Selective Serotonin Reuptake Inhibitors for Stroke Recovery
A Systematic Review and Meta-analysis

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Each year, about 16 million people in the world experience a first-ever stroke. Of these, about 5.7 million die and another 5 million remain disabled.1 Although there are effective treatments that restore brain perfusion and minimize complications and recurrent stroke, there is no treatment proven to facilitate neurological recovery after stroke.

A recent small trial demonstrated that the selective serotonin reuptake inhibitor (SSRI) fluoxetine, commonly used to treat depression, improved motor recovery and reduced dependency after stroke when given to people without depression.2 Experimental studies reporting neurogenic and neuroprotective effects of SSRIs3,4 provide a plausible mechanism of action.

Our objective was to systematically review and perform a meta-analysis of all (published and unpublished) randomized controlled trials of SSRI compared with control, given within the first year of stroke, to determine the effect on dependency, disability, and other important clinical outcomes.

Methods

Searches and Study Selection
Extensive literature searches were performed between August 2011 and March 2012 (see Data in online-only Data Supplement); this included searching the gray literature. Two review authors scrutinized the searches of Cochrane Stroke Group, CENTRAL, CCDAN and the trials registers, and applied inclusion criteria. One review author scrutinized the other searches and applied inclusion criteria.

We included all randomized controlled trials in patients with a clinical diagnosis of stroke, in which SSRIs were given within the first year of stroke, for any clinical indication. The control arm included usual care or a placebo.

Any drug classified as an SSRI (for example fluvoxamine, fluoxetine, sertraline, citalopram, escitalopram, and paroxetine) given at any dose, by any mode of delivery, was included. Drugs with mixed effects were not included.

Two review authors independently extracted data, except for papers in Chinese, for which 1 review author extracted data.

Outcomes

The primary outcomes were dependence and disability. The secondary outcomes were neurological impairments, depression, anxiety, quality of life, fatigue, healthcare cost, death, leaving the trial early, death, and adverse events including gastrointestinal side effects, bleeding, and seizures.

Risk of Bias
The Cochrane Collaboration’s risk of bias tool assessed risk of bias in relation to randomization, allocation concealment, blinding, incomplete outcome data, and selective reporting.6 A Funnel plot assessed publication bias.

Synthesis of Results
For trials with a control arm and 2 active arms, data from the control arm and the SSRI arm were included. Review Manager (RevMan 5.1) software7 calculated summary statistics at the end of intervention and at the end of follow-up. Statistical heterogeneity between trials and subgroups was assessed by I² statistic and interpreted according to The Cochrane Handbook.8

Summary Measures
Random effects meta-analyses were performed, using risk ratios (RRs) for dichotomous data and for ordinal scales with a recognized cut point. Standardized mean difference (SMD) was used for ordinal scales and continuous data.

Additional Analyses
Subgroup analyses were performed according to type of SSRI, depression or not as an inclusion criterion and time since stroke at recruitment. Sensitivity analyses explored the influence of randomization, allocation concealment, blinding, incomplete outcome data, and selective reporting on effect sizes.

Results

Study Selection
After removal of duplicates, there were 4164 records. Two hundred twenty-four full texts were retrieved for scrutiny (Figure 1).

Study Characteristics
Four trials fulfilled inclusion criteria but provided no data for meta-analysis. A further 51 completed trials provided data.
for meta-analysis, 1 of which reported data separately for depressed and nondepressed people, therefore we considered this as 2 separate trials.

Thus, there were 52 trials randomizing 4059 patients to SSRI or control; 28 used fluoxetine,7,27–32 7 used sertraline,33–39 10 used paroxetine,40–49 5 used citalopram,50–54 1 used escitalopram,55 and 1 used either sertraline or fluoxetine.56 The usual care arm was not the same in all the trials because of geographical variation in the management of stroke. In some of the Chinese trials, usual care included agents such as free radical scavengers, hyperbaric oxygen, acupuncture, Ginkgo biloba, deproteinized calf blood, and Vitamin E. These drugs were generally not given as routine care in the trials from the West.

**Subject Characteristics**

Of the 52 trials included in the meta-analysis, the mean age of patients ranged from 55 years to 77 years. Most excluded those with dementia or communication difficulties.

**Risk of Bias Within Trials**

In a substantial number of trials, there was high or unclear risk of bias for each risk of bias item (Figure 1).

**Results: At End of Treatment**

**Dependence**

One trial recruited 118 patients and reported modified Rankin score at 90 days after randomization in 112 patients. Random allocation to SSRI was associated with reduction in dependence (modified Rankin score >3) (74% SSRI versus 91% placebo; RR, 0.81; 95% confidence interval [CI], 0.68 to 0.97).2

**Disability**

Figure 3 shows that among 22 randomized controlled trials that measured disability at the end of treatment in a total of 1343 participants, the SMD in disability score was 0.91 (95% CI, 0.60 to 1.22) among participants assigned SSRI compared with placebo. However, there was substantial heterogeneity among the trials (I²=86%; P<0.00001) and moderate heterogeneity between the SSRIs (I²=58%; P=0.7).5 There was also substantial heterogeneity according to time between stroke onset and randomization (I²=89%; P<0.00001), with the largest effect size when time since stroke was not reported.

Figure 4 shows that the magnitude of the effect of SSRI versus placebo on disability was greater in trials that recruited people with depression (SMD, 1.11; 95% CI, 0.71 to 1.51) compared with people who did not have depression at randomization (SMD, 0.49; 95% CI, 0.17 to 0.80; F=83%, P=0.02). Several disability scales were used including the Barthel, modified Barthel, and functional independence measure. Some Chinese papers used an activities of daily living score that was not referenced.

**Neurological Deficit Score**

The SMD was −1.00 (95% CI, −1.26 to −0.75; 29 trials, 2011 participants), with high heterogeneity among trials (I²=86%; P=0.02) between type of SSRI and low heterogeneity according to time since stroke (I²=26%; P=0.26). Effect sizes were larger if depression was present at recruitment (F=89%; P<0.00001).

**Cognition**

SMD was 0.32 (95% CI, −0.23 to 0.86; 7 trials, n=425) with high heterogeneity among trials (I²=86%; P<0.00001) and between type of SSRI (I²=92.6%; P<0.00001), no heterogeneity according to time since stroke (F=0%; P=0.64), and moderate heterogeneity according to depression at recruitment (F=49.8%; P=0.16).
Motor Deficits
SMD was −0.33 (95% CI, −1.22 to 0.56; 2 trials, n=145), with heterogeneity in relation to time since stroke (I²=80%; P=0.02).

Continuous Depression
SMD was −1.91 (95% CI, −2.34 to −1.48; 39 trials, 2728 participants) with high heterogeneity among trials (I²=95%; P<0.00001) and between type of SSRI (I²=78%; P=0.001), with the largest effect for paroxetine and the smallest for sertraline. There was no heterogeneity according to time since stroke (I²=0%; P=0.66), and moderate heterogeneity between subgroups according to presence of depression at recruitment, (I²=35.5%; P=0.21).

Dichotomous Depression Scores
RR was 0.43 (95% CI, 0.24 to 0.77; 8 trials n=771), with high heterogeneity among trials (I²=77%; P<0.00001) and no heterogeneity between SSRIs (I²=0%). There was high heterogeneity according to time since stroke (I²=93%; P=0.00001), with the larger effect size seen in the trials that recruited patients within the first 3 months of stroke. Effect sizes were larger if depression was present at recruitment (I²=86.5%; P=0.007).

Anxiety
SMD was −0.77 (95% CI, −1.52 to −0.02; 8 trials, n=413) with high heterogeneity among trials (I²=92%; P<0.00001) and among type of SSRI (I²=70.6%; P=0.03), with the largest effect seen for paroxetine. Depression at recruitment did not influence effect sizes (I²=29.7%; P=0.23).

Death
RR was 0.76 (95% CI, 0.34 to 1.70; 46 trials, n=3344). There was no heterogeneity among trials (I²=0%; P=0.85), type of SSRI (I²=0%; P=0.69) or according to time since stroke (I²=0%; P=0.56) and depression at onset (I²=0%; P=0.66).

Seizures
RR was 2.67 (95% CI, 0.61 to 11.63; 7 trials, n=444) in favor of control, with no heterogeneity among trials (I²=0%) or between subgroups.

Gastrointestinal Side Effects
RR was 1.90 (95% CI, 0.94 to 3.85; 14 trials, n=902), with low heterogeneity among trials (I²=31%; P=0.14), moderate heterogeneity among type of SSRI (I²=48.9%; P=0.14), and no heterogeneity among the other subgroups.

Bleeding
RR was 1.63 (95% CI, 0.2 to 13.05; 2 trials, n=347), with no heterogeneity.

Premature Trial Withdrawal (Before the End of Treatment)
RR was 1.02 (95% CI, 0.86 to 1.21; 49 trials, n=3851) in favor of control, with no heterogeneity among trials or subgroups.

Follow-up Beyond Treatment End
Only 8 trials7,10,13,26,33,34,36 followed-up participants beyond the treatment period; 1 did not provide any long-term data.34 For disability (2 trials, n=155), and neurological impairment (4 trials, n=275), there were nonsignificant benefits of SSRI (SMD, 1.78; 95% CI, −1.01 to 4.57 and SMD, −0.63; 95% CI, −1.30 to 0.04), respectively. SSRI improved continuous depression scores, (SMD, −1.10; 95% CI, −2.16 to −0.04; 4 trials, n=275) but not dichotomous depression scores (RR, 0.77 [95% CI, 0.34 to 1.76]; 1 trial, n=99). There were no statistically significant differences between SSRI and control for dependence and cognition.

Sensitivity Analyses
Sensitivity analyses for dependence could not be performed because there was only 1 trial.3 For trials at low risk of bias for each of randomization, allocation concealment, patient/personnel blinding, outcome assessor blinding, incomplete data reporting, and selective reporting, effect sizes were smaller for disability and for all the secondary outcomes, whereas the risk of seizures and gastrointestinal side effects remained similar. Data are available on request. The funnel plot for one of the primary outcomes (disability at the end of treatment) appeared to be asymmetrical on visual inspection (Figure 5).3

Discussion
This is the most comprehensive and up-to-date systematic review of SSRIs in stroke. It includes 52 completed trials in which 4059 patients were recruited. We had not expected to identify such a large number of trials, based on our knowledge of previous reviews. Much of the literature is from China. At the end of treatment, patients allocated an SSRI were less likely to be dependent, disabled, neurologically impaired, depressed, or anxious. The favorable effects of SSRIs on disability, dichotomous depression scores, and neurological deficit scores were greater in participants who were depressed at randomization, but this may have been confounded by study quality—we noted that trials recruiting people with depression tended to have a higher risk of bias than the trials.
recruiting patients without depression at onset (data available on request). Participants who were allocated an SSRI manifested a trend toward a higher risk of gastrointestinal side effects, seizures, and bleeding. We noted that there was some heterogeneity between type of SSRI (eg, paroxetine appeared to have larger effects sizes on neurological deficit, but this may have been confounded by a higher risk of bias in the paroxetine trials).

The SMD of 0.91 (95% CI, 0.60 to 1.22) for disability represents a favorable and potentially important clinical effect of SSRIs. However, the precision and external validity of the estimates are potentially compromised by the substantial clinical heterogeneity.
and methodological heterogeneity among the many trials. Further, the magnitude of the effect of SSRIs was smaller when only trials at low risk of bias were included.

The strengths of our study are that we performed extensive searches, included a wide range of important clinical outcomes, and performed prespecified subgroup and sensitivity analyses. We were unable to identify a second review author who was fluent in Chinese to perform double data extraction, but the majority of Chinese papers had English abstracts, which were checked by a second review author, so it unlikely that there were any important errors in data extraction.

The potential weaknesses of our study are that trials had methodological limitations: most were small, there was patchy reporting of outcomes other than depression, none of the trials reported fatigue or health care costs, only 8 trials followed-up patients after completion of treatment, and there were multiple sources of bias, leading to overestimation of effect sizes. There was substantial heterogeneity among trials; there are several possible reasons for this, including differences in the clinical characteristics of patients (eg, age, socioeconomic status, unmeasured difference in baseline variables, time since stroke, depression or not at recruitment, type of SSRIs), process of stroke care, duration of treatment with SSRIs or placebo, and methodological quality of the trials. The heterogeneity among the trials means that the results become less reliable. We considered whether there was too much heterogeneity for some of the outcomes (eg, disability, neurological impairment, depression, anxiety) to combine results in a meta-analysis and produce a pooled estimate. However, we noted that there was no heterogeneity in the analyses of seizures, gastrointestinal side effects, which suggests that the patient population and treatments were sufficiently similar (at least in the trials that reported these outcomes) to combine data. The use of SMD in meta-analysis assumes that the differences in standard deviations among studies reflect differences in measurement scales and not real differences in variability among study populations. We decided that the trials were sufficiently similar in terms of population (stroke) and drugs (SSRI) to use SMD.

The alternative to performing a meta-analysis would have been to perform a narrative review of the 52 studies, but this would have been less easy for the reader to interpret. Furthermore, it would have also been susceptible to subjective interpretation of the data by the review authors.

The results of the meta-analysis are in broad agreement with older systematic reviews that all had much narrower

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The results of the meta-analysis are in broad agreement with older systematic reviews that all had much narrower
research questions. Our sensitivity analyses suggest that other reviews may have overestimated effect sizes because of the inclusion of less methodologically robust trials.67–69 Two previous Cochrane reviews of interventions (including SSRIs) to treat and prevent depression after stroke excluded studies that provided usual care without a placebo as the comparator and reported smaller effects than in the current review.

The included trials mostly recruited patients aged between 60 and 70 years who were able to consent for themselves. This is an important limitation of the existing data, because the risks and benefits of SSRIs may be different for patients with aphasia or cognitive impairment. Data for hemorrhagic and ischemic stroke were not reported separately. Current practice is often to give an antidepressant (often an SSRI) to stroke survivors with depression; the results of this review tentatively support the use of SSRIs in stroke survivors with depression.

This review provided tantalizing evidence of benefits of SSRIs in patients without depression (Figure 4). If the effects are real, and if the risk of adverse events is sufficiently low, SSRIs would become an important (and low cost) treatment for stroke patients. Several ongoing trials were identified (see Data in the online-only Data Supplement) that should together provide the necessary evidence to support or refute the routine prescription of SSRI for patients early after stroke, including those with cognitive impairment and aphasia.

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Disclosures

All authors have completed the Unified competiting interest form at http://www.icmje.org/co_disclosure.pdf. Dr Mead is a coprincipal investigator of FOCUS trial. Drs Hankey and Hackett are coprincipal investigators of AFFINITY Trial. Dr Hankey has received consultancy fees from Bayer Health Care, Boehringer Ingelheim, and Johnson and Johnson. The other authors have no conflicts to report.

References


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List of databases and other sources of information that were searched

Cochrane Stroke Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2011, Issue 8), MEDLINE (from 1948), EMBASE (from 1980), CINAHL (from 1982), AMED (Allied and Complementary Medicine) (from 1985) and PsycINFO (from 1967), Cochrane Depression Anxiety and Neurosis Group (CCDAN) Trials Register, Psychological Database for Brain Impairment Treatment Efficacy (www.psycbite.com/), online Clinical Trial Results and Clinical Trial Registries for Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Novartis, Pfizer, Roche, and Lundbeck, Stroke Trials Registry (www.strokecenter.org/trials), ClinicalTrials.gov (www.ClinicalTrials.gov), Current Controlled Trials (http://www.controlled-trials.com), EU Clinical Trials Register (https://www.clinicaltrialsregister.eu). Reference lists of included trials and relevant reviews were scrutinised. Contact was made with authors and researchers in the field. Science Citation Index Cited Reference Search (February 2012) was used for forward tracking of 32 included trials that were listed in Science Citation Index.

The Medline search (below) was adapted for other databases.

**Search strategy for Medline (Ovid)**

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. hemiplegia/ or exp paresis/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. exp Gait Disorders, Neurologic/
8. or/1-7
9. exp Serotonin Uptake Inhibitors/
10. ((serotonin or 5-HT or 5 HT or 5-hydroxytryptamine or 5 hydroxytryptamine) adj5 (uptake or reuptake or re-uptake) adj5 inhib$).tw.
11. SSRI$1.tw.
12. (alaproclat$ or cericlamin$ or citalopram or dapoxetin$ or escitalopram or femoxetin$ or fluoxetin$ or fluvoxamin$ or paroxetin$ or sertralin$ or trazodone or vilazodone or zimelidine).tw.
13. (alaproclat$ or cericlamin$ or citalopram or dapoxetin$ or escitalopram or femoxetin$ or fluoxetin$ or fluvoxamin$ or paroxetin$ or sertralin$ or trazodone or vilazodone or zimelidine).nm.
14. 9 or 10 or 11 or 12 or 13
15. 8 and 14
16. exp animals/ not humans.sh.
17. 15 not 16
18. Randomized Controlled Trials as Topic/
19. random allocation/
20. Controlled Clinical Trials as Topic/
21. control groups/
22. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
23. Clinical Trials Data Monitoring Committees/
24. double-blind method/
25. single-blind method/
26. Placebos/
27. placebo effect/
28. cross-over studies/
29. Multicenter Studies as Topic/
30. Therapies, Investigational/
31. Drug Evaluation/
32. Research Design/
33. Program Evaluation/
34. evaluation studies as topic/
35. randomized controlled trial.pt.
36. controlled clinical trial.pt.
37. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
38. multicenter study.pt.
40. meta analysis.pt.
41. meta-analysis as topic/
42. random$.tw.
43. (controlled adj5 (trial$ or stud$)).tw.
44. (clinical$ adj5 trial$).tw.
45. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
46. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
47. ((multicenter or multicentre or therapeutic) adj5 (trial$ or stud$)).tw.
48. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure
References to ongoing trials


Assessment of Fluoxetine in Stroke recovery (AFFINITY) trial. An Australasian-lead, investigator-initiated, prospective, parallel group, double-blind, placebo-controlled, multi-centre, randomised, controlled trial to establish the effect(s) of routine administration of fluoxetine (20mg once daily) in patients with recent stroke. Australia New Zealand Clinical trials register.