6 trials n=3113 SMD -0.16 (-0.23 to -0.09) p<0.0001, I² 92%), fewer diagnoses of depression (2 trials n=3194 RR 0.77 (0.65 to 0.90) p=0.001, I²=53%) but more seizures (7 trials n=3815, 3.9% vs 2.6% RR 1.49 (1.05 to 2.11) p=0.03, I²=0). Random effects models gave broadly similar results. FOCUS identified a slight excess of bone fractures in the fluoxetine group which was statistically significant. No other trial reported fractures.

**End of follow-up**

Two trials (n=2924) reported disability at end of follow up: SMD was 0.11 (-0.17 to 0.40) p=0.45, I²=85% (fixed effects).
Sensitivity analyses: high quality trials only (table 3), fixed effects

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

Subgroup analyses

We did not perform subgroup analyses because all trials except two (n=68) recruited patients within three months of stroke onset.
Discussion

This systematic review of fluoxetine for stroke recovery identified 14 trials recruiting more than 4000 patients of which four (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, better depression scores 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 better (lower) depression scores at the end of treatment.

We used fixed effect models as these give appropriate weight to larger trials. The sensitivity analysis using random effects models found a spuriously large benefit of fluoxetine on independence (RR 1.87) because of the disproportionate weight given to smaller trials. Fixed and random effect 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 [3, 8, 28]. This current meta-analysis, which included many more patients than previous reviews, has not confirmed these promising effects. Although one of the reviews [28] strongly recommended fluoxetine to promote neurological recovery, this recommendation was based on the results of just four reports [4, 14, 15, 22], only one of which was high quality [4].

Thus, these data do not support the routine prescription of fluoxetine early after stroke in order to reduce dependency and disability [29,30]. Clinicians and patients may wish to
consider the routine use of fluoxetine early after stroke for its small effects on depression, but this would need to be weighed up against the excess of seizures and bone fractures.

There are some limitations at study and outcome level: only four trials were of high methodological quality, not all had been registered prospectively or 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) [31] are using the same measures as FOCUS. A future meta-analysis will report mean difference for continuous data.

We did not register the review in PROSPERO, but we used almost the same methods as the 2012 Cochrane review. We used sensitive searches developed by Cochrane Stroke, there was complete retrieval of identified research, no language restrictions and inclusion of unpublished data [12].

About three-quarters of the patients were from the FOCUS trial performed in the National Health Service, UK. There was quite marked heterogeneity, even for the high quality trials (table 3); this might be explained by the different types of patients and healthcare settings. Five of the low quality trials were from China [15, 17, 21, 22, 23]; the three reporting disability all found favourable effects of fluoxetine. As the evidence base increases, it may be possible to perform meta-regression analyses to determine the factors (such as country, healthcare setting and trial quality) associated with good outcome.

Ongoing trials will provide information about the external validity of these results in other stroke populations with respect to ethnicity, background treatment and healthcare systems. AFFINITY [31] is recruiting patients from Vietnam and includes Asian populations. Also, further information is needed on other outcomes (e.g. depression, anxiety, cognition, bone
fractures, fatigue, health care costs and other potential adverse effects) that are of importance to patients, clinicians and policy makers, and to determine whether any benefits or harms at the end of treatment persist to the end of follow-up.

When AFFINITY and EFFECTS are published, we will update the meta-analysis of fluoxetine for stroke recovery, and will also perform an individual patient meta-analysis.

Our searches identified several completed trials of other SSRIs in stroke patients with and without depression and other mood disorders, which will be included in the next update of the Cochrane review of SSRIs for stroke recovery.

Finally, it would be a significant waste of resources if further trials of fluoxetine in stroke are started before ongoing trials have reported and been included in a future meta-analysis [32].

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<th>Study</th>
<th>Country</th>
<th>Participants (pathological type and time since stroke)</th>
<th>Number recruited</th>
<th>Number included at end of treatment</th>
<th>Dose and duration of fluoxetine</th>
<th>Control</th>
<th>Outcomes reported by the trial authors</th>
<th>Follow-up period</th>
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<td>Birchenall 2018</td>
<td>France</td>
<td>Stroke or brain haemorrhage, day 3 to day 15</td>
<td>6 (study terminated early)</td>
<td>6</td>
<td>20mg daily for 3 months</td>
<td>Placebo</td>
<td>Several clinical and TMS measurements, death.</td>
<td>End of treatment and at month 6</td>
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<td>Chollet 2011</td>
<td>France</td>
<td>Ischaemic stroke, 5-10 days</td>
<td>118</td>
<td>113</td>
<td>20mg daily for 3 months</td>
<td>Matching placebo</td>
<td>Primary outcome: FMMS. Secondary endpoints: NIHSS, mRS and MADRS at 0, 30 and 90 days. AEs</td>
<td>End of treatment</td>
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<td>Dam 1996</td>
<td>Italy</td>
<td>Ischaemic stroke, 1-6 months</td>
<td>35</td>
<td>33</td>
<td>20mg daily for 12 weeks</td>
<td>Matching placebo</td>
<td>HDRS, HSS (total, gait and motor scores), BI, death, AEs</td>
<td>End of treatment</td>
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<td>FOCUS collaborators 2018</td>
<td>UK</td>
<td>Any stroke, 2-15 days</td>
<td>3127</td>
<td>3106</td>
<td>20mg daily for 6 months</td>
<td>Matching placebo</td>
<td>Primary: mRS. Secondary: SIS, depression, MHI5, fatigue, Euroqol 5D 5L, health care costs HAMD, SSS. AEs</td>
<td>End of treatment and then 6 months later</td>
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<td>He 2004</td>
<td>China</td>
<td>First ever stroke, all pathological types. Mean time 3.1 days in fluoxetine and 3.5 days in control</td>
<td>84</td>
<td>71</td>
<td>20mg daily for 8 weeks</td>
<td>Usual stroke care</td>
<td>NIHSS, BI; AEs</td>
<td>End of treatment</td>
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<td>He 2016</td>
<td>China</td>
<td>Ischaemic stroke, within 1 week</td>
<td>374</td>
<td>350</td>
<td>20mg for 90 days</td>
<td>Usual care</td>
<td>NIHSS, BI; AEs</td>
<td>End of treatment</td>
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<td>Study</td>
<td>Country</td>
<td>Condition</td>
<td>Days</td>
<td>Dose</td>
<td>Comparator</td>
<td>Outcome Measures</td>
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<td>Kong 2006</td>
<td>China</td>
<td>Any pathological type, within 7 days</td>
<td>90</td>
<td>20mg for 8 weeks</td>
<td>Matching placebo</td>
<td>HAMD, BI, NIHSS.</td>
<td>End of treatment</td>
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<td>Li 2004</td>
<td>China</td>
<td>Any pathological type, mean time to recruitment was 2 days</td>
<td>67</td>
<td>20mg daily for 4 weeks</td>
<td>Routine stroke care</td>
<td>Somatic side effects and hyponatraemia</td>
<td>End of treatment</td>
<td></td>
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<tr>
<td>Marquez-Romero 2013</td>
<td>Mexico</td>
<td>Intracerebral haemorrhage within 10 days</td>
<td>32</td>
<td>20mg daily for 90 days</td>
<td>Matching placebo</td>
<td>Primary: FMMS, mRS</td>
<td>End of treatment</td>
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<tr>
<td>Pariente 2001</td>
<td>France</td>
<td>Lacunar ischaemic stroke</td>
<td>8</td>
<td>Single 20mg dose</td>
<td>Placebo</td>
<td>Secondary: NIHSS, BI, AEs Finger tapping and clinical scales presented only as graphs. fMRI activation location</td>
<td>Post-treatment</td>
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<tr>
<td>Robinson 2000 (follow up reported in Mikami 2011)</td>
<td>USA and Argentina</td>
<td>All pathological types, within 6 months</td>
<td>33</td>
<td>Dose increased over 3 weeks from 10mg to 30mg daily; total 12 weeks 10mg for one week, increased to 20mg after one week,</td>
<td>Matching placebo</td>
<td>HDRS, mRS, FIM, MMSE, JHFI, death, AEs</td>
<td>End of treatment</td>
<td></td>
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<td>Shah 2016</td>
<td>India</td>
<td>Haemorrhagic stroke, 5-10 days after onset</td>
<td>89</td>
<td>10mg for one week, increased to 20mg after one week, 'similar' to fluoxetine</td>
<td>Inert capsule 'similar' to fluoxetine</td>
<td>Primary outcome: FMMS</td>
<td>End of treatment</td>
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<td>Reference</td>
<td>Country</td>
<td>Diagnosis</td>
<td>Treatment Details</td>
<td>Comparator</td>
<td>Outcome Measures</td>
<td>End of Treatment</td>
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<tr>
<td>Zhao 2011</td>
<td>China</td>
<td>Stroke with aphasia,</td>
<td>82 mg for 12 weeks</td>
<td>Standard care</td>
<td>MESS, ADL</td>
<td>End of treatment</td>
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<td></td>
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<td>‘early treatment with fluoxetine’, precise time not stated</td>
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ADL: Activities of Daily Living  
AE: Adverse Events  
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-Asberg Depression Rating Scale  
MMSE: Mini Mental State Examination  
MESSS: Modified Edinburgh-Scandinavian Stroke Scale  
mRS: modified Rankin Score  
MHIS: Mental Health Inventory 5  
NIHSS: National Institutes of Health Stroke Scale  
SSS: Scandinavian Stroke Scale  
SIS: Stroke Impact Scale  
TMS: Transmagnetic stimulation
Table 2 Effects sizes from meta-analysis of primary and secondary outcomes; end of treatment; from all trials using fixed effects models, where at least two trials provided data that could be included.

<table>
<thead>
<tr>
<th></th>
<th>Number of trials (number of participants) contributing to the meta-analysis</th>
<th>Effect size (RR or SMD) and 95% CI</th>
<th>P value</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent (modified Rankin score 0-2)</td>
<td>3 trials (n=3249)</td>
<td>RR1.00 (0.91 to 1.09)</td>
<td>0.99</td>
<td>78%</td>
</tr>
<tr>
<td>Disability</td>
<td>7 trials (n=3404)</td>
<td>SMD 0.05 (-0.02 to 0.12)</td>
<td>0.15</td>
<td>81%</td>
</tr>
<tr>
<td>Neurological deficit score</td>
<td>8 trials (n=803)</td>
<td>SMD -0.28 (-0.42 to -0.14)</td>
<td>&lt;0.0001</td>
<td>77%</td>
</tr>
<tr>
<td>Depression-continuous data</td>
<td>6 trials (n=3113)</td>
<td>SMD -0.16 (-0.23 to -0.09)</td>
<td>&lt;0.0001</td>
<td>92%</td>
</tr>
<tr>
<td>Depression-dichotomous</td>
<td>2 trials (n=3194)</td>
<td>RR 0.77 (0.65 to 0.90)</td>
<td>0.001</td>
<td>53%</td>
</tr>
<tr>
<td>Motor score</td>
<td>5 trials (n=3079)</td>
<td>SMD 0.06 (-0.02 to 0.13)</td>
<td>0.12</td>
<td>95%</td>
</tr>
<tr>
<td>Cognition</td>
<td>2 trials (n=2834)</td>
<td>SMD -0.04 (-0.11 to 0.03)</td>
<td>0.32</td>
<td>0%</td>
</tr>
<tr>
<td>Death</td>
<td>11 trials (n=3824)</td>
<td>RR 1.0 (0.79 to 1.26)</td>
<td>1.00</td>
<td>0%</td>
</tr>
<tr>
<td>Cognition</td>
<td>2 trials (n=2793)</td>
<td>SMD -0.04 (-0.11 to 0.03)</td>
<td>0.3</td>
<td>0%</td>
</tr>
<tr>
<td>Seizures</td>
<td>7 trials (n=3815)</td>
<td>RR 1.49 (1.05 to 2.11)</td>
<td>0.03</td>
<td>0%</td>
</tr>
<tr>
<td>Gastrointestinal symptoms (nausea, diarrhoea, abdominal pain)</td>
<td>7 trials (n=688)</td>
<td>RR 1.38 (0.99 to 1.94)</td>
<td>0.06</td>
<td>8%</td>
</tr>
<tr>
<td>Serious bleeding</td>
<td>2 trials (n=3477)</td>
<td>RR 1.10 (0.72 to 1.62)</td>
<td>0.67</td>
<td>0%</td>
</tr>
<tr>
<td>Leaving before the end of first follow-up</td>
<td>11 trials (n=3972)</td>
<td>RR 0.92 (0.61 to 1.40)</td>
<td>0.71</td>
<td>0%</td>
</tr>
</tbody>
</table>

RR: relative risk
SMD: standardised mean difference
Table 3

Summary effect sizes for trials at low risk of bias, at end of treatment, where at least two trials reported the outcome of interest. Fixed effects models

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of trials and participants contributing to the meta-analysis</th>
<th>Effect size</th>
<th>P value</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent (modified Rankin score 0-2)</td>
<td>3 trials (n=3269)</td>
<td>RR 1.00 (0.91 to 1.09)</td>
<td>0.99</td>
<td>78%</td>
</tr>
<tr>
<td>Disability</td>
<td>2 trials (n=2853)</td>
<td>SMD -0.01 (-0.09 to 0.06)</td>
<td>0.75</td>
<td>0%</td>
</tr>
<tr>
<td>Neurological deficit score</td>
<td>2 trials (n=142)</td>
<td>SMD -0.30 (-0.63 to 0.04)</td>
<td>0.08</td>
<td>0%</td>
</tr>
<tr>
<td>Depression (continuous data)</td>
<td>2 trials (n=2861)</td>
<td>SMD -0.11 (-0.19 to -0.04)</td>
<td>0.002</td>
<td>69%</td>
</tr>
<tr>
<td>Motor score</td>
<td>3 trials (n=2936)</td>
<td>SMD 0.02 (-0.05 to 0.09)</td>
<td>0.58</td>
<td>88%</td>
</tr>
<tr>
<td>Death</td>
<td>4 trials (n=3260)</td>
<td>RR 0.99 (0.79 to 1.25)</td>
<td>0.95</td>
<td>0%</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>2 trials (n=148)</td>
<td>RR 2.19 (1.0 to 4.76)</td>
<td>0.05</td>
<td>0%</td>
</tr>
<tr>
<td>Leaving the trial before first follow-up</td>
<td>4 trials (n=3283)</td>
<td>RR 1.01 (0.48 to 2.10)</td>
<td>0.98</td>
<td>0%</td>
</tr>
<tr>
<td>Seizures</td>
<td>3 trials (n=3275)</td>
<td>RR 1.47 (0.99 to 2.18)</td>
<td>0.06</td>
<td>0%</td>
</tr>
</tbody>
</table>
References


intracerebral hemorrhage (FMRICH): study protocol for a randomized, double-blind, placebo-controlled, multicenter trial. *Trials* 2013; 14:77


Acknowledgements

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 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 of authors

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

Lynn Legg searched for studies selected studies for inclusion, collected data, assessed risk of bias, managed studies through the review process, 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.
Figure 1

3413 references imported for screening

2988 studies screened

2488 studies irrelevant

500 full-text studies assessed for eligibility

480 references excluded
150 duplicate reference
117 review no new trials
68 commentaries
30 wrong comparator
29 wrong study design
21 wrong patient population
32 wrong drug
13 wrong intervention
6 conference proceedings no new trials
5 old reviews (2011 or earlier)
4 the trial never started
2 follow up of original trial
1 registry Database Link
1 wrong outcomes
1 book-no new studies

One study identified by contact with experts

Seven new studies included (in addition to the six we had identified in the 2012 Cochrane review)

10 studies ongoing
3 studies awaiting classification
1 study terminated
Figure 2

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Fluoxetine Mean</th>
<th>Fluoxetine SD</th>
<th>Fluoxetine Total</th>
<th>Weight</th>
<th>IV, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4.1 Trials before FOCUS</td>
<td>61.9</td>
<td>13</td>
<td>16</td>
<td>54.1</td>
<td>21.1</td>
<td>16</td>
<td>0.9%</td>
<td>0.43 [0.27, 1.14]</td>
<td>1996</td>
</tr>
<tr>
<td>Dam 1996</td>
<td>60.5</td>
<td>10.8</td>
<td>13</td>
<td>63.1</td>
<td>8.2</td>
<td>15</td>
<td>0.8%</td>
<td>-0.27 [-1.01, 0.48]</td>
<td>2000</td>
</tr>
<tr>
<td>Robinson 2000b</td>
<td>60.4</td>
<td>12.5</td>
<td>37</td>
<td>52.3</td>
<td>13.6</td>
<td>36</td>
<td>2.1%</td>
<td>0.62 [0.15, 1.09]</td>
<td>2007</td>
</tr>
<tr>
<td>Kong 2007</td>
<td>-27.0</td>
<td>-7.1</td>
<td>37</td>
<td>-34.8</td>
<td>5.2</td>
<td>34</td>
<td>1.8%</td>
<td>1.11 [0.60, 1.61]</td>
<td>2011</td>
</tr>
<tr>
<td>Zhao 2011</td>
<td>65</td>
<td>21.4</td>
<td>14</td>
<td>49</td>
<td>73.15</td>
<td>16</td>
<td>0.9%</td>
<td>0.35 [-0.37, 1.07]</td>
<td>2013</td>
</tr>
<tr>
<td>Manrique-Romero 2013</td>
<td>178.81</td>
<td>14.69</td>
<td>177</td>
<td>84.74</td>
<td>16.85</td>
<td>170</td>
<td>10.2%</td>
<td>0.24 [0.03, 0.45]</td>
<td>2016</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>294</td>
<td>287</td>
<td>16.6%</td>
<td>0.37 [0.21, 0.54]</td>
<td>2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 4.42 (P < 0.00001)

Heterogeneity: $\chi^2 = 13.56, df = 5 (P = 0.02); I^2 = 0\%$

1.4.2 FOCUS 2018

<table>
<thead>
<tr>
<th>FOCUS collaboration 2018</th>
<th>59.86</th>
<th>31.16</th>
<th>1413</th>
<th>60.15</th>
<th>31.5</th>
<th>1410</th>
<th>83.4%</th>
<th>-0.02 [-0.09, 0.06]</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal (95% CI)</td>
<td>1413</td>
<td>1410</td>
<td>83.4%</td>
<td>-0.02 [-0.09, 0.06]</td>
<td>2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect: Z = 0.42 (P = 0.68)

| Total (95% CI) | 1767 | 1697 | 100.6% | 0.05 [-0.02, 0.12] | 2018 |

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 3

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fluoxetine</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>1.2.1 Trials before FOCUS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chollet 2011</td>
<td>15</td>
<td>57</td>
<td>2.95 [1.15, 7.56]</td>
</tr>
<tr>
<td>Marquez-Romero 2013</td>
<td>8</td>
<td>14</td>
<td>3.05 [1.20, 9.31]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>23</td>
<td>86</td>
<td>2.98 [1.45, 6.16]</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.96 (P = 0.003)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2.2 FOCUS 2018</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOCUS collaboration 2018</td>
<td>572</td>
<td>1553</td>
<td>0.97 [0.89, 1.07]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1553</td>
<td>1553</td>
<td>0.97 [0.89, 1.07]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1624</td>
<td>1625</td>
<td>1.00 [0.91, 1.09]</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>595</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.23, df = 2 (P = 0.010); I² = 78%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.02 (P = 0.99)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subroup differences: Chi² = 9.04, df = 1 (P = 0.003); I² = 88.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours control  Favours fluoxetine
Fluoxetine for stroke recovery: meta-analysis of randomised controlled trials

Gillian E Mead, MD, FRCP. Professor of Stroke and Elderly Care Medicine, University of Edinburgh

Lynn Legg, PhD. Senior researcher, Department of Medicine for the Elderly, Royal Alexandra Hospital, Paisley

Russel Tilney, MD, Department of Neuroscience, Mater Dei Hospital, Malta

Cheng Fang Hsieh, MD, Division of Geriatriecs and Gerontology, Department of Internal Medicine and Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

Simiaio Wu, MD, PhD, Department of Neurology, West China Hospital, Sichuan University, Chengdu, China 610041

Erik Lundström, Associate Professor of Neurology; Karolinska Institutet, Department of Clinical Neuroscience, and adjunct senior lecturer at Department of Neuroscience, Neurology, Uppsala University, Sweden

Ann Sofie Rudberg MD, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Mansur Kutlubaev MD, PhD, Department of Neurology, G.G. Kuvatov Republican Clinical Hospital; Department of Neurology, Bashkir State Medical University, Ufa, Russia

Martin S Dennis Professor of Stroke Medicine. University of Edinburgh

Babak Soleiman MB ChB Clinical Fellow, NHS Lothian

Amanda Barugh PhD. Consultant Stroke Physician. NHS Lothian

Maree L. Hackett PhD. Program Head Mental Health. Professor, Faculty of Medicine, UNSW Sydney. Professor of Epidemiology, The University of Central Lancashire, United Kingdom. The George Institute for Global Health, UNSW, Australia

Graeme J. Hankey MD, FRACP Professor of Neurology, Medical School, The University of Western Australia

Search terms: stroke, fluoxetine, recovery, rehabilitation

Word count of paper: 2904

Corresponding author

Gillian E Mead, Centre for Clinical Brain Sciences, University of Edinburgh, Royal Infirmary, Little France Crescent, Edinburgh EH16 4SA gillian.e.mead@ed.ac.uk
Tables and figures

Table 1 Characteristics of the randomised controlled trials (RCTs) that are included in this review

Table 2 Effects sizes from meta-analysis of primary and secondary outcomes; end of treatment; from all trials using fixed effects models, where at least two trials provided data that could be included

Table 3 Summary effect sizes for trials at low risk of bias, at end of treatment, where at least two trials reported the outcome of interest. Fixed effects models

Figure 1. Flow diagram showing selection of studies

Figure 2 Risk of Bias

Figure 3. Forest plot, mRS (0-2) at end of treatment

Figure 4. Forest plot, disability at end of treatment
Objective: To determine whether fluoxetine, at any dose, given within the first year after stroke to patients who did not have to have mood disorders at randomisation reduced disability, dependency, neurological deficits and fatigue; improved motor function, mood, and cognition at the end of treatment and follow-up, with the same number or fewer adverse effects.

Methods: Searches (from 2012) in July 2018 included databases, trials registers, reference lists, contact with experts. Co-primary outcomes were dependence and disability. Dichotomous data were synthesised using risk ratios (RR) and continuous data using standardised mean differences (SMD). Quality was appraised using Cochrane risk of bias methods. Sensitivity analyses explored influence of study quality.

Results: The searches identified 3412 references of which 491 full texts were assessed for eligibility. Six new completed RCTs (n=3710) were eligible, and were added to the seven trials identified in a 2012 Cochrane review (total: 13 trials, n=4145). There was no difference in the proportion independent (3 trials, n=3249, 36.6% fluoxetine vs 36.7% control; RR 1.00, 95% confidence interval 0.91 to 1.09, p=0.99, I² 78%) nor in disability (7 trials n=3404, SMD 0.05, -0.02 to 0.12 p=0.15, I²=81%) at end of treatment. Fluoxetine was associated with better neurological scores and less depression. Among the four (n=3283) high quality RCTs, the only difference between groups was lower depression scores with fluoxetine.

Conclusion: This class I evidence demonstrates that fluoxetine does not reduce disability and dependency after stroke but improves depression.
Background and purpose (word count 240)

Worldwide, stroke is the second leading cause of death, the third leading cause of disability [1], and results in 6.5 million years being lived with disability [2]. Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) which has been used for many years to treat mood disorders, including post-stroke depression. A 2010 systematic review suggested that fluoxetine might improve recovery in stroke patients without depression [3]. In 2011, a randomised controlled trial (RCT) recruiting 118 patients with hemiparesis due to recent (5-10 days previously) ischaemic stroke reported better motor recovery and reduced dependency with 3 months treatment with fluoxetine [4], possibly by promotion of neurogenesis [5], neuroprotection [6], modulation of cerebral motor activity [7] and prevention of depression. A 2012 Cochrane systematic review of SSRIs for stroke recovery suggested that fluoxetine reduced disability after stroke even in patients without depression, but poor methodological trial quality probably introduced bias [8]. In December 2018, one very large (n=3127) trial of fluoxetine for stroke recovery was published [9]. Meta-analyses should be updated as soon as there are new studies that might change the conclusions of the review. In this paper, we report the meta-analysis of fluoxetine for stroke recovery. The Cochrane review of SSRI for stroke recovery will be updated subsequently.

Objective

We sought to determine whether fluoxetine, at any dose, given within the first year after stroke to patients who did not have to have mood disorders at randomisation, reduced disability, dependency, neurological deficits and fatigue, and improved motor function, mood, and cognition at the end of treatment and follow-up, with the same number or fewer adverse effects.
Methods

Protocol and registration

We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). Data supporting this review are available from the corresponding author.

We did not register this review on PROSPERO as we used the same methods as the 2012 Cochrane review, except for a) including only fluoxetine trials b) excluding trials requiring patients to have mood disorders at randomisation, c) 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, d) excluding trials comparing fluoxetine plus another ‘active treatment’ versus the ‘active treatment’ and e) defining incomplete outcome data reporting as systematic differences in withdrawals between groups rather than a total of >5%. These five criteria (a-e) 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 independent (modified Rankin score, mRS 0-2) rather than the proportion dependent (mRS 3-5).

Random effects models had been used in the 2012 Cochrane review because we assumed that the included studies would represent a random sample of the effect sizes that could be observed. As the large Fluoxetine or Control Under Supervision (FOCUS) trial had systematically different results from the smaller trials, a random effects model would have given disproportionate weight to smaller studies [10]. Therefore we report fixed effects models. We performed 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 more than 24 hours [11]. 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 arm was usual care or a placebo. We excluded studies comparing fluoxetine plus another 'active treatment' versus 'active treatment' alone, because of possible interactions.

Outcomes We pre-specified two co-primary outcomes: independence or disability at the end of treatment (using any measure). Improvements in disability (performance of activities of daily living) could be important to patients even without a change in overall dependence.

Secondary outcomes: independence and disability at the end of follow-up. Neurological score, depression, anxiety, cognition, quality of life, fatigue, healthcare 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

Searches were performed:

Cochrane Stroke Group Trials Register (17 July 2018);

* Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2018, Issue 6);

* MEDLINE Ovid (from 1948 to 17 July 2018);
* Embase Ovid (from 1980 to 17 July 2018);

* CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; from 1982 to 17 July 2018);

* AMED (Allied and Complementary Medicine; from 1985 to 17 July 2018);

* PsycINFO Ovid (from 1967 to 17 July 2018).

* US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov); and * World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch) on 26th June 2018.

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 (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 beginning and end, we assumed 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 drop-outs 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 using the same criteria as previously [8]. 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.

Pre-specified sensitivity analyses

Sensitivity analyses explored the influence of bias by excluding studies with unclear or high risk of bias across one or more key domains [10].

Summary measures and synthesis of results

Risk ratios (RRs) were used for dichotomous data and for ordinal scales with an established cut-point. Standardised mean differences (SMD) were used for continuous data and ordinal scales with no standard cut-point. We pre-specified our interpretation of SMD: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect [10].

One trial [12] reported medians, interquartile ranges and ranges. We estimated the mean and standard deviation (SD) using the best available method [13].

Risk of bias across studies
Funnel plot was used to investigate publication bias. When available, we scrutinised protocols to investigate selective reporting.

Subgroup analyses

Because 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 less than three months, three to six months, six to nine months, nine to 12 months.
Results

From the database searches, we identified 3412 references, removed 426 duplicates, screened 2988 references, and assessed 500 full texts for eligibility (figure 1). Three published papers had the same grant number [14-16], very similar inclusion criteria and recruited patients from the same hospital during overlapping time periods; one appeared to be the three year follow-up data [16] from one of the earlier publications [15]. Thus we included the publication with the largest number of patients reporting our pre-specified outcomes [15] and categorised the other two [14,16] as ‘awaiting assessment’ pending further information. We identified three further new eligible trials from the database searches [12, 17, 18] and one by contact with experts [19]. We also included FOCUS [9].

These six new trials (n=3710) [9, 12, 15, 17-19] were added to seven eligible trials [4, 20-25] (n=435) identified in the 2012 Cochrane review (total 13 completed trials, n=4145, table 1). One further registered trial was withdrawn because it recruited no patients [27].

Several ongoing RCTs together aim to recruit about 3775 patients (appendix).

Risk of Bias

There were four high quality trials (n=3283) with a low risk of bias across important quality criteria [4, 9,12,18] (figure 2). One terminated early having recruited 6 patients, and reported no deaths [18]. The Funnel plot for disability showed no clear evidence of publication bias (available on request).

Results of studies and synthesis of results

Co-primary outcomes: independence and disability at end of treatment (figures 3 and 4).
Three trials (n=3249) reported independence. Fixed effects meta-analysis found no difference in the proportion independent (36.6% in fluoxetine vs 36.7% control; RR 1.00, 95% confidence interval 0.91 to 1.09, p=0.99, I² 78%) and no difference in disability (7 trials n=3404, SMD 0.05 (-0.02 to 0.12) p=0.15, I²=81%).

Two other trials [19, 26] 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 on disability (SMD 0.34, 0.04 to 0.64, p=0.03, I²=81%); and a higher RR (RR 1.87 (0.74 to 4.56; p=0.19, I²=78%) of being independent than the fixed effects models because of the greater weight given to smaller positive trials.

Secondary outcomes at end of treatment: summary effect sizes (table 2)

Fluoxetine was associated with better neurological scores (8 trials, n=803, SMD -0.28 (-0.42 to -0.14) p=<0.001, I² 77%), better depression scores (6 trials n=3113 SMD -0.16 (-0.23 to -0.09) p<0.0001, I² 92%), fewer diagnoses of depression (2 trials n=3194 RR 0.77 (0.65 to 0.90) p=0.001, I²=53%) but more seizures (7 trials n=3815, 3.9% vs 2.6% RR 1.49 (1.05 to 2.11) p=0.03, I²=0). Random effects models gave broadly similar results. FOCUS identified a slight excess of bone fractures in the fluoxetine group which was statistically significant. No other trial reported fractures.

End of follow-up

Two trials (n=2924) reported disability at end of follow up: SMD was 0.11 (-0.17 to 0.40) p=0.45, I²=85% (fixed effects).
Sensitivity analyses: high quality trials only (table 3), fixed effects

Fixed effects models found a small, but statistically significant effect on depression scores at end of treatment (2 trials, n=2861, -0.11 (-0.19 to -0.04) p=0.002, I²=69%). Random effects found a slightly larger effect size for depression which was not statistically significant (-0.23 (-0.56 to 0.10) p=0.07, I² 61%).

Subgroup analyses

We did not perform subgroup analyses because all trials except two (n=68) recruited patients within three months of stroke onset.
Discussion

This systematic review of fluoxetine for stroke recovery identified 14 trials recruiting more than 4000 patients of which four (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, better depression scores 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 better (lower) depression scores at the end of treatment.

We used fixed effect models as these give appropriate weight to larger trials. The sensitivity analysis using random effects models found a spuriously large benefit of fluoxetine on independence (RR 1.87) because of the disproportionate weight given to smaller trials. Fixed and random effect 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 [3, 8, 28]. This current meta-analysis, which included many more patients than previous reviews, has not confirmed these promising effects. Although one of the reviews [28] strongly recommended fluoxetine to promote neurological recovery, this recommendation was based on the results of just four reports [4, 14, 15, 22], only one of which was high quality [4].

Thus, these data do not support the routine prescription of fluoxetine early after stroke in order to reduce dependency and disability [29,30]. Clinicians and patients may wish to consider the routine use of fluoxetine early after stroke for its small effects on depression, but
this would need to be weighed up against the excess of seizures and bone fractures. **This review has not addressed the question about whether fluoxetine is of benefit to stroke survivors with mood disorders**-this will be addressed by other systematic reviews and meta-analyses which are currently being updated.

There are some limitations at study and outcome level: only four trials were of high methodological quality, not all had been registered prospectively or 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) [31] are using the same measures as FOCUS. A future meta-analysis will report mean difference for continuous data.

We did not register the review in PROSPERO, but we used almost the same methods as the 2012 Cochrane review. We used sensitive searches developed by Cochrane Stroke, there was complete retrieval of identified research, no language restrictions and inclusion of unpublished data [12].

About three-quarters of the patients were from the FOCUS trial performed in the National Health Service, UK). **In FOCUS, entry criteria were broad and patients did not have to have motor deficits, as in the FLAME trial. However, the subgroup analysis of patients with motor deficits recruited to FOCUS found no evidence of an effect on either the mRS or motor score of the Stroke Impact Scale.**

There was quite marked heterogeneity, even for the high quality trials (table 3); this might be explained by the different types of patients and healthcare settings. Five of the low quality trials were from China [15, 17, 21, 22, 23]; the three reporting disability all found favourable effects of fluoxetine. As the evidence base increases, it may be possible to perform meta-
regression analyses to determine the factors (such as country, health care setting and trial quality) associated with good outcome. **We did not pre-specify other outcomes that might plausibly be influenced by fluoxetine such as sleep quality and irritability, though we noted that the included trials did not measure these outcomes.**

**Ongoing trials with a very similar protocol to FOCUS, which have recruited patients from different parts of the world, will provide information about the external validity of these results in other stroke populations with respect to ethnicity, background treatment and healthcare systems.** AFFINITY [31] recruited patients from Vietnam and includes Asian populations and EFFECTS recruited from Sweden. Also, further information is needed on other outcomes (e.g. depression, anxiety, cognition, bone fractures, fatigue, health care costs and other potential adverse effects) that are of importance to patients, clinicians and policy makers, and to determine whether any benefits or harms at the end of treatment persist to the end of follow-up.

When AFFINITY and EFFECTS are published, we will update the meta-analysis of fluoxetine for stroke recovery, and will also perform an individual patient meta-analysis.

Our searches identified several completed trials of other SSRIs in stroke patients with and without depression and other mood disorders, which will be included in the next update of the Cochrane review of SSRIs for stroke recovery.

**Finally, before any further trials of fluoxetine for stroke recovery are started/funded, it would be prudent to wait for the results of AFFINITY and EFFECTS [32].**
FUNDING

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This review was not funded.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Participants (pathological type and time since stroke)</th>
<th>Number recruited</th>
<th>Number included at end of treatment</th>
<th>Dose and duration of fluoxetine</th>
<th>Control</th>
<th>Outcomes reported by the trial authors</th>
<th>Follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birchenall 2018</td>
<td>France</td>
<td>Stroke or brain haemorrhage, day 3 to day 15</td>
<td>6 (study terminated early)</td>
<td>6</td>
<td>20mg daily for 3 months</td>
<td>Placebo</td>
<td>Several clinical and TMS measurements, death.</td>
<td>End of treatment and at month 6</td>
</tr>
<tr>
<td>Chollet 2011</td>
<td>France</td>
<td>Ischaemic stroke, 5-10 days</td>
<td>118</td>
<td>113</td>
<td>20mg daily for 3 months</td>
<td>Matching placebo</td>
<td>Primary outcome: FMMS. Secondary endpoints: NIHSS, mRS and MADRS at 0, 30 and 90 days. AEs</td>
<td>End of treatment</td>
</tr>
<tr>
<td>Dam 1996</td>
<td>Italy</td>
<td>Ischaemic stroke, 1-6 months</td>
<td>35</td>
<td>33</td>
<td>20mg daily for 12 weeks</td>
<td>Matching placebo</td>
<td>HDRS, HSS (total, gait and motor scores), BI, death, AEs</td>
<td>End of treatment</td>
</tr>
<tr>
<td>FOCUS collaborators 2018</td>
<td>UK</td>
<td>Any stroke, 2-15 days</td>
<td>3127</td>
<td>3106</td>
<td>20mg daily for 6 months</td>
<td>Matching placebo</td>
<td>Primary: mRS. Secondary: SIS, depression, MHI5, fatigue, Euroquol 5D 5L, health care costs HAMD, SSS. AEs</td>
<td>End of treatment and then 6 months later</td>
</tr>
<tr>
<td>He 2004</td>
<td>China</td>
<td>First ever stroke, all pathological types. Mean time 3.1 days in fluoxetine and 3.5 days in control</td>
<td>84</td>
<td>71</td>
<td>20mg daily for 8 weeks</td>
<td>Usual stroke care</td>
<td>NIHSS, BI; AEs</td>
<td>End of treatment</td>
</tr>
<tr>
<td>He 2016</td>
<td>China</td>
<td>Ischaemic stroke, within 1 week</td>
<td>374</td>
<td>350</td>
<td>20mg for 90 days</td>
<td>Usual care</td>
<td>NIHSS, BI; AEs</td>
<td>End of treatment</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Diagnosis</td>
<td>Duration</td>
<td>Dose</td>
<td>Comparator</td>
<td>Primary Outcomes</td>
<td>Secondary Outcomes</td>
<td>Endpoint</td>
</tr>
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<td>---------------</td>
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</tr>
<tr>
<td>Kong 2006</td>
<td>China</td>
<td>Any pathological type, within 7 days</td>
<td>90</td>
<td>20mg</td>
<td>Matching</td>
<td>HAMD, BI, NIHSS.</td>
<td>Somatic side effects and hyponatraemia</td>
<td>End of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>73</td>
<td></td>
<td>placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li 2004</td>
<td>China</td>
<td>Any pathological type, mean time to recruitment was 2 days</td>
<td>67</td>
<td>20mg</td>
<td>Routine</td>
<td>HAMD, CSS; AEs in fluoxetine group</td>
<td></td>
<td>End of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>67</td>
<td></td>
<td>stroke care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marquez-Romero 2013</td>
<td>Mexico</td>
<td>Intracerebral haemorrhage within 10 days</td>
<td>32</td>
<td>20mg</td>
<td>Matching</td>
<td>Primary: FMMS, mRS</td>
<td>Secondary: NIHSS, BI, AEs</td>
<td>End of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td></td>
<td>placebo</td>
<td>Finger tapping and clinical scales presented only as graphs. fMRI activation location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pariente 2001</td>
<td>France</td>
<td>Lacunar ischaemic stroke</td>
<td>8</td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td>Post-treatment</td>
</tr>
<tr>
<td>Robinson 2000 (follow up reported in Mikami 2011)</td>
<td>USA and Argentina</td>
<td>All pathological types, within 6 months</td>
<td>33</td>
<td>Dose</td>
<td>Matching</td>
<td>HDRS, mRS, FIM, MMSE, JHFI, death, AEs</td>
<td></td>
<td>End of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>28</td>
<td>increased over 3 weeks from 10mg to 30mg daily; total 12 weeks</td>
<td>placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shah 2016</td>
<td>India</td>
<td>Haemorrhagic stroke, 5-10 days after onset</td>
<td>89</td>
<td>10mg</td>
<td>Inert capsule ‘similar’ to fluoxetine</td>
<td>Primary outcome: FMMS</td>
<td>mRS and AEs</td>
<td>End of treatment</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Diagnosis</td>
<td>Treatment</td>
<td>Duration</td>
<td>Comparator</td>
<td>Outcome Measures</td>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
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<td></td>
</tr>
<tr>
<td>Zhao 2011</td>
<td>China</td>
<td>Stroke with aphasia, ‘early treatment with fluoxetine’, precise time not stated</td>
<td>82</td>
<td>71</td>
<td>Standard care</td>
<td>MESS, ADL</td>
<td>End of treatment</td>
<td></td>
</tr>
</tbody>
</table>

ADL: Activities of Daily Living  
AE: Adverse Events  
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-Asberg Depression Rating Scale  
MMSE: Mini Mental State Examination  
MESSS: Modified Edinburgh-Scandinavian Stroke Scale  
mRS: modified Rankin Score  
MHI5: Mental Health Inventory 5  
NIHSS: National Institutes of Health Stroke Scale  
SSS: Scandinavian Stroke Scale  
SIS: Stroke Impact Scale  
TMS: Transmagnetic stimulation
Table 2 Effects sizes from meta-analysis of primary and secondary outcomes; end of treatment; from all trials using fixed effects models, where at least two trials provided data that could be included.

<table>
<thead>
<tr>
<th>Number of trials (number of participants) contributing to the meta-analysis</th>
<th>Effect size (RR or SMD) and 95% CI</th>
<th>P value</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent (modified Rankin score 0-2)</td>
<td>RR1.00 (0.91 to 1.09)</td>
<td>0.99</td>
<td>78%</td>
</tr>
<tr>
<td>Disability</td>
<td>SMD 0.05 (-0.02 to 0.12)</td>
<td>0.15</td>
<td>81%</td>
</tr>
<tr>
<td>Neurological deficit score</td>
<td>SMD -0.28 (-0.42 to -0.14)</td>
<td>&lt;0.0001</td>
<td>77%</td>
</tr>
<tr>
<td>Depression-continuous data</td>
<td>SMD -0.16 (-0.23 to -0.09)</td>
<td>&lt;0.0001</td>
<td>92%</td>
</tr>
<tr>
<td>Depression-dichotomous</td>
<td>RR 0.77 (0.65 to 0.90)</td>
<td>0.001</td>
<td>53%</td>
</tr>
<tr>
<td>Motor score</td>
<td>SMD 0.06 (-0.02 to 0.13)</td>
<td>0.12</td>
<td>95%</td>
</tr>
<tr>
<td>Cognition</td>
<td>SMD -0.04 (-0.11 to 0.03)</td>
<td>0.32</td>
<td>0%</td>
</tr>
<tr>
<td>Death</td>
<td>RR 1.0 (0.79 to 1.26)</td>
<td>1.00</td>
<td>0%</td>
</tr>
<tr>
<td>Cognition</td>
<td>SMD -0.04 (-0.11 to 0.03)</td>
<td>0.3</td>
<td>0%</td>
</tr>
<tr>
<td>Seizures</td>
<td>RR 1.49 (1.05 to 2.11)</td>
<td>0.03</td>
<td>0%</td>
</tr>
<tr>
<td>Gastrointestinal symptoms (nausea, diarrhoea, abdominal pain)</td>
<td>RR 1.38 (0.99 to 1.94)</td>
<td>0.06</td>
<td>8%</td>
</tr>
<tr>
<td>Serious bleeding</td>
<td>RR 1.10 (0.72 to 1.62)</td>
<td>0.67</td>
<td>0%</td>
</tr>
<tr>
<td>Leaving before the end of first follow-up</td>
<td>RR 0.92 (0.61 to 1.40)</td>
<td>0.71</td>
<td>0%</td>
</tr>
</tbody>
</table>

RR: relative risk
SMD: standardised mean difference
Table 3

Summary effect sizes for trials at low risk of bias, at end of treatment, where at least two trials reported the outcome of interest. Fixed effects models

<table>
<thead>
<tr>
<th></th>
<th>Number of trials and participants contributing to the meta-analysis</th>
<th>Effect size</th>
<th>P value</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent (modified Rankin score 0-2)</td>
<td>3 trials (n=3269)</td>
<td>RR 1.00 (0.91 to 1.09)</td>
<td>0.99</td>
<td>78%</td>
</tr>
<tr>
<td>Disability</td>
<td>2 trials (n=2853)</td>
<td>SMD -0.01 (-0.09 to 0.06)</td>
<td>0.75</td>
<td>0%</td>
</tr>
<tr>
<td>Neurological deficit score</td>
<td>2 trials (n=142)</td>
<td>SMD -0.30 (-0.63 to 0.04)</td>
<td>0.08</td>
<td>0%</td>
</tr>
<tr>
<td>Depression (continuous data)</td>
<td>2 trials (n=2861)</td>
<td>SMD -0.11 (-0.19 to -0.04)</td>
<td>0.002</td>
<td>69%</td>
</tr>
<tr>
<td>Motor score</td>
<td>3 trials (n=2936)</td>
<td>SMD 0.02 (-0.05 to 0.09)</td>
<td>0.58</td>
<td>88%</td>
</tr>
<tr>
<td>Death</td>
<td>4 trials (n=3260)</td>
<td>RR 0.99 (0.79 to 1.25)</td>
<td>0.95</td>
<td>0%</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>2 trials (n=148)</td>
<td>RR 2.19 (1.10 to 4.76)</td>
<td>0.05</td>
<td>0%</td>
</tr>
<tr>
<td>Leaving the trial before first follow-up</td>
<td>4 trials (n=3283)</td>
<td>RR 1.01 (0.48 to 2.10)</td>
<td>0.98</td>
<td>0%</td>
</tr>
<tr>
<td>Seizures</td>
<td>3 trials (n=3275)</td>
<td>RR 1.47 (0.99 to 2.18)</td>
<td>0.06</td>
<td>0%</td>
</tr>
</tbody>
</table>
References


after acute intracerebral hemorrhage (FMRICH): study protocol for a randomized, double-blind, placebo-controlled, multicenter trial. Trials 2013;14():77


[23] Li J, He Q-Y, Han M-F. Recent effect of fluoxetine in improving neurologic impairment and preventing post-stroke depression in the early stage. Chinese Journal of Postgraduate Medicine 2004;8(7):1208-9


[32] Chalmers I, Bracken MB, Djulbegovic B, Garattini S, Grant J, Gülmezoglu AM, Howells DW, Ioannidis JPA, Oliver S. Lancet 2014; 383: 156–65 How to increase value and reduce waste when research priorities are set
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Maureen Harding obtained articles for full text review

Dr Juan Marquez Romero provided unpublished data from the 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 of authors

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

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

Legends for figures

Figure 1. Flow diagram showing selection of studies

Figure 2 Risk of Bias

Figure 3. Forest plot, mRS (0-2) at end of treatment

Figure 4. Forest plot, disability at end of treatment
Seven new studies included (in addition to the six we had identified in the 2012 Cochrane review)