Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)


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Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

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Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery

Lynn A Legg1, Ann-Sofie Rudberg2, Xing Hua3, Simiao Wu3, Maree L Hackett4, Russel Tilney5, Linnea Lindgren6, Mansur A Kutlubaev7, Cheng-Fang Hsieh8, Amanda J Barugh9, Graeme J Hankey10, Erik Lundström6, Martin Dennis11, Gillian E Mead11

1NHS Greater Glasgow and Clyde Health Board, Paisley, UK. 2Division of Neurology, Department of Clinical Sciences, Karolinska Institutet Danderyd Hospital, Stockholm, Sweden. 3Department of Neurology, West China Hospital, Sichuan University, Chengdu, China. 4Professor, Program Head, Mental Health, The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia. 5Department of Medicine, Mater Dei Hospital, Msida, Malta. 6Department of Neuroscience, Neurology, Uppsala University, Uppsala, Sweden. 7Department of Neurology, Neurosurgery and Medical Genetics, Bashkir State Medical University, Ufa, Russian Federation. 8Division of Geriatrics and Gerontology, Department of Internal Medicine and Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan. 9Department of Geriatric Medicine, University of Edinburgh, Edinburgh, UK. 10Medical School, Faculty of Health and Medical Sciences, The University of Western Australia, Perth, Australia. 11Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

Contact: Gillian E Mead, gillian.e.mead@ed.ac.uk.

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ABSTRACT

Background
Selective serotonin reuptake inhibitors (SSRIs) might theoretically reduce post-stroke disability by direct effects on the brain. This Cochrane Review was first published in 2012 and last updated in 2019.

Objectives
To determine if SSRIs are more effective than placebo or usual care at improving outcomes in people less than 12 months post-stroke, and to determine whether treatment with SSRIs is associated with adverse effects.

Search methods
We searched the Cochrane Stroke Group Trials Register (last searched 7 January 2021), Cochrane Controlled Trials Register (CENTRAL, Issue 7 of 12, 7 January 2021), MEDLINE (1946 to 7 January 2021), Embase (1974 to 7 January 2021), CINAHL (1982 to 7 January 2021), PsycINFO (1985 to 7 January 2021), and AMED (1985 to 7 January 2021). PsycBITE had previously been searched (16 July 2018). We searched clinical trials registers.

Selection criteria
We included randomised controlled trials (RCTs) recruiting stroke survivors within the first year. The intervention was any SSRI, at any dose, for any period, and for any indication. The comparator was usual care or placebo. Studies reporting at least one of our primary (disability score or independence) or secondary outcomes (impairments, depression, anxiety, quality of life, fatigue, cognition, healthcare cost, death, adverse events and leaving the study early) were included in the meta-analysis. The primary analysis included studies at low risk of bias.
Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

Review question
What are the effects of selective serotonin uptake inhibitor (SSRI) drugs on recovery from stroke?

Background
Stroke is a major cause of disability. Stroke-related disability can include difficulty with daily tasks such as toileting, washing, and walking. Sometimes disability is so severe that a person becomes dependent on others for performing basic activities (this is known as 'dependence'). We previously published an update of this Cochrane Review which aimed to find out whether SSRIs (a class of drug usually used to treat mood problems, which work by changing the level of chemicals in the brain) might improve recovery after stroke.

Since the update in 2019, two large studies have now been completed and so it is necessary to perform a further update of this review. In our main analyses we included only high-quality trials, that is those which used rigorous methods to avoid biases (such as the person assessing outcome being aware of whether the stroke survivor received the active drug or placebo). We refer to these studies as 'low risk of bias' studies.

Main results
We identified 76 eligible studies (13,029 participants); 75 provided data at end of treatment, and of these two provided data at follow-up. Thirty-eight required participants to have depression to enter. The duration, drug, and dose varied. Six studies were at low risk of bias across all domains; all six studies did not need participants to have depression to enter, and all used fluoxetine. Of these six studies, there was little to no difference in disability between groups (MD -0.0; 95% CI -0.05 to 0.05; 5 studies, 5436 participants, high-quality evidence) or in independence (RR 0.98; 95% CI 0.93 to 1.03; 5 studies, 5926 participants; high-quality evidence) at the end of treatment.

In the studies at low risk of bias across all domains, SSRIs slightly reduced the average depression score (SMD 0.14 lower, 95% CI 0.19 lower to 0.08 lower; 4 studies; 5356 participants, high-quality evidence) and there was a slight reduction in the proportion with depression (RR 0.75, 95% CI 0.65 to 0.86; 3 studies, 5907 participants, high-quality evidence).

Cognition was slightly better in the control group (MD -1.22, 95% CI -2.37 to -0.07; 4 studies, 5373 participants, moderate-quality evidence).

Only one study (n = 30) reported neurological deficit score (MD -0.39, 95% CI -1.12 to 0.33; low-quality evidence).

SSRIs resulted in little to no difference in motor deficit (SMD 0.03, -0.02 to 0.08; 6 studies, 5518 participants, moderate-quality evidence).

SSRIs slightly increased the proportion leaving the study early (RR 1.57, 95% CI 1.03 to 2.40; 6 studies, 6090 participants, high-quality evidence).

SSRIs slightly increased the outcome of a seizure (RR 1.40, 95% CI 1.00 to 1.98; 6 studies, 6080 participants, moderate-quality evidence) and a bone fracture (RR 2.35, 95% CI 1.62 to 3.41; 6 studies, 6080 participants, high-quality evidence).

One study at low risk of bias across all domains reported gastrointestinal side effects (RR 1.71, 95% CI 0.33, to 8.83; 1 study, 30 participants).

There was no difference in the total number of deaths between SSRI and placebo (RR 1.01, 95% CI 0.82 to 1.24; 6 studies, 6090 participants, moderate quality evidence).

SSRIs probably result in little to no difference in fatigue (MD -0.06; 95% CI -1.24 to 1.11; 4 studies, 5524 participants, moderate-quality of evidence), nor in quality of life (MD 0.00; 95% CI -0.02 to 0.02, 3 studies, 5482 participants, high-quality evidence).

When all studies, irrespective of risk of bias, were included, SSRIs reduced disability scores but not the proportion independent.

There was insufficient data to perform a meta-analysis of outcomes at end of follow-up.

Several small ongoing studies are unlikely to alter conclusions.

Authors' conclusions
There is high-quality evidence that SSRIs do not make a difference to disability or independence after stroke compared to placebo or usual care, reduced the risk of future depression, increased bone fractures and probably increased seizure risk.

Plain Language Summary
Selective serotonin reuptake inhibitors for stroke recovery

Review question
What are the effects of selective serotonin uptake inhibitor (SSRI) drugs on recovery from stroke?

Background
Stroke is a major cause of disability. Stroke-related disability can include difficulty with daily tasks such as toileting, washing, and walking. Sometimes disability is so severe that a person becomes dependent on others for performing basic activities (this is known as 'dependence'). We previously published an update of this Cochrane Review which aimed to find out whether SSRIs (a class of drug usually used to treat mood problems, which work by changing the level of chemicals in the brain) might improve recovery after stroke.

Since the update in 2019, two large studies have now been completed and so it is necessary to perform a further update of this review. In our main analyses we included only high-quality trials, that is those which used rigorous methods to avoid biases (such as the person assessing outcome being aware of whether the stroke survivor received the active drug or placebo). We refer to these studies as 'low risk of bias' studies.
We also wanted to find out whether SSRIs had other benefits, for example improving the severity of any arm or leg weakness, mood, anxiety, cognition, quality of life, and whether SSRIs were associated with side effects such as bleeding or seizures.

**Study characteristics**
In total we found 76 studies recruiting 13,029 stroke survivors within one year of their stroke. There was a wide age range. About half the studies required participants to have depression to enter the trial. The duration, drug, and dose varied between studies. However, only six of these studies were at low risk of bias; the participants in these studies did not have to be depressed to enter the study, and they were all recruited soon after their stroke.

**Key results**
When we combined data from these six studies at low risk of bias, SSRIs did not reduce disability or dependency. SSRIs reduced the risk of future depression by about a quarter, but led to a slight increase in the risk of seizures and also increased the risk of bone fractures. The evidence is current until January 2021.

**Quality of the evidence**
We are very confident that the results are reliable for the effect on disability, dependency and bone fractures, and moderately confident about the effect on seizure risk.
### Summary of findings 1. Fluoxetine versus control at end of treatment, for stroke recovery, using data from high quality trials only

**Fluoxetine versus control at end of treatment, by SSRI, for stroke recovery**

**Patient or population:** people with stroke recovery  
**Settings:** hospital  
**Intervention:** fluoxetine versus control at end of treatment

*Summary of findings table based on studies with low risk of bias.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disability (primary analysis)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>SMD 0.0 (-0.05, 0.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine versus control at end of treatment</td>
<td></td>
<td>5436 (5 studies)</td>
<td>⊕⊕⊕⊕ High</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

| **Independent on modified Rankin score (mRS 0 to 2) (primary analysis)** | **Study population** | | | |
|------------------------------------------------------------------------|---------------------|----------------|--------------------------|-------------------------------|--------------------------------------------------------------------------|
|                                                                         | 1541/2971 (i.e. 52 per hundred) | 1498/2955 (i.e. 51 per hundred) | RR 0.98 (0.93 to 1.03) | 5926 (5 studies) | ⊕⊕⊕⊕ High | - |

| **Neurological deficit score** | | | | |
|---------------------------------|----------------|--------------------------|--------------------------|-------------------------------|--------------------------------------------------------------------------|
| SMD -0.39 (95% CI (-1.12 to 0.33) | | | | |

| **Depression (continuous data)** | | | | |
|---------------------------------|----------------|--------------------------|--------------------------|-------------------------------|--------------------------------------------------------------------------|
| SMD -0.14 (-0.19 to -0.08)     | | | | |

| **Death**                      | **Study population** | | | |
|---------------------------------|---------------------|-----------------------------|--------------------------|-------------------------------|--------------------------------------------------------------------------|
| 168/3029 (i.e. 55 per thousand) | 170/3061            | RR 1.01 (0.82 to 1.24)      | 6090 (6 studies)         | ⊕⊕⊕⊕ Moderate               | This is a small effect (based on the 'rule-of-thumb' method for interpreting SMD)
### Study population

<table>
<thead>
<tr>
<th>Number of seizures</th>
<th>RR</th>
<th>Number of studies</th>
<th>GRADE</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>54/3024 (i.e. 18 per thousand)</td>
<td>1.40</td>
<td>6 (studies)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>76/3056 (i.e. 25 per thousand)</td>
<td>1.40</td>
<td>6 (studies)</td>
<td>Moderate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bone fractures</th>
<th>RR</th>
<th>Number of studies</th>
<th>GRADE</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>40/3024 (i.e. 13 per thousand)</td>
<td>2.35</td>
<td>6 (studies)</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>93/3056 (i.e. 30 per thousand)</td>
<td>2.35</td>
<td>6 (studies)</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the mean control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio; SMD: standardised mean difference

**GRADE Working Group grades of evidence**

**High quality:** further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** we are very uncertain about the estimate.

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*a* Neurological deficit from only one trial of 30 people so we have downgraded for imprecision (GRADE 2013).

*b* Death downgraded for imprecision.

*c* Seizures downgraded for imprecision.

Note that because we included only the low risk of bias studies in our review, none of the evidence was downgraded because of study quality.

A range of different outcome scales were used for disability (including Barthel Index and daily activities subscale of the Stroke Impact Scale), and depression (including emotional role function of the Stroke Impact Scale).
Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

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Description of the condition

Worldwide, stroke is the second leading cause of death, the third leading cause of disability (Johnson 2016), and results in 6.5 million years being lived with disability (GBD 2015). Although major advances in the early reperfusion of ischaemic stroke have been achieved in recent years (e.g. by intravenous thrombolysis, thrombectomy), and more is known about prevention of recurrent stroke), effective, safe and widely accessible and affordable treatments that facilitate early and sustained recovery after stroke are urgently needed to further reduce the burdens of disability and dependency after stroke.

Description of the intervention

Selective serotonin reuptake inhibitors (SSRIs) are drugs that have been available for many years. There are several different SSRIs which all increase brain serotonin levels by preventing its reuptake by the presynaptic neurons. They are widely used to treat mood disorders, including those that occur after stroke, such as depression and emotional lability (i.e. emotional behaviour that is outside normal control and that occurs in situations that previously would not have provoked such behaviour) (Allida 2019). SSRIs are sometimes used to manage anxiety.

Small studies have suggested that fluoxetine, one of the SSRIs, might have a favourable effect on motor recovery after stroke (Chollet 2011; Yi 2010), even in people without mood disorders. Our 2019 Cochrane Review of SSRI for stroke recovery included 63 studies of SSRIs recruiting 9168 stroke survivors within one year of their stroke, where SSRIs were used in people with or without depression (Legg 2019). Combining the studies suggested a benefit on recovery but this benefit was not apparent when low-quality studies were excluded from the meta-analysis.

How the intervention might work

In animal studies, multiple potentially beneficial effects of SSRIs have been demonstrated in both normal and diseased brains. First, SSRIs have a neurotrophic effect. Neurotrophins are a family of proteins that are involved in embryogenesis (formation of an embryo) and organogenesis (development of organs). They control neural plasticity (ability to change, or easily changed or shaped) in adults, regulate synaptic activity and neurotransmitter synthesis, and are essential for the regeneration of nerves (Lang 2004). The development of new nerve cells in adults is generally restricted to specific areas of the brain, namely the subependymal cells of the ventricular system and the subgranular zone of the dentate gyrus in the hippocampus (Ming 2005). SSRIs increase neurogenesis and expression of neurotrophic or growth factors in the adult hippocampus (Schmidt 2007), and this is likely to account for the behavioural benefits of antidepressants in animals (Santarelli 2003). Importantly, several studies have shown that migration of new neurons to damaged areas of brain may occur (Wiltrout 2007), and that neurogenesis can also occur within areas of damaged brain, for example in people with Alzheimer’s disease and in animal models of Alzheimer’s disease (Taupin 2006).

Second, fluoxetine may have a neuroprotective effect (i.e. protect nerve cells when the brain is damaged, e.g. by a stroke). In animals, there may be several mechanisms for neuroprotective effects of SSRIs, such as reducing inflammation (e.g. repression of microglia activation) (Lim 2009), and by enhancement of specific protein expression (hypoxia inducible factor–1 alpha, heme oxygenase-1) (Shin 2009).

Third, SSRIs can indirectly affect an important hormonal system in the body, the adrenergic system, through up-regulation (i.e. increase a cellular component of a cell, such as ribonucleic acid (RNA) or protein, in response to an external variable) of beta1 receptors (Pålviimäki 1994).

In healthy humans, functional magnetic resonance imaging (fMRI) studies have demonstrated that fluoxetine can modulate cerebral motor activity (Loubinoux 1999). For example, in eight chronic stroke participants in (Zittel 2008), a single dose of citalopram 40 mg led to improvements in dexterity. A 2017 review paper discussed the hypothesis that SSRI might modulate inhibitory pathways, and that this modulation might enhance reorganisation and reestablishment of excitatory-inhibitory control, and thus promote motor recovery after stroke (Pinto 2017).

SSRIs may also improve recovery after stroke simply through their effect on preventing or treating depression and anxiety, and through improving sleep and alertness.

Why it is important to do this review

Our 2012 Cochrane Review of SSRIs for stroke recovery showed that SSRIs appeared to reduce dependence, disability, neurological impairment, anxiety, and depression after stroke, even in participants without depression, but when we included only those studies at low risk of bias, effect sizes were much smaller (Mead 2012). The review generated the hypothesis that SSRIs might promote recovery after stroke.

SSRIs interact with platelet function and clotting, and therefore may have adverse effects in people with stroke, particularly those with haemorrhagic stroke, and these adverse effects might outweigh any potential benefits.

Three large collaborative studies (AFFINITY 2020; EFFECTS 2020; FOCUS 2019), were designed based on the results of the 2012 Cochrane Review (Mead 2012), to test the hypothesis that fluoxetine given early after stroke would improve recovery, or in other words, lead to less dependency and less disability at follow-up. The 2019 Cochrane review Legg 2019 included the results of FOCUS 2019, which recruited over 3000 participants; in the 2019 update, meta-analysis of the studies at low risk of bias indicated that SSRIs did not improve recovery from stroke. There were improvements in disability only when studies at high risk of bias were included.

Cochrane Reviews should be updated regularly (ideally every two years when substantial new evidence becomes available). In 2020, the results of two large studies (AFFINITY 2020; EFFECTS 2020) were published and therefore we decided to update this review.

OBJECTIVES

To determine if selective serotonin reuptake inhibitors (SSRIs) are more effective than placebo or usual care at improving outcomes in people less than 12 months post-stroke, and to determine whether treatment with SSRIs is associated with adverse effects.
METHODS
Criteria for considering studies for this review

Types of studies
We included all randomised controlled trials (RCTs) in people with a clinical diagnosis of stroke (Hatano 1976), where an SSRI had been given within the first year of stroke onset i.e. 1) studies had to state that participants were recruited within 12 months of stroke onset, or 2) studies where the mean (or median) time since stroke was less than 12 months. Studies had to have reported at least one of our outcomes of interest in order to be included in the meta-analysis. For those studies which did not report data in a form that we could use, we attempted to get the raw data from the authors, and if this was not possible, we retained the studies in the list of included studies, even though they could not be included in the meta-analysis.

We included studies:
• with more than two arms (e.g. SSRI versus another active treatment versus placebo). We included data from the SSRI arm and the placebo arm (or usual-care arm if a placebo was not used), and discarded data from the other active treatment arms;
• in all languages.

We excluded studies:
• using a quasi-experimental design (i.e. where investigators describe a non-random component in the sequence generation process, such as date of admission);
• using a cross-over design.

There was no restriction on the eligibility of RCTs on the basis of sample size or duration of follow-up.

Types of participants
We included studies that had recruited survivors of a stroke, defined as a sudden-onset focal neurological disturbance, assumed to be vascular in origin, and lasting more than 24 hours (Hatano 1976). Studies had to recruit participants within 12 months of stroke onset, or the mean/median time since stroke had to be less than 12 months. We intended to include studies in subarachnoid haemorrhage and perform a subgroup analysis but we did not find any such studies. We intended to exclude trials of mixed populations (e.g. stroke and head injury) unless separate results for those with stroke were available, but we found no such studies.

Types of interventions
We included any drug classified as a SSRI (e.g. fluvoxamine, fluoxetine, sertraline, citalopram and paroxetine). We included any dose or mode of delivery, given for any duration and for any reason (e.g. to aid neurological recovery, to treat depression or anxiety or emotionalism, or to prevent depression or anxiety or other mood disorders). We did not include drugs that have mixed effects that include SSRI actions.

The comparator arm could include usual care or a placebo.

We excluded studies in which an SSRI was compared with another active intervention (e.g. another type of drug or herb or acupuncture). We also excluded studies that combined an SSRI with another active treatment and compared with the active treatment alone, because of the potential for interaction between the SSRI and other active treatment.

If studies had two SSRI arms, we combined these and compared with control.

Types of outcome measures
We included several outcomes.

Primary outcomes
We had two co-primary outcomes:
• independence at end of treatment. In stroke trials this is typically measured using the modified Rankin Scale (mRS), with a score of 0 to 2 conventionally considered to represent independence;
• disability score at the end of treatment. Measures included, but were not limited to, Barthel index (BI) or Functional Independence Measure (FIM). If FIM or Barthel was not measured, we included an outcome reported in the trial that reported a construct as similar as possible to FIM or Barthel. For the trials which reported the Stroke Impact Scale, we used the daily activities subscale as a measure of disability.

Although disability scores and independence (or not) are arguably measuring the same concept, disability scores provide a more detailed description of functional outcome than simply using a dichotomous outcome such as independence. In other words, we were interested in performance in personal activities of daily living (ADL)/disability (measured using disability scores) and also independence in performance in personal ADL/disability measured using dichotomous outcome (independent or not).

Note that 'end of treatment' depends on the duration of treatment, and so the outcome might be measured at different time points in different studies. But we justified this approach because we were interested in whether an SSRI, given for any duration, led to better outcomes immediately after completing the course of the SSRI. However, to be included, the outcome measure had to be assessed at the same time in the control and SSRI group.

Secondary outcomes
• Impairments (which can include neurological deficit scores such as the National Institute of Health Score, Motor deficit scores such as the Fugl-Meyer motor score). If the total score was reported, and also motor deficit alone, we performed two separate meta-analyses. For the trials which reported Stroke Impact Scale, we elected to use the self-reported 'strength' domain for motor deficit.
• Depression. We accepted any depression score. We did not decide which score to prioritise as we anticipated that trials would use only one depression score. We included both continuous and dichotomous scores and analysed these separately.
• Anxiety. We intended to accept any anxiety score. We intended to include both continuous and dichotomous scores and analyse these separately.
• Quality of life. We accepted any score.
• Fatigue. This could include any fatigue score, or the vitality component of the SF-36 (Short Form Survey).
• Healthcare cost.
Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

We searched the following electronic bibliographic databases.

- Cochrane Stroke Group Trials Register (7 January 2021)
- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 1) in the Cochrane Library (searched 7 January 2021) (Appendix 1)
- MEDLINE (from 1948 to 7 January 2021) (Appendix 2)
- Embase Ovid (from 1980 to 7 January 2021) (Appendix 3)
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1982 to 7 January 2021) (Appendix 4)
- AMED Ovid (Allied and Complementary Medicine) (from 1985 to 7 January 2021) (Appendix 5)
- PsycINFO Ovid (from 1967 to 7 January 2021) (Appendix 6)
- PsyCBITE Psychological Database for Brain Impairment Treatment Efficacy (www.psycbite.com/) (16 July 2018)

In addition, we searched the following ongoing trials registers (Appendix 7).

- Stroke Trials Registry (www.strokecenter.org/trials) (26 June 2018)
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch) (7 September 2020)

Evidence for this update included search results from the previous version of this review, combined with results from the above searches. In Mead 2012 there had been no date limits and searches had been applied from inception of databases.

Following editorial review, one review author (GM) searched the WHO ICTRP using the term 'stroke' on 8 August 2021 to identify any new trials registered after 7 July 2020 i.e. > 1 year since last search.

**Searching other resources**

In an effort to identify further published, unpublished and ongoing studies, we:

- searched reference lists of included trials and relevant reviews when full texts were retrieved for detailed scrutiny;
- contacted researchers in the field.

**Data collection and analysis**

**Selection of studies**

Joshua Cheyne (Cochrane Stroke Group Information Specialist), ran the searches of CENTRAL, MEDLINE, Embase, CINAHL, AMED, and PsycINFO, and downloaded the resulting references into Reference Manager. These were imported into Covidence, which automatically removed some, but not all, of the duplicates.

Any two review authors (from GM, EL, LAL, MK, SW, RT, A-SR, LL, C-FH, MH or XH) independently scrutinised the resulting titles and abstracts and excluded obviously irrelevant reports and duplicates. We obtained full texts of potentially eligible studies. Any two review authors (from GM, AB, EL, LAL, MK, SW, RT, A-SR, LL, C-FH or XH) independently applied inclusion and exclusion criteria; if there was lack of consensus, a third review author (usually GM unless she had already scrutinised the paper) also applied inclusion and exclusion criteria.

We include a flow diagram that includes the number of unique references identified by the searches, the number of records excluded after preliminary screening of titles and abstracts, the number of records retrieved in full text, and the number of studies fulfilling our inclusion criteria (Figure 1).
Figure 1. PRISMA flow diagram for this update

63 studies included in previous version of review

446 records identified through database searching

5 records identified through other sources

1600 records from updated search of WHO ICTRP on 8.8.2021

2114 records after duplicates removed, 9 could not be found for screening

2105 records screened

1999 records excluded

90 full text articles excluded.

26 Additional references to known study

17 Systematic review-no new trials

11 duplicate references

9 Wrong intervention

7 Wrong study design

5 Narrative review, no new references

5 Wrong comparator

4 Commentary no new references

2 Wrong patient population

1 Quasi-experimental design

1 Systematic review - new studies found and
Data extraction and management

For the new eligible studies that we had identified, any two review authors (from GM, EL, LAL, MK, MH, SW, RT, LL, A-SR, LL, C-FH or XH) independently extracted data from each new study.

We extracted the following data:

- the report: author, year and source of publication;
- the study: sample characteristics, social demography;
- the participants: stroke sequence (first-ever versus recurrent), social situation, time since stroke onset, prior history of psychiatric illness, current neurological status, stroke severity, whether people with aphasia were recruited, the proportion with depression at baseline (if recorded by trialists), we did not extract information on location or size of lesion as this was unlikely to have been recorded by the trialists, and brain imaging often does not show a visible infarct in people with minor strokes;
- the research design and features: adherence, non-response and length of follow-up;
- the intervention: type, duration, dose, timing and mode of delivery;
- the effect size: sample size, nature of outcome, estimate and standard deviation (SD) (or standard error (SE));
• source of funding.

Methods in previous versions were broadly similar and are fully reported in previous versions (Legg 2019; Mead 2012)

Assessment of risk of bias in included studies

We assessed risks of bias using the Cochrane 'Risk of bias' tool (Higgins 2017). We assessed the methods used in each study to control for the following potential sources of bias: sequence generation (selection bias); allocation concealment (selection bias); blinding of participants, personnel and outcome assessors (performance and detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and other potential threats to validity.

Where there was a disagreement between the two review authors on risk of bias, a third review author (LAL, GM) reviewed the data and reached a consensus in discussion with the first two review authors.

For incomplete outcome data, we categorised as 'low risk' if missing data were imputed using appropriate methods or if missing outcome data overall were less than 5%. For this update, we decided to categorise studies as low risk of bias if more than 5% of data were missing providing the number of participants with missing data was balanced between groups and the reasons for missing data were unrelated to treatment allocation.

We extracted data on source of funding, and listed this under 'Other sources of bias'. If the source of funding was not given, or if there were links with the pharmaceutical industry and no explicit statement that the funder had no input into the design or analysis of the study, we classified this as 'unclear risk'. We also recorded any other potential threats to validity.

We also extracted data on how adverse effects were reported, and listed these in the descriptions of the studies.

If a study author was also one of the review authors, a review author who was not involved in the study extracted data and assessed quality.

For this 2021 update, we contacted study authors to obtain more information to enable us to make judgements about risk of bias if this was unclear from the paper, and if this was going to influence whether a study was categorised as low risk of bias across all seven domains i.e. changing a judgement of 'uncertain' to 'low risk' of bias.

Measures of treatment effect

For dichotomous data, we reported risk ratios (RRs). For ordinal scales, where there was a well-recognised cut-point in the scale (e.g. mRS) we analysed the data as a dichotomous outcome (dependent or independent).

For ordinal scales with no recognised cut-point, we analysed the data as continuous data. The data required for meta-analyses of continuous data in Review Manager 5 are means and standard deviations (SDs) (Review Manager 2014). When extracting continuous data from the study reports, we checked whether trials reported the SD or the standard error (SE). We had planned to use the SE or 95% confidence interval (CI) to compute the SD when SDs were missing, but this was not needed as all the trials reported SDs.

For ordinal scales and continuous data, we calculated standardised mean differences (SMDs), because different scales were used for the same outcomes (e.g. Barthel Index (BI) and Functional Independence Measure (FIM) for disability score, the Beck Depression Inventory (BDI) or the Hamilton Rating Scale for Depression (HAM-D) for depression). The SMD does not correct for differences in the direction of the scale. Some scales increase with disease severity and others decrease, so we multiplied the mean value from one set of trials by –1. For example, in the National Institute of Health Stroke Scale (NIHSS), a low score indicates a less severe stroke, whilst a low score in the Scandinavian Stroke Scale (SSS) indicates a more severe stroke.

If there was more than one outcome measure in the same domain (e.g. two different depression scales), we made a post-hoc decision to select the one with the most complete data.

Unit of analysis issues

The number of observations in the analysis should match the number of 'units' that were randomised. We considered outcomes measured at the end of treatment and at the end of follow-up in separate analyses. For side effects, we considered the number of participants developing a specified side effect rather than the total number of side effects in each group.

Dealing with missing data

For this update, we contacted authors of new trials to obtain any data that we needed for our meta-analysis that had not been included in a published full-text article or an abstract.

Note that for some analyses, the sample size is slightly different for different outcomes, this is because of the missing responses for some outcomes.

Assessment of heterogeneity

We assessed whether there was evidence of inconsistency in our results by considering possible clinical, methodological, and statistical heterogeneity. We assessed clinical and methodological heterogeneity by comparing similarities in our included studies between study designs, participants, interventions, and outcomes.

We quantified the effect of heterogeneity using the I² statistic. We assessed statistical heterogeneity by visually examining forest plots. Thresholds for the interpretation of the I² statistic can be misleading, since the importance of inconsistency depends on several factors. A rough guide to interpretation in the context of meta-analyses of randomised trials is as follows: (Section 9.5.2; Deeks 2021):

• 0% to 40% is not considered important;
• 30% to 60% suggests moderate heterogeneity;
• 50% to 90% suggests substantial heterogeneity;
• 75% to 100% is considerable heterogeneity.

Assessment of reporting biases

We searched clinical trials registers to identify published protocols for each of our included studies. We checked for selective reporting of results by comparing the published protocol with the published full-text article and by scrutinising the aims and methods of the trials and comparing these with outcomes reported. We found several papers by the same authors, and contacted the authors
to check whether the publications were duplicates or to check if the included study populations were unique. If it was not possible to determine whether different publications reported overlapping groups of participants, we included just one of the papers and listed the others as awaiting assessment.

If we had identified a sufficient number of included studies at low risk of bias (i.e. more than 10 studies (Sterne 2017)), we would have generated a funnel plot of low risk of bias studies, to assess risk of publication bias, an asymmetrical funnel plot might have suggested publication of only positive results (Egger 1997). We made a post-hoc decision to perform a funnel plot for all studies, irrespective of risk of bias, for the co-primary outcome of disability.

We deployed a comprehensive search strategy in an effort to avoid reporting biases in our review methodology. See Search methods for identification of studies.

We tried to avoid language bias by including all trials, irrespective of language: we sought translation where needed.

**Data synthesis**

We completed meta-analysis of outcomes for which we had comparable effect measures from more than one study, and when measures of heterogeneity indicated that pooling of results was appropriate. We used the statistical calculator provided in Review Manager 5 to perform meta-analysis (Review Manager 2014).

We used a fixed-effect model (Mantel 1959), rather than a random-effects model because of the dominance of the three largest trials (AFFINITY 2020, EFFECTS 2020; FOCUS 2019); random effects would have given too much weight to the smaller trials. The dominance of the three large trials makes a fixed-effect model a more reliable indicator of the effect than the average across the smaller trials. We assessed the robustness of the results to choice of model using a sensitivity analysis for our primary outcomes.

In the initial 2012 review, we had performed multiple meta-analyses of all the primary and secondary outcomes, included all trials irrespective of risk of bias, and then explored the influence of each aspect of bias on estimates of effects in a series of sensitivity analyses.

In the 2019 review we limited our analyses of all outcome measures to studies at low risk of bias (Higgins 2017), as we wanted reliable data, not confounded by bias, to find out whether SSRIs were more effective than placebo or usual care at improving a range of important outcomes. Also, had we included all studies, irrespective or risk of bias, for all available outcomes, the number of analyses would have become unmanageable within the resources we had. However, in the 2019 review, we performed a sensitivity analysis by using data on our two primary outcomes (disability and independence) from all trials, irrespective of risk of bias. For this current update, we use the same approach.

We reached decisions on overall risk of bias by study by consideration of six risk of bias domains: sequence generation, allocation concealment, blinding of participants and trial personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other risk of bias. We required a study to have a judgement of low risk of bias in all domains in order to categorise it as having an overall low risk of bias.

**Subgroup analysis and investigation of heterogeneity**

If there had been at least two studies at low risk of bias across all six domains of risk of bias, we would have explored variability in the participants, interventions, and outcomes among studies using the following subgroups.

- Type of SSRI.
- Studies with depression at baseline as an inclusion criterion and those where depression was not an inclusion criterion.
- Time since stroke at recruitment. We categorised these as less than three months (0 - 90 days), three to six months (91 to 108 days), six to nine months (181 to 271 days) or nine to 12 months (272 to 365 days).

Finding high statistical heterogeneity ($I^2 > 50\%$) would not have prevented us from performing a subgroup analysis, rather we would have considered the reason for this heterogeneity. We did not perform subgroup analyses by type of SSRI or time since stroke as all studies included in the main analyses were similar with regard to these characteristics.

**Sensitivity analysis**

We explored the potential effects of decisions made as part of the review process as follows.

- We included all studies regardless of risk of bias judgement for our primary outcomes of disability score and independence.
- We conducted meta-analysis using the alternate meta-analytical effects model (fixed-effect or random-effects) for just those studies at low risk of bias across all six domains.
- We intended to conduct a meta-analysis using the alternate 'last available follow-up' time point if studies had reported more than one follow-up after the end of treatment, but none of the included studies did this.
- We compared effect estimates from the above results with effect estimates from the main analysis. We reported differences that altered the interpretation of effects.

**Summary of findings and assessment of the quality of the evidence**

We created a summary of findings table using the following outcomes: disability; dependent according to the mRS; neurological deficit score; depression (continuous data); death; seizures; and gastrointestinal side effects (Summary of findings 1). We chose these outcomes as they are of high clinical relevance. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used methods and recommendations described in Chapter 11 of the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2017), using GRADEproGDT software (GRADEproGDT 2015). We justified all decisions to downgrade the quality of studies using footnotes, and made comments to aid the reader’s understanding of the review where necessary.
Summary of findings and assessment of the certainty of the evidence

We created a ‘Summary of findings’ table using the following outcomes: disability; dependent according to the mRS; neurological deficit score; depression (continuous data); death; seizures; and gastrointestinal side effects (Summary of findings 1). We chose these outcomes as they are of high clinical relevance. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used methods and recommendations described in Chapter 11 of the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2017), using GRADEproGDT software (GRADEproGDT 2015). We justified all decisions to downgrade the quality of studies using footnotes, and made comments to aid the reader’s understanding of the review where necessary.

RESULTS

Description of studies

For substantive descriptions of studies see: Characteristics of included studies, Characteristics of excluded studies, Studies awaiting classification, and Characteristics of ongoing studies.

Results of the search

For this update, we screened 221 references from database searches and accessed the available full-text reports for 10 6 studies. This included a systematic review from which we identified five new studies from China (Chen 2015; Hu 2018; Li 2007; Li 2017; Wang 2009).

As a final check for new studies, WHO ICTRP was searched by one review author (GM) on 8 August 2021 and 1600 citations screened.

The flow diagram is shown in Figure 1. This includes the results of the August 2021 search of the WHO ICTRP.

The 2019 version of this review (Legg 2019), identified 63 completed studies recruiting 9168 stroke survivors within one year of their stroke; and 16 ongoing studies (AFFINITY 2020; Asadollahi 2018; Bembenek 2020; Dike 2019; EFFECTS 2020; EudraCT 2005-005266-37; Bonin Pinto 2019; IRCT20112228490N1; IRCT2012101011062N1; IRCT2017041720258N37; NCT02386475; NCT02737930; NCT02767999; NCT02865642; NCT03448159; NCT03826875).

Of these 16 previously ongoing studies, six have now been published (AFFINITY 2020; Asadollahi 2018; Bembenek 2020; Dike 2019; EFFECTS 2020; Bonin Pinto 2019); we excluded one of these at it recruited patients within two years (not one year) of stroke (Bonin Pinto 2019). One trial which we had previously listed as ‘excluded’ has been moved to our list of included studies; this study recruited only 17 patients and was terminated due to slow recruitment and lack of funding to expand to other sites (NCT02737930).

Based on information provided in trials registers: we found the following.

- There are no results for IRCT201112228490N1; the authors were contacted on 20 April 2021 but no response was received; this trial is also listed as ongoing.
- Three studies are completed but the results are not yet available; these are still listed as ongoing (IRCT2012101011062N1; IRCT2017041720258N37; NCT02386475).

Our January 2021 searches identified two new completed studies (Cao 2020; Gong 2020) and three new ongoing studies (ChiCTR1800019467; CTRI/2018/12/016568; TCTR20181216001). An additional study identified in the January 2021 searches did not start due to the COVID 19 pandemic (ACTRN12619000573156).

The flow of search results for the previous version of the review are reported in Legg 2019. We report details of the search for this update in a PRISMA flow chart (Figure 1). This includes our additional searches of WHO ICTRP on 8 August 2021, to identify any new ongoing studies, where we used the broad search term ‘STROKE’ which identified 1600 records, of which two records which were scrutinised in detail; one of these is now included as an ongoing study (IRCT20210307050617N1).

Included studies

In the previous version of the review (Legg 2019), there were 63 included studies recruiting a total of 9168 randomised participants. One study had previously been included in the list of excluded studies, but for this review we included it in our list of included studies as it now reports having recruited 17 participants although the results are not available (NCT02737930).

For the current 2021 update, we identified a further 12 completed studies providing data for meta-analysis and recruiting a total of 3845 more participants (AFFINITY 2020; Asadollahi 2018; Bembenek 2020; Cao 2020; Chen 2015; Dike 2019; EFFECTS 2020; Gong 2020; Hu 2018; Li 2007; Li 2017; Wang 2009). Five of these studies (Chen 2015; Hu 2018; Li 2007; Li 2017; Wang 2009), were identified from the reference list of a 2020 systematic review (Li 2020). For Cao 2020, there are two reports (one reporting 97 participants and the other reporting 100 participants, with overlapping periods for recruitment, almost identical stroke subtypes in the control and citalopram groups, the same funding source, and identical text in some sections of the papers); the author did not respond to our request for clarification, and the editors of the journals in which they were published also did not receive a response from the authors, so to avoid the possibility of double-counting the same participants, we included just one paper reporting 100 participants.

Overall, we now have a total of 76 included studies recruiting 13,029 participants (Figure 1). Of these, 22 contributed to the quantitative syntheses; the remaining studies were not of sufficiently high quality to be included in the main analyses, or did not report our co-primary outcomes of disability, or independence, or did not report any results.

Of the 76 included studies:

- 38 studies used fluoxetine (AFFINITY 2020; Bembenek 2020; Birchennall 2019; Brown 1998; Chen 2001; Cheng 2003; Chollet 2011; Dam 1996; Dike 2019; EFFECTS 2020; Feng 2004; FOCUS 2015; Fruehwald 2003; Gong 2020; He 2004; He 2016; Hu 2002; Huang 2002; Kong 2007; Li 2004a; Li 2004b; Li 2008; Marquez Romero 2013; NCT01674868; NCT02737930; Pariente...
Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

• Eight studies used sertraline (Almeida 2006; Burns 1999; Guo 2009; Meara 1998; Murray 2005; NCT00177424; Rasmussen 2003; Xie 2005);

• Thirteen studies used paroxetine (Chen 2002; Chen 2005b; GlaxoSmithKline 1998; He 2005; Lai 2006; Li 2007; Pan 2018; Wang 2005; Xu 2006; Yang 2002; Yang 2011; Ye 2004);

• Nine studies used citalopram (Acler 2009; Andersen 1994; Andersen 2013; Chen 2015; Gao 2017; Li 2006; Liu 2006; Miao 2004; Savadi Oskouie 2012)

• Five studies used escitalopram (Cao 2020; Hu 2018; Kim 2017; Li 2017; Robinson 2008);

• One study used either sertraline or fluoxetine (Jia 2005);

• Two studies used citalopram or fluoxetine (Chen 2005a; Asadollahi 2018).

Baseline sociodemographic and clinical characteristics

The mean age of participants ranged from 51 ± 7 years (Song 2006), to 75.6 years (Wang 2003), with most studies recruiting participants in their 60s. There are more men than women. Patients with ischaemic stroke and/or primary intracerebral haemorrhage were included.

Mean time since stroke

Of the 76 included studies: (numbers below add up to 76 not 75).

• Forty-four studies report recruiting participants between 0 and 90 days after stroke onset (AFFINITY 2020; Acler 2009; Almeida 2006; Andersen 1994; Andersen 2013; Bembrmek 2020; Birchennall 2019; Chen 2001; Chen 2005b; Cheng 2003; Chollet 2011; Dike 2019; EFFECTS 2020; Feng 2004; FOCUS 2019; Fruehwald 2003; Gao 2017; Gong 2020; He 2004; He 2016; Hu 2002; Huang 2002; Asadollahi 2018; Kim 2017; Kong 2007; Li 2004a; Li 2004b; Li 2008; Marquez Romero 2013; Pan 2018; Rasmussen 2003; Robinson 2008; Savadi Oskouie 2012; Shah 2015; Song 2006; Wen 2006; Wiart 2000; Xie 2005; Xu 2001; Xu 2006; Yang 2011; Ye 2004; Zhao 2011; Zhou 2008).

• Five studies described participants as having an ‘acute stroke’; so we have included these in the zero-to-three-month group (Cao 2020; He 2005; Lai 2006; Li 2006; NCT02737930).

• Two further studies reported that the mean time since stroke was between five and 16 weeks, so we included these in the zero-to-three-month group (Robinson 2000a; Robinson 2000b).

• One study, which did not recruit any participants, had an inclusion criterion of less than 15 days before stroke (NCT01674868).

• Four studies report recruiting participants three to six months (91 to 108 days) after stroke onset: Dam 1996 (described as participants being one to six months), Miao 2004, Murray 2005, and Yang 2002 (‘recovery phase of stroke’ two to six months).

• Two studies report recruiting participants at six to nine months (181 to 271 days) after stroke onset (Guo 2009; Li 2006).

• No study reported recruiting participants between nine and 12 months after stroke.

• One study reported the experimental and control group being median 10.5 months and 5.5 months after stroke, respectively (Burns 1999).

• Seventeen studies did not report the precise time (Brown 1998; Chen 2002; Chen 2005a; Chen 2015; GlaxoSmithKline 1998; Hu 2018; Jia 2005; Li 2005; Li 2007; Li 2017; Meara 1998; NCT00177424; Pariente 2001; Razazian 2014; Restifo 2001; Wang 2003; Wang 2009).

Depression as an inclusion criterion

Thirty-seven studies included participants affected by depression (i.e. depression used as an inclusion criterion) (Andersen 1994; Chen 2001; Chen 2002; Chen 2005a; Chen 2005b; Chen 2015; Cheng 2003; Fong 2004; Fruehwald 2003; GlaxoSmithKline 1998; Guo 2009; He 2005; Hu 2002; Hu 2018; Huang 2002; Jia 2005; Lai 2006; Li 2004a; Li 2004b; Li 2005; Li 2006; Li 2017; Liu 2006; Meara 1998; Miao 2004; Murray 2005; Robinson 2000a; Song 2006; Wang 2009; Wiart 2000; Xie 2005; Xu 2001; Yang 2002; Yang 2011; Ye 2004).

Thirty-nine studies did not use depression as an inclusion criterion (Acler 2009; AFFINITY 2020; Almeida 2006; Andersen 2013; Bembrnek 2020; Birchennall 2019; Brown 1998; Burns 2003; Cao 2020; Chollet 2011; Dam 1996; Dike 2019; EFFECTS 2020; FOCUS 2019; Gao 2017; Gong 2020; He 2004; He 2016; Asadollahi 2018; Kim 2017; Kong 2007; Li 2007; Marquez Romero 2013; NCT0177424; NCT01674868; NCT02737930; Pan 2018; Pariente 2001; Rasmussen 2003; Razazian 2014; Restifo 2001; Robinson 2000b; Robinson 2008; Savadi Oskouie 2012; Shah 2016; Wen 2006; Xu 2006; Zhao 2011; Zhou 2008).

The criteria for diagnosing depression varied between studies.

Excluded studies

Our table of excluded studies is as brief as possible and does not list studies that obviously do not fulfil the inclusion criteria. There are a total of 28 excluded studies.

We describe a total of 28 studies in our table of excluded studies (ACTRN12619000573156; Andersen 1993; Andersen 2012; Andersen 2002; Anonymous 2012a; Anonymous 2012b; Berends 2009; Chen 2019; Choi Kwon 2008; Finkenzellner 2009; Foster 2019; Bonin Pinto 2019; Gourab 2019; Graffagnino 2002; Ji 2000; Kitagao 2020; Li 2002; Liang 2003; Liu 2004; Liu 2020; Morsarrezai 2018; NCT01963832; Robinson 2011; Sitter 2002; Sun 2015; Vogel 2020; Xu 2007; Zhou 2003). Eight of these studies were excluded during this update (ACTRN12619000573156; Chen 2019; Foster 2019; Bonin Pinto 2019; Kitagao 2020; Mosarrezai 2018; Vogel 2020).

Ongoing studies

The following studies are either ongoing or are completed but have not yet published results (ChiCTR1800019467; CTRI/2018/12/016568; EudraCT 2005-005266-37; ICTR20111228490N1; ICTR201201011062N1; ICTR2017041720258N37; RCT20210307050617N1; NCT02386475; NCT02767999; NCT02865642; NCT03448159; NCT03826875; TCTR20181216001). See Characteristics of ongoing studies.

Studies awaiting classification

The same studies that were listed as ‘awaiting classification’ in the previous version of the review of Legg 2019 continue to be listed as ‘awaiting classification’ as no new information is available to change these classification (Guo 2016; He 2018;

Risk of bias in included studies

All 76 studies were randomised controlled trials (RCTs). We could not assess risk of bias in one study as there are no published data, just information on a trials register (NCT02737930). Thirty-two studies were at low risk of bias for random sequence generation and 44 at unclear risk. See Figure 2 and Figure 3.
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.
Figure 2. (Continued)

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Figure 3. 'Risk of bias' graph: review authors’ judgements about each 'risk of bias' item presented as percentages across all included studies.

Allocation

For allocation concealment, we assessed 21 studies to be at low risk of bias and 55 studies to be at unclear risk. Figure 2 and Figure 3 demonstrate selection bias.

Blinding

For performance bias, we assessed 26 studies to be at low risk of bias, 23 studies to be at unclear risk of bias, and 26 studies to be at high risk of bias for blinding of participants.

For blinding of outcome we assessed 25 studies to be a low risk of bias, 48 studies to be at unclear risk of bias, and two studies to be at high risk of bias. Figure 2 and Figure 3 demonstrate blinding.

Incomplete outcome data

For incomplete outcome data we assessed 28 studies to be at low risk of bias, 20 studies to be at unclear risk of bias, and 27 studies to be at high risk of bias. Figure 2 and Figure 3 demonstrate attrition bias.

Selective reporting

We assessed 20 studies to be at low risk of bias, 46 studies to be at unclear risk of bias, and nine studies to be at high risk of bias for selective outcome reporting. Figure 2 and Figure 3 demonstrate reporting bias.

Other potential sources of bias

Other sources of bias

These are shown in the final column of Figure 2 and Figure 3. There were 23 studies at low risk of bias, seven at high risk, and the rest were at unclear risk.

Low risk of bias across all domains

Six trials were at low risk of bias across all domains (AFFINITY 2020; Asadollahi 2018; Bembenek 2020; EFFECTS 2020; FOCUS 2019; Marquez Romero 2013) (Figure 2; Figure 3). For two of these trials, the final judgement was made after obtaining further information from the trialists (Asadollahi 2018; Bembenek 2020).

Following editorial review, one trial that had been included as low risk of bias across all domains in the previous review was re-categorised as unclear risk of bias for ‘other sources of bias’ as there were baseline differences in motor scores (Chollet 2011).

Publication bias

We performed a funnel plot for the outcome of disability, for all trials irrespective of risk of bias (Figure 4). This suggests publication bias, with a cluster of studies in the upper left portion of the graph.
Figure 4. Funnel plot, all studies irrespective or risk of bias, for disability at end of treatment.

Effects of interventions

See: Summary of findings 1 Fluoxetine versus control at end of treatment, for stroke recovery, using data from high quality trials only

Primary outcomes (low risk of bias trials only)

Disability score at the end of treatment

Of the six studies at low risk of bias in all seven domains, two reported Barthel score as median and interquartile range (QR) (Bembenek 2020; Marquez Romero 2013). For one study (Marquez Romero 2013), we converted the median Barthel score and IQR to mean and standard deviation (SD) using a method described in Wan 2014.

For Bembenek 2020, AFFINITY 2020, EFFECTS 2020, and FOCUS 2019 the authors supplied the mean and SD of the activities of daily living score (five questions about activities done during a typical day) of the Stroke Impact Scale.

One did not report disability or independence and so is not included in the analyses of disability and independence (Asadollahi 2018).

There was no difference in measures of disability between selective serotonin reuptake inhibitors (SSRIs) and placebo (Analysis 1.1): the standard mean difference (SMD) with a fixed-effect model (SMD −0.00, 95% CI −0.05 to 0.05; P = 0.98; 5 studies, 5436 participants; high-quality evidence) with no heterogeneity (I² = 0%).

Independent on modified Rankin score (mRS 0 to 2) at the end of treatment

We combined data from the five studies at low risk of bias across all seven domains for the outcome of independent on mRS 0 to 2 using a risk ratio with a fixed-effect model (RR 0.98, 95% CI 0.93 to 1.03; P = 0.37; 5 studies, 5926 participants, high-quality evidence). The I² was 32%, moderate heterogeneity (Analysis 1.2).

Secondary outcomes (low risk of bias trials only)

Impairments: neurological deficit score at the end of treatment

One study (30 participants) of high quality reported neurological deficit scores. The study authors reported no difference in neurological score for participants who received and SSRI compared with those who received a placebo (Analysis 1.3).
Impairments: motor deficits at end of treatment

We combined data for the six low risk of bias studies that reported motor deficits, using the SMD with a fixed-effect model. The analysis found no difference between SSRI and placebo (SMD = 0.03, 95% CI −0.02 to 0.08; P = 0.23; 6 studies, 5518 participants, I² = 75%, substantial heterogeneity, moderate-quality evidence) (Analysis 1.4).

We downgraded the evidence to 'moderate' as the data from several trials were by self-report rather than by an objective assessment of deficits. Note that data from Marquez Romero 2013 are means and SDs estimated from reported medians and interquartile ranges using a method described in Wan 2014.

Depression severity at end of treatment (continuous data)

We combined data from the four studies with an overall low risk of bias for the outcome of depression severity using the SMD with a fixed-effect model (SMD −0.14, 95% CI −0.19 to −0.08; P < 0.01; 4 studies, 5356 participants; high-quality evidence). Participants who received fluoxetine had significantly lower end-of-treatment scores on measures of depression than those participants receiving placebo (Analysis 1.5) with moderate heterogeneity (I² = 36%, P < 0.01).

Depression at the end of treatment (dichotomous data)

Data were available for three studies at low risk of bias (Analysis 1.6). Risk of depression was lower in the SSRI group (RR 0.75, 95% CI 0.65 to 0.86; 3 studies, 5907 participants, P < 0.01), with no important heterogeneity (I² = 0%). This was assessed as high-quality evidence.

Anxiety severity at end of treatment (continuous data)

No studies at low risk of bias reported measures of anxiety.

Anxiety severity at end of treatment (dichotomous data)

No studies at low risk of bias reported number of diagnoses of anxiety.

Death at end of treatment

We combined data for the six studies with an overall low risk of bias for the outcome of death, using a risk ratio with a fixed-effect model. The analysis found no difference in the total number of deaths between SSRI and placebo (RR 1.01, 95% CI 0.82 to 1.24; P = 0.98; 6 studies, 6090 participants, moderate quality evidence), with no evidence of heterogeneity (I² = 0%) (Analysis 1.7).

Side effects: seizures at end of treatment

We combined data for the six studies with an overall low risk of bias for the outcome of seizures, using a risk ratio with a fixed-effect model. The analysis showed more patients had seizures in the SSRI than control group (RR 1.40, 95% CI 1.00 to 1.98; P = 0.05; 6 studies, 6080 participants, moderate-quality evidence because wide confidence intervals), with moderate heterogeneity (I² = 45%) (Analysis 1.8).

Gastrointestinal side effects at end of treatment

One study (30 high quality reported 'gastrointestinal side effects' at the end of treatment. The study authors reported no difference in 'gastrointestinal side effects' for participants who received and SSRI compared with those who received a placebo (Analysis 1.9).

Side effects: bleeding at end of treatment

We combined data from the six studies at low risk of bias using a risk ratio with fixed-effects model (Analysis 1.10). The risk ratio was 1.08 (95% CI 0.69 to 1.70; P = 0.73, 6 trials, 6088 participants, high-quality evidence). There was no important heterogeneity (I² = 0%).

Side effects: fractures at end of treatment

We combined data from the six studies at low risk of bias. SSRIs were associated with higher risk of fractures (RR 2.35, 95% 1.62 to 3.41, 6 studies, 6080 participants, high-quality evidence, P < 0.01, I² = 0%, no important heterogeneity) (Analysis 1.11).

Cognition at end of treatment (continuous data)

Of the six studies at low risk of bias, four studies reported the memory domain of the Stroke Impact Scale (AFFINITY 2020; Bembeneck 2020; EFFECTS 2020; FOCUS 2019). MD was −1.22 (95% CI -2.37 to -0.07) in favour of control, 4 trials, 5373 participants, I² 72%, P = 0.04 (Analysis 1.12). There was substantial heterogeneity. We downgraded to moderate-quality evidence because the cognition outcomes were self-reported, not directly measured. Note that the size of the mean difference between treatment and placebo is very small.

Leaving the study early (before the end of scheduled follow-up) for reasons other than death

We combined data for studies with an overall low risk of bias for the outcome of leaving the study before the end of scheduled follow-up, using a risk ratio with a fixed-effect model. The analysis suggested a slight excess of people leaving early in the SSRI group with no evidence of heterogeneity (RR 1.57, 95% CI 1.03 to 2.40, P = 0.04, 6 studies, 6090 participants; I² = 0%, no important heterogeneity, high-quality evidence) (Analysis 1.13).

Fatigue

Four trials reported SF36 Vitality score as a measure of fatigue (AFFINITY 2020; EFFECTS 2020; Bembeneck 2020; FOCUS 2019). The mean difference between groups was -0.06 (95% CI -1.24 to 1.11; 5524 participants, P = 0.92, I² = 0%, no important heterogeneity, moderate-quality evidence). We downgraded quality because of wide confidence intervals (Analysis 1.14).

Quality of life

Three trials used EQ5 5DL and reported mean and standard deviation in each group which enabled us to perform a meta-analysis. (FOCUS 2019; AFFINITY 2020; EFFECTS 2020 ). The mean difference between groups was -0.00 (95% CI -0.02 to 0.02), 5482 participants, P = 0.93; I² = 0, no important heterogeneity, high-quality evidence) (Analysis 1.15).

Healthcare costs

No trial reported healthcare costs.

Outcomes at the end of follow-up

We repeated the analyses above for all outcomes reported at the end of follow-up for the studies at low risk of bias across all domains. Four studies collected data on outcomes 12 months after
completing the intervention and so we selected this time point for our analyses (AFFINITY 2020; Bembenek 2020; EFFECTS 2020; FOCUS 2019). Two studies have not yet published their 12-month data and so are not included in this meta-analysis (AFFINITY 2020; EFFECTS 2020). We analysed available data for other two studies (Bembenek 2020; FOCUS 2019).

These analyses are shown in Analysis 2.1 to Analysis 2.10. There was no clear evidence of differences between SSRI and control for any outcome.

**Subgroup analyses by intervention characteristics and subsets of participant**

We did not perform preplanned subgroup analyses by intervention characteristics and subsets of participant (including with or without depression) of the studies at low risk of bias, because they all used fluoxetine and all did not require participants to have depression to enter the trial.

**Sensitivity analysis**

**Inclusion of all studies regardless of ‘Risk of bias’ judgement for the co-primary outcomes**

We included all studies reporting disability, regardless of ‘Risk of bias’ judgement for the co-primary outcome of disability at the end of treatment using a SMD and a fixed-effect model.

For disability, participants who received an SSRI intervention had significantly lower end-of-treatment scores than those participants receiving placebo or standard care/practice (SMD -0.18, 95% CI -0.23 to -0.14; P < 0.00001; 32 studies, 7667 participants) with considerable heterogeneity (I² = 94%) (Analysis 1.16). Our post-hoc analysis (Funnel plot, Figure 4) demonstrated an absence of studies in the right hand side of the plot, consistent with publication bias.

We included all studies regardless of risk of bias judgement for the co-primary outcome of independence.

Note that previously Andersen 2013 had the mRS data entered as a continuous variable for disability; for this update we have entered it only as dichotomous data for mRS.

The mRS 0 to 2 at the end of treatment was similar in the two groups (RR 0.97, 95% CI 0.93 to 1.01; P = 0.18, I² = 59%, 8 studies, 6792 participants) (Analysis 1.17).

**Meta-analysis using the alternate meta-analytical effects model (fixed-effect or random-effects) for the primary outcomes from the high-quality studies**

We re-analysed the data for our primary outcomes (disability score and independence (0-2 on mRS) using the random-effects analysis for the high-quality studies. This made no difference to the results (Table 1).

**DISCUSSION**

**Summary of main results**

For this update we included 76 studies with 13,029 participants, of which 38 used fluoxetine and the remaining studies used other selective serotonin reuptake inhibitors (SSRIs) Data from our co-primary outcomes (disability, independence) were not collected in many of the studies.

Six studies were at low risk of bias across all key domains; these all recruited participants who were less than 90 days after stroke onset, none used depression as an inclusion criterion; and they all compared fluoxetine with placebo. Comparing fluoxetine to placebo in these trials, we found high-quality evidence of no beneficial effects of fluoxetine on our co-primary outcomes (disability and independence) at end of treatment. We found high-quality evidence that fluoxetine reduced the severity of depression evaluated using a continuous outcome and the number of participants with depression at end of treatment. We found an excess of participants having seizures and bone fractures amongst those allocated to fluoxetine. Cognition was lower at the end of treatment in the SSRI group. As we included only high-quality studies in our main analyses, we did not downgrade for quality of trials; the main reason for downgrading quality was because of imprecision.

There are data on outcomes at end of follow-up for two trials (Bembenek 2020; FOCUS 2019); follow-up data will be available for two other studies in due course (AFFINITY 2020; EFFECTS 2020).

When we performed a meta-analysis of disability for all studies irrespective of risk of bias, we found a small beneficial effect of SSRI but with high heterogeneity. There was no difference in the proportion of participants independent at follow-up; for this outcome there was evidence of publication bias on our funnel plot.

**Overall completeness and applicability of evidence**

This review includes studies from different settings (e.g. countries; high-, middle- and low-income settings; healthcare systems), with different criteria for selecting participants (e.g. methods of pre-randomisation diagnosis and investigation, inclusion and exclusion criteria), that may reflect differences between the trial protocol and routine clinical practice (e.g. inclusion of participants based on a diagnosis of stroke made using brain imaging: brain imaging is unlikely to be either available or affordable in routine clinical care in many low- and middle-income country settings); and different characteristics of randomised participants (e.g. baseline demographic and clinical characteristics, stroke severity, time since stroke onset, presence or absence of depression, severity of depression). These study characteristics may in part explain the heterogeneity of results, but we know from our previous review that the most probable cause of heterogeneity is study quality.

There is a discordance between the results for disability (one of our co-primary outcomes) between the studies at low risk of bias, which showed no effect, and all studies irrespective of bias (a positive effect). This is because trials at high risk of bias tended to be positive.

The results of the meta-analysis of the seven studies at low risk of bias are applicable to clinical practice throughout the world, for both ischaemic and haemorrhagic stroke.

There is a theoretical risk that SSRIs might carry particular risks in people with haemorrhagic stroke, due to their effects on platelet aggregation and bleeding, but there was no evidence of this based on data from the individual studies; to explore this further we are planning an individual patient meta-analysis (EFFECTS 2020; FOCUS 2019). We noted that those allocated control had better cognition at the end of treatment, although the effect size was
very small, and of uncertain clinical relevance. According to the NHS in the UK, confusion is a rare side effect of SSRIs (NHS 2021), but on the other hand, there is also systematic review evidence that fluoxetine might improve cognition in people with dementia (Xie 2019). Our finding might also have been due to chance. We plan to explore in more detail the impact of fluoxetine on cognition when we perform our individual patient data meta-analysis from the three large studies.

There were no data on anxiety from the studies, even though anxiety is a common problem after stroke.

We were unable to explore the influence of the type of SSRI, as all the high-quality trials used fluoxetine.

The full searches were last performed in January 2021; the lead review author (GM) searched WHO ICTRP in August 2021 and did not find any further new eligible studies. We are not aware of any other new studies published since January 2021 that are likely to change the results of the review.

We have data on follow-up after treatment end for only two studies (Bembenek 2020; FOCUS 2019). Two large studies have unpublished data for outcome six months after treatment end (12 months after randomisation) (AFFINITY 2020; EFFECTS 2020); these data will be incorporated into an individual patient data meta-analysis in due course (Mead 2020).

We did not include studies which combined an SSRI with another active treatment (either drugs or another type of intervention), and either compared with control or the active treatment alone. It is possible that SSRIS could modify (either enhance or reduce) training-induced brain plasticity and hence functional recovery. Thus, the absence of an effect of SSRIs on disability might have been because the SSRI was not coupled with a domain-specific behavioural rehabilitation intervention. In the future, a systematic review of SSRIs plus training would be of interest.

Quality of the evidence

For the evaluation of quality of the evidence, we contacted authors of primary studies as yet unpublished for data on outcomes. For studies which we thought would fall into the category of being at low risk of bias across all the domains, but where some of the methodology was not reported in sufficient detail to enable us to make a final judgement, we contacted authors to clarify methodology. We also contacted authors of primary studies when it appeared that the same (or similar) group of patients had been described in more than one publication, in order to avoid double counting participants, and for one study, we also contacted the editors of the respective journals.

We used the Cochrane risk of bias tool to assess study methods. As in the previous update (Legg 2019), we restricted our meta-analyses to studies at low risk of bias, because in the first review, Mead 2011, there was evidence that the apparently beneficial effects of SSRIs on recovery was due to methodological limitations of the included trials. This observation was confirmed by the sensitivity analyses that we performed for these two previous reviews.

The meta-analysis of the high-quality studies is dominated by three trials (AFFINITY 2020; EFFECTS 2020; FOCUS 2019). All three of these trials were neutral for their primary outcome (modified Rankin score (mRS) at six months).

We performed sensitivity analyses of our two co-primary outcomes (disability and independence) by including all the available outcome data, irrespective of risk of bias. Like our initial (hypothesis-generating) Cochrane Review (Mead 2011), we found that SSRIs reduced disability at the end of treatment. However, it is highly likely that this positive effect is due to biases in trial quality. Publication bias might also be a problem, as suggested by the funnel plot (Figure 4).

We also performed sensitivity analyses to explore whether a random-effects model would make any difference to outcome, but it did not (Table 1).

Potential biases in the review process

We conducted the review using robust Cochrane methodology, with two review authors independently assessing studies for eligibility, extracting data, and carrying out risk of bias assessment. As five review authors (MD, GEM, EL, GH, MH) were also authors of the AFFINITY 2020, FOCUS 2019, and EFFECTS 2020 trials, we ensured that assessment of risk of bias and data extraction for these trials was not performed by these review authors; except for unpublished data on mean (SD) for the Stroke Impact Scale scores, fatigue and quality of life, which were provided by the trial statisticians and entered into forest plots by one review author (GEM).

Our searches identified one systematic review that included several trials from China that we had not identified in the previous review (Li 2020). These trials are now included. Thus, it is possible, though unlikely, that there are other trials that have been published since the Li 2020 review that our searches might not have identified.

After editorial review in July 2021, we decided to perform a final check of the WHO ICTRP (that had last been searched about a year previously) to check for any new ongoing studies. This search was done by one review author only (GEM) and so it is possible, though very unlikely, that new studies were missed.

Agreements and disagreements with other studies or reviews

This review has demonstrated that SSRIs do not improve recovery after stroke. This is in contrast with several other meta-analyses which showed that SSRIs might improve recovery, but these meta-analyses did not include two recently published large high-quality trials which were both neutral (AFFINITY 2020; EFFECTS 2020). In this meta-analysis, we were also able to explore the influence of SSRIs on other important outcomes, that previous reviews had not done, because there had previously been insufficient data.

AUTHORS’ CONCLUSIONS

Implications for practice

Based on our meta-analysis of the studies at low risk of bias, most of which provided selective serotonin reuptake inhibitors (SSRIs) early after stroke and did not require participants to have depression, there is currently no indication for the routine prescription of SSRIs in order to reduce disability and increase independence after stroke. Fluoxetine, which was the most commonly used SSRI and used in the three largest trials, reduces the risk of depression and the severity of depression, but this is probably not a sufficiently strong rationale to give all people with stroke a six-month course
of the drug, particularly as there is an increased risk of seizures and fractures. As the studies at low risk of bias all did not require patients to have depression at entry, we do not know for certain whether SSRIs might reduce disability in people who do have depression after stroke. Also, we do not know what effect SSRIs other than fluoxetine might have on recovery after stroke.

Implications for research

This review found high-quality evidence that SSRIs do not improve recovery after stroke and provided reliable evidence about their risks, though this conclusion is based mainly on evidence about fluoxetine. Thus, further trials of SSRI for stroke recovery are almost certainly not needed, unless they are designed only to include people with depression. This is because all the studies in this review which were at low risk of bias did not require participants to have depression at entry.

We have published a protocol for an individual patient data meta-analysis of the three largest studies included in this review, all of which were of high quality (AFFINITY 2020; EFFECTS 2020; FOCUS 2019). This individual patient data meta-analysis may provide more precise estimates of treatment effects and may be able to identify any differences in outcome related to country or ethnicity. We are also planning to publish a series of other papers, using these data, which we have already described (Mead 2020).

We have carefully considered whether to update this review again. Currently there are several small ongoing studies but, because they are small, the results will not make a material difference to the results of this review. Thus, we think that it is unlikely that further updates of this Cochrane Review will be needed. However, if further large studies are established in the future, we will reconsider this decision.

ACKNOWLEDGEMENTS

For this update, we are grateful to the following people.

Joshua Cheyne, Cochrane Stroke Information Specialist, ran the literature searches.

Maureen Harding obtained articles for full-text review.

Dr Jan Bembenek and Professor Anna Czlonkowska provided further unpublished information about FOCUS-Poland, and additional data on SIS.

Dr Qilong Yi provided additional data for means (SD) of SIS, SF-36 vitality and quality of life from AFFINITY.

Professor Osvaldo Almeida provided additional information about Almeida 2006

Dr Per Näsmann provided data for means (SD) of SIS, SF-36 vitality and quality of life from AFFINITY.

Dr Ehsan Karimi provided further information about Asadollahi 2018.

Bernhard Sabel (Editor in Chief of Restorative Neurology and Neuroscience) and Dr João Pereira Leite, Editor of Brazilian Journal of Medical and Biological Research, wrote to the authors of the two publications relating to Cao 2020; these papers were very similar. No response was received; the two editors kindly checked the text of the two papers and decided that it was likely that the two papers described overlapping groups of patients.

We are also grateful to the peer reviewers and editors in Cochrane Stroke for their comments.

This updated review was funded by the National Institute for Health Research (NIHR) [NIHR Cochrane Review Incentive Scheme 2020 (NIHR133254)]. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.
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Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

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Chen 2005b (published data only)

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Dike 2019 (published data only)


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Wang 2003 (published data only)

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Wen 2006 (published data only)

Wiart 2000 (published data only)

Xie 2005 (published data only)

Xu 2001 (published data only)

Xu 2006 (published data only)

Yang 2002 (published data only)

Yang 2011 (published data only)

Ye 2004 (published data only)


Zhou 2011 (published data only)

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Andersen 2012 (published data only)
Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)


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Anonymous 2012b (published data only)

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IRCT2017041720258N37 [published data only]

IRCT20210307050617N1 [published data only]

NCT02386475 [published data only]

NCT02767999 [published data only]

NCT02865642 [published data only]
**Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)**

**Hattano 1976**


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**Higgins 2017**


**Johnson 2016**


**Lang 2004**


**Legg 2019**


**Li 2020**


**Lim 2009**


**Loubinoux 1999**


**Mantel 1959**


**Mead 2020**


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**NCT03448159 (published data only)**


**NCT03826875 (published data only)**


**TCTR20181216001 (published data only)**

TCTR20181216001. Randomized controlled trial of fluoxetine or placebo on quality of life after acute ischemic stroke. www.thaicalclinicaltrials.org/show/TCTR20181216001 (first received 16 December 2018).

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**GRADE 2013**


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Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

Ming 2005

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NHS 2021

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Pinto 2017

Review Manager 2014 [Computer program]

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Schmidt 2007

Schüinemann 2017

Shin 2009

Sterne 2017

Taupin 2006

Wan 2014

Wiltzou 2007

Xie 2019

Yi 2010

Zittel 2008

References to other published versions of this review

Legg 22019

Mead 2011

Mead 2012

* Indicates the major publication for the study
### Characteristics of included studies [ordered by study ID]

**Acler 2009**

#### Study characteristics

**Methods**
- **Study type:** interventional (clinical trial)
- **Intervention model:** parallel assignment
- **Primary purpose:** treatment

**Participants**
- **20 participants**
  - **Location:** Italy
  - **Setting:** inpatient
  - **Inclusion criteria:** first-ever ischaemic stroke, CT or MRI documenting a single monohemispheric lesion, age below 80 years, within 3 months of onset
  - **Exclusion criteria:** major affective disorders, alcohol abuse and dementia leading to un-cooperative behaviour, pacemakers, metal in the head, concomitant neuropathies, systemic vasculopathies, major affective disorders
  - **Treatment:** 10 people, mean age 68 ± 7 years, 6 men
  - **Control:** 10 people, mean age 65 ± 7 years, 6 men

**Interventions**
- **Citalopram 10 mg daily**
- **Placebo: identical pill daily**
- **Duration of treatment:** at least 4 months
- **Duration of follow-up:** not stated

**Outcomes**
- **Motor cortex excitability**
- **NIHSS**
- **Lindmark Scale**
- **BI**
- **HDRS**
- **BDI**
- **No data on death, GI upset, bleeds or seizures**

**Funding source**
- **Source of funding not stated; unclear whether or not a drug company was involved in the study**

**Notes**
- **Dates of study not stated. Any conflicts of interest not stated**

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>

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Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)  
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Acler 2009 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low</td>
<td>Computer-generated random numbers</td>
</tr>
<tr>
<td>(selection bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear</td>
<td>Method of allocation concealment not stated</td>
</tr>
<tr>
<td>(selection bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and</td>
<td>Low</td>
<td>Stated blinded, placebo was 'an identical pill'</td>
</tr>
<tr>
<td>personnel (performance bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low</td>
<td>Stated blinded</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Unclear</td>
<td>It is not stated whether data from all recruited participants are reported</td>
</tr>
<tr>
<td>(attrition bias)</td>
<td></td>
<td></td>
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<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High</td>
<td>Side effects were not reported although they were assessed</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear</td>
<td></td>
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</tbody>
</table>

### AFFINITY 2020

#### Study characteristics

**Methods**
- Multicentre
  - Study type: interventional (clinical trial)
  - Allocation: randomised
  - Intervention model: parallel assignment
  - Masking: quadruple (participant, care provider, investigator, outcomes assessor)
  - Primary purpose: treatment

**Participants**
- 1280 participants
  - Country: Australia (n = 532), New Zealand (n = 42), and Vietnam (n = 706)
  - Setting: inpatient
  - At randomisation number allocated: N = 1280: fluoxetine (n = 642); placebo (n = 638)
  - % male: fluoxetine (64%); placebo (62%)
  - Age: mean age = 63.5 ± 12.5; placebo = 64.6 ± 12.2
  - Subtype of stroke
    - Total anterior circulation infarct: fluoxetine (9%); placebo (9%)
    - Partial anterior circulation infarct: fluoxetine (49%); placebo (52%)
    - Lacunar infarct: fluoxetine (21%); placebo (105%)
    - Posterior circulation infarct: fluoxetine (114%); placebo (103%)
• Uncertain: fluoxetine (2%); placebo (1%)

Inclusion criteria

• Age > 18 years
• Clinical diagnosis of stroke 2 to 15 days previously
• Brain imaging consistent with ischaemic or haemorrhagic stroke (including normal CT brain scan)
• Persisting measurable focal neurological deficits causing a functional deficit at the time of randomisation

Exclusion criteria:

• History of epileptic seizures
• History of bipolar disorder
• History of drug overdose or attempted suicide
• Ongoing treatment with any selective serotonin reuptake inhibitor
• Allergy or contra-indication to fluoxetine
• Use of medications that may interact seriously with fluoxetine
• Not available for follow-up over the next 365 days e.g. no fixed home address
• Life-threatening illness (e.g. advanced cancer) that is likely to reduce 365-day survival
• Pregnant, breast-feeding or of child-bearing potential and not using contraception
• Enrolled in another interventional clinical research trial involving an investigational product (medicine) or device

Interventions
Fluoxetine 20 mg once daily or matching placebo capsules for 6 months

Outcomes
Primary outcome

• Functional outcome as measured by the mRS at 180 days after randomisation

Secondary outcomes at 180 and 365 days after randomisation

• Survival
• Mood (PHQ-9)
• Cognitive function (TICSm)
• Communication (SIS)
• Motor function (SIS)
• Overall health status (SIS)
• Health-Related Quality of Life (HRQoL) (EuroQol)
• Functional recovery (smRSq) at the 365-day assessments
• New diagnosis of depression requiring treatment with antidepressants
• Fatigue (vitality domain of the SF-36)
• Serious adverse events at any time during follow-up including new stroke, acute coronary syndrome, epileptic seizures, fall, new fractures or death

Funding source
The AFFINITY trial was funded by the Australian NHMRC Project Grant 1059094. The minimisation algorithm was provided by The Stroke Research Group, Division of Clinical Neuroscience, University of Edinburgh, Edinburgh, UK

Notes
ACTRN1261100174921Recruitment January 11, 2013, and June 30, 2019. GJH has received grants from the NHMRC of Australia, Vetenskapsrådet (The Swedish Research Council), and UK National Institute for Health Research Technology, during the conduct of the study; and personal fees from the American Heart Association, outside of the submitted work. MLH, CE-B, LB, and TL have received grants from the NHMRC of Australia during the conduct of the study. CSA has received grants from the NHMRC of Australia, and grants and personal fees from Takeda, outside of the submitted work. All other members of the writing group declare no competing interests.
### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;The patient’s clinician entered the patient’s baseline data into a secure, password-protected, centralised, web-based randomisation system that checked the data for completeness and consistency and generated a unique study identification number and treatment pack number corresponding to fluoxetine or placebo in a 1:1 ratio.&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;All patients, carers, investigators, and outcome assessors were masked to the allocated treatment by use of placebo capsules that were visually identical to the fluoxetine capsules even when broken open. Success of masking was not assessed.&quot;</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: &quot;All patients, carers, investigators, and outcome assessors were masked to the allocated treatment by use of placebo capsules that were visually identical to the fluoxetine capsules even when broken open. Success of masking was not assessed.&quot;</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: &quot;All patients, carers, investigators, and outcome assessors were masked to the allocated treatment by use of placebo capsules that were visually identical to the fluoxetine capsules even when broken open. Success of masking was not assessed.&quot;</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Less than 5% dropped out or died and there is no compelling evidence of a difference between the 2 groups</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes in protocol were reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>The study appears to be free of other sources of bias</td>
</tr>
</tbody>
</table>

### Study characteristics

**Almeida 2006**

#### Methods

- **Parallel design**
- Analysis: ITT (last observation carried forward), withdrawn owing to becoming depressed, AE, treating practitioner started antidepressant, medical advice, no reason given, not contactable - numbers not included

#### Participants

- **Location:** Australia
- **Setting:** inpatient
- **Treatment:** 55 people, mean ± SD age 68 ± 13 years, 67% men
- **Control:** 56 people, mean ± SD age 67 ± 13 years, 62% men
- **Stroke criteria:** acute ischaemic or haemorrhagic stroke, diagnosis by clinical signs (ICD-10) and CT (100% imaged, 10/111 CT scan did not show acute ischaemia); stroke on average < 2 weeks prior to randomisation
- **Not depressed:** (HADS-D had to be over 7)
Other entry criteria: not stated

Comparability of treatment groups: more participants in treatment group with previous heart attack and stroke, also higher levels of hypertension

Exclusion criteria: severe communication difficulties, unstable medical condition, severe cognitive impairment and depression (MMSE < 10), taking antidepressants within 4 weeks of stroke, contraindication to sertraline, previous reaction to sertraline, could not speak English

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Treatment: sertraline 50 mg daily (night)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control: matched placebo</td>
</tr>
<tr>
<td></td>
<td>Duration: treatment continued for 24 weeks</td>
</tr>
<tr>
<td></td>
<td>Duration of follow-up (post-treatment to study end): 28 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Depression: change in scores from baseline to end of treatment on HDRS, proportion depressed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change in MMSE scores</td>
</tr>
<tr>
<td></td>
<td>mRS</td>
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<tr>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>Leaving the trial early</td>
</tr>
<tr>
<td></td>
<td>Check list of possible AEs read out to participant by a research nurse</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Funding source</th>
<th>Funded by an unrestricted grant from Rotary Health Research Fund</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notes</td>
<td>Recruitment June 2004 to June 2006</td>
</tr>
<tr>
<td></td>
<td>Conflicts of interest not stated</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer-generated random numbers</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Centralised</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Stated in paper, matched placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Not stated in paper</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Performed last observation carried forward</td>
</tr>
</tbody>
</table>
| Selective reporting (reporting bias)           | Low risk           | Trial protocol published on [www.strokecentre.org/trials](http://www.strokecentre.org/trials). This weblink is no longer available so we have been unable to check whether all the outcomes
were reported. We have contacted the author to check this—who confirm that all endpoints were reported

### Other bias

<table>
<thead>
<tr>
<th>Other bias</th>
<th>Low risk</th>
<th>No other obvious biases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Andersen 1994

#### Study characteristics

**Methods**
Parallel design
Analysis (ITT) last observation carried forward and per protocol: death (1 treatment, 1 control) withdrawn owing to AE (6 treatment, 1 control), all excluded from analysis

**Participants**
Location: Denmark
Setting: mixed
Treatment: 33 people, mean ± SD age 68 ± 4 years, 36% men
Control: 33 people, mean ± SD age 66 ± 9 years, 66% men
Stroke criteria: ischaemic stroke and PICH; diagnosis via clinical signs and CT (100%); stroke 2 to 52 weeks prior to randomisation (average time 12 weeks)
Depression criteria: HDRS score > 12 (score transformed to appropriate DSM-III-R criteria)
Other entry criteria: none stated
Comparability of treatment groups: balanced
Exclusion criteria: depression within last year, receiving current treatment for depression, severe dementia or communication problems, degenerative or expansive neurological disease, decreased consciousness

**Interventions**
Experimental: citalopram 10 mg in participants > 66 years, 20 mg in participants < 67 years daily; dose doubled if no response to treatment within 3 weeks
Comparator: matched placebo
Duration: treatment continued for 6 weeks
Duration of follow-up (post-treatment to study end): 0
Note that although the protocol on www.strokecentre.org/trials states that mood scores were measured up to 1 year post-stroke, this probably refers to the time since stroke at the time of randomisation

**Outcomes**
Depression: change in scores from baseline to end of treatment on HDRS
Melancholia scale
Proportion no longer meeting entry criteria (< 13 on HDRS)
50% reduction in HDRS score
Additional: leaving the study early
Death
AEs (unwanted drug effects were registered and evaluated at the same intervals using a side effect scale)
### Andersen 1994 (Continued)

**Funding source**
Funded by Lundbeck Foundation, Medical Research Foundation for North Jutland County, The Aalborg Diocese Research Foundation, Consultant Otorhinolaryngologist Kopp’s Foundation and Stine and Martinus Sorensen’s Foundation. Lundbeck Pharma A/S provided the citalopram and placebo; thus we have classified this as 'unclear risk'.

**Notes**
Recruitment 1 February 1991 to 29 February 1992. Conflicts of interest not stated

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Blocks of 4 used</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Centralised opaque envelopes</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Matched placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Those who were blinded were not stated</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Although there were dropouts, analysis performed both per protocol and using last observation carried forward</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Trial published on <a href="http://www.strokecentre.org/trials">www.strokecentre.org/trials</a></td>
</tr>
</tbody>
</table>

- The primary outcome was reported. We have been unable to access this record on 28 September 2021, the paper also describes the social activities index in the list of outcomes but this was not reported in the results so we have changed this to high risk of bias for this 2021 update

**Other bias**
Unclear risk

### Andersen 2013

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Multicentre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type: interventional (clinical trial)</td>
<td></td>
</tr>
<tr>
<td>Intervention model: parallel assignment</td>
<td></td>
</tr>
<tr>
<td>Primary purpose: treatment</td>
<td></td>
</tr>
</tbody>
</table>

**Participants**
642 participants

- Country: Denmark
- Setting: inpatient
At randomisation number allocated: citalopram n = 319; placebo n = 323

% male at baseline: citalopram n = 199/319 (62%); placebo n = 222/323 (69%)

Age at baseline: mean age, citalopram 68 ± 13 (n = 319); placebo 68 ± 13 (n = 323)

Subtype of stroke at baseline: not available

Severity of stroke at baseline: NIHSS, citalopram 5.3 ± 5.6; placebo 4.8 ± 4.8

Time since stroke onset: mean time from last known 'well' to first treatment 1.7 days (median 1, IQR 0 to 6)

Inclusion criteria:

• First ever ischaemic stroke
• Age ≥ 18 years

Exclusion Criteria

• Haemorrhagic stroke
• Dementia or other neurodegenerative disease
• Antidepressant medical treatment within 6 months of admission
• Acute need for antidepressant treatment
• Drug abuse or other conditions that may indicate non-compliant behaviour
• Liver failure (increased liver enzyme levels up to or more than 2 times upper limit)
• Renal failure (eGFR below 30 mL/min per 1.73 m²)
• Hyponatremia (S-potassium below 130 mmol/L
• Actively bleeding ulcer
• Fatal stroke or other severe co-morbidity that markedly decreases expected life span
• Prolonged corrected QT-interval (QTc above 480 ms)
• Ongoing treatment with drugs known to prolong the QTc interval

Interventions

Experimental: citalopram 20 mg (10 mg if aged ≥ 65 years or having reduced liver/kidney function) or placebo once daily for 6 months

Comparator: ½ to 2 tablets with no intrinsic drug activity per day for 6 months

Outcomes

Primary outcomes

• Vascular death, TIA/stroke and myocardial infarction within 6 months
• Functional status at 6 months (mRS)

Secondary outcomes within or at 6 months

• Vascular death
• Death of any cause
• TIA/stroke
• Bleeding
• Myocardial infarction
• Disability/dependence (mRS and BI)
• Physical activity (PASE)
• Cognitive and organic cerebral impairment (MMSE and the Symbol Digit Modalities Test)
• Fatigue (Multidimensional Fatigue Inventory)
• Post-stroke depression (Major Depression Inventory test (MDI), Global depression scale (self and clinician and Hamilton Depression Scale - 6 item (HAM-D6))
• Pathological crying (Pathological Crying Scale)
• Lesion size (FLAIR positive lesion size on MRI 24 hours after treatment with Alteplase)
Andersen 2013 (Continued)

Funding source

TrygFonden, the Danish Council for Independent Research, the Regional Medicine Fund, and the Aarhus University Research Foundation

Notes

Dates study conducted: September 2013 to December 2016

Declarations of Interest: Dr Kraglund received speaker honoraria from Bristol-Meyers Squibb and Pfizer. Dr Iversen received speaker honoraria from Boehringer Ingelheim, Bristol-Myers Squibb, Bayer, AstraZeneca, and Pfizer and has previously participated in advisory board meetings for Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Bayer, AstraZeneca, and Amgen. Dr Grove has received speaker honoraria from AstraZeneca, Baxter, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, and Pfizer and has previously participated in advisory board meetings for AstraZeneca, Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb. Dr Andersen reports other from MSD, personal fees from AstraZeneca, outside the submitted work

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: ”A computer-generated randomization code was used to randomize patients in blocks of 10.”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: ”Citalopram was commercially available (Sandoz, Denmark) and production of the placebo and randomization was prepared by a pharmacy independently of the investigators (Glostrup Pharmacy, Denmark). The tablets were indistinguishable and were supplied in numbered containers.”</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Blinding of participant, care provider, and investigator assured and unlikely that the blinding could have been broken</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Blinding of outcome assessor assured and unlikely that the blinding could have been broken</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Attrition/exclusions reported with reasons provided (including did not start on study medication, consent withdrawn, side effects, indication for open label, other reasons (no detail provided)). At &lt; 31 days of study medication, twice as many participants in the citalopram group withdrew consent (n = 29/318 (9%)) compared to the placebo group (n = 14/320 (4%)). However, at &lt; 31 days twice as many participants in the placebo group (n = 12/318(4%)) compared to the citalopram group (n = 6/320 (2%)) were switched to open label. Attrition/exclusions: 51/319 (16%) in the citalopram group and 39/319 (11%) in the placebo group. The investigators use LOCF in their intention-to-treat analysis. LOCF assumes that missing values are missing completely at random and ignores improvements or deteriorations in the participants condition since dropout and therefore stops improvements or declines in outcome measures. LOCF introduces risk of false or biased conclusions (Molnar 2008)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>The study protocol is available and all of the study’s prespecified (primary and secondary) outcomes that are of interest to the review have been reported in the prespecified way</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>The study appears to be free of other sources of bias</td>
</tr>
</tbody>
</table>
**Study characteristics**

**Methods**
- RCT

  **Study type:** interventional (clinical trial)
  **Allocation:** randomised
  **Intervention model:** parallel assignment
  **Masking:** double (participant, outcomes assessor)
  **Primary purpose:** treatment

**Participants**
- 90 participants
  - **Country:** Iran
  - **Setting:** inpatient
  - **At randomisation number allocated:** N = 90: citalopram (n = 30); fluoxetine (n = 30); placebo (n = 30)
  - **% male:** citalopram (60%); fluoxetine (50%); placebo (56.6%)
  - **Age:** mean age: citalopram = 61.7 ± 9.6; fluoxetine = 60.2 ± 8.52; placebo = 58.7 ± 8.56

**Inclusion criteria**
- > 18 years of age
- suffering from hemiparesis or hemiplegia as a result of a first-time acute ischaemic stroke within the past 24 hours
- an initial Fugl-Meyer Motor Scale score of under 55

**Exclusion criteria**
- NIHSS score < 5
- Prior disabilities including aphasia, cognitive disorders and motor disorders due to stroke, or any other neurodegenerative disease
- Pregnancy or breastfeeding
- Currently taking antidepressants
- Contraindications of therapy, including renal insufficiency (glomerular filtration rate < 30mL/min), abnormal liver function tests, hyponatremia, and a long QT interval on an electrocardiogram
- Any significant adverse effects (agitation, hypertension, or other signs of serotonin syndrome) after initiation of treatment

**Interventions**
- Participants were randomly allocated to 1 of 3 groups: Group A received 20 mg orally of fluoxetine daily, Group B received 20 mg orally of citalopram daily, and Group C received a placebo orally. The duration of the therapy was 90 days. In addition to the medications, all of the participants received physiotherapy

**Outcomes**
- FMMS

**Funding source**
- No financial support received

**Notes**
- IRCT20141116019971N3. Recruitment January 2015 to January 2016. Authors declared no conflicts of interest

**Risk of bias**
Asadollahi 2018 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Quote: “A computer-generated schedule was used by investigators to assign the patients into one of three groups by block randomization: Group A—20mg P.O. daily of citalopram, Group B—20mg P.O. daily of fluoxetine, and Group C—a placebo (microcrystalline cellulose).”</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>Computer-generated schedule confirmed with authors</td>
</tr>
<tr>
<td>Blinding of participants</td>
<td>Low risk</td>
<td>Quote: “All of the drugs for each group of subjects were over-encapsulated by a pharmacist.”</td>
</tr>
<tr>
<td>and personnel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome</td>
<td>Low risk</td>
<td>Quote: “Three evaluators were used in our study, namely, neurology residents who were blind to the interventions.”</td>
</tr>
<tr>
<td>assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>5/90 discontinued medication due to moving away—but this would not have introduced because the reasons for missing data are unlikely to be related to the true outcome (Quote: &quot;The main reason for participants leaving the study was noncompliance in terms of taking their drugs regularly (10 subjects stopped taking the treatment but completed their follow-up), while five participants intentionally failed to attend follow-up after two months because they were resident in other cities distant from the location of the study.&quot;)</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Low risk</td>
<td>There was just one outcome measure planned (see reference on Iranian clinical trials register) and this was reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>The study appears to be free of other sources of bias</td>
</tr>
</tbody>
</table>

Bembenek 2020

Study characteristics

Methods

- Study type: interventional (clinical trial)
- Actual enrolment: 61
- Allocation: randomised
- Intervention model: parallel assignment
- Masking: double (participant, care provider)
- Primary purpose: treatment

Participants

- 61 participants
- Country: Poland
- Setting: inpatient

At randomisation number allocated: N = 61: fluoxetine (n = 30); placebo (n = 31)

% male: fluoxetine (73.3%); placebo (58.1%)

Age: mean age: fluoxetine = 66.6 ± 12.6; placebo = 66.35 ± 12.46
Subtype of stroke

- Total anterior circulation infarct: fluoxetine (40.0%); placebo (38.7%)
- Partial anterior circulation infarct: fluoxetine (23.3%); placebo (35.5%)
- Lacunar infarct: fluoxetine (6.7%); placebo (0.0%)
- Posterior circulation infarct: fluoxetine (20.0%); placebo (16.1%)
- Uncertain: fluoxetine (2%); placebo (2%)

Severity of stroke: NIHSS, Median (IQR) fluoxetine (5 (3 to 8)); placebo (6 (4 to 8))

Inclusion criteria

- Age ≥ 18 years
- Ischaemic or haemorrhagic stroke confirmed by neuroimaging
- Within 2 to 15 days from the stroke onset
- Evidence of neurological deficit at randomisation

Exclusion criteria

- Subarachnoid haemorrhage (unless secondary to intracerebral bleeding)
- High probability that the patient would not be available during follow-up (e.g. another life-threatening illness)
- Pregnant or breast-feeding or of child bearing age not taking contraception
- History of epileptic seizures
- Attempted suicide or self-harm
- Allergy or contra indication to fluoxetine
- Taken a monoamine oxidase inhibitor in last 5 weeks
- Current or recent depression requiring treatment with selective serotonin reuptake inhibitor
- Already participating in a CTIMP
- Current use of drugs that cause significant interactions with fluoxetine: history of epileptic seizures; history of allergy to fluoxetine; suicide attempt or self-harm; hepatic impairment (ALT > 3 above the upper normal limit) and renal impairment (creatinine > 180 micromol/L)

Interventions

Fluoxetine 20 mg daily (1 capsule) for 6 months (180 capsules) vs placebo

Outcomes

The primary outcomes at 6 months

- mRS

Secondary endpoints

- SIS at 6 months
- NIHSS at baseline, 6 and 12 months
- Brunnstrom scale at 6 month follow-up
- Medical Research Council scale at 6 month follow-up
- BI at 6 and 12 month follow-up
- EuroQol 5D-5L
- MHI-5
- Overall recovery on a VAS
- Diagnosis of new depression
- Compliance with drug intake
- Treatment effects and the occurrence of possible adverse reactions are assessed up to 12 months

Funding source

POLPHARMA S.A. manufactured and donated fluoxetine and placebo for this study. Anna Członkowska, Jan Bembenek, and Katarzyna Kurczych were supported by statutory activity of the Institute of Psychiatry and Neurology, Warsaw, Poland
Bembenek 2020 (Continued)

Notes
Recruitment 19 December 2014 and 13 March 2018. Authors declared no conflicts of interest

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Patients were randomly assigned in a 1:1 ratio to receive either fluoxetine or a placebo, by use of a computer-based permuted block randomisation</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Allocation was concealed (further information obtained from the study author Jan Bembenek to confirm this)</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: &quot;Clinicians involved in randomisation and outcome assessments, the patients, and their families, were all masked so as to be unaware of treatment allocation. The placebo capsules were visually identical to the fluoxetine capsules, even when broken open.&quot;</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: &quot;Clinicians involved in randomisation and outcome assessments, the patients, and their families, were all masked so as to be unaware of treatment allocation&quot;</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>5 withdrew consent (8%) before 6 months but the withdrawals are balanced between groups (3 in the fluoxetine group and 2 in the control group) From personal communication with the author: a further 2 patients dropped out between 6 and 12 months</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Trial was registered and all outcomes were reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>The study appears to be free of other sources of bias</td>
</tr>
</tbody>
</table>

Birchenall 2019

Study characteristics

Methods
Study type: interventional (clinical trial)
Intervention model: parallel assignment
Primary Purpose: treatment

Participants
6 participants
Country: France
Setting: inpatient
At randomisation number allocated: 6 although unclear as to which group
% male: not available
Age: not available
Subtype of stroke: not available
Severity of stroke: not available
Time since stroke onset: not available
Inclusion criteria

- Age 18 to 80 years
- Social security affiliation
- Day 3 to day 15 after stroke or brain haemorrhage
- Hemiparesis with upper limb motor deficit (Fugl-Meyer score - hand ≤ 10)
- Informed consent

Exclusion criteria

- NIHSS > 20
- Depression (criteria DSM5-R) with MADRS score > 19
- History of recurrent bipolar or depressive disorders
- History of behavior or suicidal idea
- Family history of extension of the interval QT or congenital long interval QT
- History of clinical stroke
- Aphasia preventing correct evaluation of motor and depression scales.
- Patients treated by antidepressant drugs, IMAO, and neuroleptics in the past month
- Benzodiazepines within 48 hours preceding inclusion.
- Intolerance or allergy to fluoxetine (Sandoz® 20 mg pill)
- Severe swallowing disorders preventing oral administration of the treatment
- Planned carotid surgery
- Pregnant or breast-feeding woman
- Hepatic failure (TGO and TGP > 2N); severe renal failure (creatinine > 180 micromol/L)
- Concomitant severe disease not allowing follow-up
- Participation to another therapeutic study
- Contraindication to MRI and TMS

Withdrawal criteria: not stated

Interventions

Experimental: fluoxetine; 1 pill of 20 mg/day, during 3 months
Comparator: placebo of fluoxetine; 1 pill of 20 mg/day, during 3 months

Outcomes

Primary outcome

- Slope of the curve of recruitment of the MEPs at 3 months

Secondary outcomes recorded at 3 and 6 months

- Slope of recruitment of the MEPs (effect of a first dose of fluoxetine on the slope of recruitment of the MEPs)
- Slope of recruitment of the MEPs (persistence of fluoxetine effect on the slope of recruitment of the MEPs to month 6)
- Index finger force control in paretic hand
- Index finger force control in non-paretic hand

Funding source

Not stated

Notes

No published data, unpublished data say 6 patients, none of whom died, so we have used this information

Dates study conducted: February 2014 to August 2015

Declarations of Interest: none reported
## Birchenall 2019 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No information available</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information available</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>No information available</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>No information available</td>
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<td>All outcomes</td>
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<td>Selective reporting (reporting bias)</td>
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<td>No information available</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No information available</td>
</tr>
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</table>

## Brown 1998

### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis: per protocol: 1 withdrawn (treatment), excluded from analysis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Diagnosis: stroke, time from stroke to randomisation not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomised 10 to treatment and 10 to control</td>
</tr>
<tr>
<td></td>
<td>Treatment: 9 completed treatment, mean ± SD age 61.4 ± 8.6 years, 55% men</td>
</tr>
<tr>
<td></td>
<td>Control: 10 people completed placebo, mean ± SD age 63.7 ± 5.4 years, 60% men</td>
</tr>
<tr>
<td></td>
<td>Emotionalism criteria: emotionalism of at least 4 weeks' duration assessed during semi-structured interview using a modified Lawson and MacLeod rating scale, in addition to frequency of outbursts</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: cognitive impairment, dysphasia, major depressive disorder</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Treatment: fluoxetine 20 mg daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control: matched placebo</td>
</tr>
<tr>
<td></td>
<td>Duration: 10 days</td>
</tr>
<tr>
<td></td>
<td>Duration of follow-up: (end of treatment to end of study) 0</td>
</tr>
</tbody>
</table>

| Outcomes      | Used leaving the study early    |
Brown 1998 (Continued)

Unable to use data from HDRS, Lawson and MacLeod Scale, self-rating scales (mean and SD not presented)
Also reported emotional outbursts; we have not used these in our analyses
AEs: not presented

Funding source
Funder not stated

Notes
Dates of study not stated; conflicts of interest not stated

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation method not stated</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Randomised by independent statistician</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>States blinding of patients and nursing staff, matched placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>States blinding of rating clinicians</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Only 1 withdrawn (5% of participants); we categorised this as low risk</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Insufficient information to make judgement</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other obvious biases, baseline balanced</td>
</tr>
</tbody>
</table>

Burns 1999

Study characteristics

Methods
Parallel design
Analysis: ITT: 2 withdrawn and 1 death (treatment), 1 death (placebo), last value carried forward

Participants
Diagnosis: stroke.
Months from stroke: median (range) 10.5 months (1 ± 156) in sertraline group and 5.5 months (1.5 ± 48) in the control group
Treatment: 14 people
Control: 14 people
Exclusion criteria: less than 1 month since stroke, depression or dementia using the DSM III-R criteria
### Burns 1999 (Continued)

#### Interventions
- **Treatment:** sertraline 50 mg daily
- **Control:** matched placebo
- **Duration:** treatment continued for 8 weeks
- **Duration of follow-up:** 2 weeks off treatment. All scores became non-significant (though data not reported so could not be used in the analysis)

#### Outcomes
- **Able to use**
  - improved score on lability scale
  - improved score on clinician’s interview based impression of change
  - diminished tearfulness
  - leaving the study early
  - death
  - AEs

Method of collecting AEs was not stated

Unable to use: MADRS, BI, MMSE (data not presented)

#### Funding source
- Funded by an unrestricted personal grant from Pfizer, the manufacturers of sertraline

#### Notes
- Dates of study not stated, conflicts of interest not stated

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Blocks of 4 using list produced by medical statistics department</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not stated</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Matched placebo, both active drug and placebo were packed in gelatine capsules with an identical appearance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Run-out was single-blind, treatment was double-blind, but unclear whether outcome assessors were blind</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Analysis: ITT, LOCF 4/28 did not complete the study (14%)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Trial details published on <a href="http://www.strokecentre.org/trials">www.strokecentre.org/trials</a>, although unable to use data from MADRS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Given that the main aim was to explore effect on emotionalism, this is unlikely to have biased results</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Placebo group younger, uncertain influence on bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Statistical analysis was carried out independently by the Applied Statistics Research Unit in Canterbury</td>
</tr>
</tbody>
</table>
### Study characteristics

**Methods**
- RCT
- Study type: interventional (clinical trial)
- Primary purpose: prevention

**Participants**
- 100 participants
- January 2013 to April 2016
- Country: China
- Setting: inpatient
- At randomisation number allocated: N = 99: escitalopram (n = 52); usual care (n = 47)
- % male: escitalopram (%); usual care (%)

**Inclusion criteria**
- First ever acute anterior circulation cerebral infarction
- Met the American Heart Association/American Stroke Association diagnostic criteria for stroke
- Hospitalised within 1 week of stroke onset
- Stroke confirmed cranial MRI

**Exclusion criteria**
- Recurrent stroke, haemorrhagic stroke and posterior circulation stroke
- Pre-stroke depression, history of depression, or receiving mood stabilisers, antipsychotics, or any antidepressant before enrolment
- Depression caused by other organic brain diseases, or depression caused by psychoactive substances and non-addictive substances
- Consciousness disorder, aphasia, and dementia
- HAMD of ≥ 17
- NIHSS score of ≥ 20
- History of cancer and psychosis
- Chronic obstructive pulmonary disease, heart failure, pulmonary, hepatic, or renal failure, or other severe chronic diseases
- Serious suicidal tendencies
- Laboratory and accessory examinations revealing coagulation dysfunction
- Patients who refuse to participate or cooperate

**Interventions**
- Experimental: prophylactic escitalopram in addition to the basic therapies. Started with 5 mg and gradually titrated to 10 mg/d, oral administration in the morning for 90 days
- Comparator: usual care. Secondary prevention of cerebral infarction, brain protection therapy and rehabilitation, without any antidepressants. People with difficulty sleeping could receive Zolpidem or benzodiazepines for a short period of time

**Outcomes**
- Primary and secondary outcome measures not stated
  - 17-item HAMD
  - NIHSS
  - MMSE
  - BI
### Notes

No trial registration information

Dates study conducted: All patients were hospitalised patients treated for acute ischaemic stroke from January 2013 to April 2016

Declarations of Interest: none reported

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Random number table</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information available to permit a judgement of ‘low risk’ or ‘high risk’. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Control group did not receive a placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Treatment evaluation conducted by a physician blind to patient's clinical data, but it does not state whether the physician was blind to treatment allocation. So the judgement was that the risk of bias was unclear</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>There are two publications-the numbers initially included in the two papers do not match; also two patients out of 49 randomised to escitalopram dropped out. Given the inconsistency in the numbers reported, we judge that there is the potential for high risk of bias</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol is available</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>The authors did not reply to questions and so we have graded this as unclear</td>
</tr>
</tbody>
</table>

### Chen 2001

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim:</td>
<td>to observe effects of integrative Chinese herb YuLeShu and fluoxetine on the depressive symptoms and rehabilitation of neurological impairment in patients with post-stroke depression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Country: China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting:</td>
<td>not described</td>
</tr>
<tr>
<td>Participants:</td>
<td>internal carotid system cerebral infarction or haemorrhage within previous 2 months</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine: 19 people, mean age 61.71 ± 8.13 years, 8 men</td>
</tr>
<tr>
<td></td>
<td>Control: 18 people, mean age 62.85 ± 7.32 years, 7 men</td>
</tr>
</tbody>
</table>
Depression: diagnosis of depression according to DSM-IV

Inclusion criteria: HDRS ≥ 20 but < 35 and/or Zung SDS ≥ 41

Exclusion criteria: HDRS > 35, previous depression, aphasia, severe cardiac, pulmonary, hepatic and renal diseases, previous stroke

### Interventions

3 groups: fluoxetine plus usual care versus YuLeShu plus usual care versus usual care. We are using the fluoxetine plus usual care versus usual care alone in the comparison

### Outcomes

- HDRS
- Zung SDS
- BI

Scandinavian Neurological Stroke Scale (also known as CSS)

Stated no side effects, but not clear which side effects were sought, or how they were sought. They were reported at 4, 8 and 12 weeks after treatment

### Funding source

Funded by a local scientific academic fund, drug company not involved

### Notes

- 

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: “using a computer”, but method not described. Insufficient information about the sequence generation process available to permit a judgement of ‘low risk’ or ‘high risk’</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>The method of concealment is not described or not described in sufficient detail to allow a definite judgement of ‘low risk’ or ‘high risk’</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient information about blinding of outcome assessment available to permit a judgement of ‘low risk’ or ‘high risk’</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Dropouts: 2 people dropped out of the fluoxetine group, 1 dropped out of the YuLeShu group and 2 dropped out of the control group</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Protocol not published. Insufficient information available to permit a judgement of ‘low risk’ or ‘high risk’</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Reported that of the people who completed the tests, there were no differences in baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No comment on whether there were differences in baseline for the entire group</td>
</tr>
</tbody>
</table>
## Study characteristics

### Methods
Parallel group (3 groups: doxepin, paroxetine, placebo; we used the paroxetine and placebo data in our review)

**Aim**: treat depression and determine effect on neurological function

### Participants
Country: China  
Setting: unclear  
Stroke diagnosis: diagnostic criteria of the 4th National Meeting of the Cerebrovascular Diseases proved by CT or MRI  
Time since stroke: not known  
Depression diagnosis: Classification and Diagnosis of Psychosis in China (2nd edition)  
Treatment: 24 people, age and gender not given  
Control: 24 people, age and gender not given  
Exclusion: pre-stroke mental disease, cognition disorder (MMSE < 24), marked deterioration in depression during treatment (HAMD > 24) or suicide mood, intolerance to drug

### Interventions
Treatment: paroxetine 20 mg 3 times per day  
Control: placebo guvitamine once per day  
Duration of treatment: 8 weeks  
Duration of follow-up (post-treatment to study end): unclear: follow-up is performed 'after treatment' so we assume this is at 8 weeks (so post-treatment to study end = 0)

### Outcomes
- HAMD  
- BI  
- CSS  
- Death/side effects/leaving the trial early  
- Method of reporting side effects not stated

### Funding source
Funder not stated, unclear if there was drug company involvement

### Notes
-

## Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information about the sequence generation process available to permit a judgement of ‘low risk’ or ‘high risk’</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>The method of concealment is not described to allow a definite judgement of ‘low risk’ or ‘high risk’</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Insufficient information available to permit a judgement of ‘low risk’ or ‘high risk’</td>
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</tbody>
</table>
### Chen 2002 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient information about blinding of outcome assessment available to permit a judgement of ‘low risk’ or ‘high risk’</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Dropouts: 4 in placebo and 0 in paroxetine</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Insufficient information available to permit a judgement of ‘low risk’ or ‘high risk’</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Demographic data not provided, so we cannot determine whether the baseline was balanced</td>
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</tbody>
</table>

### Chen 2005a

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>To observe the changes of neurotransmitter in people with post-stroke depression by using encephalofluctuography technology, and observe the effect of antidepressant treatment on the activity of neurotransmitter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>48 participants with post-stroke depression</td>
</tr>
<tr>
<td>Interventions</td>
<td>Treatment: 24 people received citalopram 20 mg plus usual care, or fluoxetine if side effects such as nausea, emesis Control: 24 people usual care alone</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Encephalofluctuography technology</td>
</tr>
<tr>
<td></td>
<td>Level of sympathetic and 5-hydroxytryptamine at 4 weeks and 3 months after treatment started</td>
</tr>
<tr>
<td>Funding source</td>
<td>Not stated</td>
</tr>
<tr>
<td>Notes</td>
<td>No data from our endpoints of interest, so data not included in a meta-analysis</td>
</tr>
<tr>
<td></td>
<td>Recruitment March 2001 to December 2001</td>
</tr>
<tr>
<td></td>
<td>Conflicts of interest not stated</td>
</tr>
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</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: “Randomly divided” but method not stated. Insufficient information about the sequence generation process available to permit a judgement of ‘low risk’ or ‘high risk’</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>The method of concealment is not described or not described in sufficient detail to allow a definite judgement of ‘low risk’ or ‘high risk’</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
</tbody>
</table>
Chen 2005a (Continued)

<table>
<thead>
<tr>
<th>All outcomes</th>
<th>Blinding of outcome assessment (detection bias) All outcomes</th>
<th>Unclear risk</th>
<th>Not described</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not described</td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Unclear</td>
<td></td>
</tr>
</tbody>
</table>

Chen 2005b

**Study characteristics**

**Methods**

Parallel group
Analysis: according to allocated treatment group

**Participants**

Country: China
Setting: inpatient
Stroke criteria: first ever stroke, onset time ≤ 7 days, haemorrhagic and ischaemic, clinical diagnosis plus confirmation by imaging (though not clear whether a stroke lesion had to be present), at least 1 limb with muscle power grade 3 or less, BI ≤ 50, no consciousness disturbance
Mood criteria: HAMD > 16
Treatment: 40 people, mean age 63.5 years, 29 men
Control: 38 people, mean age 65.8 years, 25 men
No difference in baseline depression and BI between treatment and control group
Excluded: severe cardiac, hepatic and renal organic diseases, psychiatric disorders

**Interventions**

Treatment: paroxetine 20 mg daily plus routine stroke medication, nerve nutritional agents, acupuncture and rehabilitation
Control: routine stroke medication, nerve nutritional agents, acupuncture and rehabilitation
Duration of treatment: 12 weeks
Duration of follow-up (post-treatment to study end): 0 weeks

**Outcomes**

HAMD
BI
Death
Number completing the trial
AEs not reported
Chen 2005b (Continued)

Funding source  No description of funding

Notes  –

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method not described</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not stated</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Dropouts: none</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No obvious risks, baseline similar</td>
</tr>
</tbody>
</table>

Chen 2015

Study characteristics

Methods  To investigate the effect of early antidepressant intervention on the acute depression and rehabilitation of neurological function after stroke

Participants  96 acute depression patients after stroke were selected and randomly divided into study group and control group. Stroke diagnosed according to the diagnostic criteria of stroke by the 4th Congress of Chinese Cerebrovascular Diseases, which requires both clinical and imaging criteria to be met. HAMD ≥ 17. Excluded patients with mental disorders. Range of disease: 2-9 months

Interventions  The study group orally took the antidepressant (citalopram) and the control group took placebo for 8 weeks

Outcomes  Depression (HAMD), neurological function (NIHSS), ADL (BI). Substance P and neuropeptide Y

Funding source  No information regarding funding

Notes

Risk of bias
### Chen 2015 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Random number table</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Information not provided</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Information not provided</td>
</tr>
<tr>
<td>All outcomes</td>
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<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Information not provided</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
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<td>Information not provided</td>
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<tr>
<td>All outcomes</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Information not provided</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No information provided e.g. on source of funding</td>
</tr>
</tbody>
</table>

### Cheng 2003

**Study characteristics**

#### Methods
- Parallel design
- **Aim:** to treat depression and augment rehabilitation
- Analysis: according to allocated treatment group

#### Participants
- Location: China
- Setting: inpatient
- Treatment: 25 people
- Control: 32 people
- Whole group (including non-depression group, depression control group and depression treatment group): 132 (mean age 62 ± 12 years, 79 men)
- Stroke: ischaemic stroke or PICH, clinical diagnosis plus confirmation on brain imaging (not clear that a stroke lesion had to be present), clear consciousness
- Depression diagnosis (at 2 weeks after stroke onset): psychiatric interview, DSM IV criteria
- Excluded: major psychological trauma history in previous 1 year, severe mental retardation, severe impairment of lingual expression or comprehension, major complicated medical event in previous 1 year

#### Interventions
- Treatment: fluoxetine 20 mg daily
- Control: no fluoxetine
Duration of treatment: 6 months
Duration of follow-up (post-treatment to study end): 6 months

Outcomes

- SSS
- ADL
- HAMD
- Zung SDS
- Zung SAS
- No deaths, none left trial early
- No data on AEs

Funding source
No description of funding

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method not described</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>59 participants were diagnosed to have depression by symptoms but only 57 were included in the results table</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>No protocol, no report of the results of the self-rating anxiety scale</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No clear description of differences between the treatment and control group</td>
</tr>
</tbody>
</table>

Chollet 2011

Study characteristics

Methods
Randomised parallel-group trial

Participants
Location: France
Setting: stroke units

Inclusion criteria: aged 18 to 85 years with FMMS of 55 or less, acute ischaemic stroke with hemiparesis or hemiplegia, 5 to 10 days after stroke onset, unclear if there had to be a visible lesion on brain imaging

Treatment: 59 people, mean ± SD age 66.4 ± 11.7 years; 63% men

Control: 59 people, mean ± SD age 62.9 ± 13.4 years; 59% men

Comparability of treatment groups: total FMMS score fluoxetine 17.1 compared with 13.4 in placebo

Previous stroke more common in the fluoxetine group; fluoxetine group had more diabetes

Exclusions: clinical depression or treatment with antidepressants, MADRS > 19, aphasia severe enough to mask detection/assessment of depression, pregnancy, patient on neuroleptics/benzodiazepines, owing to undergo carotid endarterectomy, other major diseases that would prevent follow-up

**Interventions**

| Treatment: fluoxetine 20 mg daily for 90 days |
| Control: identical capsules to active drug |

| Duration of treatment: 90 days |
| Duration of follow-up (treatment end to study end): 0 days |

**Outcomes**

Primary outcome: the mean change of FMMS score between inclusion (day 0) and day 90 after the start of the study drug

Secondary endpoints were NIHSS, mRS and MADRS measured at days 0, 30 and 90

**Funding source**

Funded by French national programme for clinical research: the sponsor had no involvement in study design, data collection, data analysis, data interpretation or writing the report

**Notes**

Recruitment 14 March 2005 to 9 June 2009. Authors state "no conflicts of interest"

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Balanced by centre with an allocation based on a block size of 4 generated with a computer random-number generator</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Sequentially-numbered opaque envelopes</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>All outcomes: Low risk</td>
<td>Identical capsules for control arm</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>All outcomes: Low risk</td>
<td>All study site investigators and all investigators were masked to treatment allocation</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>All outcomes: Low risk</td>
<td>Dropouts: 2 participants died (1 in each group) and 3 dropped out; not stated how missing outcome data were dealt with</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Trial protocol published on <a href="http://www.strokecentre.org/trials">www.strokecentre.org/trials</a>, all outcomes were reported</td>
</tr>
</tbody>
</table>
Other bias | Unclear risk | Note difference in baseline; particularly for the total FMMS score (17.1 in fluoxetine and 13.4 in the placebo): it is not clear what effect this had on results, so we have classified this as 'unclear risk'.

---

### Dam 1996

#### Study characteristics

| Methods | Parallel design |
| Analysis: per protocol: withdrawn because of AEs (2 treatment), all excluded from analysis |

| Participants | Location: Italy |
| Setting: unclear |
| Treatment: 18 people, mean ± SD age 68 ± 9 years, 44% men |
| Control: 17 people, mean ± SD age 68 ± 5.5 years, 44% men |
| Stroke criteria: ischaemic, unilateral MCA territory stroke, diagnosis via clinical signs and CT (100%), stroke 1 to 6 months prior to randomisation (average time 3 months) |
| Other inclusion criteria: unable to walk |
| Comparability of treatment groups: balanced |
| Exclusion: history of major affective disorders; alcohol abuse; or a history or evidence or both of severe heart, lung, kidney or liver diseases or mental deterioration |

| Interventions | Treatment: fluoxetine 20 mg daily |
| Control: matched placebo |
| Duration: treatment continued on average 74 ± 6 days, duration not reported for control group |
| Duration of follow-up (treatment end to study end): 0 |

| Outcomes | Depression: change in scores from baseline to end of treatment on HDRS |
| Additional: graded neurological scale (HSS), BI |
| Leaving the study early |
| Death |
| AEs including seizures - unclear if these were reported systematically |

| Funding source | Funding source not stated |

| Notes | Dates of recruitment and conflicts of interest not stated |

#### Risk of bias

| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear risk | No description |
**Dam 1996** (Continued)

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment</td>
<td>Unclear</td>
<td>No description</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low</td>
<td>Quote: &quot;Examining neurologists blind to treatment&quot;. Comment: Unclear if this refers to outcome assessors or the neurologist caring for the participant. However, placebo was 'matched' so this is low risk as the treating physician and the participants would have been blind</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear</td>
<td>See above</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>High</td>
<td>2/35 dropouts (5.7%), per-protocol analysis</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Low</td>
<td>Trial available, including results on <a href="http://www.strokecentre.org/trials">www.strokecentre.org/trials</a>: all specified outcome measures were reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Baseline characteristics similar in the 2 groups</td>
</tr>
</tbody>
</table>

**Dike 2019**

**Study characteristics**

- **Methods**
  - Study type: interventional (clinical trial)
  - Allocation: randomised
  - Intervention model: parallel assignment
  - Masking: single (investigator)
  - Primary purpose: treatment

- **Participants**
  - 60 participants
  - Country: Nigeria
  - Setting: inpatient
  - At randomisation number allocated: N = 1500: fluoxetine (n = 750); placebo (n = 750)
  - % male: fluoxetine (53.3%); placebo (43.3%)
  - Age: mean age: fluoxetine = 59 ± 11; placebo = 62 ± 9
  - Inclusion criteria
    - 18 to 85 years of age
    - Ischaemic stroke, unilateral, supra-tentorial confirmed by neuroimaging
    - Presentation within first 14 days of stroke onset
    - NIHSS score ≤ 16
    - Hemiparesis or hemiplegia
    - FMMS ≤ 55
    - Informed consent
**Exclusion criteria**
- Haemorrhagic stroke on CT
- Glasgow coma score < 8
- NIHSS score > 16
- Cardiovascular/metabolic/respiratory instability: hypertensive emergency or hypotension/acidosis or alkalosis/RR > 24 cycles per minute
- Previous central/peripheral nerve injury
- Current use of a medication likely to have an adverse interaction with fluoxetine
- Concurrent medications interacting with SSRI
- Substantial premorbid disability
- Depression (MADRS score > 19)
- Current use of antidepressant medication
- Pregnancy

**Interventions**
- Experimental: 20 mg fluoxetine for 30 days plus standard treatment
- Comparator: standard treatment

**Outcomes**
- **Primary outcome**
  - Changes in FMMS at day 14 and day 30
- **Secondary outcomes**
  - NIHSS at day 30
  - mRS at day 30

**Funding source**
- No funding

**Notes**
- PACTR201412000967245. Recruitment between January 2015 and May 2016. All authors declare no conflicts of interest

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Block randomization was used in the assignment of study participants. Permutated blocks of six (6) for two groups were drawn up. A random selection of possibilities was done using a list of random numbers generated with STATA 12.”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Allocation concealment was done using sequentially numbered envelopes.”</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Quote: “This was a single-blind randomized controlled trial that compared motor recovery between 2 groups of stroke patients: those on fluoxetine 20mg daily + standard therapy; and the control group who received standard therapy only.” Thus the participants would have known their treatment allocation</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>No information provided</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>22/60 lost to follow-up (presumably including the 7 in the intervention group and the 8 in the control group who died). 6 in fluoxetine group stopped treatment but were still included in the analysis. It is unclear what effect this would have had, hence the judgement about unclear risk of bias</td>
</tr>
</tbody>
</table>
**Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)**

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Multicentre RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type: interventional (clinical trial)</td>
<td></td>
</tr>
<tr>
<td>Allocation: randomised</td>
<td></td>
</tr>
<tr>
<td>Intervention model: parallel assignment</td>
<td></td>
</tr>
<tr>
<td>Masking: quadruple (participant, care provider, investigator, outcomes assessor)</td>
<td></td>
</tr>
<tr>
<td>Primary purpose: treatment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>1500 participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: Sweden</td>
<td></td>
</tr>
<tr>
<td>Setting: inpatient</td>
<td></td>
</tr>
<tr>
<td>At randomisation number allocated: N = 1500; fluoxetine (n = 750); placebo (n = 750)</td>
<td></td>
</tr>
<tr>
<td>% male: fluoxetine (62%); placebo (62%)</td>
<td></td>
</tr>
<tr>
<td>Age: mean age: fluoxetine = 70.6 ± 11.3; placebo = 71.0 ± 10.5</td>
<td></td>
</tr>
</tbody>
</table>

**Subtype of stroke**

- Total anterior circulation infarct: fluoxetine (27%); placebo (29%)
- Partial anterior circulation infarct: fluoxetine (46%); placebo (44%)
- Lacunar infarct: fluoxetine (15%); placebo (16%)
- Posterior circulation infarct: fluoxetine (10%); placebo (9%)
- Uncertain: fluoxetine (x2%); placebo (2%)

**Inclusion criteria**

- Age ≥ 18
- Informed consent can only be obtained from a patient who according to the trial investigator is mentally capable of decision-making and who, after having received information and got answers to their questions, wants to participate in the trial
- Brain imaging is compatible with intracerebral haemorrhage or ischaemic stroke
- Randomisation can be performed between 2 and 15 days after stroke onset and by the research group at the person's local/emergency hospital
- Persisting focal neurological deficit is present at the time of randomisation severe enough to warrant treatment from the physicians and the patient's and relative's perspective

**Exclusion criteria**

- Subarachnoidal haemorrhage (except where secondary to a primary intracerebral haemorrhage)
- Unlikely to be available for follow-up for the next 12 months e.g. no fixed home address
- Unable to speak Swedish and no close family member available to help with follow-up forms
- Other life-threatening illness (e.g. advanced cancer) that will make 12-month survival unlikely
Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)  

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**Interventions**  
Fluoxetine (20 mg once daily) for 6 months with oral capsules

**Outcomes**  
Outcomes collected at 6 months and 12 months

**Primary outcome**  
- mRS

**Secondary outcomes**  
- Death from all causes  
- HRQoL (EQ5D-5L)  
- Depression and anxiety (MHI-5)  
- Level of fatigue (vitality subscale of the Health Questionnaire)  
- Recovery from stroke (SIS)  
- New diagnosis of depression since randomisation  
- Adverse events (including participant-completed diary)  
- Health and social care utilisation  
- Adherence to trial medication  
- Motor function (NIHSS)  
- Aphasia (NIHSS), aphasia (Norsk Grunntest for Afasi)  
- Depression (MADRS + DSM-IV/DSM-V)  
- Cognitive function (MoCA)

**Funding source**  
The Swedish Research Council, the Swedish Heart-Lung Foundation, the Swedish Brain Foundation, the Swedish Society of Medicine, King Gustav V and Queen Victoria’s Foundation of Freemasons, and the Swedish Stroke Association (STROKE-Riksförbundet)

**Notes**  

BN has received honoraria for data monitoring committee work in the SOCRATES and THALES trials (AstraZeneca) and the NAVIGATE-ESUS trial (Bayer). HW has received grants from the Swedish Medical Research Council (Vetenskapsrådet) during the conduct of the study; the grant was for the study that is presented in the submitted manuscript. GJH has received grants from the National Health and Medical Research Council (NHMRC) of Australia, Vetenskapsrådet, and UK National Institute for Health Research Technology, during the conduct of the study; and personal fees from American Heart Association, outside of the submitted work. MD reports that the University of Edinburgh received some funding from the grants for EFFECTS (Vetenskapsrådet) in relation to its provision of a randomisation system. MLH has received grants from the NHMRC of Australia, outside of the submitted work. All other authors declare no competing interests

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Random sequence generation (selection bias) | Low risk           | Quote: “A physician or nurse entered patients’ baseline data into a secure web-based randomisation system. The system checked the data for completeness and consistency and allocated each patient an identification number and a
treatment number. Patients were randomly assigned in a 1:1 ratio to either oral fluoxetine 20 mg once daily or placebo for 6 months."

| Allocation concealment (selection bias) | Low risk | Quote: "secure web-based randomisation system"
| Blinding of participants and personnel (performance bias) | Low risk | Quote: "Patients, their families, health-care personnel, investigators, outcomes assessors, and staff in the coordinating centre (Karolinska Institutet, Department of Clinical Sciences Danderyd Hospital, Stockholm, Sweden), and the pharmacy were masked to treatment allocation. The placebo capsules were visually identical to the fluoxetine capsules, even when broken open. The success of the masking procedure was not assessed. An emergency unmasking system was available but was designed so that the coordinating centre and staff doing follow-up continued to be masked throughout the study."
| Blinding of outcome assessment (detection bias) | Low risk | Quote: "Patients, their families, health-care personnel, investigators, outcomes assessors, and staff in the coordinating centre (Karolinska Institutet, Department of Clinical Sciences Danderyd Hospital, Stockholm, Sweden), and the pharmacy were masked to treatment allocation"
| Incomplete outcome data (attrition bias) | Low risk | Only 11 dropped out; 2 crossed over; the rest were included in the analysis
| Selective reporting (reporting bias) | Low risk | All outcomes that were prespecified were reported
| Other bias | Low risk | The study appears to be free of other sources of bias

**Feng 2004**

**Study characteristics**

**Methods**

Aim: to study the influence of Jieyu Huoxue decoction on rehabilitation of patients with depression after cerebral infarction

**Participants**

Country: China

4 groups: fluoxetine plus usual care, Jieyu Huoxue decoction plus usual care, usual care in people with depression, usual care in people with no depression

We are using data from 'fluoxetine plus usual care' versus 'usual care in people with depression'

Setting: mixed inpatient and outpatient

Stroke criteria: ischaemic stroke within 1 month of stroke onset, clinical diagnosis plus confirmation by imaging. Did not state whether a visible lesion was needed to make a diagnosis

Depression: psychiatric interview using DSM IV, Zung SDS ≥ 41

Included those with no previous psychiatric history

54 participants with post-stroke depression were randomised

18 received fluoxetine plus usual care, 18 received usual care only and 18 received Jieyu Huoxue decoction

Of the 54 participants with depression randomised, mean age: 71.5 ± 6.7 years, 24 men
### Feng 2004 (Continued)

<table>
<thead>
<tr>
<th>Excluded: previous stroke, previous depression, and severe cardiac, pulmonary, hepatic and renal diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interventions</strong></td>
</tr>
<tr>
<td>Treatment: fluoxetine 20 mg daily plus usual stroke care</td>
</tr>
<tr>
<td>Control: usual stroke care</td>
</tr>
<tr>
<td>Duration of treatment: 60 days</td>
</tr>
<tr>
<td>Duration of follow-up (post-treatment to study end): 0 weeks</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td>Zung SDS</td>
</tr>
<tr>
<td>ADL: although score not referenced, so not used in analysis</td>
</tr>
<tr>
<td>MESSS</td>
</tr>
<tr>
<td>Reported side effects in fluoxetine group but not in the control group</td>
</tr>
<tr>
<td>Unclear how side effects were collected</td>
</tr>
<tr>
<td><strong>Funding source</strong></td>
</tr>
<tr>
<td>Funding source not stated</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
</tr>
<tr>
<td>–</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method not stated</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No description</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High risk</td>
<td>No blinding</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>8 participants dropped out (2 in fluoxetine group, 2 in the depression control group, 1 in the Jieyu Huoxue decoction, 3 in no-depression control)</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Baseline balanced</td>
</tr>
</tbody>
</table>

### FOCUS 2019

**Study characteristics**

| Methods | Multicentre RCT |
Study type: interventional (clinical trial)
Primary purpose: treatment

Participants
3127 participants
Country: UK
Setting: inpatient
At randomisation number allocated: N = 3127: fluoxetine (n = 1564); placebo (n = 1563)
% male: fluoxetine (62%); placebo (61%)
Age: mean age: fluoxetine = 71.2 ± 12.4; placebo = 71.5 ± 12.1

Subtype of stroke
- Total anterior circulation infarct: fluoxetine (20%); placebo (20%)
- Partial anterior circulation infarct: fluoxetine (36%); placebo (35%)
- Lacunar infarct: fluoxetine (20%); placebo (18%)
- Posterior circulation infarct: fluoxetine (12%); placebo (15%)
- Uncertain: fluoxetine (2%); placebo (2%)

Severity of stroke: NIHSS, Median (IQR) fluoxetine (6 (3 to 11)); placebo (6 (3 to 11))
Time since stroke onset: mean days: fluoxetine 6.9 ± 3.6; placebo 7.0 ± 3.6

Inclusion criteria
- Age > 18 years
- Brain imaging consistent with intracerebral haemorrhage or ischaemic stroke
- Randomisation can be performed between 2 and 15 days after stroke onset
- Persisting focal neurological deficit is present at the time of randomisation

Exclusion criteria
- SAH
- Unlikely to be available for follow up at 12 months
- Patient and/or carer unable to understand spoken or written English
- Other life-threatening illness
- Pregnant or breast-feeding or of child bearing age not taking contraception
- History of epileptic seizures
- Attempted suicide or self-harm
- Allergy or contra indication to fluoxetine
- Taken a monoamine oxidase inhibitor in last 5 weeks
- Current or recent depression requiring treatment with selective serotonin reuptake inhibitor
- Already participating in a CTIMP

Interventions
Experimental: 20 mg orally once daily for 6 months
Comparator: matching placebo orally once daily for 6 months

Outcomes
Primary outcome
- mRS at 6 months

Secondary outcome measures
- Deaths from all causes at 6 and 12 months
- mRS at 12 months
### Focus 2019 (Continued)

- SIS
- Euroqol 5D-5L
- MHI-5
- Vitality subscale of SF36 (as an assessment of fatigue)
- Diagnosis of depression
- Other AEs
- Adherence to the trial medication
- Health and social care resources used during follow-up

<table>
<thead>
<tr>
<th>Funding source</th>
<th>MHRA approval granted. Start-up phase funded by The Stroke Association. Main phase funded by NIHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notes</td>
<td>ISRCTN83290762. Recruitment 10 September 2012 to 31 March 2017. Authors declared no conflicts of interest</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Patients were randomly assigned in a 1:1 ratio to receive fluoxetine or placebo, by use of a centralised randomization system.”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Patients were randomly assigned in a 1:1 ratio to receive fluoxetine or placebo, by use of a centralised randomization system.”</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: “Patients, their families, and the health-care team including the pharmacist, staff in the coordinating centre, and anyone involved in outcome assessments were all masked to treatment allocation by use of a placebo capsule that was visually identical to the fluoxetine capsules even when broken open.”</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: “Patients, their families, and the health-care team including the pharmacist, staff in the coordinating centre, and anyone involved in outcome assessments were all masked to treatment allocation by use of a placebo capsule that was visually identical to the fluoxetine capsules even when broken open.”</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>For the primary outcome of mRS at 6 months data were available for fluoxetine n = 1553/1564 (99.3%) and placebo n = 1553/1563 (99.3%)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>The study protocol is available and all of the study’s prespecified (primary and secondary) outcomes that are of interest in the review have been reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>The study appears to be free of other sources of bias</td>
</tr>
</tbody>
</table>

#### Fruehwald 2003

#### Study characteristics

- Methods: Parallel design
- Analysis: per protocol
- Withdrawals: death (1 treatment), withdrawn owing to AEs (1 treatment, 2 control), all excluded from analysis
Participants
Location: Austria
Setting: inpatients
Treatment: 28 people, mean ± SD age 65 ± 14 years, 46% men
Control: 26 people, mean ± SD age 64 ± 14 years, 71% men
Stroke criteria: ischaemic stroke and PICH; diagnosis via clinical signs and CT (100%); stroke on average 11 days prior to randomisation
Depression criteria: psychiatric interviews, HDRS score > 15
Other entry criteria: not stated
Comparability of treatment groups: non-significant trend towards more women and right-sided strokes in treatment group
Exclusion criteria: MMSE < 20, more than mild communication deficit, diseases of the central nervous system and previous neurodegenerative or expansive neurological disorders

Interventions
Treatment: fluoxetine 20 mg daily, dose escalation at 4 weeks if HDRS score > 13
Control: matched placebo
Duration of treatment: 12 weeks
Duration of follow-up (end of treatment to study end): 15 months

Outcomes
Depression: change in scores from baseline to end of treatment of HDRS, BDI, and CGI (item 1)
Proportion of responders (< 13 HDRS)
Additional: SSS
Death
AEs (selected data)
Unable to use: RS, BI, MMSE (data not presented at follow-up)
AEs data on dizziness, nausea and cephalalgia (data not presented by group)

Funding source
The medication was supplied by Lannacher Heilmittel, Lannach, Austria

Notes
Recruitment 1 June 1998 to 31 December 1998. Conflicts of interest not stated

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computerised randomisation, using random permuted block design</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Centralised concealment</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>States blinded, used matching placebo</td>
</tr>
</tbody>
</table>

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)
### Fruehwald 2003 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blinding of outcome assessment (detection bias)</strong></td>
<td>Low</td>
<td>States blinded</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incomplete outcome data (attrition bias)</strong></td>
<td>High</td>
<td>4/54, per protocol analysis</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Selective reporting (reporting bias)</strong></td>
<td>Unclear</td>
<td>No protocol</td>
</tr>
<tr>
<td><strong>Other bias</strong></td>
<td>Unclear</td>
<td>Baseline balanced</td>
</tr>
<tr>
<td>All participants were randomly assigned to either fluoxetine or placebo treatment by the drug company independently of the research teams and the study centres</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Gao 2017

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Study type: interventional (clinical trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary purpose:</strong> treatment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>274 participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country:</strong></td>
<td>China</td>
</tr>
<tr>
<td><strong>Setting:</strong></td>
<td>outpatient</td>
</tr>
<tr>
<td>At randomisation number allocated: N = 274, citalopram (n = 91); placebo (n = 91); cognitive behavioural therapy (n = 92)</td>
<td></td>
</tr>
<tr>
<td>% male:</td>
<td>51.8%</td>
</tr>
<tr>
<td><strong>Age:</strong> Mean age, citalopram 66.0 ± 7.3 (n = 91); placebo 67.2 ± 9.6 (n = 91); cognitive behavioural therapy 64.9 ± 8.0 (n = 92)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtype of stroke:</strong> not available</td>
<td></td>
</tr>
<tr>
<td><strong>Severity of stroke:</strong> not available</td>
<td></td>
</tr>
<tr>
<td><strong>Time since stroke onset:</strong> acute ischaemic stroke within the previous 7 days</td>
<td></td>
</tr>
</tbody>
</table>

#### Inclusion criteria

- Age ≥ 18
- First ever ischaemic stroke meeting World Health Organization (WHO) diagnostic criteria confirmed by MRI
- No history of depression
- No antidepressant use prior to the study

#### Exclusion criteria

- No consent
- Premorbid stroke related impairment
- BI < 10

---

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

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Interventions

Experimental: citalopram 20 mg per day for a minimum of 3 months + general discussions

Comparator 1: placebo + general discussions

Comparator 2: placebo + cognitive behaviour therapy

Outcomes

- Depressive symptoms (17-item HAM-D), Bech-Rafaelsen Melancholia Scale (MES)) at 3 months
- Drug side-effects (Udvalg for Kliniske Undersogelser side-effect scale at 2, 4, and 6 weeks, and 3 months
- Performance in ADL (BI) at 3 months
- Functional impairment (FIM scale) at 3 months

Funding source

Natural Science Foundation of China [81100243, 81171131, 81272564, 81272795, 81100893, 81172197, and 81372484], the Natural Science Foundation of Liaoning Province in China [No. L2013296], and Liaoning Science and Technology Plan Projects [No. 2011225020]

Notes

This trial was particular in that recruitment happened at 4 different time points: at 0 months, 3 months, 6 months, and 9 months from discharge. Inclusion criteria required that participants suffered from post-stroke depression. Participants were invited to complete the BDI and those with a score > 10 were included, provided other criteria were met.

Group 'placebo + general discussions' and 'citalopram + general discussions' were included. No significant differences observed in the 2 included groups.

Dates study conducted: participants enrolled between October 2011 and June 2013.

Declarations of interest: none reported

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Randomization into one of three intervention groups was undertaken by an independent researcher using computer-generated random number sequences ...&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;... that were prepared in advance and placed in consecutively numbered, sealed, opaque envelopes.&quot;</td>
</tr>
</tbody>
</table>
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Study described as "single blind"
Quote: "The researcher successively opened the envelopes corresponding to different time periods and determined the intervention by patient number."
Quote: "The study therapists acted as clinical evaluators."
Quote: "The study therapists were asked not to divulge any treatment information to their patients."
Comment: Care providers, investigator and outcome assessors were all aware of allocation |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Quote: "The study therapists acted as clinical evaluators."
Quote: "The study therapists were asked not to divulge any treatment information to their patients."

Incomplete outcome data (attrition bias) All outcomes | Low risk | Quote: "in Group A [placebo + general discussions], one patient violated protocol in the second time period, one could no longer be reached, and one left the study owing to stroke recurrence in the third time period; in Group B [citalo-
pra + general discussions], persistent side-effects from the drugs led five pa-
stients to leave the study (two owing to orthostatic dizziness, one owing to pal-
pitation, and two owing to constipation)"

Comment: Attrition reported for each intervention group and reasons given

Group A (placebo + general discussions) 3/91 = 3% attrition
Group B (citalopram + general discussions) 5/91 = 5% attrition
Overall = 4% attrition

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Unclear risk</th>
<th>There is no study protocol available. Therefore insufficient information to judge high or low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>The study appears to be free from other sources of bias</td>
</tr>
</tbody>
</table>

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

Study characteristics

Methods
Parallel group
Analysis: according to treatment group

Participants
Location: not stated
Setting: not stated
Stroke criteria: "documented diagnosis of stroke within 12 months prior to screening"
Mood: MADRS score > 17
Treatment: 112 people, age 64.3 ± 11.4 years, 61 men
Control: 117 people, 65.6 ± 10.5 years, 64 men

Excluded: concurrent psychiatric disorders, concurrent psychotropic pharmacotherapy, patients who posed a suicidal risk, patients with substance abuse/dependence, concurrent psychotropic pharmacotherapy, MMSE < 24, participating in another clinical trial, serious medical condition or clinically significant finding on screening or baseline evaluation that would preclude the administration of paroxet-ine and an intolerance to paroxetine

Interventions
Treatment: paroxetine 20 to 50 mg daily
Control: placebo (not stated whether matching)
Duration of treatment: 8 weeks
Duration of follow-up (treatment to study end): 0 weeks

Outcomes
Change from baseline to endpoint in MADRS
Proportion of participants scoring < 8 on the MADRS total score at the endpoint (we used this in our analysis)
Changes from baseline to endpoint on the BI
Change from baseline to endpoint on RS score
**GlaxoSmithKline 1998** (Continued)

Change from baseline to endpoint on the Clinical Global Improvement Severity of Illness Score (CGI-S) Proportion of responders based on CGI-Globall Improvement (CGI-G) score (score of < 4) at endpoint

GI side effects reported, but unclear whether these are 'events' or 'participants', so we cannot use these data. It is not clear how the side effects were collected

Withdrawal from study

**Funding source**

Source of funding not stated, but we assume it was funded by GlaxoSmithKline

**Notes**


---

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
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<td>Randomisation method not described</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Blinding not described, used placebo but not stated whether identical</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Blinding not described</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>20 in each group dropped out</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Insufficient information to make clear judgement</td>
</tr>
</tbody>
</table>

---

**Gong 2020**

### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type: interventional (clinical trial)</td>
<td></td>
</tr>
<tr>
<td>Allocation: randomised</td>
<td></td>
</tr>
<tr>
<td>Intervention model: parallel assignment</td>
<td></td>
</tr>
<tr>
<td>Masking: double (participant, outcomes assessor)</td>
<td></td>
</tr>
<tr>
<td>Primary purpose: treatment</td>
<td></td>
</tr>
</tbody>
</table>
The study was designed as a double-blind, randomized clinical trial in order to obtain evidence for using Shu-Gan-JieYu capsule as an integrative, anti-depressive treatment for motor recovery in post-stroke patients.

**Participants**

254 participants

Country: China

Setting: inpatient

At randomisation number allocated: N = 254:

- Group A (Shu-Gan-Jie-Yu only (n = 64), Group B (fluoxetine n = 64), Group C (Shu-Gan-Jie-Yu and fluoxetine (n = 64)), and Group D (placebo (n = 62))

% male: Group A (Shu-Gan-Jie-Yu only (n = 68.5%), Group B (fluoxetine n = 64.2%), Group C (Shu-Gan-Jie-Yu and fluoxetine (n = 67.3%)), and Group D (placebo (n = 61.0%))

Age: mean age:

- Group A (Shu-Gan-Jie-Yu only (58.36 ± 15.28), Group B (fluoxetine 56.68 ± 17.59), Group C (Shu-Gan-Jie-Yu and fluoxetine (55.95 ± 19.66), and Group D (placebo (57.79 ± 17.54)

**Inclusion criteria**

- Age ≥ 18
- Suffering from hemiparesis or hemiplegia as a result of a first-time acute ischemic stroke within the past 24 hours
- Initial FMMS score lower than 55

**Exclusion criteria**

- NIHSS score less than 5
- Prior disabilities, including aphasia, cognitive disorders, and motor disorders due to stroke, or any other neurodegenerative disease
- Pregnant or breastfeeding
- Currently taking antidepressants
- Recurrent suffering from acute stroke
- Met the recombinant tissue plasminogen activator (tPA) treatment and treated by thrombolysis
- Contraindications for therapy, including renal insufficiency (glomerular filtration rate < 30 mL/min), abnormal liver function tests, hyponatremia, or a long QT interval on an electrocardiogram

**Interventions**

Group A (Shu-Gan-Jie-Yu only), Group B (fluoxetine), Group C (Shu-Gan-Jie-Yu and fluoxetine), and Group D (placebo)

**Outcomes**

mRS: categorised as (0&1), (2&3), (> 4)

Fugl-Meyer: continuous

**Funding source**

Supported by a grant from The National Natural Science Foundation of China (81373619) and the Plateau Discipline of Neurology of Integrated Traditional Chinese and Western Medicine in Pudong New Area (PDZY-2018-0606)

**Notes**

No trial registration number. Recruitment from July 2015 to December 2018. The authors declare that they have no conflicts of interest

Please note: final per protocol number stated as 222, but Table 1 baseline only includes 219; Table 2 mRS n=291; Table 3 30 & 90 days n=222

Denominators change for each outcome – even different for mRS 90 day and Fugel-Meyer 90 day
**Gong 2020 (Continued)**

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Simple randomization method … computer-generated schedule to assign the patients who met the criteria into one of four groups by block randomization, in a ratio of 1:1:1:1, without stratification&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>The method of allocation concealment is not described to allow a definite judgement</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: &quot;All capsules looked identical ... in order to guarantee the consistency of capsule appearance. All of the patients were told the effects of the drugs ... could improve motor recovery even if they did not have a depressive disorder.&quot;</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Three neurology residents who were blinded to the interventions served as evaluators in the study. The evaluators obtained the patients’ FM-MS and mRS scores at enrollment and follow-up on day 30 and day 90 after the start of the intervention. They also recorded any adverse events observed during the study.”</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Final per protocol number stated as 222, but Table 1 baseline only includes 219; Table 2 mRS n = 291; Table 3 30 and 90 days n = 222. Denominators change for each outcome – and are different for mRS 90 day and Fugel-Meyer 90 day</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No published protocol to cross check for selective reporting</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Non-standard analysis of outcomes</td>
</tr>
</tbody>
</table>

**Guo 2009**

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel group, 3-arm trial, comparing sertraline plus routine care versus routine care versus acupuncture plus routine care. We are using the sertraline plus routine care versus routine care in this review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim</td>
<td>to treat depression</td>
</tr>
<tr>
<td>Analysis</td>
<td>according to allocated treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Country: China</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting</td>
<td>unknown</td>
<td>Stroke criteria: first ever stroke, clinical diagnosis plus relevant lesion on imaging, age $\geq$ 60 years old</td>
</tr>
<tr>
<td>Depression criteria</td>
<td>HAMD score $\geq$ 8, no depression prior to stroke</td>
<td>Treatment: 40 people, mean age $67.6 \pm 12.43$ years, 23 men</td>
</tr>
<tr>
<td>Treatment</td>
<td>Control: 40 people, mean age $64.5 \pm 12.07$ years, 22 men</td>
<td></td>
</tr>
</tbody>
</table>
### Guo 2009 (Continued)

Exclusions: psychiatric disorders or family psychiatric disorders, severe cognitive impairment, global aphasia, sensory aphasia, apraxia, severe cardiac, hepatic, renal, lung or other severe somatic disorder, consciousness disturbance, severe deafness, family or patient unable to comply

### Interventions

**Treatment:** sertraline 50 mg daily plus stroke care (acute, secondary prevention, rehabilitation and psychotherapy)

**Control:** stroke care (acute, secondary prevention, rehabilitation and psychotherapy)

Duration of treatment: 6 weeks

Duration of follow-up: (treatment end to study end): 6 months

### Outcomes

**HAMD**

**NIHSS**

**FIM** (reported cognition and mobility scores only)

**SF-36**

**AEs not reported**

### Funding source

Funded by a local scientific academic fund

### Notes

−

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
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<td>Low risk</td>
<td>Random-number table</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Outcome assessor blind</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>No dropouts, analysed by allocated treatment</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No obvious risk, balance baseline</td>
</tr>
</tbody>
</table>
### Study characteristics

| Methods | Parallel group  
| Analysis: according to treatment allocation |
| Participants | Location: China  
| Setting: inpatient  
| Inclusion criteria: all pathological types of stroke, clinical diagnosis plus confirmation by imaging (did not state that a visible lesion was needed to make the diagnosis), first ever stroke  
| Depression diagnosis: ‘HAMD scores’. Translation of paper: did not have to have depression at recruitment  
| Treatment: 36 people, mean age 70.8 ± 6.7 years, 25 men  
| Control: 35 people, mean age 70.4 ± 6.8 years, 23 men  
| Exclusion: psychiatric disorders, dysphasia, consciousness disturbance, agnosia, severe dementia |
| Interventions | Treatment: fluoxetine 20 mg daily plus usual stroke care  
| Control: usual stroke care  
| Duration of treatment: 8 weeks  
| Duration of follow-up (treatment end to study end): 0 |
| Outcomes | HAMD  
| SSS  
| No description of how side effects were collected |
| Funding source | Funded by local scientific academic fund |
| Notes | Reported that there were no AEs, so we have assumed no seizures or GI side effects |

### Risk of bias

| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear risk | Not described |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | No placebo |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote: "Outcome assessors blind" |
| Incomplete outcome data (attrition bias) | High risk | 13 dropped out after randomisation |
He 2004 (Continued)

All outcomes

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Unclear risk</th>
<th>No protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Balanced baseline, no obvious risks</td>
</tr>
</tbody>
</table>

He 2005

Study characteristics

Methods
Parallel design. 3 groups: paroxetine, paroxetine plus psychotherapy, control. We are using paroxetine and control data in this review
Analysis: according to treatment group

Participants
Location: China
Setting: inpatient
Stroke criteria: first ever stroke; ischaemic and haemorrhagic, timing: "acute", clinical diagnosis plus confirmation by imaging (though not clear whether a stroke lesion had to be present or not)
Mood criteria: meets ICD-10 organic depression and organic anxiety diagnostic criteria on psychiatric interview, HAMD score ≥ 17 and HAMA score ≥ 14
Treatment: 27 people, mean age 62.4 ± 6.1 years, 14 men
Control: 27 people, mean age 63.2 ± 5.7 years, 16 men
Exclusion: previous psychiatric disorder, antidepressants and "nerve block agents" in recent 3 months, severe cognitive impairment, aphasia, severe cardiac, hepatic and renal function impairment, allergy to paroxetine, severe suicidal behaviour

Interventions
Treatment: paroxetine 20 mg plus routine stroke treatment
Control: routine stroke treatment
Duration of treatment: 6 weeks
Duration of follow-up: end of treatment to study end: 0

Outcomes
SSS
BI
HAMD
HAMA
TESS
Also reported GI upset and dizziness. They did not list any seizures in the list of AEs, so we are assuming no seizures in either groups
Unclear how side effects were collected

Funding source
Funded by a local scientific academic fund
### He 2005 (Continued)

**Notes**
The authors mentioned using the SDS and the SAS for evaluation, but they did not report the results of SDS and SAS

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method not described</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No dropouts, analysed according to treatment group</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>No protocol, the authors mentioned using the SDS and the SAS for evaluation but they did not report the results</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Balanced baseline</td>
</tr>
</tbody>
</table>

### He 2016

#### Study characteristics

**Methods**
Study type: interventional (clinical trial)
Primary purpose: prevention

**Participants**
374 participants
Country: China
Setting: inpatient
At randomisation numbers allocated: N = 300
Experimental group 1: fluoxetine immediately after enrolment n = 100; comparator group 1: fluoxetine 7 days after enrolment n = 100; comparator group 2: no fluoxetine n = 100
% male: unclear
Age: experimental, unclear; comparator 1, unclear; comparator 2, unclear
Subtype of stroke: unclear
Severity of stroke NIHSS score at baseline: unclear
Experimental: unclear
Comparator 1: unclear
Comparator 2: unclear

Time from stroke onset: within 1 week after onset of cerebral infarction

Inclusion criteria
- ICD-10 diagnostic criteria for acute cerebral infarction
- Age 18 to 80 years
- First onset of stroke within 1 week
- NIHSS score > 2
- Stroke related impairment
- Informed consent by patients or legal representative

Exclusion criteria
- Coma
- Haemorrhagic stroke
- Previous neurological impairment
- Use of antidepressants over previous 3 months
- Use of benzodiazepines over previous 2 weeks
- Self-harm, suicidal ideation or need for antidepressants
- Abnormal liver enzymes or creatinine levels
- Gastrointestinal disorders affect drug absorption seriously
- Life-threatening illness (e.g. malignancy)
- Allergic
- Mental health disorders
- Pregnant or breast feeding
- Allergic
- Enrolled in another interventional clinical research trial within previous 3 months
- Scheduled endovascular intervention

Withdrawal criteria
- Unblinding
- Serious adverse reactions e.g. anaphylactic shock
- Need for immediate stroke-related surgery
- Complications
- Antidepressant use
- Self-harm, suicidal intention, urgent need for antidepressants
- Withdrawal from the study

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Experimental: 20 mg of fluoxetine a day for 90 days and conventional therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator:</td>
<td>conventional therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Primary outcome at days 15, 90 and 180</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIHSS score</td>
</tr>
<tr>
<td></td>
<td>Secondary outcome at days 90 and 180</td>
</tr>
<tr>
<td></td>
<td>BI score</td>
</tr>
</tbody>
</table>
**He 2016 (Continued)**

**Funding source**
This study was funded by Science and Technology Department of Guangdong, China (grant number: 2011B031800130), Science and Technology Innovation Committee of Shenzhen, China (grant number: 201101020), and Health and Family Planning Committee of Shenzhen, China (grant number: 201501009). It was registered on the Chinese Clinical Trial Registry (number: ChiCTR-TRC-12002078)

**Notes**
Dates study conducted: unclear. Either from June 2011 to December 2012 (ChiCTR-TRC-12002078) or from December 2015 to June 2016 (ChiCTR-IPR-15007658)

Declarations of Interest: none reported

Trial registration detail (ChiCTR-TRC-12002078) does not match but rather matches ChiCTR-IPR-15007658.

Baseline demographic and clinical characteristics for each group not presented, but rather the baseline demographic and clinical characteristics for those completing the trial (i.e. a subset of all those randomised at baseline) are presented

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Table of random numbers&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information on method of allocation concealment to judge high or low</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement of high or low</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: &quot;The evaluator was banned from participation in the treatment or from querying of the randomisation data.&quot;</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>For the primary outcome of NIHSS score at 15, 90 and 180 days there was 8/187 (4%) lost to follow-up in the experimental group; 16/187 (15%) in the comparator group. Twice as many participants in the comparator group (16/187[9%]) compared to the fluoxetine group (8/187 [4%]) were lost to follow-up. Attrition and exclusions were not fully reported, &gt; 5% lost to follow-up</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>The trial registration number/protocol does not match the study design presented, but rather matches ChiCTR-IPR-15007658</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>The baseline data presented in table 1: comparison of data at baseline between control group and the treatment group are not true baseline characteristics (i.e. at randomisation). The data presented in table 1 are the baseline characteristics of all those completing the trial which is a subgroup of all participants randomised. We cannot tell if there is whether there was any baseline imbalance in important demographic or clinical characteristics</td>
</tr>
</tbody>
</table>

**Hu 2002**

**Study characteristics**
### Methods

Parallel design

**Aim:** to study effect of antidepressants on depressive symptoms and nervous function

### Participants

- **Country:** China  
- **Setting:** inpatient  
- **Stroke criteria:** all pathological stroke types, clinical diagnosis plus confirmation by imaging (though unclear whether a relevant lesion had to be visible), onset of stroke 0.5 to 2 months, no obvious aphasia  
- **Depression:** according to CCMD-II-R  
- **Treatment:** 42 people, mean age 61.4 ± 3.6 years, 32 men  
- **Control:** 30 people, mean age 60 ± 4.8 years, 23 men

### Interventions

- **Treatment:** fluoxetine 20 mg daily  
- **Control:** no other antidepressant  
- **Duration of treatment:** 8 weeks  
- **Duration of follow-up (end of treatment to study end):** 0

### Outcomes

- **HAMD**  
- **MESSS**  

However, these data were not usable, as they were reported as proportions above or below "decrement levels"

- **Reported side effects but unclear how this was done**  
- **None left the trial early**

### Funding source

**Source of funding not stated**

### Notes

- **−**

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation method not described</td>
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<tr>
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<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No dropouts</td>
</tr>
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</table>
### Hu 2002 (Continued)

<table>
<thead>
<tr>
<th>All outcomes</th>
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</thead>
<tbody>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Balanced baseline, no other obvious risks</td>
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### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Aim: to explore the effect of escitalopram on the neural function and cognitive function of patients with post-stroke depression</th>
<th>RCT</th>
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<tbody>
<tr>
<td>Participants</td>
<td>82 stroke patients selected who were in hospital from October 2016 to October 2017. Met diagnostic criteria for stroke. Both haemorrhagic and ischaemic stroke included. Patients also met the diagnostic criteria of depression in Chinese classification of mental disorders; Patients did not take other antidepressants before; HAMD Score &gt; 18</td>
<td></td>
</tr>
<tr>
<td>Exclusions: 1) patients with transient cerebral ischaemia, secondary cerebral ischaemia and cerebral infarction; 2) patients with haematological diseases, coagulation dysfunction, arteriovenous malformations; 3) patients with severe organ diseases, respiratory failure; 4) patients taking other antidepressants recently; 5) patients with severe depression and cognitive impairment; 6) patients allergic to the study drugs, and dropped out of the study</td>
<td></td>
<td></td>
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<td>Interventions</td>
<td>Both groups were given usual medical care, the treatment group was given escitalopram oxalate tablets (H20103327, Shandong Jingwei Pharmaceutical Co., Ltd. 10mg*7 tablets) 10mg, once per day, for 12 weeks</td>
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<tr>
<td>Outcomes</td>
<td>HAMD score</td>
<td>NIHSS score</td>
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<td>Funding source</td>
<td>Scientific research program of Shandong Provincial Department of Health (Funding number: 2012ws1783)</td>
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### Risk of bias

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<td>Incomplete outcome data</td>
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<tr>
<td>(attrition bias) All outcomes</td>
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<tr>
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<tr>
<td>bias)</td>
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<tr>
<td>Other bias</td>
<td>Unclear risk</td>
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</table>

### Hu 2018

#### Study characteristics

**Methods**
- Parallel design
- **Aim:** efficacy and tolerance of fluoxetine in early post-stroke depression
- **Analysis:** according to treatment group

**Participants**
- **Country:** China
- **Setting:** inpatient
- **Stroke criteria:** first ever stroke, with single unilateral lesion, clinical diagnosis with imaging consistent with stroke, both ischaemic and haemorrhagic, recruited 2 weeks after stroke onset
- **Depression criteria:** CCMD II-R depression diagnosis
- **Treatment:** 40 people, age and gender not stated
- **Control:** 40 people, age and gender not stated
- **Participants in the treatment and control groups were selected from a group of 168 first-ever acute stroke patients with average age of 62 ± 8.1 years, 76 men**

**Interventions**
- **Treatment:** fluoxetine 20 mg daily
- **Control:** placebo
- **Duration of treatment:** 4 weeks
- **Duration of follow-up (treatment end to study end):** 0

**Outcomes**
- HAMD
- CSS
- Did not report death
- Unclear how AEs were reported: no obvious AEs were found, but they did not specifically report seizures

**Funding source**
- Source of funding not stated

**Notes**
- —
Huang 2002 (Continued)

Risk of bias

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<td>Not described</td>
</tr>
<tr>
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<td>Low risk</td>
<td>No dropouts, analysed according to treatment group</td>
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<tr>
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<td>Unclear risk</td>
<td>No description of the differences between treatment and control group in baseline characteristics</td>
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</table>

Jia 2005

Study characteristics

Methods

- Parallel design
- Aim: to determine the effect of early intervention for post stroke depression on movement after 3 months of stroke

Participants

- Country: China
- Setting: inpatient
- Inclusion: aged 40 to 75 years, all pathological types of stroke, clinical diagnosis plus confirmation by imaging (did not state whether a relevant lesion had to be present to make a diagnosis), able to give informed consent
- Depression diagnosis: Zung SDS > 41 for screening for depression, HDRS for evaluation of the depression severity level
- Treatment: 92 people randomised, 90 accepted allocation, mean age 55.6 ± 6.5 years, 60 men
- Control: 92 people randomised, 90 accepted allocation, mean age 55.1 ± 6.8, 55 men
- Excluded: organic psychiatric disorders such as Alzheimer’s disease or degenerative disease, functional disorders such as schizophrenia and affective disorders

Interventions

- Treatment: either fluoxetine or sertraline (given sertraline if also had anxiety) plus routine stroke care
Jia 2005 (Continued)

Control: routine stroke care

Duration of treatment: 3 months
Duration of follow-up: 3 years but the authors did not describe the extent of neurological function damage and HAMD scores in the third year

Outcomes

<table>
<thead>
<tr>
<th>HAMD</th>
<th>Extent of neurological damage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recurrent stroke</td>
</tr>
<tr>
<td></td>
<td>Death</td>
</tr>
</tbody>
</table>

Did not report AEs

Funding source

Source of funding not stated

Notes

−

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tr>
<td>Allocation concealment (selection bias)</td>
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</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
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<td>No placebo</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
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</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>No blinding</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Dropouts: 6 in treatment group (2 refused allocation), 4 in control group (2 refused allocation)</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Balanced baseline</td>
</tr>
</tbody>
</table>

Kim 2017

Study characteristics

Methods

Multicentre

Study type: interventional (clinical trial)

Intervention model: parallel assignment
**Kim 2017 (Continued)**

**Primary purpose:** prevention

**Participants**  
478 participants  
Country: South Korea  
Setting: inpatient at neurology departments in 17 university hospitals throughout South Korea  
At randomisation number allocated: N = 478, escitalopram (n = 241); placebo (n = 237)  
% male at baseline: unclear  
Age at baseline: unclear  
Subtype of stroke at baseline: unclear  
Severity of stroke at baseline: unclear  
Time since stroke onset: acute ischaemic stroke or intracerebral haemorrhage within the previous 21 days

**Inclusion criteria**

- Age > 20 years  
- Patients with acute stroke (ischaemic stroke or cerebral haemorrhage) confirmed by neuroimaging within 21 days after stroke onset  
- Patients with haemorrhagic transformation of infarcted tissue will not be included, but if investigators judge the risk of bleeding is small (i.e. reduced amount of blood in follow-up neuroimaging) those patients can be enrolled  
- Patients with mRS ≥ 2 on screening  
- Patients without definite history of depression  
- Patients who fulfil the following criteria in the K-MADRS test: The combined score of the 9th question (pessimistic thoughts) and the 10th question (suicidal idea) ≤ 7 The score of the 10th question < 6  
- Patients without serious communication problem  
- Consent

**Exclusion criteria**

- MRS 0 or 1 on screening  
- History of depression or have taken antidepressants  
- Diagnosis of bipolar disorder or other psychiatric disorders  
- Severe dementia or aphasia and unable to communicate  
- Taken migraine medication on screening or expected to take migraine medication frequently due to severe migraine  
- Suicidal ideation on screening test or those who express their wish to be treated for depression  
- Depression requiring treatment diagnosed by physician  
- SSRI medication required for other reasons  
- Taken antiepileptic drugs on screening  
- History of traumatic brain injury, brain tumour, or other brain disease (except stroke) within 30 days prior to screening  
- Uncommon causes of stroke (e.g. subarachnoid haemorrhage, venous thrombosis, arteriovenous malformation, or Moyamoya disease)  
- Bleeding diathesis, haemophilia, or thrombocytopenia  
- Severe concomitant illness (e.g. liver disease, renal disease, malignancy)  
- Patients with abnormal blood tests, renal insufficiency, heart failure  
- Pregnant or breastfeeding  
- Participating in another clinical (interventional) trial

**Withdrawal criteria:** not stated
Interventions
Experimental: escitalopram: first week 5 mg, 2nd week ~ 12 week: 10 mg
Comparator: "sugar pill". First week 5 mg, 2nd week ~ 12 week: 10 mg

Outcomes
Primary outcomes collected at 3 months
- Occurrence rate of depression (MADRS score ≥ 16)
Secondary outcomes
- Prevention of depression at 3 months
- Prevention of emotional incontinence (modified Kim’s criteria) at 3 and 6 months
- Prevention of anger proneness (modified Spielberger trait anger scale) at 3 and 6 months
- Recovery of neurologic dysfunction (NIHSS, mRS, BI, motor function test from Hemispheric Stroke Scale at 3 months)
- Improvement of cognitive function (MoCA) at 3 and 6 months
- Improvement of quality of life (Stroke Specific Quality of Life scale) at 3 and 6 months
- Improvement of caregiver burden (Sense of Competence Questionnaire scores) at 3 and 6 months

Funding source
Dong-A Pharmaceutical Company, grants from the Ministry for Health, Welfare, and Family Affairs, South Korea

Notes
NCT01278498
Baseline demographic and clinical characteristics for each group not presented, but rather the baseline demographic and clinical characteristics for those completing the trial (i.e., a subset of all those randomised at baseline) are presented
Dates study conducted: January 2011 to December 2015
Declarations of Interest: none reported

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Quote: &quot;Eligible patients were enrolled by investigators at each centre, and randomly assigned in a 1:1 ratio using a web-based system to the escitalopram group or the placebo group after being assigned a subject number. Randomisation was done with random permuted blocks of sizes four to six, and was stratified by centre. The placebo was identical in appearance to escitalopram&quot;</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>Quote: &quot;Eligible patients were enrolled by investigators at each centre, and randomly assigned in a 1:1 ratio using a web-based system to the escitalopram group or the placebo group after being assigned a subject number. Randomisation was done with random permuted blocks of sizes four to six, and was stratified by centre&quot;</td>
</tr>
<tr>
<td>Blinding of participants and</td>
<td>Low risk</td>
<td>Quote: &quot;The placebo was identical in appearance to escitalopram&quot;</td>
</tr>
</tbody>
</table>
| personnel (performance bias)  |                    | Quote: "The individual treatment code was stored separately by the main medical statistician (E-JL) and two designated statisticians. All investigators including interviewers and assessors of the outcome, participants, and care providers were masked to treatment assignment throughout the study. The code could be unblinded only with the approval of the steering committee."
| Blinding of outcome assessment| Low risk           | Quote: "All investigators including interviewers and assessors of the outcome, participants, and care providers were masked to treatment assignment" |
Incomplete outcome data (attrition bias)  
All outcomes  
High risk  
The following participants were excluded from the 'full analysis set' post-randomisation from both escitalopram group and placebo group:  
- did not take at least 1 dose of study medication (escitalopram = 4, placebo = 6)  
- did not undergo at least 1 assessment of the primary endpoint (escitalopram = 27, placebo = 36)  

Reasons for attrition were reported (withdrew consent, violated protocol, considered for treatment for depression, death). Numbers were similar in both groups  
At 12 weeks, escitalopram group 67/241 (28%) attrition and placebo 73/237(31%) attrition  
Attrition much greater than 5%  
It is not clear how missing data were imputed for the intention-to-treat analysis; Quote: "we used latest available records for analysis."  

Selective reporting (reporting bias)  
Low risk  
The study protocol is available and all the study's prespecified (primary outcomes and secondary outcomes) that are of interest in the review have been reported in the prespecified way.  

Other bias  
High risk  
The baseline data presented in table 1: comparison of data at baseline between control group and the treatment group are not true baseline characteristics (i.e. at randomisation). The data presented in table 1 are the baseline characteristics of all those completing the trial which is a subgroup of all participants randomised. We cannot tell if there is whether there was any baseline imbalance in important demographic or clinical characteristics.

### Kong 2007

**Study characteristics**

**Methods**  
Parallel  
Aim: to study whether fluoxetine could prevent post-stroke depression and improve neurological function  

**Participants**  
Country: China  
Setting: inpatient  
Stroke: met diagnostic criteria of various cerebrovascular diseases formulated in the 4th National Cerebrovascular Disease conference and confirmed as stroke by CT or MRI, all hemiplegic, within 7 days of onset  
HAMD score of no depression  
Treatment: 48 people, mean age 64 ± 7 years, 60% men  
Control: 42 people, mean age 62 ± 7 years, 57% men  
Exclusion: major depression, current antidepressants, allergy to fluoxetine, substance abuse, bipolar disorder, schizophrenia, MMSE ≤ 23/30, substance abuse, obvious liver and renal deficit
Kong 2007 (Continued)

Interventions
Treatment: fluoxetine 20 mg daily
Control: matching placebo capsules
Duration of treatment: 8 weeks
Duration of follow-up (end of treatment to end of study): 0

Outcomes
HAMD
BI
NIHSS
Reported "somatic side effects and hyponatraemia" but not death or other side effects
Authors state that "side effect rating was assessed at each visit" but unclear how this was done

Funding source
Source of funding not stated. Fluoxetine and placebo were supplied by Lilly Pharmaceutical Company

Notes
−

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tr>
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<td>Low risk</td>
<td>Identical capsules, participants blinded</td>
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<td>Low risk</td>
<td>States that researchers were blinded</td>
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<td>High risk</td>
<td>17/90 dropouts</td>
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</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Balanced baseline</td>
</tr>
</tbody>
</table>

Lai 2006

Study characteristics

Methods
Parallel design

Analysis: analysed according to allocated treatment groups
### Participants

Location China  
Setting: inpatients  
Treatment: 40 people  
Control: 40 people  
Total: mean age 60 ± 14 years, 43 men  
Stroke criteria: unclear stroke types, clinical diagnosis plus brain imaging (though not clear that stroke lesion had to be present), acute stroke  
Depression criteria: HAMD at least 7, or Zung SDS > 53, but no clear description about using which scale for inclusion criteria  
Other entry criteria: none stated  
Comparability of treatment groups: unclear  
Exclusion criteria: unclear

### Interventions

Treatment: paroxetine 20 mg daily  
Control: placebo  
Duration: treatment continued for 2 months  
Duration of follow-up (end of treatment to end of study): 0

### Outcomes

Depression: HAMD, Zung SDS (abnormal if the score is > 53)  
Additional: Zung SAS (abnormal is the score is > 50)  
Death  
The author described that they recorded AEs but they did not report any AEs

### Funding source

Source of funding not stated

### Notes

−

### Risk of bias

<table>
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<th>Bias</th>
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<th>Support for judgement</th>
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<td>Placebo used, not stated if matching</td>
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### Lai 2006 (Continued)

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<tr>
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<th>Support for judgement</th>
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<tr>
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<td>No participant dropped out</td>
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<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>No protocol, stated that they would evaluate side effects but these were not reported</td>
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<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Demographic details at baseline not described</td>
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</table>

### Li 2004a

**Study characteristics**

**Methods**
- Parallel group
- Aim: to study effects of fluoxetine on neurological impairment and post-stroke depression

**Participants**
- Location: China
- Setting: inpatient
- Stroke: inclusion: all pathological types, clinical diagnosis plus confirmation by imaging that relevant lesion visible, CSS 16 to 30
- Depression criteria: HAMD scores ≥ 17 and DSM IV diagnostic criteria
- Treatment: 33 people, mean age 60.33 years, 24 men
- Control: 34 people, mean age 60.44 years, 23 men
- Excluded severe psychiatric disorders, severe cardiac, pulmonary, hepatic and renal disease

**Interventions**
- Treatment: fluoxetine 20 mg daily plus routine acute stroke care
- Control: routine acute stroke care
- Duration of treatment: 4 weeks
- Duration of follow-up (end of treatment to end of study): 0

**Outcomes**
- CSS
- Depression incidence
- Laboratory monitoring parameters
- AEs (method of reporting not stated)

**Funding source**
- Source of funding not stated

**Notes**
- –

**Risk of bias**

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</tr>
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### LI 2004b

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel design</th>
</tr>
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<tbody>
<tr>
<td>Aim</td>
<td>to treat depression</td>
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<table>
<thead>
<tr>
<th>Participants</th>
<th>Country: China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting</td>
<td>inpatient</td>
</tr>
<tr>
<td>Stroke criteria</td>
<td>ischaemic stroke, clinical diagnosis plus imaging confirmation (though not clear that a relevant lesion had to be seen), stroke onset time ≤ 7 days</td>
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<tr>
<td>Depression criteria</td>
<td>HAMD score ≥ 8</td>
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<tr>
<td>Treatment</td>
<td>37 people, age 48 to 87 years, 17 men</td>
</tr>
<tr>
<td>Control</td>
<td>36 people, age 53 to 82 years, 15 men</td>
</tr>
<tr>
<td>Exclusion</td>
<td>previous depression or psychiatric interview, dementia (according to MMSE scores), aphasia, severe cardiac, pulmonary, hepatic, renal function impairment, consciousness disturbance</td>
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<table>
<thead>
<tr>
<th>Interventions</th>
<th>Treatment: fluoxetine 20 mg daily plus usual stroke care</th>
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<tr>
<td></td>
<td>Control: usual stroke care</td>
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<td>Duration: 8 weeks</td>
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<td>Duration of follow-up (treatment end to study end): 0</td>
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<table>
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<tr>
<td></td>
<td>CSS (cannot use as reported as a categorical variable)</td>
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<td></td>
<td>MMSE (reported as a dichotomous variable)</td>
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</table>
Li 2004b (Continued)

BI (reported as a dichotomous variable)
Data for continuous variables not provided
Death reported
Side effects in treatment group only reported, not control group. Method of reporting side effects not stated

Funding source
Source of funding not stated

Notes
Note that the sum of numbers in each category of HAMD at 8 weeks in the control group adds up to 30, not 32

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method not described</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Method not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not stated</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Dropouts: 6 in treatment and 4 in control group. Total dropouts = 10/73 (14%)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Baseline balanced</td>
</tr>
</tbody>
</table>

Li 2005

Study characteristics

Methods
Parallel design
Improvement of post-stroke depression and augmentation of rehabilitation

Participants
Country: China
Setting: inpatient
Stroke criteria: all stroke, clinical diagnosis plus confirmation on imaging (though not clear whether a relevant lesion had to be present)
Depression according to CCMD-II-R
Li 2005 (Continued)

Treatment: 74 participants
Control: 74 participants

Participants in the treatment and control groups were selected from a group of 368 stroke patients with an average age of 57 ± 11.8 years, age range 33 to 84 years, 240 men

Excluded: previous psychiatric disorders, severe dementia, aphasia, consciousness disturbance

Interventions
- Treatment: paroxetine 20 mg daily plus routine stroke treatment
- Control: routine stroke treatment
- Duration of treatment: 4 weeks
- Duration of follow-up (end of treatment to study end): 0

Outcomes
- HAMD
- SSS
- Deaths
- Side effects not recorded

Funding source
Source of funding not stated

Notes
-

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
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<td>Unclear risk</td>
<td>Randomisation method not described</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No description</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not stated whether blinded</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Analysed according to allocated treatment group, no participant dropped out</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No description of differences between treatment and control group</td>
</tr>
</tbody>
</table>
### Li 2006

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>All pathological types of stroke, CT or MRI needed for diagnosis&lt;br&gt; Inclusion criteria: depression diagnosed by Chinese Classification of Mental Disorders 3 and HAMD ≥ 18, no previous organic brain disorder, and no previous psychiatric history, clear consciousness, no comprehension problems, normal language, first acute stroke, first episode of depression&lt;br&gt; Treatment: 52 people, mean ± SD age 61.12 ± 10.25, 32 men&lt;br&gt; Control: 53 people, mean ± SD age 60.89 ± 9.12, 35 men</td>
</tr>
<tr>
<td>Interventions</td>
<td>Treatment: citalopram 20 mg daily plus usual care&lt;br&gt; Control: usual care&lt;br&gt; Duration of treatment: 12 weeks&lt;br&gt; Duration of follow-up (end of treatment to end of study): 0</td>
</tr>
<tr>
<td>Outcomes</td>
<td>HDRS (also known as HAMD)&lt;br&gt; BI&lt;br&gt; CSS&lt;br&gt; MMSE&lt;br&gt; Side effects reported according to the participant’s complaints and observation, no description of who recorded AEs; and reported only for the treatment group</td>
</tr>
<tr>
<td>Funding source</td>
<td>Source of funding not stated</td>
</tr>
<tr>
<td>Notes</td>
<td>–</td>
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</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No description</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>No description</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>2 dropouts in treatment group, 4 in control group. 1 in treatment group died, and 2 in the control group died (i.e. &gt; 5%)</td>
</tr>
</tbody>
</table>
Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

Li 2006 (Continued)

Selective reporting (reporting bias) | Unclear risk | No protocol
---|---|---
Other bias | Low risk | Baseline balanced

Li 2007

**Study characteristics**

**Methods**
Aim: to investigate the efficacy and safety of paroxetine in the treatment of post-stroke depression. Patients randomly divided into two groups

**Participants**
Stroke diagnosis: 4th Congress of Chinese Cerebrovascular Diseases, with brain CT or MRI to confirm the diagnosis.

30 cases of ischemic stroke and 14 cases of hemorrhagic stroke in the treatment group, and 31 cases of ischemic stroke and 11 cases of hemorrhagic stroke in the control group.

Patients with prior depression, anxiety and schizophrenia were excluded

HAMD Score ≥ 18

**Interventions**
Both groups were given usual medical care, the treatment group was give paroxetine tablets (Zhejiang Huahai Pharmaceutical Co., Ltd.), 20mg, once per day orally in the morning for 8 weeks; the control group was given the placebo, dose not reported, once per day orally in the morning for 8 weeks

**Outcomes**
Depression score at treatment of 2-week, 4-week and 8-week

Neurological deficiency score at treatment of 2-week, 4-week and 8-week

**Funding source**
Unclear

**Notes**

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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<tbody>
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<td>Unclear risk</td>
<td>No information provided</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information provided</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>No information provided</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>No information provided</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>No information provided</td>
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</table>
**Li 2007 (Continued)**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No information provided</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No information provided</td>
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</tbody>
</table>

**Li 2008**

**Study characteristics**

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Parallel trial, 3 (fluoxetine versus &quot;free and easy wandering&quot; versus placebo), we are using the fluoxetine versus placebo comparison in this review</td>
</tr>
<tr>
<td>Participants</td>
<td>Country: China</td>
</tr>
<tr>
<td></td>
<td>Setting: unclear</td>
</tr>
<tr>
<td></td>
<td>Stroke criteria: by neuroimaging, ischaemic or PICH</td>
</tr>
<tr>
<td></td>
<td>Depression diagnosis: &quot;each patient was evaluated by a psychiatrist&quot;, HAMD &gt; 20 included</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine group: 60 people, mean age 69.2 ± 3.5 years, men 41.6%</td>
</tr>
<tr>
<td></td>
<td>Control: 30 people, mean age 67.8 ± 3.9 years, men 56.7%</td>
</tr>
<tr>
<td></td>
<td>Excluded psychiatric illness other than depression, antidepressants within previous 2 weeks, MMSE &lt; 23, severe aphasia</td>
</tr>
<tr>
<td>Interventions</td>
<td>Treatment: fluoxetine 20 to 40 mg daily</td>
</tr>
<tr>
<td></td>
<td>Control: placebo</td>
</tr>
<tr>
<td></td>
<td>Duration of treatment: 8 weeks</td>
</tr>
<tr>
<td></td>
<td>Duration of follow-up (treatment end to study end): 0</td>
</tr>
<tr>
<td>Outcomes</td>
<td>HAMD</td>
</tr>
<tr>
<td></td>
<td>BI</td>
</tr>
<tr>
<td></td>
<td>Description of why participants left the trial early</td>
</tr>
<tr>
<td></td>
<td>AEs (reported by participant or observed/elicted by physician at each visit)</td>
</tr>
<tr>
<td>Funding source</td>
<td>Funded by the Natural Science Foundation of Shandong Province, People’s Republic of China. None of authors had financial ties with the companies producing the medications in this study</td>
</tr>
<tr>
<td>Notes</td>
<td>Note twice as many in fluoxetine as in control group</td>
</tr>
<tr>
<td></td>
<td>Study conducted between March 2006 to September 2007. None of the authors or departments involved in the study had financial ties with the companies producing the medications used in this study</td>
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</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer-generated random numbers</td>
</tr>
<tr>
<td>Study characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>Aim: to investigate the effect of escitalopram oxalate in the early treatment of post-stroke depression, cognition and neurological function</td>
<td></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>The diagnosis of ischaemic stroke was based on the Chinese guidelines for the diagnosis and treatment of acute ischaemic stroke (2010), and the diagnosis of haemorrhagic stroke was based on the Chinese diagnostic criteria for adult spontaneous cerebral haemorrhage (2010). Patient met the Chinese diagnostic criteria for mental disorders and depression, with HAMD ≥ 17 points. MMSE was used to screen the patients with post-stroke cognitive impairment. The patients with unstable vital signs, severe cognitive impairment, severe depression, severe aphasia and unconsciousness were excluded</td>
<td></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Both groups received routine medicine and rehabilitation exercise. The treatment group was additionally treated with escitalopram oxalate tablets (Lexpro, produced by Lingbei pharmaceutical factory of Denmark, Xi’an Janssen Pharmaceutical sub package), 10 mg orally after breakfast every day for 24 weeks; the control group was additionally treated with placebo, 1 tablet each time, orally after breakfast for 24 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>HAMD, MMSE, NIHSS and FIM were used to evaluate depression, cognitive function, neurological deficit and the patients' ability to live independently respectively, by 2 psychiatrists and 2 neurologists who were uninformed of the treatment. Above scales were respectively before treatment, 4 weeks and 24 weeks after treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Funding source</strong></td>
<td>Unclear</td>
<td></td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allocation concealment (selection bias)</strong></td>
<td>Unclear risk</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Blinding of participants and personnel (performance bias)</strong></td>
<td>Unclear risk</td>
<td>Paper states blinded, used placebo (though unclear if matching, thus unclear (had a matching placebo been used then it would have been low)</td>
</tr>
<tr>
<td><strong>Blinding of outcome assessment (detection bias)</strong></td>
<td>Low risk</td>
<td>Blinded</td>
</tr>
<tr>
<td><strong>Incomplete outcome data (attrition bias)</strong></td>
<td>Unclear risk</td>
<td>4/90 dropped out (&lt; 5%)</td>
</tr>
<tr>
<td><strong>Selective reporting (reporting bias)</strong></td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td><strong>Other bias</strong></td>
<td>Low risk</td>
<td>Balanced baseline</td>
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</table>
### L1 2017 (Continued)

<table>
<thead>
<tr>
<th>Bias Source</th>
<th>Risk</th>
<th>Information</th>
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</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No information</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>No information</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Outcome assessed by 2 neurologist and 2 psychiatrists unaware of treatment allocation</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>No information</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No information</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No information</td>
</tr>
</tbody>
</table>

### Liu 2006

**Study characteristics**

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Parallel design</td>
</tr>
<tr>
<td>Aim</td>
<td>to study effect of citalopram on post-stroke depression and neurological functional rehabilitation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>China</td>
</tr>
<tr>
<td>Setting</td>
<td>inpatient</td>
</tr>
<tr>
<td>Stroke criteria</td>
<td>stroke during &quot;recovery phase&quot; at 6 to 9 months, NIHSS score ≥ 13, HAMD score ≥ 17</td>
</tr>
<tr>
<td>Demographics</td>
<td>60 people randomised, of whom 38 were men, mean age 60.7 ± 8.6 years. Demographics for treatment and control groups were not provided</td>
</tr>
<tr>
<td>Treatment</td>
<td>30 people, age and gender not stated</td>
</tr>
<tr>
<td>Control</td>
<td>30 people, age and gender not stated</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>previous psychiatric disorder, dementia, aphasia, consciousness disturbance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>citalopram 20 mg daily plus routine stroke care</td>
</tr>
<tr>
<td>Control</td>
<td>routine stroke care</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>(treatment end to study end): 0</td>
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<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>HAMD</td>
<td></td>
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<tr>
<td>NIHSS</td>
<td></td>
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### Liu 2006 (Continued)

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<thead>
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<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
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<td>Method not described</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not stated</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>No dropouts</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Baseline balance reported by authors</td>
</tr>
</tbody>
</table>

### Marquez Romero 2013

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Multicentre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type: interventional (clinical trial)</td>
<td></td>
</tr>
<tr>
<td>Primary purpose: supportive care</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>32 participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: Mexico</td>
<td></td>
</tr>
<tr>
<td>Setting: inpatient</td>
<td></td>
</tr>
<tr>
<td>At randomisation number allocated: N = 32: fluoxetine (n = 15); placebo (n = 17)</td>
<td></td>
</tr>
<tr>
<td>% men: 50%</td>
<td></td>
</tr>
<tr>
<td>Age: mean age 55.1 ± 12.2</td>
<td></td>
</tr>
</tbody>
</table>
**Subtype of stroke:** not available

**Severity of stroke:** NIHSS, Median (IQR): fluoxetine (12 (5)); placebo (14 (5))

**Time since stroke onset:** within 10 days

**Inclusion criteria**
- Age > 18 years
- Patients who had an acute intracerebral haemorrhage within the past 10 days causing hemiparesis or hemiplegia
- FMMS scores of ≤ 55
- Written informed consent

**Exclusion criteria**
- NIHSS score > 20
- Premorbid disability, evidenced by residual motor deficit from a previous stroke
- Comprehension deficit or severe aphasia
- Previous diagnosis of depression or one of the following: HADS score ≥ 11 points; taking antidepressant drugs 2 weeks before inclusion
- Use of neuroleptic drugs or benzodiazepines 2 weeks before inclusion
- Other life-threatening illnesses

**Withdrawal criteria**
- Detection of eligibility violations
- Poor compliance (< 90%) or noncompliance
- Use of any medication or treatment during the trial that could affect the study results
- Occurrence of a serious adverse event:
  - participant has an acute reaction (allergy, shock) to the investigational product
  - participant develops depression, evidenced by HADS score ≥ 11 points at visit
  - participant withdraws consent or is uncooperative

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Experimental: fluoxetine 20 mg orally once daily for 90 days</th>
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</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>matching placebo orally once daily for 90 days</td>
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<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FMMS score (baseline and 90 days): change from baseline in FMMS score at 90 days</td>
</tr>
</tbody>
</table>

**Secondary outcomes**
- BI (baseline and 90 days): change from baseline in BI at 90 days
- mRS (baseline and 90 days): change from baseline in mRS at 90 days
- NIHSS (baseline and 90 days): change from baseline in NIHSS at 90 days

**Funding source**
Psicofarma S.A. de C.V.

**Notes**
NCT01737541
Terminated (study recruitment was suspended due to lack of funding)
Dates study conducted: November 2012 to August 2014
Declarations of Interest: none reported

**Risk of bias**
### Marquez Romero 2013 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Random sequence generation (selection bias) | Low risk           | Quote: "A pharmaceutical laboratory (Psicofarma™ S.A. de C.V.) will be responsible for the manufacture and randomization of the investigational product, which will be achieved using a web-based randomization program. This program will be set to assign participants equally to each site at a ratio of 1:1."
| Allocation concealment (selection bias)   | Low risk           | Quote: "Each of the sites will be assigned 22 participants. The manufacturer will then deliver the pre-randomized bottles containing the investigational product to each recruiting center. Study subjects who satisfy the eligibility criteria at each recruiting center will receive the investigational product corresponding to a consecutive number assigned according to their entrance to the study."
| Blinding of participants and personnel (performance bias) | Low risk           | Quote: "Fluoxetine and placebo tablets will be identical in form, color, odor and packaging."
| All outcomes                              |                    | "Both the investigator and the subject will be blinded to the assignment of the study drugs. The manufacturer of the tablets will label the investigational drugs by the randomization code number. The labeled experimental products will be provided to the recruiting centers by the manufacturer. An envelope containing all randomization codes will be delivered to the principal investigator and will be kept sealed until the conclusion of the trial."
| Blinding of outcome assessment (detection bias) | Low risk           | Blinding of participants and key study personnel ensured, and unlikely that blinding could have been broken
| Incomplete outcome data (attrition bias)  | Low risk           | Aimed to recruit 44 per group (total of 88) 35 in each group + 20% to allow for predicted 20% loss to follow-up
| All outcomes                              |                    | Actual enrolment N = 32. Quote: "Two patients (one in each group) did not take any medication returning the unopened bottles at visit 1 and had to be excluded from analysis." We judged that this is unlikely to have influenced bias, as there is one missing from each group and this represents a similar proportion in each group
| Selective reporting (reporting bias)      | Low risk           | The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported
| Other bias                                | Low risk           | The study appears to be free of other sources of bias

### Meara 1998

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel design</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Analysis: unclear</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Location: Wales, UK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Setting: inpatient</td>
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<tr>
<td></td>
<td>Treatment: unclear</td>
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</table>
### Meara 1998 (Continued)

<table>
<thead>
<tr>
<th>Control: unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke criteria: ischaemic stroke &gt; 11 weeks prior to randomisation</td>
</tr>
<tr>
<td>Depression criteria: GDS (15-item) score &gt; 4</td>
</tr>
<tr>
<td>Other entry criteria: not stated</td>
</tr>
<tr>
<td>Exclusion criteria: moderate to severe dementia, severe aphasia, communication difficulties, poorly controlled epilepsy</td>
</tr>
</tbody>
</table>

#### Interventions

- **Treatment:** sertraline 50 mg daily, dose escalation to 100 mg for non-responders at 2 weeks
- **Control:** matched placebo
- **Duration:** treatment continued for 6 weeks

#### Outcomes

- **Depression:** change in scores from baseline to end of treatment on GDS
- **Unable to use:** GDS, BI, MMSE, FAI, FAST
- **Leaving trial early**
- **Death**
- **AEs**

#### Funding source

- Source of funding not stated

#### Notes

- Contacted author for more details but no response
- We could not use the data in our meta-analysis
- Dates of study not stated. Conflicts not stated

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
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<td>Method not described</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Double-blind reported, those who were blind not described</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Double-blind reported, those who were blind not described</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Insufficient data to make a judgement</td>
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</table>
### Meara 1998 (Continued)

#### Risk of bias

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<thead>
<tr>
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<th>Support for judgement</th>
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<tbody>
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<td>Quote: &quot;Simple random sampling&quot;</td>
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<td></td>
<td></td>
<td>Comment: no further description given</td>
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</table>

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 not allocated (5 in treatment group refused allocation, 4 in the control group refused allocation)</td>
</tr>
<tr>
<td>Participants</td>
<td>Country: China, Setting: mixed inpatient and outpatient</td>
</tr>
<tr>
<td></td>
<td>All stroke pathological types, clinical diagnosis plus confirmation by imaging that a relevant lesion was visible, 2 to 8 months after stroke, clear consciousness, no comprehension problem, 1 lesion in 1 hemisphere, normal language comprehension</td>
</tr>
<tr>
<td></td>
<td>Mood: depression after stroke onset, HAMD score ≥ 20</td>
</tr>
<tr>
<td></td>
<td>Participants: 90 randomised, 34 in each group at treatment end</td>
</tr>
<tr>
<td></td>
<td>Treatment: 34 people, age 58.16 ± 8.49 years, 19 men</td>
</tr>
<tr>
<td></td>
<td>Control: 34 people, age 62.45 ± 8.24 years, 18 men</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: other organic brain disorders and other aetiologies-related depression</td>
</tr>
<tr>
<td>Interventions</td>
<td>Treatment: citalopram 20 mg daily plus usual stroke care</td>
</tr>
<tr>
<td></td>
<td>Control: usual stroke care</td>
</tr>
<tr>
<td></td>
<td>Duration of treatment: 6 weeks</td>
</tr>
<tr>
<td></td>
<td>Duration of follow-up (treatment end to study end): 0</td>
</tr>
<tr>
<td>Outcomes</td>
<td>HAMD</td>
</tr>
<tr>
<td></td>
<td>SDS</td>
</tr>
<tr>
<td></td>
<td>Efficacy</td>
</tr>
<tr>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>AEs (only in the citalopram group)</td>
</tr>
<tr>
<td></td>
<td>Method of recording AEs was not stated</td>
</tr>
</tbody>
</table>

#### Funding source

Source of funding not stated

#### Notes

−
### Miao 2004 (Continued)

<table>
<thead>
<tr>
<th>Study characteristic</th>
<th>Risk Evaluation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Allocation not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Blinding described</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>9 not allocated after randomisation, 13 dropouts</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Baseline balanced</td>
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### Murray 2005

**Study characteristics**

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Parallel design</td>
</tr>
<tr>
<td>Analysis: ITT (last observation carried forward) and per-protocol; death (2 control), no efficacy (16 treatment, 22 control), withdrawn owing to AE (8 treatment, 5 control), withdrew consent (1 control), all excluded from analysis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location: Sweden</td>
<td></td>
</tr>
<tr>
<td>Setting: mixed</td>
<td></td>
</tr>
<tr>
<td>Treatment: 62 people, mean ± SD age 71 ± 10 years, 52% men</td>
<td></td>
</tr>
<tr>
<td>Control: 61 people, mean ± SD age 71 ± 10 years, 44% men</td>
<td></td>
</tr>
<tr>
<td>Stroke criteria: all subtypes, diagnosis by WHO criteria and CT (100%); stroke 3 to 367 days prior to randomisation (average time 128 days)</td>
<td></td>
</tr>
<tr>
<td>Depression criteria: psychiatric interview (DSM-IV, major and minor) and MADRS &gt; 9</td>
<td></td>
</tr>
<tr>
<td>Other entry criteria: &gt; 17 years of age, stroke within the previous 12 months</td>
<td></td>
</tr>
<tr>
<td>Comparability of treatment groups: significant trend towards more left-hemisphere lesion strokes in treatment group</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: under 18 years of age, severely impaired communication, apparent difficulties adhering to study protocol, acute myocardial infarction, other psychiatric illnesses other than depression, significant risk of suicide, antidepressants during the month after randomisation, current use of psychotropic medication or opiate analgesic drugs</td>
<td></td>
</tr>
<tr>
<td>Participants with &lt; 20% reduction in MADRS score at 6 weeks were excluded</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment: sertraline 50 mg daily; possible dose escalation to 100 mg after 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Control: matching placebo</td>
<td></td>
</tr>
</tbody>
</table>
### Murray 2005 (Continued)

Duration of treatment: 26 weeks
Duration of follow-up: (treatment end to study end): 0

**Outcomes**

- Depression: change in scores from baseline to end of treatment on MADRS
- Additional: leaving the study early
- Death

Unable to use: Scandinavian Supervision Stroke Scale, BI, Stroke Unit Mental Status, Examination social performance, treatment costs, mortality, relative's situation, neuropsychological performance, neurological recovery (data not presented)

AEs (selected data presented) using a modified version of the Udvalg for Kliniske Undersogelser side effect rating scale

**Funding source**

Funded by an unrestricted grant, study drug and placebo from Pfizer AG Sweden and grants from the AFA Insurances and Marianne and Marcus Wallenberg Foundation

**Notes**

Recruitment September 1998 to January 2001. Conflicts stated; some of the authors have received grants from pharmaceutical companies

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Block randomisation</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Centralised randomisation</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>States blinding and used matching placebo</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>States blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>123 enrolled. 69 completed. Last observation carried forward</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>No protocol, paper stated that ADL data and SSS data were collected, but these were not reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Balanced baseline except that more participants had left hemisphere brain lesion in sertraline group than in placebo group (statistically significant)</td>
</tr>
</tbody>
</table>

### NCT00177424

**Study characteristics**

**Methods**

Study type: interventional (clinical trial)
Primary purpose: prevention

Participants
Number of participants: unclear
Country: USA
Setting: inpatient
At randomisation number allocated: unclear
% male: unclear
Age: unclear
Subtype of stroke: unclear
Severity of stroke: unclear
Time since stroke onset: unclear

Inclusion criteria
• Age > 40 years old
• Ischaemic stroke within 3 months of study entry
• Admitted to a University of Pittsburgh Medical Center hospital for acute inpatient treatment or rehabilitation of stroke
• English-speaking
• Women willing to use an effective form of birth control throughout the study

Exclusion criteria
• Major depressive episode (DSM-IV-TR criteria)
• History of any bipolar disorder
• Psychotic or history of a psychotic disorder
• Alcohol or substance abuse or dependence (DMS-IV TR criteria) within 3 months of study entry
• Current treatment with antidepressant medication for any reason (e.g. anxiety disorder, neuropathic pain)
• Primary haemorrhagic stroke
• Language impairment severe enough to prevent assessment
• CNS disease other than prior stroke or psychiatric illness (e.g. head trauma, multiple sclerosis, HIV with CNS involvement)
• Pulse < 50 or > 100 beats per minute
• Significant hyponatraemia (Na < 130 meq)
• Current hypothyroid state
• Medically unstable including symptoms of delirium
• History of sensitivity to sertraline
• Pregnant or breastfeeding

Interventions
Experimental: sertraline 12.5 mg/d for 3 days, increased to 25 mg/d for 4 days, then 50 mg/day for 7 days, then increased to 75 mg/day. Target dose = 75 mg per day for the remainder of participation in the study
Comparator: matched placebo

Outcomes
Primary outcome collected at 12 months
• Major depression at 12 months

Secondary outcomes collected at 12 months:
• Severity of depressive symptoms post-stroke as measured by the HDRS
NCT00177424

(Continued)

- Level of disability as measured by the FIM

Funding source
None stated

Notes
Terminated (recruitment goals could not be met). Last update 27 June 2014

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement</td>
</tr>
</tbody>
</table>

NCT01674868

Study characteristics

Methods
Study type: interventional (clinical trial)
Intervention model: parallel assignment
Primary purpose: treatment

Participants
0 participants (aimed to recruit 25 participants)
Country: USA
Setting: inpatient
At randomisation number allocated: 0
% male: not available
Age: not available
Subtype of stroke: not available
Severity of stroke: not available
Time since stroke onset: not available

Inclusion criteria
- Ischaemic infarction within 15 days
- Admission NIHSS item 5 score ≥ 2
- Able to give informed consent, with surrogate consent acceptable

Exclusion criteria
- Pre-stroke mRS score equal or ≥ 3
- Pregnant or lactating
- Taking an SSRI on admission
- Taking a medication likely to have adverse interaction with an SSRI
- Unable to return for follow-up testing days 90, 180
- Concurrent medical condition likely to worsen patient’s functional status over next 6 months
- Unable to competently participate in testing for 45 minutes to 2 hours with rest breaks
- for MRI substudy: contraindication to MRI

Interventions
Experimental: fluoxetine 20 mg daily for 90 days starting day 5 to 10 after stroke
Comparator: placebo participants will take 1 placebo pill daily for 90 days

Outcomes
Primary outcome measure
- FMMS (baseline to 90 days, baseline to 180 days)

Secondary outcome measures
- Western Aphasia Battery (baseline to 90 days)
- Behavioral Inattention Test (baseline to 90 days, baseline to 180 days)
- FIM (baseline to discharge)
- Fatigue Severity Scale (baseline to 90 days, baseline to 180 days)
- BDI (baseline to 90 days, baseline to 180 days)
- Western Aphasia Battery (baseline to 180 days)
- mRS (baseline to 90 days, baseline to 180 days)

Funding source
Not stated

Notes
NCT01674868
Withdrawn: unable to find patients meeting inclusion/exclusion criteria
Dates study conducted: April 2013 to December 2015 (estimated completion date)
Declarations of Interest: none reported

Risk of bias

<table>
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<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<td>Random sequence generation (selection bias)</td>
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<td>Withdrawn: unable to find patients meeting inclusion/exclusion criteria</td>
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<tr>
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<td>Withdrawn: unable to find patients meeting inclusion/exclusion criteria</td>
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Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
**NCT01674868** (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Withdrawn: unable to find patients meeting inclusion/exclusion criteria</td>
</tr>
<tr>
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<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Withdrawn: unable to find patients meeting inclusion/exclusion criteria</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Withdrawn: unable to find patients meeting inclusion/exclusion criteria</td>
</tr>
<tr>
<td>All outcomes</td>
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<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Withdrawn: unable to find patients meeting inclusion/exclusion criteria</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Withdrawn: unable to find patients meeting inclusion/exclusion criteria</td>
</tr>
</tbody>
</table>

**NCT02737930**

**Study characteristics**

**Methods**
RCT

**Participants**
Acute stroke
18 Years to 85 years
MRI-confirmed acute ischaemic stroke resulting in an isolated homonymous visual field loss
17 enrolled up to August 2020. No results published

**Interventions**
Fluoxetine 20mg for 90 days or matching placebo

**Outcomes**
Improvement in size of visual field deficit (degrees) (primary outcome)
Secondary outcomes: improvement in size of visual field deficit (square degrees), Improvement in parametric mean deviation
Functional field score
Visual Function Questionnaire-25 score
Patient Health Questionnaire-9 score
mRS score
Post-stroke changes in cortical visual representation as measured by functional MRI
Post-stroke changes in retinal nerve fibre layer thickness

**Funding source**
Bogachan Sahin

**Risk of bias**
NCT02737930 (Continued)

Random sequence generation (selection bias)
Unclear risk
No published data

Allocation concealment (selection bias)
Unclear risk
No published data

Pan 2018

Study characteristics

Methods
Study type: interventional (clinical trial)
Primary purpose: treatment

Participants
170 participants
Country: China
Setting: inpatient
At randomisation number allocated: 170, paroxetine (n = 85); usual care (n = 85)
% male: paroxetine (71.8); usual care (unclear)
Age: mean age paroxetine = 65.6 ± 7.56; placebo = unclear
Subtype of stroke: not stated.
Severity of stroke: NIHSS, Median (IQR): paroxetine 8 (6 – 10); usual care (unclear)
Time since stroke onset: within 1 week
Inclusion criteria
• Age between 50 and 80 years old
• Diagnostic criteria met (Fourth National Cerebrovascular Disease Conference) and confirmation by MRI
• Ability to participate in assessments within 1 week of stroke onset
• FMMS score of < 55 points
• MoCA score of < 26 points
Exclusion criteria
• NIHSS score > 20 points
• Aphasia
• History of pre-stroke depression and taken antidepressants or benzodiazepines
• HAMD score > 7 points
• Receipt of thrombolytic therapy
• Complications such as infection, bed sores, or heart failure that might affect rehabilitation
Withdrawal criteria: not stated

Interventions
Experimental: orally administrated paroxetine at dosages of 10 mg/day during week 1 and 20 mg/day thereafter, for a total treatment duration of 3 months
Comparator: usual care

Outcomes
Outcomes were collected at 15, 90 and 180 days
• Movement assessed using FMMS
• Cognitive impairment assessed using the MoCA
• Depression assessed using HAMD

Funding source
No grant funding from any grant funding agency, commercial or not-for-profit organisations

Notes
There is no study protocol/trial register reference
Baseline sociodemographic and clinical characteristics are provided only for those who completed the study
The authors state that one of the inclusion criteria is MOCA score of < 26 points. In the Results section they state that there were "72 cases of cognitive impairment" (i.e., a MoCA score of < 26 points) in the comparator group and 82 in the experimental group at days 15, 90 and 180. This suggests that either that the inclusion criteria were not strictly adhered to or if 100% of participants had a MoCA score of < 26 points at baseline then 10/82 participants in the comparator group and 3/85 in the experimental group have improved on the MoCA between days 0 and 15.

Dates study conducted: participants recruited between January 2012 and June 2014
Declarations of interest: none reported

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Random number table&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information to judge high or low</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient information to judge high or low</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: &quot;All scale evaluators were trained and tested by the main investigator and were blind to the group assignment.&quot;</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>All data available for all participants in the experimental group (n = 85/85) and data available for (n = 82/85) participants in the comparison group for the Fugl–Meyer Motor Scale and the HAMD score For the MoCA (see 'Other bias' below) &lt; 5% overall loss to follow-up</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>There is no study protocol/trial register reference, so insufficient information to judge high or low</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>The authors state that one of the inclusion criteria is Montreal Cognitive Assessment (MoCA) score of &lt; 26 points. In the Results section they state that there were &quot;72 cases of cognitive impairment&quot; (i.e., a MoCA score of &lt; 26 points) in the comparator group and 82 in the experimental group at days 15, 90 and 180. This suggests that either that the inclusion criteria were not strictly adhered to or, if 100% of participants had a MoCA score of &lt; 26 points at baseline then 10/82 participants in the comparator group and 3/85 in the experi-</td>
</tr>
</tbody>
</table>
mental group have improved on the MoCA between days 0 and 15. The results 'Comparison of MoCA scores' and table 3 suggests otherwise

Pan 2018 (Continued)

Pariente 2001

Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Prospective double-blind cross-over placebo-controlled study of 8 people with pure motor hemiparesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Lacunar ischaemic stroke, assessed by brain CT</td>
</tr>
<tr>
<td>Quote</td>
<td>&quot;Early phase of recovery&quot;</td>
</tr>
<tr>
<td>Interventions</td>
<td>Single dose of fluoxetine</td>
</tr>
<tr>
<td>Outcomes</td>
<td>fMRI (raw data provided)</td>
</tr>
<tr>
<td></td>
<td>Finger tapping (presented as a graph, no raw data)</td>
</tr>
<tr>
<td></td>
<td>NIHSS, motoricity index, BI, trunk control test, Ashworth Scale, somatosensory scale (no data)</td>
</tr>
<tr>
<td>Funding source</td>
<td>Source of funding not stated</td>
</tr>
<tr>
<td>Notes</td>
<td>We could not use these data in our meta-analyses. The authors reported that fluoxetine led to hyper-activation in the ipsi-lesional (i.e. on the same side as the stroke lesion) primary motor cortex during a motor task; moreover, fluoxetine significantly improved motor skills of the affected side</td>
</tr>
<tr>
<td></td>
<td>Dates of recruitment not given. Conflicts not stated</td>
</tr>
</tbody>
</table>

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Randomisation code kept at the centre and broken at the end of the study</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Randomisation code kept at the centre and broken at the end of the study</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Double-blind, placebo given</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Double-blind</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Data on fMRI appears complete</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Data on clinical outcomes were not reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Balanced baseline</td>
</tr>
</tbody>
</table>
### Rasmussen 2003

#### Study characteristics

| Methods | Parallel design  
Analysis: ITT (last observation carried forward) and per-protocol: details of those excluded from analyses (35 treatment, 35 control) unclear |
|---------|---------------------------------------------------------------|
| Participants | Location: Denmark  
Setting: unclear  
Treatment: 70 people, mean ± SD age 72 ± 9, 50% men  
Control: 67 people, mean ± SD age 68 ± 11, 51% men  
Stroke criteria: ischaemic and PICH; diagnosis by clinical signs and symptoms; stroke 0 to 4 weeks prior to randomisation  
Other entry criteria: not stated  
Comparability of treatment groups: participants in treatment group older on average |
| Interventions | Treatment: sertraline 50 mg daily; at any time after 2 weeks dose could be increased in 50 mg increments up to 150 mg daily; average dose 62.9 mg daily  
Control: matched placebo  
Duration of treatment: 12 months  
Duration of follow-up (end of treatment to end of study): 0 |
| Outcomes | Depression: change in scores from baseline to end of treatment on HDRS  
Proportion scoring > 2 on the CGI or > 16 on the GDS at end of treatment  
Additional: leaving the study early. Did not report death  
Unable to use: HDRS, GDS, aphasia severity rating scale, European Stroke Scale, MMSE, Cambridge Cognitive Examination, SF-36, BI (data not presented)  
AEs (detailed data not presented) evaluated by using the Udvalg for Kliniske Undersogelser Side Effect Rating Scale  
Did not report death |
| Funding source | Funding from Pfizer A/S, Gert Jorgensen legat and the Brain Cause. It is unclear whether the drug companies had input into the design and analysis of the study |
| Notes | Recruitment January 1996 to May 1998. Conflicts not stated |

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method not stated</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Method not stated</td>
</tr>
</tbody>
</table>
### Rasmussen 2003 (Continued)

<table>
<thead>
<tr>
<th>Blinding of participants and personnel (performance bias) All outcomes</th>
<th>Low risk</th>
<th>Matched placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not stated</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>No data on patients who dropped out. Used ITT analysis and last observation carried forward</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Trial details published on <a href="http://www.strokecentre.org/trials">www.strokecentre.org/trials</a></td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Those given sertraline were slightly older (by 4 years) but this is unlikely to introduce bias. There was no significant difference between groups</td>
</tr>
</tbody>
</table>

### Razazian 2014

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type: interventional (clinical trial)</td>
</tr>
<tr>
<td>Primary purpose: treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>172 participants</td>
</tr>
<tr>
<td>Country: Iran (Islamic Republic of)</td>
</tr>
<tr>
<td>Setting: inpatient</td>
</tr>
<tr>
<td>At randomisation number allocated: fluoxetine n = 86; placebo n = 86</td>
</tr>
<tr>
<td>% male: unclear</td>
</tr>
<tr>
<td>Age: fluoxetine group = unclear; placebo = unclear</td>
</tr>
<tr>
<td>Subtype of stroke: not available</td>
</tr>
<tr>
<td>Severity of stroke: not available</td>
</tr>
<tr>
<td>Time since stroke onset: not available</td>
</tr>
<tr>
<td>Inclusion criteria</td>
</tr>
<tr>
<td>• Middle cerebral artery stroke (documented with imaging)</td>
</tr>
<tr>
<td>• Hemiplegia, monoplegia or paresis</td>
</tr>
<tr>
<td>• No coma</td>
</tr>
<tr>
<td>• Consent</td>
</tr>
<tr>
<td>• Suitable for discharge</td>
</tr>
<tr>
<td>• Not admitted to Intensive care unit</td>
</tr>
<tr>
<td>Exclusion criteria</td>
</tr>
<tr>
<td>• Death from any cause during study</td>
</tr>
</tbody>
</table>
Razazian 2014 (Continued)

- Irregular use of drugs
- Irregular return for re-examinations
- Seizures
- Severe diarrhoea, vomiting.
- Severe insomnia
- Metabolic disorder
- History of psychiatric disorder or severe depression prior to stroke
- SAH, lobar ICH, brain tumour or stroke in other vascular territories
- Use of any MAOI, selegiline, cyproheptadine

Withdrawal criteria: not stated

Interventions
Experimental: fluoxetine, 20 mg once a day for 90 days
Comparator: placebo fluoxetine for 90 days
All participants received 30 sessions of routine physiotherapy during the rehabilitation period

Outcomes
Primary outcomes collected at day 45 and day 90
- Motor deficit (BI)
- Psychiatric disorder (HDRS)

Funding source
Kermanshah University of Medical Sciences

Notes
IRCT201312088323N7
Baseline demographic and clinical characteristics for each group not presented, but rather the baseline demographic and clinical characteristics for those completing the trial (i.e. a subset of all those randomised at baseline) are presented
Dates study conducted: participants recruited between June 2013 and September 2014
Declarations of Interest: none reported

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Random sequence generation (selection bias) | Unclear risk       | Quote: "random permuted blocks"
Comment: insufficient information about the block randomisation to permit judgement |
| Allocation concealment (selection bias)   | Unclear risk       | Insufficient information to permit judgement of high or low                            |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk           | Quote: "placebo that was identical to the active drug in appearance and packaging"     |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk       | Insufficient information to permit judgement of high or low                            |
| Incomplete outcome data (attrition bias) All outcomes | High risk          | 13% attrition at 90 days. 13% (n = 11/86) from the experimental group and 13% (n = 11/86) from the comparator group were excluded form the full set analysis at 90 days follow-up. Reasons for attrition reported |
### Razazian 2014 (Continued)

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Low risk</th>
<th>Protocol available and all the study's prespecified outcomes that are of interest to the review have been reported in a prespecified way</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>The baseline data presented in table 1: patients demographic characteristics and risk factors and not true baseline characteristics (i.e. at randomisation). The data presented in table 1 are the characteristics of the full analysis set which is a subgroup of all participants randomised. We cannot tell if there is whether there was any baseline imbalance in important demographic or clinical characteristics</td>
</tr>
</tbody>
</table>

### Restifo 2001

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Double-blind study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>10 participants with disabling hemiplegia owing to hemispheric ischaemic stroke in territory of left MCA</td>
</tr>
<tr>
<td>Interventions</td>
<td>Treatment: fluoxetine 20 mg daily for 3 months plus usual care (including Bobath rehabilitation)</td>
</tr>
<tr>
<td></td>
<td>Control: usual care including Bobath rehabilitation</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Transmagnetic stimulation to establish motor reorganisation</td>
</tr>
<tr>
<td></td>
<td>The authors reported that fluoxetine might modulate the primary motor cortex reorganisation</td>
</tr>
<tr>
<td>Funding source</td>
<td>Source of funding not stated</td>
</tr>
<tr>
<td>Notes</td>
<td>Abstract only, full paper could not be found by our searches. Dates of study and conflicts of interest not stated</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;Random allocation&quot;; method not described</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;Random allocation&quot;; method not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>A placebo was used, not clear if it was matching</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Unclear from abstract</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Unclear from abstract</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Unclear from abstract</td>
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### Other bias

<table>
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<th>Support for judgement</th>
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<tr>
<td>Unclear risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear from abstract</td>
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### Robinson 2000a

#### Study characteristics

**Methods**
- Parallel design
- Comparison of fluoxetine, nortriptyline and placebo. We are using the fluoxetine and placebo data
- Analysis: per protocol, number excluded from analyses varied
- Data provided for depressed and non-depressed separately. We are labelling the depressed group as Robinson 2000a (this trial), and the non-depressed group as Robinson 2000b

**Participants**
- Location: USA and Argentina
- Setting: mixed
- Treatment: 23 people with depression, mean ± SD age 65 ± 14 years; 17 men
- Control: 17 people with depression, mean ± SD age 73 ± 10 years; 9 men
- Stroke criteria: all subtypes, diagnosis by clinical signs and CT (100%), stroke within 6 months of recruitment, 18 to 85 years of age
- Stroke on average 16 weeks (fluoxetine) and 6 weeks (placebo) prior to randomisation
- Exclusion criteria: other significant medical illness, severe comprehension deficit, prior history of head injury, prior history of other brain disease (with the exception of stroke), participants on antidepressants (other than fluoxetine) were allowed to stop their antidepressant for a 2-week washout period

**Interventions**
- Treatment: fluoxetine 10 mg daily (3 weeks), 20 mg daily (3 weeks), 30 mg daily (3 weeks), 40 mg daily (3 weeks)
- Control: matched placebo
- Duration: treatment continued for 12 weeks
- Duration of follow-up (end of treatment to end of study): 0

**Outcomes**
- Depression: change in scores from baseline to end of treatment on HDRS
- Additional: MMSE, JHFI
- Death
- AEs (method of reporting these was not stated)

**Funding source**
- Funded by NIMH grants and grants from the Raul Carrea Institute of Neurological Research and Fundación Perez Companc. Eli Lilly and company supplied the fluoxetine and placebo

**Notes**
- Note difference in time since stroke between treatment groups
- Dates of recruitment not stated. Conflicts not stated

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
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### Robinson 2000a (Continued)

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<th>Description</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Random-number table</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Concealment held by independent person</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Matched placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Not stated</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Per-protocol and ITT analyses</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Protocol published <a href="http://www.strokecentre.org/trials">www.strokecentre.org/trials</a></td>
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<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Imbalance in treatment groups for time since stroke and gender</td>
</tr>
</tbody>
</table>

### Robinson 2000b

#### Study characteristics

**Methods**

- Parallel design
- Comparison of fluoxetine, nortriptyline and placebo. We are using the fluoxetine and placebo data
- Analysis: per protocol, number excluded from analyses varies
- Data provided for depressed and non-depressed separately. We are labelling the depressed group as Robinson 2000a, and the non-depressed group as Robinson 2000b (this trial)

**Participants**

- Location: USA and Argentina
- Setting: mixed
- Treatment: 17 non-depressed people, mean ± SD age 66 ± 13 years, 15 men
- Control: 16 non-depressed people, mean ± SD age 67.9 years, 12 men
- Stroke criteria: all subtypes, diagnosis by clinical signs and CT (100%), stroke within 6 months of recruitment, aged 18 to 85 years of age
- Stroke on average 8 weeks (treatment) and 5 weeks (control) prior to randomisation
- Comparability of treatment groups: unclear
  - Exclusion criteria: other significant medical illness, severe comprehension deficit, prior history of head injury, prior history of other brain disease (with the exception of stroke), participants on antidepressants (other than fluoxetine) were allowed to stop their antidepressant for a 2-week washout period

**Interventions**

- Treatment: fluoxetine 10 mg daily (3 weeks), 20 mg daily (3 weeks), 30 mg daily (3 weeks), 40 mg daily (3 weeks)
Robinson 2000b  (Continued)

Control: matched placebo
Duration: treatment continued for 12 weeks
Duration of follow-up (end of treatment to end of study): 0

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Depression: change in scores from baseline to end of treatment on HDRS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Additional: MMSE, JHFI</td>
</tr>
<tr>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>AEs (method of reporting these was not stated)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funded by NIMH grants and grants from the Raul Carrea Institute of Neurological Research and Fundación Pérez Compancc. Eli Lilly and company supplied the fluoxetine and placebo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Note difference in time since stroke between groups</td>
</tr>
<tr>
<td>Dates of recruitment not stated. Conflicts of interest not stated</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Random-number table</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Concealment held by independent person</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Matched placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Not stated</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>ITT and per-protocol</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Trial on <a href="http://www.strokecentre.org/trials">www.strokecentre.org/trials</a></td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Note imbalance in time since stroke and in gender</td>
</tr>
</tbody>
</table>

Robinson 2008

### Study characteristics

Methods

Parallel group, 3-arm (escitalopram, placebo, problem-solving therapy group). We are using the escitalopram versus placebo arm in this review

Analysis: ITT
Participants
Country: USA
Setting: mixed: neurology department and newspaper advertisements
Stroke criteria: ischaemic or haemorrhagic stroke not because of complications of intracranial aneurysm or intracranial vascular malformation; within 3 months of index stroke
Mood: excluded if DSM IV for major or minor depression or HAMD > 17
Treatment (escitalopram): 59 people, mean ± SD age 61.2 ± 13.7, 38 men
Control (matched placebo): 58 people, mean ± SD age 63.9 ± 11.1, 37 men
Exclusion: acute coronary syndrome, neurodegenerative disorders, DSM IV criteria for alcohol or substance abuse

Interventions
Treatment: escitalopram 5 mg to 10 mg (depending on age - lower dose given to > 65 years old)
Control: matched placebo
Duration of treatment: 12 months
Duration of follow-up (treatment end to study end): 0

Outcomes
Diagnosis of depression
HAMD (dichotomised)
FIM (though no raw data provided in the paper for meta-analysis)
Social functioning examination
Repeatable Battery for Neuropsychological Status
The Iowa subset provided detailed information about cognition
Participants, family members and primary care physicians were asked about AEs at 3 monthly intervals or sooner if an individual reported an AE using a standardised checklist

Funding source
The initial report states that “This work was supported solely by National Institute of Mental Health Grant R01MH-65134. All the study medications were purchased using NIMH grant funds.” In a subsequent letter to the Journal, the authors disclosed honoraria and expenses from pharmaceutical companies, and that 1 of the authors owned Pfizer stock. However, the authors stated that the design and analysis of any of the expenses of the study were supported by monies, materials or any intellectual input from Forest Laboratories

Notes
The escitalopram group had significantly more diabetes than the placebo group
Financial disclosures: see above
Recruitment: 9 July 2003 to 1 October 2007

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Randomised blocks of 3, 6, and 9</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
</tbody>
</table>

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)
Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Robinson 2008 (Continued)

<table>
<thead>
<tr>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Low risk</th>
<th>Identical placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Low risk</th>
<th>Outcome assessors were blinded</th>
</tr>
</thead>
<tbody>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incomplete outcome data (attrition bias)</th>
<th>Low risk</th>
<th>ITT analyses, all participants used in analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>All outcomes</td>
<td></td>
<td>Dropouts: 5 in placebo and 7 drop-outs in escitalopram</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Low risk</th>
<th>All specified outcome data reported. Trial published on <a href="http://www.strokecentre.org/trials">www.strokecentre.org/trials</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>There was more diabetes in the escitalopram group than placebo group</td>
</tr>
</tbody>
</table>

### Savadi Oskouie 2012

**Study characteristics**

**Methods**
- Study type: interventional (clinical trial)
- Primary purpose: treatment

**Participants**
- 144 participants
  - Country: Islamic Republic of Iran
  - Setting: inpatient
  - At randomisation number allocated: N = 144; citalopram (n = 72); placebo (n = 72)
  - % male at baseline: citalopram n = unclear; placebo n = unclear
  - Age at baseline: citalopram (n = unclear); placebo (n = unclear)
  - Subtype of stroke at baseline: unclear
  - Severity of stroke at baseline: unclear
  - Time since stroke onset: within 7 days

**Inclusion criteria**
- Acute ischaemic stroke
- No previous use of citalopram or other antidepressants in the month prior to stroke onset
- Pre-stroke NIHSS < 20
- No depression MADRS > 18

**Exclusion criteria**
- Request of patients to leave the study
- Previous chronic disease likely to interfere with assessment of effects of citalopram including: chronic infections, liver or kidney failure, cancer
- Previous stroke-related disability
- Pregnancy or breastfeeding or any conditions that makes follow-up impossible
Savadi Oskouie 2012 (Continued)

- Severe loss of consciousness
- Thrombolytic therapy
- Endarterectomy
- Depression (MADRS > 18)

Withdrawal criteria: not stated

Interventions

Experimental: oral citalopram 20 mg once daily  
Comparator: placebo

Outcomes

Primary outcome
- 50% reduction in NIHSS score at 3 months compared to baseline

Secondary outcome
- mRS score at 3 months
- 50% reduction in NIHSS (motor) score at 3 months compared to baseline
- 50% reduction in NIHSS (language) score at 3 months compared to baseline
- Mortality

Funding source

Neurosciences Research Center (NSRC) of Tabriz University of Medical Sciences

Notes

IRCT201203192150N2

Baseline demographic and clinical characteristics for each group not presented, rather the baseline demographic and clinical characteristics for those completing the trial (i.e. a subset of all those randomised at baseline) are presented

Dates study conducted: May 2012 to January 2014

Declarations of interest: none reported

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;A total of 144 patients were randomized through an allocation sequence based on 2 blocks with size of 72, generated with a computer random number generator.&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Allocation was concealed using the sequentially numbered black envelopes.&quot;</td>
</tr>
</tbody>
</table>
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk       | Not explicitly stated that key study personnel and care providers were blinded, although implied by:  
Quote: "The blinding code remained confidential until the end of the study."  
Quote: "placebo of the same shape and full packaging during the first day after hospital admission." |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk       | Not explicitly stated that outcome assessors were blinded, although perhaps implied by the fact:  
Quote: "The blinding code remained confidential until the end of the study." |
| Incomplete outcome data (attrition bias) All outcomes | High risk          | Primary outcome data were available for 58 (81%) of the citalopram group and 50 (69%) of the placebo group. Reasons for attrition are reported but there are differences between groups: number of participants in the placebo group (n =
11) dead compared to the citalopram group (n = 4). 3 times the number of participants in the placebo group were depressed (n = 6) compared to the citalopram group (n = 2). Did not want to continue (placebo group (n = 5), citalopram group (n = 8)

Intention-to-treat analyses were carried out (suppl table) assuming that 1. those lost to follow-up had a poor outcome (i.e. did not improve their NIHSS scores from baseline) and 2. those participants in the placebo group who did not want to continue had a good outcome

Overall loss of > 5%

| Selective reporting (reporting bias) | Low risk | The study protocol is available and all the study's prespecified (primary outcomes and secondary outcomes) that are of interest in the review have been reported in the prespecified way |
| Other bias | High risk | The baseline data presented in table 1: comparison of demographic and baseline variables and not true baseline characteristics (i.e. at randomisation). The data presented in table 1 are the characteristics of the full analysis set at 3 months which is a subgroup of all participants randomised. We cannot tell if there is whether there were any baseline imbalance in important demographic or clinical characteristics. However, given that approximately 3 times the number of participants in the placebo group (n = 11) died compared to the citalopram (n = 4) and 3 times the number of participants in the placebo group were depressed (n = 6) compared to the citalopram group (n = 2), this suggests that there may have been important group differences in clinical characteristics at baseline |

Shah 2016

**Study characteristics**

| Methods | Study type: interventional (clinical trial) |
|         | Primary purpose: supportive care |
| Participants | 89 participants |
| Country: India |
| Setting: inpatient |
| At randomisation number allocated: N = 89: fluoxetine (n = 45); placebo (n = 44) |
| % male: unclear |
| Age: unclear |
| Subtype of stroke: unclear |
| Severity of stroke: unclear |
| Time since stroke onset: within 5 to 10 days |
| Inclusion criteria |
| • Age 18 to 80 years old |
| • Patients who had an acute ICH within the past 5 to 10 days causing hemiparesis or hemiplegia |
| • FMMS scores of 55 or less |
Shah 2016 (Continued)

Exclusion criteria

- NIHSS score > 20
- Diagnosis of depression MADRS score > 19 points
- Premorbid disability, evidenced by residual motor deficit from a previous stroke
- Use of neuroleptic drugs or benzodiazepines 4 weeks before inclusion
- Other life-threatening illnesses that would prevent follow-up
- Pregnancy

Withdrawal criteria: not stated

Interventions

Experimental: fluoxetine 20 mg orally once daily for 90 days
Comparator: matching placebo orally once daily for 90 days

Outcomes

Primary outcome

- FMMS score (baseline and 90 days): change from baseline in FMMS score at 90 days

Funding source

Not stated

Notes

Baseline demographic and clinical characteristics for each group not presented, rather the baseline demographic and clinical characteristics for those completing the trial (i.e. a subset of all those randomised at baseline) are presented

Dates study conducted: January 2014 to January 2015

Declarations of Interest: none reported

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information about the sequence generation process to permit judgement of high or low</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information about the method of allocation concealment to permit judgement of high or low</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Quote: “Patients, attendants, study staff and investigators were masked to treatment allocation.” However, “matching was done on a 1:1 basis for age, sex, severity of stroke”, which suggests that some key study personnel were not blinded and this non-blinding is likely to introduce bias</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement of high or low</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>3/45 (7%) participants in the fluoxetine and 2/44 (5%) in the placebo group were lost to follow-up. Reasons for attrition/exclusion not reported. 6% lost to follow-up</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No study protocol available. Insufficient information to permit judgement of high or low</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>The use of matching suggests a matched case control design rather than an RCT design</td>
</tr>
</tbody>
</table>
Shah 2016 (Continued)

We cannot tell whether there was any baseline imbalance in important demographic or clinical characteristics.

Song 2006

Study characteristics

Methods

Aim: to evaluate changes in depression and cognitive impairment in people with post-stroke depression treated with fluoxetine
Parallel trial

Participants

Country: China
Setting: inpatient
Stroke diagnosed by clinical criteria and "proved on CT" (though not clear if lesion had to be visible)
Depression: diagnosed in accordance with the CCMD-II-R
Treatment: 41 people, mean age 51 ± 7 years, 25 men), time since stroke: 3.5 days
Control: 41 people, mean age 50 ± 8 years, 24 men), time since stroke: 3.7 days
Excluded: previous mental disorders, previous "neurological disorder", if other psychiatric drugs had been taken, these had to be stopped for 1 week before fluoxetine was administered

Interventions

Treatment: fluoxetine 20 mg daily
Control: placebo (although not stated whether this was identical to fluoxetine)
Duration of treatment: 6 weeks
Duration of follow-up (treatment end to study end): 0
Side effects not reported

Outcomes

SDS
P300 (an event-related potential)
Although the stated aim was to assess cognitive impairment, it is not clear how this was measured

Funding source

Source of funding not stated

Notes

Recruitment: December 1999 to June 2003. Conflicts of interest not stated

Risk of bias

Bias

Authors' judgement
Support for judgement

Random sequence generation (selection bias)
Unclear risk
Method not described

Allocation concealment (selection bias)
Unclear risk
Not described

Blinding of participants and personnel (performance bias)
Unclear risk
Placebo, but not clear whether identical
**Song 2006 (Continued)**

### Study characteristics

**Methods**

- Parallel design

- 3-arm trial: routine care, fluoxetine plus routine care, amitriptyline plus routine care. We are using the routine care and fluoxetine plus routine care in this analysis

- Aim: to observe effects of antidepressant therapy on post-stroke and neurological rehabilitation in the elderly

**Participants**

- Country: China

- Setting: inpatient

- Stroke criteria: ischaemic stroke, clinical diagnosis plus confirmation by imaging (although not clear whether a stroke lesion had to be present)

- Depression diagnosed according to CCMD-II-R diagnostic criteria, HAMD ≥ 18

- Treatment: 64 people, mean age 75.6 ± 19.7 years, 39 men

- Control: 56 people, mean age 74.9 ± 20.8 years, 29 men

- Excluded: psychiatric disorder history, severe cardiac, pulmonary, hepatic and renal diseases

**Interventions**

- Treatment: fluoxetine 20 mg to 80 mg daily (start at 20 mg/day, increase dosage at 3 weeks if poor therapeutic effect and no AE), plus usual stroke care

- Control: usual stroke care

- Duration of treatment: 12 to 24 weeks

- Duration of follow-up (treatment end to study end): 6 to 9 months

**Outcomes**

- HAMD

- Neurological function impairment score

- BI

- AEs not recorded

---

**Wang 2003**

**Methods**

- Parallel design

- 3-arm trial: routine care, fluoxetine plus routine care, amitriptyline plus routine care. We are using the routine care and fluoxetine plus routine care in this analysis

- Aim: to observe effects of antidepressant therapy on post-stroke and neurological rehabilitation in the elderly

**Participants**

- Country: China

- Setting: inpatient

- Stroke criteria: ischaemic stroke, clinical diagnosis plus confirmation by imaging (although not clear whether a stroke lesion had to be present)

- Depression diagnosed according to CCMD-II-R diagnostic criteria, HAMD ≥ 18

- Treatment: 64 people, mean age 75.6 ± 19.7 years, 39 men

- Control: 56 people, mean age 74.9 ± 20.8 years, 29 men

- Excluded: psychiatric disorder history, severe cardiac, pulmonary, hepatic and renal diseases

**Interventions**

- Treatment: fluoxetine 20 mg to 80 mg daily (start at 20 mg/day, increase dosage at 3 weeks if poor therapeutic effect and no AE), plus usual stroke care

- Control: usual stroke care

- Duration of treatment: 12 to 24 weeks

- Duration of follow-up (treatment end to study end): 6 to 9 months

**Outcomes**

- HAMD

- Neurological function impairment score

- BI

- AEs not recorded
**Wang 2003** (Continued)

<table>
<thead>
<tr>
<th>Funding source</th>
<th>Source of funding not stated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notes</td>
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</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method not described</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>13 dropped out of fluoxetine group, and 9 dropped out of control group</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Baseline appeared balanced but no statistical comparison between groups</td>
</tr>
</tbody>
</table>

**Wang 2009**

**Study characteristics**

| Methods | Aim: to investigate the efficacy of paroxetine in the treatment of post-stroke depression  
Parallel RCT design. Placebo-same appearance as paroxetine |
|---------|-----------------------------------------------------------------------------------------------|
| Participants | Diagnosis of stroke: all patients underwent CT or MRI examination, and the diagnosis was in accordance with the Chinese diagnostic criteria formulated by the Second National Conference of Cerebrovascular Disease in 1986;  
Depression diagnosis: HAMD ≥ 18, SDS (self-rating depression scale) ≥ 50  
Excluded: patients with medical history of mental illness, aphasia, epilepsy, glaucoma and drug allergy before stroke or used other antipsychotics or antidepressants in the past 2 weeks |
| Interventions | The treatment group was given paroxetine 20mg/day in the morning, which could be increased to 40 mg/day according to the condition, for a total of 2 months; the control group was given placebo with the same appearance. No other antipsychotics were used during the study period and benzodiazepines were given to patients with severe insomnia |
| Outcomes | HAMD |
**Wang 2009**  (Continued)

<table>
<thead>
<tr>
<th>AEs</th>
</tr>
</thead>
</table>

**Funding source**  Unclear

**Notes**  The data in Table 2 were different to the data in the Results section. Possibly the data of treatment group were mistakenly listed for the control group. Thus there is a high risk of incorrect data reporting

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
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<td>Unclear risk</td>
<td>No information provided</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
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<td>No information provided</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>No information provided</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>No information provided</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>No information provided</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No information provided</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No information provided</td>
</tr>
</tbody>
</table>

### Wen 2006

**Study characteristics**

**Methods**  Parallel trial

Aim: to explore effects of prophylactic anti-depression therapy on nerve functional rehabilitation after stroke

Analysis: according to treatment group

**Participants**  Country: China

Setting: inpatient

Stroke criteria: acute stroke of all pathological subtypes, clinical diagnosis plus confirmation by imaging (although not clear whether a stroke lesion had to be present)

Treatment: 42 people, mean age 56.8 years, men 19

Control: 42 people, mean age 57.2 years, men 16
### Wen 2006 (Continued)

Excluded those with primary psychiatric impairment and premorbid mood disorders, pre-existing neurological disease causing confusion, severe systematic diseases and pulmonary, hepatic and renal failure.

#### Interventions

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Treatment: fluoxetine 20 mg daily plus routine stroke care</th>
<th>Control: routine stroke care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duration of treatment: 8 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration of follow-up (end of treatment to end of study): 0</td>
<td></td>
</tr>
</tbody>
</table>

#### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>HAMD</th>
<th>MESSS</th>
<th>AEs (method of obtaining data not stated)</th>
<th>Death</th>
</tr>
</thead>
</table>

#### Funding source

Source of funding not stated

#### Notes

−

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method not described</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Analysed according to treatment group, no dropouts</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Balanced baseline</td>
</tr>
</tbody>
</table>

### Wiart 2000

#### Study characteristics

Purpose: to treat early depression
Wiart 2000 (Continued)

Parallel design

Analysis: ITT (last observation carried forward), withdrawn owing to AE (1 treatment), protocol violation (1 treatment)

<table>
<thead>
<tr>
<th>Participants</th>
<th>Location: France</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting: unclear</td>
<td></td>
</tr>
<tr>
<td>Treatment: 16 people, mean ± SD age 66 ± 7 years, 65% men</td>
<td></td>
</tr>
<tr>
<td>Control: 15 people, mean ± SD age 66 ± 12 years, 40% men</td>
<td></td>
</tr>
<tr>
<td>Stroke criteria: ischaemic stroke and PICH, diagnosis by clinical signs and CT (100%); stroke on average 47 ± 22 days (treatment group) and 48 ± 20 days (control group)</td>
<td></td>
</tr>
<tr>
<td>Depression criteria: psychiatric interview (ICD-10 criteria) and MADRS score &gt; 19</td>
<td></td>
</tr>
<tr>
<td>Other entry criteria: all antidepressant or neuroleptic drugs stopped 10 days prior to enrolment</td>
<td></td>
</tr>
<tr>
<td>Comparability of treatment groups: balanced</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: severe psychiatric problems which required hospitalisation, severe aphasia, previous stroke, severe cognitive impairment, chronic alcoholism, chronic associated handicapping pathology, contraindication to fluoxetine</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Treatment: fluoxetine 20 mg daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control: matched placebo</td>
<td></td>
</tr>
<tr>
<td>Duration of treatment: 45 days</td>
<td></td>
</tr>
<tr>
<td>Duration of follow-up (treatment end to study end): 0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Depression: change in scores from baseline to end of treatment of MADRS, 50% reduction in MADRS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional: FIMs</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
</tr>
<tr>
<td>Motricity Index</td>
<td></td>
</tr>
<tr>
<td>Leaving the study early</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>AEs (&quot;evaluated qualitatively and quantitatively&quot;. Complete blood count, liver test and renal function test were carried out at each assessment visit)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Funding source</th>
<th>Lilly France Laboratory provided methodological and financial support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notes</td>
<td>Dates of recruitment not stated. Conflicts of interest not stated</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method of randomisation not stated</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Method not stated</td>
</tr>
</tbody>
</table>
**Wiart 2000 (Continued)**

<table>
<thead>
<tr>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Low risk</th>
<th>Quote: &quot;Identical white capsules&quot; given</th>
</tr>
</thead>
<tbody>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Method of blinding not stated</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Used last observation carried forward; 2/31 (both in fluoxetine group) dropped out. This is &gt; 5%</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Trial published on <a href="http://www.strokecentre.org/trials">www.strokecentre.org/trials</a>. The primary outcome was reported</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Baseline balanced</td>
</tr>
</tbody>
</table>

**Xie 2005**

**Study characteristics**

**Methods**

Aim: to study the effect of treatment with sertraline in elderly patients with post-stroke depression  
Parallel study

**Participants**

- **Country:** China  
- **Setting:** unclear  
- Recruited quote: "clinically stable stroke patients with post-stroke depression"  
- **Mood:** Zung SDS score ≥ 40 or GDS score 5 to 10  
- **Treatment:** 65 people, mean age 69.8 years, 29 men  
- **Control:** 65 people, mean age 70.7 years, 27 men  
- **Time since stroke:** mean 87.8 days, range 48 to 142 days

**Interventions**

- **Treatment:** sertraline 50 mg/day plus usual stroke care  
- **Control:** usual stroke care  
- **Duration of treatment:** 12 weeks  
- **Duration of follow-up:** 0

**Outcomes**

- Zung SDS, GDS, ADL score  
- AEs were not reported

**Funding source**

Local scientific academic fund funded the study

**Notes**

-
### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
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<td>Method not described</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>No dropouts</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No clear description between treatment and control</td>
</tr>
</tbody>
</table>

### Study characteristics

#### Methods
- **Parallel**
- **Aim:** to study the effect of fluoxetine on depression in early recovery stage of cerebral infarction

#### Participants
- **Country:** China
- **Setting:** outpatient in rehabilitation clinic
- **Stroke:** first acute cerebral infarction, no description of the diagnostic criteria and the need for imaging confirmation, excluded large cerebral infarction or lacunar infarction (clinical condition too severe or too mild); onset to recruitment time mean 30 days
- **Zung SDS ≥ 40**
- **Treatment:** 32 people
- **Control:** 31 people (no details of participant characteristics)
- **Excluded if previous antidepressants**

#### Interventions
- **Treatment:** fluoxetine 20 mg daily plus usual stroke care
- **Control:** usual stroke care
- **Duration of treatment:** 8 weeks
### Xu 2001 (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Duration of follow-up (treatment end to study end): 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zung SDS</td>
<td>ADL (BI)</td>
</tr>
<tr>
<td>Neural function deficient</td>
<td>Death</td>
</tr>
<tr>
<td>AEs not reported</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Funding source</th>
<th>Source of funding not stated</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th>–</th>
</tr>
</thead>
</table>

#### Risk of bias

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<tr>
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<td>Unclear risk</td>
<td>Not described</td>
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<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>10/62 dropouts</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No clear description of stroke criteria and imaging</td>
</tr>
</tbody>
</table>

### Xu 2006

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim: to test whether early prophylactic antidepressant treatment by paroxetine has any beneficial influence on the rate of post-stroke depression and rehabilitation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Country: China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting: inpatient</td>
<td></td>
</tr>
</tbody>
</table>
Xu 2006 (Continued)

Stroke criteria: stroke onset time ≤ 3 days, age ≤ 75 years old, no previous psychiatric disorders, no obvious cognitive impairment or aphasia

Depression diagnosis was not mentioned as an inclusion criteria, so we assumed that patients did not have to have depression to enter the trial

Treatment: 32 people, mean age 65 ± 12 years, 17 men

Control: 32 people, mean age 63 ± 11 years, 16 men

Exclusion: no severe hepatic or renal impairment, DSM IV depression not stated as an inclusion, but none met criteria for depression initially

Interventions

Treatment: paroxetine 20 mg daily

Control: placebo

Duration of treatment: 12 weeks

Duration of follow-up (treatment end to study end): 0

Outcomes

MESSS

ADL

Post-stroke diagnosis incidence of depression according to DSM IV

AEs not recorded

Funding source

Study funded by local scientific academic fund

Notes

The number of participants in Table 1 (p187) were wrong (paroxetine/placebo: N = 32/32 should be N = 28/29)

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;Sequence numbers&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Placebo used, but unclear if it was matched</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>7/64 (11%) participants dropped out</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Baseline balance</td>
</tr>
</tbody>
</table>
### Yang 2002

#### Study characteristics

**Methods**
- Parallel group
  - Aim: to study effects of antidepressant in treatment of people with post-stroke depression

**Participants**
- Country: China
- Setting: inpatients and outpatients
  - Stroke criteria: recovery phase of stroke (2 to 6 months after ischaemic stroke, and 1.5 to 6 months after haemorrhagic stroke). We included this in the 3 to 6 month group. Clinical diagnosis of stroke (not stated whether confirmation by imaging was needed)
  - Depression: HAMD > 7
  - Treatment: 64 people, mean age 64 ± 3 years, 40 men
  - Control: 57 people, mean age 63 ± 5 years, 32 men

**Interventions**
- Treatment: paroxetine 20 mg daily plus stroke treatment and rehabilitation
- Control: stroke treatment and rehabilitation
- Duration of treatment: 4 months
- Duration of follow-up: 0

**Outcomes**
- Death
  - They collected data on HAMD and CSS but did not report these data
- ADL score: did not state which one, so not used
- AEs not reported

**Funding source**
- Source of funding not reported

**Notes**
- –

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method not described</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performace bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
</tbody>
</table>
Incomplete outcome data (attrition bias)
High risk
11/121 (9%) dropouts

Selective reporting (reporting bias)
High risk
No protocol. The paper stated that ADL data and depression data were collected, but these data were not reported

Other bias
Low risk
No baseline differences between groups, no other obvious source of bias

Yang 2011

Study characteristics

Methods
Aim: to treat early post-stroke depression

Participants
Country: China
Setting: inpatient
Stroke: all pathological types, clinical diagnosis plus confirmation of lesion on imaging, no previous psychiatric and psychological disorders, age < 75 years old, stroke onset time < 72 hours, NIHSS score: 4 to 19
Mood: HAMD ≥ 8
Treatment: 20 people, mean age 64 ± 8 years, 8 men
Control: 22 people, mean age 64 ± 10 years, 13 men
Note inconsistency between abstract (20 in treatment and 22 in control, but in tables of results, there are 22 in treatment and 20 in control). We have used the data from the abstract
Excluded: functional psychiatric disorder, functional depression, psychoactive substance and addictive substance induced psychiatric disorders, infectious disease, severe cognitive impairment to affect communication, severe aphasia to affect communication, severe cardiac, pulmonary, hepatic and renal function impairment, previous organic brain disease such as brain tumour, or symptomatic stroke, encephalitis

Interventions
Treatment: paroxetine 20 mg daily plus usual stroke care
Control: usual stroke care
Duration of treatment: at least 3 months
Duration of follow-up: 0

Outcomes
HAMD score, IL-1β and IL-6 level
Death
AEs not reported

Funding source
Source of funding: local scientific academic fund

Notes
−

Risk of bias
### Yang 2011 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;Case sequence&quot; randomisation</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>No placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>No dropouts</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No difference in baseline</td>
</tr>
</tbody>
</table>

### Ye 2004

**Study characteristics**

**Methods**

Aim: to investigate whether antidepressive therapy is needed for people with post-stroke depression or not, and the effect of different antidepressive drugs on the rehabilitation of psychological and neurological function after stroke

3 groups: paroxetine, imipramine and control. We are using the paroxetine versus control arm in this review

**Participants**

Country: China

Setting: inpatient

Stroke: all pathological subtypes, clinical diagnosis plus confirmation by imaging (did not state whether a visible lesion was needed to make the diagnosis), no positive psychiatric disorders or family history, clear consciousness, no comprehension problem

Mood: inclusion criteria: HAMD score > 21, HAMA scale > 14

Treatment: 30 people, age 58.04 ± 8.28 years, 22 men

Control: 30 people, age 59.21 ± 9.52 years, 17 men

Exclusion criteria: severe cardiac, hepatic and renal diseases, multiple infarcts or haemorrhage

**Interventions**

Treatment: paroxetine 20 mg/day plus acute stroke routine care and rehabilitation

Control: acute stroke routine care plus rehabilitation

Duration of treatment: 12 weeks
### Ye 2004 (Continued)

| Outcomes | Chinese Neurological Impairment Scale, modified BI, HAMD, HAMA, Therapeutic Effect for Depression and Neurologic Function  
| Death, GI upset  
| Method of recording side effects not stated |

| Funding source | Source of funding not stated |

| Notes | Inconsistent description about the number of recruitment and randomisation between abstract (N = 90) and result part (N = 93) of the text. The number for final analysis is consistent in the text |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Used “number table”, but unclear if this was a random number table</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>The study designer was not involved in assessment and treatment, the assessors did not know the allocation</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>The participants were blinded. Not clear if those delivering the treatment were blind, but no placebo used</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Assessors were blinded</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Only 1 dropped out in paroxetine group</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Different numbers reported to have been recruited and randomised, baseline similar</td>
</tr>
</tbody>
</table>

### Zhao 2011

### Study characteristics

| Methods | Study type: interventional (clinical trial)  
| Primary purpose: treatment |
| Participants | Country: People’s Republic of China  
| Setting: inpatient  
| At randomisation number allocated: N = 82: fluoxetine (n = 41); placebo (n = 41)  
| % male: 58.5 |
Zhao 2011 (Continued)

Age: mean age 65 ± 12
Subtype of stroke: Ischaemic stroke: 61/82 (74%); haemorrhagic stroke: 21/82 (26%)
Severity of stroke: MESSS: fluoxetine 23.2 ± 6.2 (n = 37); placebo 22.8 ± 5.8 (n = 34)
Time since stroke onset: within 10 days

Inclusion criteria
- Consistent with the Diagnostic Criteria for Cerebrovascular Disease formulated by the Fourth National Conference of Chinese Medical Association in 1995, and prove with brain CT or MRI
- Obvious aphasia and unable to communicate normally after language function evaluation
- Age 75 years old or less
- Without previous psychiatric illness
- No severe cognitive impairment

Exclusion criteria: none

Withdrawal criteria: not stated

Interventions
- Experimental: fluoxetine 20 mg daily for 12 weeks
- Comparator: no fluoxetine

Outcomes
- Outcomes collected at 2nd, 4th and 12 week of treatment and 12 weeks after the end of treatment
  - Severity of stroke (MESSS)
  - Performance in ADLs

Funding source
- Not available

Notes
- Dates study conducted: 2008 to 2010
- Declarations of interest: none reported

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>The participants were randomised into 2 groups (with fluoxetine or without fluoxetine) according to the sequence number and a block randomisation table</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement of high or low</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement of high or low</td>
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<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement of high or low</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Attrition rate of fluoxetine group vs control group was 4/41 (9.8%) vs 7/41 (17.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 5% loss to follow-up</td>
</tr>
</tbody>
</table>

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

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Zhao 2011 (Continued)

Selective reporting (reporting bias) | Unclear risk | No trial protocol available. Insufficient information to permit judgement of high or low
Other bias | Low risk | The study appears to be free from other sources of bias

Zhou 2008

Study characteristics

Methods
Aim: to study effect of early paroxetine on post-stroke depression and rehabilitation
Parallel design
Analysis: according to treatment groups

Participants
Country: China
Setting: inpatient
Stroke criteria: all stroke, clinical diagnosis plus confirmation by imaging (though not clear if a relevant stroke lesion had to be visible), stroke onset time ≤ 7 days, no obvious cognitive impairment, no obvious aphasia
HAMD score < 8
Treatment: 36 people, mean age 63 ± 9.3 years, 16 men
Control: 40 people, mean age 61 ± 9.6 years, 19 men
Excluded: previous psychiatric disorders, severe hepatic and renal impairment, taking agents with obvious interaction with fluoxetine in recent 1 month

Interventions
Treatment: fluoxetine 20 mg daily plus acute stroke routine medication
Control: acute stroke routine medication
Duration of treatment: 8 weeks
Duration of follow-up: 0

Outcomes
No raw data provided for any of the following outcomes: diagnosis of depression (CCMD-3, HAMD, ADL, MESSS)
Reported no deaths in either group. Unclear how data on side effects were collected

Funding source
Source of funding not stated

Notes
–

Risk of bias

<table>
<thead>
<tr>
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</tr>
<tr>
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<td>Unclear risk</td>
<td>Not described</td>
</tr>
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</table>
## Zhou 2008 (Continued)

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High</td>
<td>No placebo</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear</td>
<td>Not described</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low</td>
<td>No dropouts, analysed according to allocated treatment group</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High</td>
<td>No protocol, no raw data provided for several of the outcomes</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low</td>
<td>Baseline similar</td>
</tr>
</tbody>
</table>

ADL: activities of daily living  
AE: adverse event  
ALT: Alanine aminotransferase test  
BDI: Beck Depression Inventory  
BI: Barthel Index  
CCMD-II-R: Chinese Classification of Mental Disorders, second edition, revised  
CCMD-3: Chinese Classification of Mental Disorders-3  
CGI: Clinical Global Impressions Scale  
CSS: Chinese Stroke Scale  
CT: computerised tomography  
CTIMP: Clinical Trial of an Investigational Medical Product  
DSM: Diagnostic and Statistical Manual of Mental Disorders  
EEG: electroencephalogram  
eFGR: estimated glomerular filtration rate  
FAI: Frenchay Activities Index  
FAST: Frenchay Aphasia Screening Test  
FIM: Functional Independence Measure  
FMMS: Fugl-Meyer Motor Scale  
fMRI: functional magnetic resonance imaging  
GDS: Geriatric Depression Scale  
GI: gastrointestinal  
HADS: Hospital Anxiety and Depression Scale  
HAM: Hamilton Anxiety scales  
HAMD/HDRS: Hamilton Depression Rating Scale  
HSS: Hemispheric Stroke Scale  
ICD: International Classification of Diseases  
ICH: intracerebral haemorrhage  
IL: interleukin  
ITT: intention-to-treat  
IQR: interquartile range  
JHFI: Johns Hopkins Functioning Inventory  
LOCF: last-observation-carried-forward  
MADRS: Montgomery-Åsberg Depression Rating Scale  
MAOI: mono-amino-oxidase inhibitor  
MCA: middle cerebral artery  
MEP: motor evoked potentials  
MESSS: Modified Edinburgh-Scandinavian Stroke Scale  
MHI-5: Mental Health Inventory  
MMSE: Mini-Mental State Examination  
MoCA: Montreal Cognitive Assessment  
MRI: magnetic resonance imaging  

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**Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)**

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Characteristics of excluded studies [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTRN12619000573156</td>
<td>Trial abandoned prior to initiating recruitment due to COVID-19 pandemic</td>
</tr>
<tr>
<td>Andersen 1993</td>
<td>Cross-over design: double-blind placebo-controlled cross-over protocol as follows: 7 days initial baseline registration, 21 days citalopram or placebo (randomised), 7 days wash-out, 7 days baseline registration, and cross-over to second 21-day treatment period</td>
</tr>
<tr>
<td>Andersen 2012</td>
<td>The trial never started</td>
</tr>
<tr>
<td>Anderson 2002</td>
<td>The trial never started</td>
</tr>
<tr>
<td>Anonymous 2012a</td>
<td>Unable to find publication after extensive searching</td>
</tr>
<tr>
<td>Anonymous 2012b</td>
<td>Unable to find publication after extensive searching</td>
</tr>
<tr>
<td>Berends 2009</td>
<td>Mean time from stroke onset to fluoxetine was 39.1 months</td>
</tr>
<tr>
<td>Bonin Pinto 2019</td>
<td>Participants were recruited within 2 years (not 1 year) of stroke</td>
</tr>
<tr>
<td>Chen 2019</td>
<td>Tandospirone + escitalopram (combination therapy) and escitalopram (monotherapy) in people with vascular depression</td>
</tr>
<tr>
<td>Choi Kwon 2008</td>
<td>Participants more than 1 year post-stroke</td>
</tr>
<tr>
<td>Finkenzeller 2009</td>
<td>SSRI plus active intervention (psychotherapy) versus active treatment (psychotherapy) alone. This trial had been included in the original 2012 review but due to the potential interaction between the SSRI and psychotherapy we decided to exclude it in this update</td>
</tr>
<tr>
<td>Foster 2019</td>
<td>2 arms: 1 with SSRI plus exercise and 1 arm with placebo plus exercise</td>
</tr>
<tr>
<td>Gourab 2015</td>
<td>Time of stroke onset &gt; 12 months</td>
</tr>
<tr>
<td>Graffagnino 2002</td>
<td>Previously listed in 'Studies awaiting classification' (Mead 2012). Unable to access any full publication and we received no response from the author. Given the insufficient information to assess eligibility and, owing to the length of time since the study abstract (2002) was published, we have now excluded this study. CRSREF: 3340767</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ji 2000</td>
<td>SSRI plus active intervention versus active treatment alone</td>
</tr>
<tr>
<td>Kitago 2020</td>
<td>Combined intervention</td>
</tr>
<tr>
<td>Li 2002</td>
<td>There is no random component in the sequence generation process</td>
</tr>
<tr>
<td>Liang 2003</td>
<td>There is no random component in the sequence generation process. This had been included in the 2012 review but on review of the methodology the review authors decided to exclude this for the update</td>
</tr>
<tr>
<td>Liu 2004</td>
<td>SSRI plus active intervention versus active treatment alone</td>
</tr>
<tr>
<td>Liu 2020</td>
<td>Wrong comparator</td>
</tr>
<tr>
<td>Mosarrezaii 2018</td>
<td>Quoted: &quot;Patients received numbered cards according to the order of hospitalization. The recipients of the cards with odd and even numbers constituted the case and control group, respectively.&quot; Allocation concealment procedure was inadequately concealed</td>
</tr>
<tr>
<td>NCT01963832</td>
<td>Study withdrawn (not funded)</td>
</tr>
<tr>
<td>Robinson 2011</td>
<td>Ineligible outcomes: prevention of generalised anxiety disorder</td>
</tr>
<tr>
<td>Sitzer 2002</td>
<td>Previously listed in 'Studies awaiting classification' (Mead 2012). Unable to access any full publication and we received no response from the author. Given the insufficient information to assess eligibility and, owing to the length of time since the study abstract (2002) was published, we have now excluded this study</td>
</tr>
<tr>
<td>Sun 2015</td>
<td>Mean time since onset 19.2 ± 3.5 months. No placebo or usual-care control group (Prozac, acupuncture, and prozac plus acupuncture)</td>
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<tr>
<td>Vogel 2020</td>
<td>Open-label single-group study</td>
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<tr>
<td>Xu 2007</td>
<td>This had been included in the 2012 review but it compares fluoxetine plus wulung capsule versus wulung capsule alone. Wulung capsule is an active comparator so we have therefore excluded this trial for this update</td>
</tr>
<tr>
<td>Zhou 2003</td>
<td>There is no random component in the sequence generation process. This trial had been included in the 2012 version of the review but for this update we excluded it</td>
</tr>
</tbody>
</table>

SSRI: selective serotonin reuptake inhibitor

**Characteristics of studies awaiting classification** [ordered by study ID]

**Guo 2016**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Study type: interventional (clinical trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Actual enrolment: 300</td>
</tr>
<tr>
<td></td>
<td>Allocation: randomised</td>
</tr>
<tr>
<td></td>
<td>Intervention model: parallel assignment</td>
</tr>
<tr>
<td></td>
<td>Masking: single (outcomes assessor)</td>
</tr>
<tr>
<td></td>
<td>Primary purpose: prevention</td>
</tr>
</tbody>
</table>
**Guo 2016 (Continued)**

**Participants**

- Country: China
- Setting: inpatient
- At randomisation numbers allocated: \( N = 300 \)
- Experimental group 1: fluoxetine immediately after enrolment \( n = 100 \)
- Comparator group 1: fluoxetine 7 days after enrolment \( n = 100 \)
- Comparator group 2: no fluoxetine \( n = 100 \)
- % male: unclear
- Age: Experimental, unclear; Comparator 1, unclear; Comparator 2, unclear
- Subtype of stroke: unclear
- Severity of stroke NIHSS score at baseline: unclear
- Time from stroke onset: within 1 week after onset of cerebral infarction

**Inclusion criteria**

- ICD-10 diagnostic criteria for acute cerebral infarction
- Age 18 to 80 years
- First onset of stroke within 1 week
- NIHSS > 2
- Stroke-related impairment
- Informed consent by participants or legal representative

**Exclusion criteria**

- Coma
- Haemorrhagic stroke
- Previous neurological impairment
- Use of antidepressants over previous 3 months
- Use of benzodiazepines over previous 2 weeks
- Self-harm, suicidal ideation or need for antidepressants
- Abnormal liver enzymes or creatinine levels
- Gastrointestinal disorders affect drug absorption seriously
- Life-threatening illness (e.g. malignancy)
- Allergic
- Mental health disorders
- Pregnant or breast feeding
- Allergic
- Enrolled in another interventional clinical research trial within previous 3 months

**Withdrawal criteria**

- Unblinding
- Serious adverse reactions e.g. anaphylactic shock
- Need for immediate stroke-related surgery
- Complications
- Antidepressant use
- Self-harm, suicidal intention, urgent need for antidepressants
Interventions

Experimental: 20 mg of fluoxetine per day for 90 days given immediately after enrolment and conventional therapy of cerebral infarction

Comparator 1: 20 mg of fluoxetine a day for 90 days given 7 days after enrolment and conventional therapy of cerebral infarction

Comparator 2: no fluoxetine and conventional therapy of cerebral infarction

Outcomes

Primary outcome at days 15, 90, and 180

- NIHSS score

Secondary outcome at days 90 and 180

- BI score

Notes

ChiCTR-TRC-15007658
xuanyi-guo@163.com

Baseline demographic and clinical characteristics for each group not presented, but rather the baseline demographic and clinical characteristics for those completing the trial (i.e. a subset of all those randomised at baseline) are presented

He 2018

Methods

Study type: interventional (clinical trial)

Actual enrolment: 404

Allocation: randomised

Intervention model: parallel assignment

Masking: single (outcomes assessor)

Primary purpose: prevention

Participants

Country: China

Setting: inpatient

At randomisation numbers allocated: N = 404

Experimental group: fluoxetine n = 202

Comparator group n = 202

% male: 70.5%

Age: Experimental: 61.14 ± 10.48; Comparator 62.72 ± 11.86

Subtype of stroke: unclear

Severity of stroke NIHSS score at baseline:

Experimental: Median 6 (IQR 4, 8)

Comparator: Median 5 (IQR 3, 8)

Time since stroke onset: mean days, fluoxetine 4.28 ± 1.89; placebo 4.08 ± 2.15
Inclusion criteria

- ICD-10 diagnostic criteria for acute cerebral infarction
- Age 18 to 80 years
- within 1 week of stroke onset
- Written informed consent by participants or legal representatives

Exclusion criteria

- Coma
- History of stroke
- Pregnant or breast feeding
- Self-injury, suicidal intention or depression and need for antidepressants
- History of peptic ulcer or gastritis
- Life-threatening illness (e.g. cardiac insufficiency, malignancy)
- Use of antidepressants over previous 3 months
- Use of benzodiazepines over previous 2 weeks
- Allergic
- Enrolled in another interventional clinical research trial within previous 3 months

Withdrawal criteria

- Violation of randomisation or blinding rules during the follow-up
- Serious adverse reactions, such as anaphylactic shock
- Serious infections or medical complications.
- Antidepressants use
- Self-injury, suicidal intention or depression and need for antidepressants
- Withdrawal from the study (participant or legal relatives)

Interventions

Experimental: 20 mg of fluoxetine a day for 90 days and conventional therapy
Comparator: conventional therapy

Outcomes

- Recurrence rate of cerebral infarction within 3 years
- Improvement of NIHSS, hypertension, diabetes, hyperlips at day 90

Notes

ChiCTR-TRC-12002078
xuanyi_guo@163.com

Jurcau 2016

Methods

Study type: interventional (clinical trial)
Actual enrolment: 89
Allocation: randomised
Intervention model: parallel assignment
Masking: unclear
Primary purpose: treatment

Participants

Country: Romania
Setting: inpatient
### Interventions

**Experimental:** escitalopram 10 mg/day for 12 weeks  
**Comparator:** ?secondary preventive treatment = 46

### Outcomes

Outcomes collected at 3, 6 and 12 months post-stroke  
- NIHSS  
- BI  
- MMSE  
- BDI  
- HAM-D17

### Notes

Does not appear to be a clinical trial register number

---

**NCT00967408**

### Methods

Study type: interventional (clinical trial)  
Estimated enrolment: 200 participants  
Allocation: randomised  
Intervention model: parallel assignment  
Masking: quadruple (participant, care provider, investigator, outcomes assessor)  
Primary purpose: treatment

### Participants

Country: Italy  
Setting: inpatient  
Inclusion criteria  
- > 18 years  
- First ischaemic or haemorrhagic stroke  
Exclusion criteria
NCT00967408 (Continued)

- Unstable medical conditions
- Unable to understand study aims and procedures
- Severe aphasia
- Other progressive neurological disease
- Previous or concomitant psychiatric illness
- Not willing to participate

Interventions

Experimental: escitalopram and rehabilitation. Escitalopram given 5 mg once a day for the first week, 10 mg once a day from the second to fourth week, and 20 mg daily until the 6th month

Comparator: placebo and rehabilitation

Outcomes

Primary outcome collected at 2 and 6 months

- FIM

Secondary outcomes collected at 2 and 6 months:

- MMSE
- Trunk Control Test
- Canadian Stroke Scale
- Motricity Index
- Token test
- The Bells Test
- Stroop Test
- Wisconsin Card Sorting test
- Verbal Fluency
- Raven’s Matrices Test
- Trail Making A-B Test
- Center for Epidemiological Studies Depression Scale

Notes

clinicaltrials.gov/ct2/show/NCT00967408

Contacted author Prof Cisari; response received; data being analysed

BDI: Beck Depression Inventory
BI: Bathel Index
FIM: Functional Independence Measure
HAM-D17: Hamilton Depression Scale
ICD-10: International Statistical Classification of Diseases, 10th revision
IQR: interquartile range
MMSE: Mini-Mental State Examination
NIHSS: National Institutes of Health Stroke Scale

Characteristics of ongoing studies [ordered by study ID]

ChiCTR1800019467

Study name

The effect and mechanism of fluoxetine on the automatic regulation of cerebral blood flow for ischemic stroke

Methods

Study type: interventional (clinical trial)

Estimated enrolment:

Allocation: randomised

Intervention model: parallel assignment
<table>
<thead>
<tr>
<th>Study name</th>
<th>An interventional study to look at efficacy of fluoxetine in patients with post-stroke anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Study type: interventional (clinical trial)</td>
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<tr>
<td></td>
<td>Estimated enrolment: 60 participants</td>
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<td>Allocation: randomised</td>
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<td>Intervention model: parallel assignment</td>
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<tr>
<td></td>
<td>Masking: triple (participant, investigator and outcome assessor)</td>
</tr>
<tr>
<td></td>
<td>Primary purpose: treatment</td>
</tr>
<tr>
<td>Participants</td>
<td>Country: India</td>
</tr>
<tr>
<td></td>
<td>Setting: inpatient</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria</td>
</tr>
<tr>
<td></td>
<td>• Age 18 years to 99 years</td>
</tr>
<tr>
<td></td>
<td>• Ischaemic stroke, haemorrhagic stroke and TIA</td>
</tr>
</tbody>
</table>

**ChiCTR1800019467 (Continued)**

<table>
<thead>
<tr>
<th>Masking: unclear</th>
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<tbody>
<tr>
<td>Primary purpose: treatment</td>
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</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria</td>
<td></td>
</tr>
<tr>
<td>• Age 30 to 80 years</td>
<td></td>
</tr>
<tr>
<td>• First-time acute (in the past 72 hours) ischaemic stroke</td>
<td></td>
</tr>
<tr>
<td>• Diagnosis of stroke confirmed by imaging</td>
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<tr>
<td>• Consent</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td></td>
</tr>
<tr>
<td>• Haemorrhagic stroke</td>
<td></td>
</tr>
<tr>
<td>• Coma</td>
<td></td>
</tr>
<tr>
<td>• Massive cerebral infarction</td>
<td></td>
</tr>
<tr>
<td>• Poor coordination of transcranial doppler ultrasonography</td>
<td></td>
</tr>
<tr>
<td>• Currently participating or have participated in other clinical trials within 3 months</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Experimental: 20 mg of fluoxetine daily for 90 days</th>
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</thead>
<tbody>
<tr>
<td>Comparator: conventional therapy</td>
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<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Baseline, 30 days after treatment, 90 days after treatment, 180 days after treatment</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Automatic regulation of cerebral blood flow</td>
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</tbody>
</table>

| Starting date |     |
|---------------|     |

<table>
<thead>
<tr>
<th>Contact information</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th></th>
</tr>
</thead>
</table>
### Interventions

**Experimental:** 20 mg of fluoxetine orally, daily for 12 weeks  
**Comparator:** standard care

### Outcomes

**Primary and secondary outcomes at 12 weeks**

- **Primary outcome**
  - Improvement in HAM-A
- **Secondary outcomes**
  - Frequency of anxiety and depression after stroke  
  - Activities of daily living measured by BI  
  - Improvement in QoL as measured by 36 item short form questionnaire (SF-36)

### Starting date

December 2018

### Contact information

Dr Deepti Vibha, deeptivibha@gmail.com

### Notes

CTRI/2018/12/016568 (Continued)
Exclusion criteria

- Dementia
- Recurrent major depression
- Major stroke
- Alcohol and drug dependency
- Pregnancy, breastfeeding
- Participating in other trials of medicinal products
- Impaired liver/kidney disease
- Life expectancy less than 6 months

Aiming to recruit 60 participants

Interventions

- Experimental: escitalopram
- Comparator: placebo

Outcomes

- Depression (MADRS) after 180 days
- Incidence of dementia after 180 days (Clinical Dementia Rating scale)
- Severity of dementia
- Zarit Burden Interview
- Incidence of depression (Depression Visual Analogue Scale)
- Severity of post-stroke depression
- Quality of life (SF-36)
- Bayer Activities of Daily Living score
- NPI

Starting date

- MHRA approval 7 April 2006; start date not known

Contact information

- Not available. National Competent Authority is Germany-BFarm
- Sponsor Name: Central Institute for Mental Health, Mannheim, Division of Gerontopsychiatry

Notes

- Details available on EudraCT website

**IRCT201112228490N1**

Study name

- Effect of fluoxetine on functional recovery of patients with cerebrovascular accident following middle cerebral artery trunk obstruction: a randomised clinical trial

Methods

- Study type: interventional (clinical trial)
- Estimated enrolment: 60 participants
- Allocation: randomised
- Intervention model: parallel assignment
- Masking: unclear
IRCT201112228490N1 (Continued)

Primary purpose: treatment

Participants

Iran (Islamic Republic of Iran)

Inclusion criteria

- Age 55 to 85 years
- Informed consent
- Unilateral occlusion of middle cerebral artery trunk
- Resident in Rasht
- Admission NIHSS < 20
- No history of alcohol abuse
- No history of insomnia
- No history of cerebral haemorrhage and heart of cerebral stroke
  
- No history of systemic diseases of other organs, including liver failure and kidney
- No cardiac pacemaker, severe neuropathy, systemic vascular disease or major affective disorders
- No concomitant stroke in an area other than the stroke of the middle cerebral artery

Exclusion criteria

- Dissatisfaction of patient during the study
- Occurrence of serious adverse drug affects at any time during drug administration
- Alcohol abuse during the study period
- Occurrence of post-stroke depression, concomitant use of the MAOIs or serotonergic drugs such as tricyclic antidepressants and SSRI

Interventions

Intervention: fluoxetine, 15 mg oral pill for the first month and 20 mg for the next 2 months

Comparator: placebo, 15 mg oral pill for the first month and 20 mg for the next 2 months

Outcomes

Primary outcomes collected at discharge, 1 and 3 months

- Disability (mRS)
- Activities of Daily Living (BI)
- Functional recovery (NIHSS)
- Depression (BDI questionnaire)

Secondary outcomes collected at discharge

- Cerebral blood flow changes of middle cerebral artery (TCD)

Starting date

5 April 2012

Contact information

Dr Babak Bakhshayesh Eghbali

Poorsina hospital, Guilan University of Medical Sciences

bakhshayesh@gums.ac.ir

Notes

IRCT201112228490N1

Contacted 7 February 2019
<table>
<thead>
<tr>
<th>Study name</th>
<th>A study of sertraline effect on quality of life in stroke inpatients</th>
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<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Study type: interventional (clinical trial)</td>
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<td>Estimated enrolment: 80 participants</td>
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<td>Intervention model: parallel assignment</td>
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<td></td>
<td>Masking: unclear</td>
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<tr>
<td></td>
<td>Primary purpose: prevention</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Iran (Islamic Republic of Iran)</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria</td>
</tr>
<tr>
<td></td>
<td>• 55 years old to 75 years old</td>
</tr>
<tr>
<td></td>
<td>• First-ever stroke</td>
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<td></td>
<td>Exclusion criteria</td>
</tr>
<tr>
<td></td>
<td>• History of stroke</td>
</tr>
<tr>
<td></td>
<td>• Renal failure</td>
</tr>
<tr>
<td></td>
<td>• Hepatic failure</td>
</tr>
<tr>
<td></td>
<td>• Cardiac failure</td>
</tr>
<tr>
<td></td>
<td>• Substance related disorders</td>
</tr>
<tr>
<td></td>
<td>Aiming to recruit 80 participants</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Experimental: 3 weeks after stroke sertraline 50 mg a day for 12 months versus</td>
</tr>
<tr>
<td></td>
<td>Comparator: 3 weeks after stroke a placebo tablet every day</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary outcomes collected at 3 months, 6 months, 9 months</td>
</tr>
<tr>
<td></td>
<td>• Quality of life (NHP)</td>
</tr>
<tr>
<td></td>
<td>Secondary outcomes collected at 3 months, 6 months, 9 months</td>
</tr>
<tr>
<td></td>
<td>• Depression (BDI)</td>
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<td><strong>Starting date</strong></td>
<td>28 November 2012. Contacted author for an update on 4 May 2021 but no response received</td>
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<tr>
<td><strong>Contact information</strong></td>
<td>Reza Pirzeh, Tabriz University of Medical Sciences, Iran (Islamic Republic of)</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:pirzehr@tbzmed.ac.ir">pirzehr@tbzmed.ac.ir</a></td>
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<td><strong>Notes</strong></td>
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<thead>
<tr>
<th>Study name</th>
<th>Evaluation of fluoxetine and standard treatment efficacy on change to side effect of stroke of ischaemic strokes in both hemispheres in anterior circulation</th>
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<tr>
<td><strong>Methods</strong></td>
<td>Study type: interventional (clinical trial)</td>
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<tr>
<td></td>
<td>Estimated enrolment: 60 participants</td>
</tr>
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</table>

---

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

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IRCT2017041720258N37 (Continued)

Allocation: randomised

Intervention model: parallel assignment

Masking: unclear

Primary purpose: treatment

Participants

Islamic Republic of Iran

Inclusion criteria

- Age 40 to 70 years
- No previous history ischaemic stroke
- Diagnosis of stroke confirmed by imaging
- Within 2 to 7 days of stroke onset

Exclusion criteria

- Not available during study period
- History of side effect of fluoxetine and other antipsychotic drugs
- Pregnant or breast feeding
- Depression in the previous month and treatment with antipsychotic drugs
- Use of any MAOI in the last 5 months

Aiming to recruit 60 participants

Interventions

Experimental: 20 milligram fluoxetine and standard treatment (antiplatelets, anticoagulant and statin)

Comparator: placebo and standard treatment (antiplatelets, anticoagulant and statin)

Outcomes

Primary outcome collected at 1 and 2 months

- Change to side effect of stroke (NIHSS questionnaire)

Starting date

11 October 2017. Trials register states it's complete but no results are available (email to author on 4 May 2021, no reply)

Contact information

Fariba Farokhi, Arak University of Medical Sciences Iran (Islamic Republic of Iran)

f.farokhi@arakmu.ac.ir

Notes

www.irct.ir/trial/17976

IRCT20210307050617N1

Study name

The efficacy comparison of fluoxetine and citalopram on motor recovery after ischemic stroke: single-blind placebo-controlled randomized clinical trial

Methods

3 arm RCT- citalopram, fluoxetine or placebo

Participants

Ischaemic stroke, at least 18 years old, hemiparesis or hemiplegia after the first ischaemic stroke in 24 hours. A score greater than 2 NIHSS on the motor items

Interventions

Fluoxetine 20 mg daily for 3 months or citalopram 10 mg for first 10 days then 20 mg daily. Placebo-starch given for 3 months

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Study name
Effect of serotonin and levodopa in ischemic stroke (SELEIS)

### Methods
- **Study type:** interventional (clinical trial)
- **Estimated enrolment:** 240 participants
- **Allocation:** randomised
- **Intervention model:** parallel assignment
- **Masking:** single (outcomes assessor)
- **Primary purpose:** treatment

### Participants
- **Country:** Spain
- **Setting:** inpatient
- **Inclusion criteria:**
  - Age > 18 years
  - NIHSS 5 to 20 points
  - mRS < 3 prior to stroke
  - Participants without prior cognitive impairment or depressive syndrome
  - Assigned treatment initiated within the first 5 days of stroke
- **Exclusion criteria:**
  - Aphasia
  - Prior myocardial or cerebral haemorrhage
  - TIA
  - History of cognitive impairment or prior depressive syndrome
  - mRS 3 or higher
  - Life-threatening illness that is likely to reduce 1-year survival
  - Use of levodopa, an antidepressant or neuroleptic

Aiming to recruit 240 participants.

### Interventions
- **Placebo comparator:** placebo
- **Active comparator:** citalopram 20 mg
- **Active comparator:** sinemet plus 100 mg
- **Sinemet plus + citalopram group**

### Outcomes
- **Rankin Scale at 12 months**
### NCT02386475 (Continued)

<table>
<thead>
<tr>
<th>Starting date</th>
<th>1 January 2015. Study completed 31 October 2019. No results available-contacted author on 4 May 2021</th>
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<td>Contact information</td>
<td>Dolores Cocho mailto:dcacho%40fhag.es?subject=NCT02386475, SELEIS, Effect of Serotonin and Levodopa in Ischemic Stroke</td>
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### NCT02767999

<table>
<thead>
<tr>
<th>Study name</th>
<th>Resting state MRI connectivity in acute ischemic stroke: serotonin selective reuptake inhibitor (SSRI) in enhancing motor recovery: a placebo controlled study</th>
</tr>
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</table>
| Methods | Study type: interventional (clinical trial)  
Estimated enrolment: 60 participants  
Allocation: randomised  
Intervention model: parallel assignment  
Masking: double (participant, investigator)  
Primary purpose: treatment |
| Participants | Country: France  
Setting: inpatient  
Inclusion criteria  
• Age 18 years to 85 years  
• First-ever ischaemic stroke  
• Cortical or subcortical stroke  
• NIHSS > 12 or motor NIHSS > 6 at inclusion  
• MRI-proved ischaemic stroke  
Exclusion criteria  
• Pregnant or breast-feeding  
• Alcoholism  
• Ongoing SSRI treatment or interruption < 1 month  
• Allergic reaction after SSRI administration  
• MRI contraindication  
• NIHSS > 22  
• Severe aphasia  
• Coma |
| Interventions | Experimental: 20 mg of fluoxetine capsule a day from day 0 to day 90 and have fMRI  
Comparator: cellulose placebo a day from day 0 to day 90 and have fMRI |
| Outcomes | Primary outcome at 90 days  
• Intracerebral connectivity in the motor network between fluoxetine and placebo group  
Secondary outcome at 90 days |

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

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### NCT02767999 (Continued)

- Intracerebral connectivity in the motor network between good responder participants (defined by 8 points gain on the NIHSS, assessed between day 0 and day 30 and between day 0 and day 90, or 2 points gain on the mRS assessed between day 0 and day 30 and between day 0 and day 90)
- Intracerebral connectivity in the motor network between non-responder participants

#### Starting date
January 2016

#### Contact information
Virgine Sattler, Dr: sattler.v@chu-toulouse.fr
Françoise Chollet, MD PhD: chollet.f@chu-toulouse.fr

#### Notes
NCT02767999

### NCT02865642

#### Study name
Cortical Ischemic Stroke and Serotonin (CISS)

#### Methods
- Study type: interventional (clinical trial)
- Estimated enrolment: 90 participants
- Allocation: randomised
- Intervention model: parallel assignment
- Masking: quadruple (participant, care provider, investigator, outcomes assessor)
- Primary purpose: supportive care

#### Participants
- Country: Switzerland
- Setting: inpatient

#### Inclusion criteria
- First-ever stroke
- Clinically significant contralesional hand plegia or paresis as a main symptom
- Involvement of the pre-and/or post-central gyri confirmed on DWI and FLAIR scans
- Written informed consent

#### Exclusion criteria
- Aphasia or cognitive deficits severe enough to preclude understanding of study purposes
- Prior cerebrovascular events
- Significant stenosis (70% to 99% according to NASCET) or occlusion of the carotid and intracranial arteries on MRA
- Purely subcortical stroke
- Known brain lesion (tumour, old cerebral haemorrhage)
- Other medical conditions interfering with task performance or SSRI-treatment, specifically: prolonged corrected QT interval (QTc) on electrocardiogram, ongoing drug/alcohol abuse
- Simultaneous intake of medications which can lead to prolonged QTc syndrome known or suspected hypersensitivity to one of the ingredients of Cipralex® or placebo
- Simultaneous administration of antidepressants
- Conditions interfering with MRI (e.g. patients with a cardiac pacemaker or cochlear implant)
- Pregnant or breastfeeding
- Women in childbearing age without sufficient birth control (at least 2 contraceptive methods)
Interventions

Experimental: escitalopram 5 mg/day at the baseline visit (day 14 ±7 post-stroke) for 7 days followed by a weekly dosage increase of 5 mg/day till target dose of escitalopram 20 mg/day. Participants remain on escitalopram 20 mg/day until visit 3 (day 90 ±14 post-stroke) followed by dosage reduction of escitalopram 10 mg/day for 1 week

Comparator: placebo 5 mg/day at the baseline visit (day 14 ±7 post-stroke) for 7 days followed by a weekly dosage of 5 mg/day until target dose of placebo 20 mg/day. Participants remain on placebo 20 mg/day until visit 3 (day 90 ±14 post-stroke) followed by placebo 10 mg/day for 1 week

Outcomes

Primary outcome

• Effect of escitalopram on sensorimotor network at month 9 (task-related fMRI (act-fMRI))

Secondary outcomes

• Imaging patterns of rs-fMRI at month 3 and month 9
• Imaging patterns of act-fMRI at month 3 and month 9
• JTT monthly from baseline to month 9
• Mean cortical volume changes at month 3 and month 9
• Serum concentration of escitalopram at month 3
• Genetic polymorphisms in genes at month 3

Other outcomes

• Glutamate/glutamine concentration at month 3 and month 9
• rTMS at month 3 and month 9
• Number of adverse events due to study medication monthly until month 9

Starting date

August 2016

Contact information

Manuela Pastore-Wapp manuela.p astore-wapp@insel.ch

Notes

NCT02865642

NCT03448159

Study name

FLuoxetine Opens Window to improve motor recovery after stroke (FLOW)

Methods

Study type: interventional (clinical trial)
Estimated enrolment: 176 participants
Allocation: randomised
Intervention model: parallel assignment
Intervention model description

• Intervention group (trial drug (fluoxetine) and exercise intervention)
• Placebo group (placebo and exercise intervention)

Masking: quadruple (participant, care provider, investigator, outcomes assessor)

Primary purpose: treatment

Participants

Country: Canada
Setting: inpatient
Inclusion criteria

- Age > 25 years
- Between 60 to 210 days post-stroke at enrolment
- Lower limb FMMS < 30

Exclusion criteria

- Subarachnoid haemorrhage
- Pre-morbid mRS > 2
- Substantial premorbid disability or pre-existing deficit or language comprehension deficit that could interfere with assessments
- Diagnosis of major depressive disorder/anxiety disorder requiring antidepressant use within 6 weeks of enrolment
- Taking neuroleptic drugs, benzodiazepines, MAOIs within 30 days of enrolment
- Unstable serious medical condition (e.g. terminal cancer, renal or liver failure, congestive heart failure)
- Resting blood pressure exceeding 180/100 mmHg
- Requires more than a one-person assist for transfer
- Planned surgery that would affect participation in the trial
- Participating in another exercise programme more than 1 day a week
- Pregnant
- Ongoing history of illicit drug use or alcohol abuse or both
- Unwilling or unable to comply with trial requirements
- Unable to understand English

Interventions

Experimental: fluoxetine hydrochloride (Prozac): 10 mg Prozac per day for 3 to 5 weeks and then 20 mg for 12 weeks (the duration of the exercise intervention)

Comparator: an over-encapsulated placebo (identical 'sugar pill'): 10 mg 'sugar pill' a day for 3 to 5 weeks and then 20 mg for 12 weeks (the duration of the exercise intervention)

Outcomes

Primary outcomes at 12 weeks

- Fugl-Meyer Lower Extremity Score at 12 weeks

Secondary outcomes at 12 weeks and 6 months

- Ambulatory function measured using 6-Minute Walk Test/10 Metre Walk Test
- Lower limb strength measured using knee strength
- Balance measured using Berg Balance Assessment
- Grip Strength
- Waist-to-Hip Ratio
- Body Mass Index
- SIS
- Fugl-Meyer Lower Extremity Score at 6 months
- Fugl-Meyer Upper Extremity Score
- PHQ-9
- Simple and Choice Reaction Time Test
- Trail Making Test - A & B
- Montreal Cognitive Assessment
- Fasting Blood Draws

Starting date

1 November 2018

Contact information

Farrell Leibovitch
### Notes

**NCT03448159**

- **Study name**: Depression in haemorrhagic stroke
- **Methods**
  - **Study type**: interventional (clinical trial)
  - **Estimated enrolment**: 224 participants
  - **Allocation**: randomised
  - **Intervention model**: parallel assignment
  - **Intervention model description**: double-blinded placebo-controlled randomised trial
  - **Masking**: triple (participant, care provider, investigator)
  - **Primary purpose**: prevention
- **Participants**
  - **Country**: USA
  - **Setting**: inpatient
  - **Inclusion criteria**
    - Age 18 to 85 years
    - Subarachnoid haemorrhage from a ruptured cerebral aneurysm
    - Consent
  - **Exclusion criteria**
    - Non-English speaking
    - Taking therapy for depression or related mental health diagnoses before admission
    - Medical contraindications to fluoxetine therapy
    - Pregnancy or considering getting pregnant during the trial period at the time of consent.
    - Active psychosis
    - Incarcerated or in police custody
    - Comorbidity or a score > 26 on the MoCA
- **Interventions**
  - **Experimental**: fluoxetine 20 mg/day for a period of 1 year
  - **Comparator**: placebo 20 mg/day for a period of 1 year
- **Outcomes**
  - **Primary outcomes at 1 year**
    - Depression measured using HAM-D
    - Depression measured using PHQ-9
  - **Secondary outcomes at 1 year**
    - Anxiety measured using Hamilton Rating Scale for Anxiety
    - Fatigue measured using Fatigue Severity Scale
    - Healthcare utilization measured using Self-Report Health Service Utilization and Medication Use
    - Social support measured using Multidimensional Scale of Perceived Social Support (MSPSS)
### NCT03826875 (Continued)

**Starting date**
1 March 2019

**Contact information**
Cory M Kelly: kellycm@neurosurgery.washington.edu

**Notes**
NCT03826875

### TCTR20181216001

<table>
<thead>
<tr>
<th>Study name</th>
<th>Randomized controlled trial of fluoxetine or placebo on quality of life after acute ischemic stroke</th>
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#### Methods
- Study type: interventional (clinical trial)
- Allocation: randomised
- Intervention model: parallel assignment
- Masking: double blind (no detail)
- Primary purpose: efficacy

#### Participants
- Country: Thailand
- Setting: inpatient
- Inclusion criteria
  - Age > 18
  - Acute ischaemic stroke patient
  - Consent
- Exclusion criteria
  - History of or current psychiatric condition - hemorrhagic complication
  - EQ-5D-5L score > 0.9
  - Language barrier

#### Interventions
- Experimental: fluoxetine 20 mg once daily for 90 days
- Comparator: matching placebo once daily for 90 days

#### Outcomes
- Primary outcomes at 3 months
  - Quality of life measured by EQ-5D-5L
- Secondary outcomes at 3 months
  - Post stroke depression measured by Thai HADS
  - Disability measured by the Modified Rankin Score

**Starting date**
1 January 2019

**Contact information**
Sirikanya Lorwatanapongs: sirikanyalor@yahoo.com

**Notes**
TCTR20181216001

BDI: Beck Depression Inventory;  
BDNF: brain-derived neurotrophic factor;
### Comparison 1. SSRI versus control at end of treatment, by SSRI

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Disability (primary outcome). Studies at low risk of bias</td>
<td>5</td>
<td>5436</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.00 [-0.05, 0.05]</td>
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<tr>
<td>1.1.1 Fluoxetine</td>
<td>5</td>
<td>5436</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.00 [-0.05, 0.05]</td>
</tr>
<tr>
<td>1.2 Independent on modified Rankin score (mRS 0 to 2) (primary outcome). Studies at low risk of bias</td>
<td>5</td>
<td>5926</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.98 [0.93, 1.03]</td>
</tr>
<tr>
<td>1.3 Neurological deficit score (studies at low risk of bias)</td>
<td>1</td>
<td>30</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.39 [-1.12, 0.33]</td>
</tr>
<tr>
<td>1.3.1 Fluoxetine</td>
<td>1</td>
<td>30</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.39 [-1.12, 0.33]</td>
</tr>
<tr>
<td>1.4 Motor deficits (studies at low risk of bias)</td>
<td>6</td>
<td>5518</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.03 [-0.02, 0.08]</td>
</tr>
<tr>
<td>1.4.1 Fluoxetine</td>
<td>6</td>
<td>5518</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.03 [-0.02, 0.08]</td>
</tr>
<tr>
<td>Outcome or subgroup title</td>
<td>No. of studies</td>
<td>No. of participants</td>
<td>Statistical method</td>
<td>Effect size</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>-------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>1.5 Depression, continuous data (studies at low risk of bias)</td>
<td>4</td>
<td>5356</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.14 [-0.19, -0.08]</td>
</tr>
<tr>
<td>1.5.1 Fluoxetine</td>
<td>4</td>
<td>5356</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.14 [-0.19, -0.08]</td>
</tr>
<tr>
<td>1.6 Depression, dichotomous data (studies at low risk of bias)</td>
<td>3</td>
<td>5907</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.75 [0.65, 0.86]</td>
</tr>
<tr>
<td>1.6.1 Fluoxetine</td>
<td>3</td>
<td>5907</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.75 [0.65, 0.86]</td>
</tr>
<tr>
<td>1.7 Death (trials at low risk of bias)</td>
<td>6</td>
<td>6090</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.01 [0.82, 1.24]</td>
</tr>
<tr>
<td>1.7.1 Fluoxetine</td>
<td>6</td>
<td>6090</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.01 [0.82, 1.24]</td>
</tr>
<tr>
<td>1.8 Seizures (studies at low risk of bias)</td>
<td>6</td>
<td>6080</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.40 [1.00, 1.98]</td>
</tr>
<tr>
<td>1.8.1 Fluoxetine</td>
<td>6</td>
<td>6080</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.40 [1.00, 1.98]</td>
</tr>
<tr>
<td>1.9 Gastrointestinal side effects (studies at low risk of bias)</td>
<td>1</td>
<td>30</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.71 [0.33, 8.83]</td>
</tr>
<tr>
<td>1.9.1 Fluoxetine</td>
<td>1</td>
<td>30</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.71 [0.33, 8.83]</td>
</tr>
<tr>
<td>1.10 Bleeding (studies at low risk of bias)</td>
<td>6</td>
<td>6088</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.08 [0.69, 1.70]</td>
</tr>
<tr>
<td>1.10.1 Fluoxetine (except for Asadol-lahi 2018)</td>
<td>6</td>
<td>6088</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.08 [0.69, 1.70]</td>
</tr>
<tr>
<td>1.11 Fractures (studies at low risk of only)</td>
<td>6</td>
<td>6080</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>2.35 [1.62, 3.41]</td>
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<tr>
<td>1.12 Cognition (trials at low risk of bias)</td>
<td>4</td>
<td>5373</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-1.22 [-2.37, -0.07]</td>
</tr>
<tr>
<td>1.13 Leaving the study before the end of scheduled follow-up for reasons other than death (trials at low risk of bias)</td>
<td>6</td>
<td>6090</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.57 [1.03, 2.40]</td>
</tr>
<tr>
<td>1.13.1 Fluoxetine</td>
<td>6</td>
<td>6090</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.57 [1.03, 2.40]</td>
</tr>
<tr>
<td>1.14 Fatigue at end of treatment (studies at low risk of bias only)</td>
<td>4</td>
<td>5524</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.06 [-1.24, 1.11]</td>
</tr>
<tr>
<td>1.15 Quality of life at end of treatment (studies at low risk of bias)</td>
<td>3</td>
<td>5482</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.00 [-0.02, 0.02]</td>
</tr>
<tr>
<td>1.16 Disability (all studies regardless of risk of bias)</td>
<td>32</td>
<td>7667</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.18 [-0.23, -0.14]</td>
</tr>
<tr>
<td>1.16.1 Fluoxetine</td>
<td>19</td>
<td>6590</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.09 [-0.13, -0.04]</td>
</tr>
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</table>
### Outcome or subgroup title
<table>
<thead>
<tr>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.16.2 Sertraline</td>
<td>1</td>
<td>130</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
</tr>
<tr>
<td>1.16.3 Paroxetine</td>
<td>5</td>
<td>293</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
</tr>
<tr>
<td>1.16.4 Citalopram</td>
<td>5</td>
<td>446</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
</tr>
<tr>
<td>1.16.5 Escitalopram</td>
<td>2</td>
<td>208</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
</tr>
<tr>
<td>1.17 Independent on modified Rankin score (mRS 0 to 2) (all studies regardless of risk of bias)</td>
<td>8</td>
<td>6792</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
</tr>
<tr>
<td>1.17.1 Fluoxetine</td>
<td>6</td>
<td>6039</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
</tr>
<tr>
<td>1.17.2 Sertraline</td>
<td>1</td>
<td>111</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
</tr>
<tr>
<td>1.17.3 Citalopram</td>
<td>1</td>
<td>642</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
</tr>
</tbody>
</table>

### Analysis 1.1. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 1: Disability (primary outcome). Studies at low risk of bias

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI Mean</th>
<th>SSRI SD</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Fixed, 95% CI</th>
<th>Std. Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>2708</td>
<td></td>
<td>2728</td>
<td></td>
<td>100.0%</td>
<td>-0.00 [-0.05, 0.05]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>2708</td>
<td></td>
<td>2728</td>
<td></td>
<td>100.0%</td>
<td>-0.00 [-0.05, 0.05]</td>
<td></td>
</tr>
</tbody>
</table>

**Footnotes**
1. Used activities of daily living component of SIS for all trials except Marquez Romero, which provided Barthel.
2. SD in Marquez Romero calculated from the median (45) and IQR (45) for control and from median (65) and IQR (13) in intervention group.
## Analysis 1.2. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 2: Independent on modified Rankin score (mRS 0 to 2) (primary outcome). Studies at low risk of bias

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>AFFINITY 2020</td>
<td>432</td>
<td>624</td>
<td>458</td>
<td>632</td>
</tr>
<tr>
<td>Bembenek 2020</td>
<td>20</td>
<td>27</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>EFFECTS 2020</td>
<td>466</td>
<td>737</td>
<td>475</td>
<td>742</td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>572</td>
<td>1553</td>
<td>588</td>
<td>1553</td>
</tr>
<tr>
<td>Marquez Romero 2013</td>
<td>8</td>
<td>14</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2955</strong></td>
<td><strong>2971</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.98 [0.93 , 1.03]</strong></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 5.84, df = 4 (P = 0.21); I² = 32%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.89 (P = 0.37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Not applicable</td>
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</tbody>
</table>

## Analysis 1.3. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 3: Neurological deficit score (studies at low risk of bias)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td><strong>1.3.1 Fluoxetine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marquez Romero 2013</td>
<td>8.5</td>
<td>3.29</td>
<td>14</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>14</strong></td>
<td><strong>16</strong></td>
<td><strong>100.0%</strong></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.07 (P = 0.29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Analysis 1.4. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 4: Motor deficits (studies at low risk of bias)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td><strong>1.4.1 Fluoxetine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFFINITY 2020</td>
<td>72.3</td>
<td>24.1</td>
<td>570</td>
</tr>
<tr>
<td>Asadollahi 2018</td>
<td>51.65</td>
<td>26.49</td>
<td>60</td>
</tr>
<tr>
<td>Bembenek 2020</td>
<td>27.16</td>
<td>28.5</td>
<td>30</td>
</tr>
<tr>
<td>EFFECTS 2020</td>
<td>69.4</td>
<td>24.7</td>
<td>694</td>
</tr>
<tr>
<td>FOCUS 2019 (1)</td>
<td>57.05</td>
<td>29.6</td>
<td>1398</td>
</tr>
<tr>
<td>Marquez Romero 2013</td>
<td>75.5</td>
<td>32.95</td>
<td>14</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>2766</strong></td>
<td><strong>2752</strong></td>
<td><strong>100.0%</strong></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 19.83, df = 5 (P = 0.001); I² = 75%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 1.19 (P = 0.23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Not applicable</td>
<td></td>
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</tr>
</tbody>
</table>

### Footnotes
1. For FOCUS, AFFINITY, EFFECTS and Bembenek we use the strength subscale of the SIS
### Analysis 1.5. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 5: Depression, continuous data (studies at low risk of bias)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
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<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
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<tr>
<td><strong>1.5.1 Fluoxetine</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFFINITY 2020</td>
<td>-77.8</td>
<td>15.2</td>
<td>570</td>
<td>-75.2</td>
</tr>
<tr>
<td>Bembenek 2020</td>
<td>-67.41</td>
<td>19.04</td>
<td>26</td>
<td>-72.43</td>
</tr>
<tr>
<td>EFFECTS 2020</td>
<td>-78.7</td>
<td>15.7</td>
<td>695</td>
<td>-75.5</td>
</tr>
<tr>
<td>FOCUS 2019 (1)</td>
<td>11.98</td>
<td>5.24</td>
<td>1372</td>
<td>12.52</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
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<td></td>
<td>2693</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 4.68, df = 3 (P = 0.20); I² = 36%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 5.05 (P &lt; 0.00001)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2663</td>
<td>2693</td>
<td>100.0%</td>
<td>-0.14 [-0.19 , -0.08]</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 4.68, df = 3 (P = 0.20); I² = 36%</td>
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</tr>
<tr>
<td>Test for overall effect: Z = 5.05 (P &lt; 0.00001)</td>
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<tr>
<td>Test for subgroup differences: Not applicable</td>
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</tbody>
</table>

Footnotes
(1) SIS emotional role used from AFFINITY, EFFECTS and Bembenek (higher score is better). FOCUS reported MHI5 (where a lower score is better). Thus a minus sign was included for AFFINITY, EFFECT and Bembenek to account for the different direction of the scales.

### Analysis 1.6. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 6: Depression, dichotomous data (studies at low risk of bias)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td><strong>1.6.1 Fluoxetine</strong></td>
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<td></td>
</tr>
<tr>
<td>AFFINITY 2020</td>
<td>33</td>
<td>642</td>
<td>46</td>
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<tr>
<td>EFFECTS 2020</td>
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<td>81</td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>210</td>
<td>1564</td>
<td>269</td>
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<td><strong>Subtotal (95% CI)</strong></td>
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<td><strong>2951</strong></td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events:</td>
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<td>396</td>
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</tr>
<tr>
<td>Heterogeneity: Chi² = 0.76, df = 2 (P = 0.68); I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 4.03 (P &lt; 0.0001)</td>
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<td></td>
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<tr>
<td>Total (95% CI)</td>
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<td>2951</td>
<td>100.0%</td>
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<tr>
<td>Total events:</td>
<td>297</td>
<td>396</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.76, df = 2 (P = 0.68); I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 4.03 (P &lt; 0.0001)</td>
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<tr>
<td>Test for subgroup differences: Not applicable</td>
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</tbody>
</table>

Footnotes
(1) SIS emotional role used from AFFINITY, EFFECTS and Bembenek (higher score is better). FOCUS reported MHI5 (where a lower score is better). Thus a minus sign was included for AFFINITY, EFFECT and Bembenek to account for the different direction of the scales.
### Analysis 1.7. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 7: Death (trials at low risk of bias)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>AFFINITY 2020</td>
<td>15</td>
<td>642</td>
<td>15</td>
</tr>
<tr>
<td>Asadollahi 2018</td>
<td>0</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Bembenek 2020</td>
<td>1</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>EFFECTS 2020</td>
<td>25</td>
<td>750</td>
<td>22</td>
</tr>
<tr>
<td>FOCUS 2019 (1)</td>
<td>129</td>
<td>1564</td>
<td>130</td>
</tr>
<tr>
<td>Marquez Romero 2013</td>
<td>0</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>3061</strong></td>
<td><strong>3029</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events: 170
Heterogeneity: $\chi^2 = 0.19$, df = 3 (P = 0.98); $I^2 = 0$
Test for overall effect: Z = 0.10 (P = 0.92)

### Analysis 1.8. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 8: Seizures (studies at low risk of bias)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>AFFINITY 2020</td>
<td>10</td>
<td>642</td>
<td>2</td>
</tr>
<tr>
<td>Asadollahi 2018</td>
<td>0</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Bembenek 2020</td>
<td>0</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>EFFECTS 2020</td>
<td>8</td>
<td>750</td>
<td>11</td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>58</td>
<td>1564</td>
<td>40</td>
</tr>
<tr>
<td>Marquez Romero 2013</td>
<td>0</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>3056</strong></td>
<td><strong>3024</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events: 76
Heterogeneity: $\chi^2 = 5.49$, df = 3 (P = 0.14); $I^2 = 45$
Test for overall effect: Z = 1.93 (P = 0.05)

### Footnotes
(1) We used the number randomised as the denominator

---

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

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## Analysis 1.9. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 9: Gastrointestinal side effects (studies at low risk of bias)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td><strong>1.9.1 Fluoxetine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marquez Romero 2013</td>
<td>3</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>14</td>
<td>16</td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 0.64$ (P = 0.52)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>14</td>
<td>16</td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 0.64$ (P = 0.52)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Analysis 1.10. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 10: Bleeding (studies at low risk of bias)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td><strong>1.10.1 Fluoxetine (except for Asadollahi 2018)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFFINITY 2020</td>
<td>4</td>
<td>642</td>
<td>2</td>
</tr>
<tr>
<td>Asadollahi 2018</td>
<td>0</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Bembenek 2020</td>
<td>0</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>EFFECTS 2020</td>
<td>10</td>
<td>750</td>
<td>8</td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>25</td>
<td>1564</td>
<td>26</td>
</tr>
<tr>
<td>Marquez Romero 2013</td>
<td>0</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>3060</td>
<td>3028</td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>39</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.77$, df = 2 (P = 0.68); $I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 0.34$ (P = 0.73)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>3060</td>
<td>3028</td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>39</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.77$, df = 2 (P = 0.68); $I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 0.34$ (P = 0.73)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Analysis 1.11. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 11: Fractures (studies at low risk of only)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>AFFINITY 2020</td>
<td>19</td>
<td>642</td>
<td>6</td>
<td>638</td>
</tr>
<tr>
<td>Asadollahi 2018</td>
<td>0</td>
<td>60</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>Bembenek 2020 (1)</td>
<td>1</td>
<td>26</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>EFFECTS 2020</td>
<td>28</td>
<td>750</td>
<td>11</td>
<td>750</td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>45</td>
<td>1564</td>
<td>23</td>
<td>1563</td>
</tr>
<tr>
<td>Marquez Romero 2013</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>16</td>
</tr>
</tbody>
</table>

Total (95% CI) | 3056 | 3024 | 100.0% | 2.35 [1.62, 3.41] |

Heterogeneity: Chi² = 0.99, df = 3 (P = 0.80); I² = 0%
Test for overall effect: Z = 4.50 (P < 0.00001)
Test for subgroup differences: Not applicable

#### Footnotes

(1) Bembenek reported one fracture; we clarified with the author that this fracture occurred within 6 months

### Analysis 1.12. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 12: Cognition (trials at low risk of bias)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>AFFINITY 2020 (1)</td>
<td>84.6</td>
<td>19.3</td>
<td>570</td>
</tr>
<tr>
<td>Bembenek 2020</td>
<td>84.89</td>
<td>17.15</td>
<td>26</td>
</tr>
<tr>
<td>EFFECTS 2020</td>
<td>84.7</td>
<td>18.3</td>
<td>696</td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>72.89</td>
<td>27.43</td>
<td>1378</td>
</tr>
</tbody>
</table>

Total (95% CI) | 2670 | 2703 | 100.0% | -1.22 [-2.37, -0.07] |

Heterogeneity: Chi² = 10.53, df = 3 (P = 0.01); I² = 72%
Test for overall effect: Z = 2.09 (P = 0.04)
Test for subgroup differences: Not applicable

#### Footnotes

(1) Used memory component of SIS from all four trials (mean and SD provided by study authors)
### Analysis 1.13. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 13: Leaving the study before the end of scheduled follow-up for reasons other than death (trials at low risk of bias)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>AFFINITY 2020</td>
<td>18</td>
<td>642</td>
<td>6</td>
<td>638</td>
</tr>
<tr>
<td>Asadollahi 2018</td>
<td>10</td>
<td>60</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>Bembenek 2020 (1)</td>
<td>3</td>
<td>30</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>EFFECTS 2020</td>
<td>13</td>
<td>750</td>
<td>7</td>
<td>750</td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>11</td>
<td>1564</td>
<td>10</td>
<td>1563</td>
</tr>
<tr>
<td>Marquez Romero 2013</td>
<td>1</td>
<td>15</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>3061</strong></td>
<td><strong>3029</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.57 [1.03 , 2.40]</strong></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td><strong>56</strong></td>
<td><strong>32</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 3.84, df = 5 (P = 0.57); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.09 (P = 0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Footnotes**

(1) For Bembenek 2020, the text in the published paper states that 2 withdrew from the placebo group between 0 and 6 months. The author kindly confirmed...

### Analysis 1.14. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 14: Fatigue at end of treatment (studies at low risk of bias only)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>AFFINITY 2020</td>
<td>68.11</td>
<td>21.54</td>
<td>642</td>
</tr>
<tr>
<td>Bembenek 2020</td>
<td>49.52</td>
<td>12.36</td>
<td>26</td>
</tr>
<tr>
<td>EFFECTS 2020</td>
<td>55.5</td>
<td>21.8</td>
<td>692</td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>56.54</td>
<td>23.54</td>
<td>1405</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2765</strong></td>
<td><strong>2759</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.50, df = 3 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable

### Analysis 1.15. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 15: Quality of life at end of treatment (studies at low risk of bias)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>AFFINITY 2020</td>
<td>0.73</td>
<td>0.32</td>
<td>642</td>
</tr>
<tr>
<td>EFFECTS 2020</td>
<td>0.65</td>
<td>0.29</td>
<td>687</td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>0.47</td>
<td>0.36</td>
<td>1412</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2741</strong></td>
<td><strong>2741</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.83, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable
Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

Analysis 1.16. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 16: Disability (all studies regardless of risk of bias)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Control</th>
<th>SSRI</th>
<th>Std. Mean Difference IV, Fixed, 95% CI</th>
<th>Std. Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Favours SSRI</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Analysis 1.16. (Continued)**

Test for overall effect: Z = 7.85 (P < 0.00001)
Test for subgroup differences: Chi² = 154.62, df = 4 (P < 0.00001), I² = 97.4%

**Footnotes**
(1) Chen 2001 reported Barthel

---

**Analysis 1.17. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 17: Independent on modified Rankin score (mRS 0 to 2) (all studies regardless of risk of bias)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.17.1 Fluoxetine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFFINITY 2020</td>
<td>430</td>
<td>624</td>
<td></td>
</tr>
<tr>
<td>Bembrer 2020</td>
<td>20</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Choller 2011</td>
<td>15</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>EFFECTS 2020</td>
<td>466</td>
<td>737</td>
<td></td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>572</td>
<td>1553</td>
<td></td>
</tr>
<tr>
<td>Marquez Romero 2013</td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>3012</strong></td>
<td><strong>3027</strong></td>
<td><strong>0.98 [0.94, 1.03]</strong></td>
</tr>
<tr>
<td>Total events:</td>
<td>1511</td>
<td>1546</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 11.37, df = 5 (P = 0.04); I² = 56%
Test for overall effect: Z = 0.67 (P = 0.50)

| **1.17.2 Sertraline** |      |         |            |
| Almeida 2006        | 55   | 55      | 1.00 [0.97, 1.04] |
| **Subtotal (95% CI)** | **55** | **56** | **1.00 [0.97, 1.04]** |
| Total events:       | 55   | 56      |            |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

| **1.17.3 Citalopram** |      |         |            |
| Andersen 2013       | 231  | 319     | 0.90 [0.82, 0.98] |
| **Subtotal (95% CI)** | **319** | **323** | **0.90 [0.82, 0.98]** |
| Total events:       | 231  | 261     |            |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.50 (P = 0.01)

**Comparison 2. SSRI versus control at end of follow up, by SSRI**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Disability (studies at low risk of bias only)</td>
<td>2</td>
<td>2591</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.24 [-2.59, 2.11]</td>
</tr>
<tr>
<td>Outcome or subgroup title</td>
<td>No. of studies</td>
<td>No. of participants</td>
<td>Statistical method</td>
<td>Effect size</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>---------------------</td>
<td>-------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>2.2 Independent on modified rankin score (0-2) (studies at low risk of bias only)</td>
<td>2</td>
<td>3137</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.03 [0.89, 1.19]</td>
</tr>
<tr>
<td>2.3 Depression, continuous data (studies at low risk of bias only)</td>
<td>2</td>
<td>2684</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.04 [-0.36, 0.44]</td>
</tr>
<tr>
<td>2.4 Depression, dichotomous (studies at low risk of bias only)</td>
<td>1</td>
<td>3083</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.87 [0.73, 1.04]</td>
</tr>
<tr>
<td>2.5 Motor deficits (studies at low risk of bias only)</td>
<td>2</td>
<td>2688</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.77 [-3.00, 1.46]</td>
</tr>
<tr>
<td>2.6 Cognition (studies at low risk of bias only)</td>
<td>2</td>
<td>2689</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.35 [-2.32, 1.62]</td>
</tr>
<tr>
<td>2.7 Death (studies at low risk of bias only)</td>
<td>2</td>
<td>3144</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.93 [0.77, 1.12]</td>
</tr>
<tr>
<td>2.8 Leaving the trial before the end of follow-up, for reasons other than death (studies at low risk of bias)</td>
<td>2</td>
<td>3188</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.90 [0.54, 1.51]</td>
</tr>
<tr>
<td>2.9 Disability, all studies irrespective of risk of bias</td>
<td>2</td>
<td>2691</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.25 [-2.56, 2.06]</td>
</tr>
<tr>
<td>2.10 Independent on mRS (0-2) all studies irrespective of risk of bias</td>
<td>2</td>
<td>3134</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.03 [0.89, 1.19]</td>
</tr>
</tbody>
</table>

Analysis 2.1. Comparison 2: SSRI versus control at end of follow up, by SSRI, Outcome 1: Disability (studies at low risk of bias only)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean SSRI</th>
<th>SD</th>
<th>Total</th>
<th>Mean Control</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bembenek 2020</td>
<td>83.33</td>
<td>19.83</td>
<td>24</td>
<td>74.25</td>
<td>26.94</td>
<td>27</td>
<td>3.3%</td>
<td>9.08 [-3.81 , 21.97]</td>
<td></td>
</tr>
<tr>
<td>FOCUS 2019 (1)</td>
<td>61.63</td>
<td>30.7</td>
<td>1227</td>
<td>62.19</td>
<td>30.78</td>
<td>1313</td>
<td>96.7%</td>
<td>-0.56 [-2.95 , 1.83]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1251</td>
<td>1340</td>
<td>100.0%</td>
<td>-0.24 [-2.59 , 2.11]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Footnotes
(1) Used the daily activities from the Stroke Impact Scale from FOCUS and Bembenek

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)
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Analysis 2.2. Comparison 2: SSRI versus control at end of follow up, by SSRI, Outcome 2: Independent on modified rankin score (0-2) (studies at low risk of bias only)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Bembenek 2020</td>
<td>20</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>FOCUS 2019 (1)</td>
<td>562</td>
<td>1539</td>
<td>557</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1565</td>
<td>1572</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total events: 582, 576
Heterogeneity: \( \chi^2 = 0.50, df = 1 (P = 0.48); I^2 = 0\%
Test for overall effect: \( Z = 0.34 (P = 0.73) \)
Test for subgroup differences: Not applicable

Footnotes
(1) mRS at 12 months for all four trials are included, denominator is the number for whom an mRS is available (this includes a score of six for those

Analysis 2.3. Comparison 2: SSRI versus control at end of follow up, by SSRI, Outcome 3: Depression, continuous data (studies at low risk of bias only)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Bembenek 2020</td>
<td>73.5</td>
<td>16.3</td>
<td>24</td>
</tr>
<tr>
<td>FOCUS 2019 (2)</td>
<td>12.36</td>
<td>5.21</td>
<td>1323</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1347</td>
<td>1337</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 1.32, df = 1 (P = 0.25); I^2 = 24\%
Test for overall effect: \( Z = 0.20 (P = 0.84) \)
Test for subgroup differences: Not applicable

Footnotes
(1) additional data from SIS provided by Jan Bembenek. We used the emotion score of the SIS for mood
(2) in focus additional data were obtained from the trial team on mean (SD) scores to enable meta-analysis

Analysis 2.4. Comparison 2: SSRI versus control at end of follow up, by SSRI, Outcome 4: Depression, dichotomous (studies at low risk of bias only)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Control</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>292</td>
<td>1539</td>
<td>327</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1539</td>
<td>1544</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total events: 292, 327
Heterogeneity: Not applicable
Test for overall effect: \( Z = 1.53 (P = 0.13) \)
Test for subgroup differences: Not applicable
Analysis 2.5. Comparison 2: SSRI versus control at end of follow up, by SSRI, Outcome 5: Motor deficits (studies at low risk of bias only)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bembenek 2020</td>
<td>83.3</td>
<td>20.2</td>
<td>24</td>
<td>78.1</td>
<td>23.97</td>
<td>27</td>
<td>3.4%</td>
<td>5.20 [-6.93, 17.33]</td>
<td></td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>55.73</td>
<td>29.76</td>
<td>1322</td>
<td>56.71</td>
<td>29.65</td>
<td>1315</td>
<td>96.6%</td>
<td>-0.98 [-3.25, 1.29]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1346</td>
<td>1342</td>
<td>100.0%</td>
<td>-0.77 [-3.00, 1.46]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.96, df = 1 (P = 0.33); I^2 = 0$
Test for overall effect: $Z = 0.68 (P = 0.50)$
Test for subgroup differences: Not applicable

Analysis 2.6. Comparison 2: SSRI versus control at end of follow up, by SSRI, Outcome 6: Cognition (studies at low risk of bias only)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bembenek 2020</td>
<td>88.54</td>
<td>15.76</td>
<td>24</td>
<td>85.85</td>
<td>17.43</td>
<td>27</td>
<td>4.7%</td>
<td>2.69 [-6.42, 11.80]</td>
<td></td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>73.26</td>
<td>26.33</td>
<td>1324</td>
<td>73.76</td>
<td>26.55</td>
<td>1314</td>
<td>95.3%</td>
<td>-0.50 [-2.52, 1.52]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1348</td>
<td>1341</td>
<td>100.0%</td>
<td>-0.35 [-2.32, 1.62]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.45, df = 1 (P = 0.50); I^2 = 0$
Test for overall effect: $Z = 0.35 (P = 0.73)$
Test for subgroup differences: Not applicable

Analysis 2.7. Comparison 2: SSRI versus control at end of follow up, by SSRI, Outcome 7: Death (studies at low risk of bias only)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bembenek 2020</td>
<td>2</td>
<td>30</td>
<td>1</td>
<td>31</td>
<td>0.5%</td>
<td>2.07 [0.20, 21.61]</td>
<td>0.92 [0.76, 1.11]</td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>182</td>
<td>1539</td>
<td>198</td>
<td>1544</td>
<td>99.5%</td>
<td>0.93 [0.77, 1.12]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1569</td>
<td>1575</td>
<td>100.0%</td>
<td>0.93</td>
<td>[0.77, 1.12]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 184
Heterogeneity: $\chi^2 = 0.45, df = 1 (P = 0.50); I^2 = 0$
Test for overall effect: $Z = 0.78 (P = 0.43)$
Test for subgroup differences: Not applicable
Analysis 2.8. Comparison 2: SSRI versus control at end of follow up, by SSRI, Outcome 8: Leaving the trial before the end of follow-up, for reasons other than death (studies at low risk of bias)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI Events</th>
<th>SSRI Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bembenek 2020 (1)</td>
<td>3</td>
<td>30</td>
<td>2</td>
<td>31</td>
<td>5.8%</td>
<td>1.61 [0.25 , 10.39]</td>
<td></td>
</tr>
<tr>
<td>FOCUS 2019 (2)</td>
<td>25</td>
<td>1564</td>
<td>29</td>
<td>1563</td>
<td>94.2%</td>
<td>0.86 [0.50 , 1.47]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 1594 1594 100.0% 0.90 [0.54 , 1.51]

Total events: 28 31

Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%

Test for overall effect: Z = 0.39 (P = 0.70)

Test for subgroup differences: Not applicable

Footnotes
(1) Need to check whether there were three withdrawals in the placebo group rather than two for Bembenek
(2) Note that a 'favourable' outcome in the Forest plot is indicated by fewer drop outs

Analysis 2.9. Comparison 2: SSRI versus control at end of follow up, by SSRI, Outcome 9: Disability, all studies irrespective of risk of bias

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI Mean</th>
<th>SSRI SD</th>
<th>SSRI Total</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bembenek 2020</td>
<td>83.3</td>
<td>19.83</td>
<td>24</td>
<td>74.2</td>
<td>16.94</td>
<td>27</td>
<td>3.2%</td>
<td>9.10 [-3.79 , 21.99]</td>
<td></td>
</tr>
<tr>
<td>FOCUS 2019 (1)</td>
<td>61.63</td>
<td>30.7</td>
<td>1327</td>
<td>62.19</td>
<td>30.78</td>
<td>1313</td>
<td>96.8%</td>
<td>-0.56 [-2.91 , 1.79]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 1351 1340 100.0% -0.25 [-2.56 , 2.06]

Heterogeneity: Chi² = 2.09, df = 1 (P = 0.15); I² = 52%

Test for overall effect: Z = 0.21 (P = 0.83)

Test for subgroup differences: Not applicable

Footnotes
(1) used the daily activities of SIS from 12 months

Analysis 2.10. Comparison 2: SSRI versus control at end of follow up, by SSRI, Outcome 10: Independent on mRS (0-2) all studies irrespective of risk of bias

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI Events</th>
<th>SSRI Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bembenek 2020</td>
<td>20</td>
<td>24</td>
<td>19</td>
<td>27</td>
<td>0.8%</td>
<td>2.11 [0.54 , 8.16]</td>
<td></td>
</tr>
<tr>
<td>FOCUS 2019</td>
<td>562</td>
<td>1539</td>
<td>557</td>
<td>1544</td>
<td>99.2%</td>
<td>1.02 [0.88 , 1.18]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 1563 1571 100.0% 1.03 [0.89 , 1.19]

Total events: 582 576

Heterogeneity: Chi² = 1.09, df = 1 (P = 0.30); I² = 8%

Test for overall effect: Z = 0.38 (P = 0.71)

Test for subgroup differences: Not applicable

Footnotes
(1) used the daily activities of SIS from 12 months

ADDITIONAL TABLES
<table>
<thead>
<tr>
<th></th>
<th>mRS (RR and 95% CI)</th>
<th>Disability (SMD and 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed-effect</td>
<td>0.98 (0.93, 1.03)</td>
<td>-0.00 (-0.05, 0.05)</td>
</tr>
<tr>
<td>Random-effects</td>
<td>0.98 (0.92, 1.04)</td>
<td>-0.00 (-0.05, 0.05)</td>
</tr>
</tbody>
</table>

CI: confidence interval  
mRS: modified Rankin Scale  
RR: risk ratio  
SMD: standardised mean difference

**APPENDICES**

**Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy**

[1] The CENTRAL search strategy looks different to the one I have stored. Please see below the correct strategy and add it into your appendices.

#1 MeSH descriptor: [Cerebrovascular Disorders] this term only  
#2 MeSH descriptor: [Basal Ganglia Cerebrovascular Disease] explode all trees  
#3 MeSH descriptor: [Brain Ischemia] explode all trees  
#4 MeSH descriptor: [Carotid Artery Diseases] explode all trees  
#5 MeSH descriptor: [ Intracranial Arterial Diseases] explode all trees  
#6 MeSH descriptor: [ Intracranial Embolism and Thrombosis] explode all trees  
#7 MeSH descriptor: [ Intracranial Hemorrhages] explode all trees  
#8 MeSH descriptor: [Stroke] explode all trees  
#9 MeSH descriptor: [Brain Infarction] explode all trees  
#10 MeSH descriptor: [Vertebral Artery Dissection] this term only  
#11 (stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc* or cva* or apoplex* or SAH):ti,ab,kw (Word variations have been searched)  
#12 ([brain* or cerebr* or cerebell* or intracran* or intracerebral] near/5 (isch?emi* or infarct* or thrombo* or emboli* or occlus*)):ti,ab,kw (Word variations have been searched)  
#13 ([brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid) near/5 (haemorrhage* or hemorrhage* or haematoma* or hematom*:or bleeding):ti,ab,kw (Word variations have been searched)  
#14 MeSH descriptor: [Hemiplegia] this term only  
#15 MeSH descriptor: [Paresis] explode all trees  
#16 (hemipleg* or hemipar* or paresis or paretic):ti,ab,kw (Word variations have been searched)  
#17 MeSH descriptor: [Gait Disorders, Neurologic] explode all trees  
#18 [or #1-#17]  
#19 MeSH descriptor: [Serotonin Uptake Inhibitors] explode all trees  
#20 ((serotonin or 5-HT or 5 HT or 5-hydroxytryptamine or 5 hydroxytryptamine) near/5 (uptake or reuptake or re-uptake) near/5 inhibit*:ti,ab,kw (Word variations have been searched)  
#21 SSRI*:ti,ab,kw (Word variations have been searched)  
#22 (alaproclat* or cericlamin* or citalopram or clomipramin* or dapoxetine* or etoperidon* or escitalopram or femoxetine* or fenfluramin* or fluoxetine* or fluvoxamin* or nonfenfluramin* or paroxetine* or sertralin*: or trazodone or vilazodone or zimelidine):ti,ab,kw (Word variations have been searched)  
#23 (Celaexa or Cipramil or Cipram or Recital or Emocal or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Esertia or Prozac or Fontex or Seromek or Seronil or Sarafem or Ladose or Motivest or Fluclot or fluvox or Lovan or Luvox or Fervari or Favoril or Movox or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanal or Paroxet or Loxamine or Zolof or Lustral or Serian or Asentra):ti,ab,kw (Word variations have been searched)  
#24 [or #19-#23]  

**Appendix 2. MEDLINE (Ovid) search strategy**

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or vertebral artery dissection/  
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH):tw.  
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral$) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)):tw.
Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

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Cochrane Database of Systematic Reviews

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$).tw.
11. SSRIS1.tw.
12. (alaprocain$ or cericlamin$ or citalopram or dapoxetin$ or escitalopram or femoxetine$ or fluoxetine$ or fluvoxamin$ or paroxetine$ or sertralin$ or trazodone or vilazodone or zimelidine).tw, nm.
13. (Celexa or Cipramil or Cipram or Recital or Emocal or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Eserita or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Fluctin or fluxor or Lovan or Luvox or Fevarin or Faverin or Favoril or Movox or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Zolof or Lustral or Serlain or Asentra).tw, nm.
14. 9 or 10 or 11 or 12 or 13
15. 8 and 14
16. exp animals/ not humans.sh.
17. 15 not 16
18. Randomized Controlled Trials as Topic/
19. random allocation/
20. Controlled Clinical Trials as Topic/
21. control groups/
22. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
23. Clinical Trials Data Monitoring Committees/
24. double-blind method/
25. single-blind method/
26. Placebos/
27. placebo effect/
28. cross-over studies/
29. Multicenter Studies as Topic/
30. Therapies, Investigational/
31. Drug Evaluation/
32. Research Design/
33. Program Evaluation/
34. evaluation studies as topic/
35. randomized controlled trial.pt.
36. controlled clinical trial.pt.
37. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
38. multicenter study.pt.
40. meta analysis.pt.
41. meta-analysis as topic/
42. random$.tw.
43. (controlled adj5 (trial$ or stud$)).tw.
44. (clinical$ adj5 trials).tw.
45. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
46. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
47. (multicenter or multicentre or therapeutic) adj5 (trial$ or stud$)).tw.
48. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
49. (singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
50. (coin adj5 (flip or flipped or toss$)).tw.
51. latin square.tw.
52. versus.tw.
53. (cross-over or cross over or crossover).tw.
54. placebo$.tw.
55. sham.tw.
56. (assign$ or alternate or allocat$ or counterbalance$ or multiple baseline).tw.
57. controls.tw.
58. (treatment$ adj6 order$).tw.
59. (meta-analy$ or metaanaly$ or meta analy$ or systematic review or systematic overview).tw.
Appendix 3. Embase (Ovid) search strategy

1. cerebrovascular disease/ or basal ganglion hemorrhage/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or cerebrovascular accident/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/ or stroke/
2. stroke unit/ or stroke patient/ 
3. (stroke or poststroke or post-stroke or cerebrovascular or brain vascular or cerebral vascular or cerebral or cva or apoplexy or SAH).tw.
4. ((brain or cerebr or cerebell or intracran or intracerebral) adj5 (isch?em? or infarct? or thrombo? or emboli? or occlus?)).tw.
5. ((brain or cerebr or cerebell or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage or hemorrhage or haematoma or hematoma or bleed?)).tw.
6. hemiparesis/ or hemiplegia/ or paresis/ 
7. (hemipleg$ or hemipar$ or paresis or paretic).tw.
8. or/1-7
9. exp serotonin uptake inhibitor/
10. ((serotonin or 5-HT or 5 HT or 5-hydroxytryptamine or 5 hydroxytryptamine) adj5 (uptake or reuptake or re-uptake) adj5 inhibit$).tw.
11. SSRI$.tw.
12. ((alaproclat$ or cericlamin$ or citalopram or dapoxetine? or escitalopram or fomoxetin$ or fluoxetine? or fluvoxamin$ or paroxetine? or sertralin$ or trazodone or vilazodone or zimelidine)).tw.
13. (Celexa or Cipramil or Cipram or Recital or Emoca or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Eserti or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Fluctin or Flux or Lovan or Luvox or Fevarin or Faverin or Favoril or Moxov or Paxil or Seroxat or Sereupin or Aropan or Deroxat or Divarius or Rextin or Xetanor or Paroxat or Loxamine or Zoloft or Lustral or Serlain or Asentra).tw,tn.
14. 9 or 10 or 11 or 12 or 13
15. 8 and 14
16. limit 15 to human
17. Randomized Controlled Trial/
18. Randomization/
19. Controlled Study/
20. control group/
21. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/ 
22. Double Blind Procedure/
23. Single Blind Procedure/ or triple blind procedure/
24. placebo/
25. "types of study"/
26. research subject/
27. random$.tw.
28. (controlled adj5 (trial$ or study$)).tw.
29. (clinical$ adj5 trial$).tw.
30. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
31. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
32. (sing?l$ or doubl$ or tripl$ or treb$ adj5 (blind$ or mask$)).tw.
33. (coin adj5 (flip or flipped or toss$)).tw.
34. versus.tw.
35. placebo$.tw.
36. controls.tw.
37. or/17-36
38. 16 and 37

Appendix 4. CINAHL (Ebsco) search strategy

S23. S12 and S22
S22. S13 or S17 or S18 or S19 or S20 or S21
S21. AB Celexa or Cipramil or Cipram or Recital or Emoca or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Eserti or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Fluctin or Flux or Lovan or Luvox or Fevarin or Faverin or Favoril or Moxov or Paxil or Seroxat or Sereupin or Aropan or Deroxat or Divarius or Rextin or Xetanor or Paroxat or Loxamine or Zoloft or Lustral or Serlain or Asentra
S20. TI Celexa or Cipramil or Cipram or Recital or Emoca or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Eserti or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Fluctin or Flux or Lovan or Luvox or Fevarin or Faverin or Favoril or Moxov or Paxil or Seroxat or Sereupin or Aropan or Deroxat or Divarius or Rextin or Xetanor or Paroxat or Loxamine or Zoloft or Lustral or Serlain or Asentra

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review)

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Appendix 5. AMED (Ovid) search strategy

1. cerebrovascular disorders/ or cerebral hemorrhage/ or cerebral infarction/ or cerebral ischemia/ or cerebrovascular accident/ or stroke/ 
2. (stroke or poststroke or post-stroke or cerebrovascular).tw. 
3. ((brain* or cerebr* or cerebell* or intracran* or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw. 
4. ((brain* or cerebr* or cerebell* or intracranial or subarachnoid).adj5 (hemorrhage$ or hemorrhage$ or haematoma$ or or bleedin$)).tw. 
5. hemicplesia/ 
6. (hemipleg$ or hemipar$ or paresis or paretic).tw. 
7. or/1-6 
8. antidepressive agents/ 
9. ((serotonin or 5-HT or 5HT or 5-hydroxytryptamine or 5-hydroxytryptamine) adj5 (uptake or reuptake or re-uptake) adj5 inhibit$)).tw. 
10. SSSI1.tw. 
11. (alaproclat$ or cericlamin$ or citalopram or dapoxygen$ or escitalopram or fomoxetin$ or fluoxetin$ or fluvoxamin$ or paroxetin$ or sertralin$ or trazodone or vilazodone or zimelidine).tw. 
12. (Celexa or Cipramil or Cipram or Recital or Emocal or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Esertia or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivate or Flucin or flux or lovan or Luvox or Favarin or Favoxil or Movox or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Lodaxine or Zoloft or Lustral or Serlair or Asentra).tw. 
13. 8 or 9 or 10 or 11 or 12 
14. 7 and 13 

Appendix 6. PsycINFO (Ovid) search strategy

1. cerebrovascular disorders/ or cerebral hemorrhage/ or exp cerebral ischemia/ or cerebral small vessel disease/ or cerebrovascular accidents/ or subarachnoid hemorrhage/ 
2. (stroke or poststroke or post-stroke or cerebrovascular).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 intracranial or subarachnoid).adj5 (hemorrhage$ or hemorrhage$ or haematoma$ or or bleedin$)).tw. 
5. hemicplesia/ 
6. (hemipleg$ or hemipar$ or paresis or paretic).tw. 
7. or/1-6 
8. exp serotonin reuptake inhibitors/
Appendix 7. Search strategy for the trial registers

World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch;search strategy)
1. Basic search: CEREBR* AND selective serotonin OR CEREBR* AND alaprocate OR CEREBR* AND cerclimine OR CEREBR* AND citalopram OR CEREBR* AND clomipramine OR CEREBR* AND dapoxtine OR CEREBR* AND etoperidone OR CEREBR* AND escitalopram OR CEREBR* AND femoxetine OR CEREBR* AND fenfluramine OR CEREBR* AND fluoxetine OR CEREBR* AND fluvoxamine OR CEREBR* AND norfenfluramine OR CEREBR* AND paroxetine OR CEREBR* AND sertraline OR CEREBR* AND trazodone OR CEREBR* AND vilazodone OR CEREBR* AND zimelidine
2. Basic search: STROKE AND selective serotonin OR STROKE AND alaprocate OR STROKE AND cerclimine OR STROKE AND citalopram OR STROKE AND clomipramine OR STROKE AND dopoxide OR STROKE AND etoperidone OR STROKE AND escitalopram OR STROKE AND femoxetine OR STROKE AND fenfluramine OR STROKE AND fluoxetine OR STROKE AND fluvoxamine OR STROKE AND norfenfluramine OR STROKE AND paroxetine OR STROKE AND sertraline OR STROKE AND trazodone OR STROKE AND vilazodone OR STROKE AND zimelidine
US National Institutes of Health Trials Register (ClinicalTrials.gov) search strategy
(“selective serotonin” OR alaprocate OR cerclimine OR citalopram OR clomipramine OR dapoxtine OR etoperidone OR escitalopram OR femoxetine OR fenfluramine OR fluoxetine OR fluvoxamine OR norfenfluramine OR paroxetine OR sertraline OR trazodone OR vilazodone OR zimelidine) AND EXACT “Interventional” [STUDY-TYPES] AND Stroke [DISEASE]

WHAT'S NEW

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 January 2021</td>
<td>New citation required and conclusions have changed</td>
<td>The conclusions are now more certain than in the previous version.</td>
</tr>
<tr>
<td>7 January 2021</td>
<td>New search has been performed</td>
<td>We updated the searches. We identified and included 13 new studies. There are now 76 included studies involving 13,029 participants. We have created a funnel plot and entered data on SF36 vitality, quality of life, and fractures.</td>
</tr>
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HISTORY

Review first published: Issue 11, 2012

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 March 2019</td>
<td>New citation required and conclusions have changed</td>
<td>We include 2 new high-quality trials. Meta-analysis of all the high-quality trials shows no effect on either of the co-primary outcomes of independence and disability. Meta-analysis of all trials irrespective of trial quality showed that SSRIs reduced disability at the end of treatment.</td>
</tr>
<tr>
<td>14 March 2019</td>
<td>New search has been performed</td>
<td>We have clarified that there are 2 primary outcomes: independence and disability.</td>
</tr>
</tbody>
</table>
For modified Rankin Score (mRS) in advance of starting this update, we decided to report the proportion of independent participants compared with the proportion dead or dependent which is the usual convention in stroke trials. In the previous version we had reported the proportion dependent and had excluded the dead participants from the analysis.

We checked the total number of participants included in the 2012 review. We had stated that the trials included 4060 participants; there were errors in the arithmetic (due to counting number allocated rather than those recruited, and omitting to count data from 2 small trials). When we recalculated the figures, there were 4109 recruited. We excluded 7 of these trials (439 participants) which had combined an SSRI with another active intervention and compared it to the active treatment alone or where there was a non-random component to sequence generation process (see list of excluded studies in text).

We added 14 new completed trials, recruiting 5498 participants.

There are now a total of 63 trials recruiting a total of 9168 participants.

We decided to restrict our primary analyses only to those trials at low risk of bias. We did this because we wished to provide a clear answer about the risks and benefits of SSRIs, which was not influenced by trial quality and because it would have been impractical, given the resources for this update, to perform analyses including all the low-quality trials. We made this decision before we knew the results of the largest trial in this review (FOCUS). We have, however, performed a sensitivity analysis for dependence and disability (our primary outcomes) using data from all trials; as in the first version of the review, this sensitivity analysis showed that when low-quality trials are included, results tend to be in favour of SSRIs.

We adhered to the MECIR standards for conduct and reporting.

We shortened our list of excluded studies in line with the Cochrane Handbook, by not listing those studies that obviously did not fulfil inclusion criteria, including those studies which clearly had an ineligible comparator, intervention or study design.

26 August 2013 Amended

The review authors identified minor errors following publication of the previous version. These errors have now been corrected and have resulted in very minor changes in SMD for disability and some I² values. The changes have not materially changed the results or conclusions of the review.

Changes made:

1) the total number of participants has been changed from 4059 to 4060;

2) Almeida 2006 recruited people without depression; this has been corrected in the 'Characteristics of included studies' table, and data have been moved to 'did not have to have depression' in the relevant subgroup analyses;
(3) disability data for Acler 2009 had been entered incorrectly; this has now been corrected.

CONTRIBUTIONS OF AUTHORS

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

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 screened citations, retrieved potentially relevant papers and screened their eligibility, assisted with data extraction, performed risk of bias assessments.

Cheng Fang Hsieh screened citations, retrieved potentially relevant papers and screened their eligibility, assisted with data extraction, performed risk of bias assessments and approved the final version.

Simiao Wu screened citations, retrieved potentially relevant papers and screened their eligibility, assisted with data extraction, performed risk of bias assessments and approved the final version.

Erik Lundström screened citations, retrieved potentially relevant papers and screened their eligibility, assisted with data extraction, performed risk of bias assessments and approved the final version.

Xing Hua screened citations, retrieved potentially relevant papers, assisted with data extraction, performed risk of bias assessments and approved the final version.

Linnea Lindgren screened citations, retrieved potentially relevant papers, assisted with data extraction, performed risk of bias assessments and approved the final version.

Ann-Sofie Rudberg screened citations, retrieved potentially relevant papers and screened their eligibility, assisted with data extraction, performed risk of bias assessments and approved the final version.

Mansur Kutlubaev screened citations, retrieved potentially relevant papers and screened their eligibility, assisted with data extraction, performed risk of bias assessments and approved the final version.

Amanda Barugh screened citations, retrieved potentially relevant papers and screened their eligibility, assisted with data extraction, drafted the manuscript for submission, performed risk of bias assessments and approved the final version.

Maree Hackett screened citations, retrieved potentially relevant papers and screened their eligibility, assisted with data extraction, performed risk of bias assessments and approved the final version.

Graeme Hankey conceived the review, provided expertise in relation to analysis methods, and approved the final version of the review.

Martin Dennis provided topic expertise, advised on methods of analysis and approved the final version.

DECLARATIONS OF INTEREST

Lynn A Legg: none known.

Ann-Sofie Rudberg: none known.

Xing Hua: none known.

Simiao Wu: none known.

Maree L Hackett: Grants and contracts: Project grant (NHMRC funding for AFFINITY trial), HTA Program (National Institute for Health Research funding for FOCUS), Framework grant (Swedish Research Council funding for EFFECTS); all funding received by the author’s institution. Payment for a fellowship: National Health and Medical Research Council (NHMRC), received by the author’s institution.

Russel Tilney: none known.

Linnea Lindgren: none known.
Mansur A Kutlubaev: none known.
Cheng-Fang Hsieh: none known.
Amanda Barugh: none known.

Graeme J Hankey: Grants and contracts: Chief Investigator for the AFFINITY trial, National Health and Medical Research Council of Australia, received by the author’s institution. Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events: Discussion about antithrombotic therapy to prevent stroke, Medscape, received by the author. Consulting fees: Consulting on design of a possible phase III trial of a new anticoagulant in atrial fibrillation, Janssen Research and Development, received by the author. Payment for participation on a Data Safety Monitoring Board, Advisory Board, or Guideline Panel: Chair or Member of Data Safety Monitoring Committees, of ACI trials of an immune therapies for Alzheimer’s disease, AC Immune, Lausanne, Switzerland, received by the author; Member of Stroke Prevention Initiative, Bayer, received by the author; Other: Associate Editor of Circulation, American Heart Association, received by the author. Published opinions in medical journals, the public press, broadcast and social media relevant to the interventions in the work: Publication, Lancet Neurology, AFFINITY Trial Collaboration. Safety and efficacy of fluoxetine on functional outcome after acute stroke (AFFINITY): a randomised, double-blind, placebo-controlled trial. Lancet Neurology 2020; 19(8): 651-660. doi: 10.1016/S1474-4422(20)30207-6. PMID: 32702334; Publication, Stroke. Declaring involvement in eligible studies: Yes, National Health and Medical Research Council of Australia (for AFFINITY trial).

Erik Lundström: Grants and contracts: Funding, STROKE-Riksförbundet, received by author’s institution. Leadership or other fiduciary role in other board, society, committee, or advocacy group: Chief Investigator of the EFFECTS trial, received by author. Declaring involvement in eligible studies: The Swedish Research Council, The Swedish Heart-Lung Fund, The Swedish Brain Fund, STROKE-Riksförbundet, The Swedish Medical Society, Konung Gustaf V:s och Drottnings Kristinas Frimurarstiftelse.

Martin Dennis: Grants and contracts: Grants received to carry out FOCUS trial - and RCT which is included in the review, NIHR, Stroke Association, received by the author’s institution

Gillian E Mead: Grants and contracts: Research grants, HTA NIHR, co-applicant on grants led by Prof Graeme Hankey and Maree Hackett, and Erik Lundstrom; NIHR incentive award for updating this review, both received by the author’s institution.

Gillian Mead, Martin Dennis, Maree Hackett, Erik Lundstrom and Graeme Hankey are investigators on the FOCUS trial (Fluoxetine or control under supervision) in the UK, the AFFINITY (Assessment of fluoxetine in stroke recovery) trial in Australia, and the EFFECTs trial in Sweden designed to assess the impact of fluoxetine on disability and dependency after stroke. None of these review authors extracted data from these three trials.

**Sources of Support**

**Internal sources**
- National Health and Medical Research Council of Australia, Australia
  - Maree Hackett: Career Development Fellowship, Population Health (Level 2), APP1141328 (1/1/18-31/12/21)

**External sources**
- Chief Scientist Office, Scotland, UK
  - The Chief Scientist Office, Scotland, provides infrastructure support for Cochrane Stroke
- Incentive grant from National Institute of Health Research, UK
  - £5000 incentive grant to support an honorarium to Lynn Legg
- NIHR Incentive grant, UK
  - £7000 to backfill some of Gillian Mead’s academic time to enable her to work on this review.

**Differences between protocol and review**

Changes to 'Criteria for considering studies for this review'
We did not change the criteria since the last update.

Changes to 'Data collection and analysis'
We included cognition as a secondary outcome.
Changes to Results

We added in new eligible studies, and updated all analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Anxiety [*drug therapy]; Citalopram [therapeutic use]; Cognition [drug effects]; Depression [*drug therapy]; Fluoxetine [therapeutic use]; Nervous System Diseases [drug therapy]; Paroxetine [therapeutic use]; Randomized Controlled Trials as Topic; Serotonin Uptake Inhibitors [adverse effects] [*therapeutic use]; Sertraline [therapeutic use]; Stroke [*drug therapy] [psychology]; Stroke Rehabilitation

MeSH check words

Adult; Humans