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

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[Intervention Review]

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery

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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.

Data collection and analysis

We extracted data on demographics, stroke type and, our pre-specified outcomes, and bias sources. Two review authors independently extracted data. We used mean difference (MD) or standardised mean differences (SMDs) for continuous variables, and risk ratios (RRs) for dichotomous variables, with 95% confidence intervals (CIs). We assessed bias risks and applied GRADE criteria.

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 SMD -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 (SMD -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.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Fluoxetine versus control at end of treatment				
Disability (primary analysis)		SMD 0.0 (-0.05, 0.05)		5436 (5 studies)	⊕⊕⊕⊕ High	-
Independent on modified Rankin score (mRS 0 to 2) (primary analysis)	**Study population**		RR 0.98 (0.93 to 1.03)	5926 (5 studies)	⊕⊕⊕⊕ High	-
	1541/2971 (i.e. 52 per hundred)	1498/2955 (i.e. 51 per hundred)				
Neurological deficit score		SMD -0.39 (95% CI (-1.12 to 0.33)		30 participants, one study	⊕⊕⊖⊖ Low[a]	This is a small effect (based on the 'rule-of-thumb' method for interpreting SMD)
Depression (continuous data)		SMD -0.14 (-0.19 to -0.08)		5356 (4 studies)	⊕⊕⊕⊕ High	This is a small effect (based on the 'rule-of-thumb' method for interpreting SMD)
Death	**Study population**		RR 1.01 (0.82 to 1.24)	6090 (6 studies)	⊕⊕⊕⊖ Moderate	-
	168/3029 (i.e. 55 per thousand)	170/3061				

		(i.e. 56 per thousand)				
Number of seizures	**Study population**		RR 1.40 (1.00 to 1.98)	6080 (6 studies)	⊕⊕⊕⊖ Moderate[c]	-
	54/3024 (i.e. 18 per thousand)	76/3056 (i.e. 25 per thousand)				
Bone fractures	**Study population**		RR 2.35 (1.62 to 3.41)	6080 (6 studies)	⊕⊕⊕ ⊕ High	-
	40/3024 (i.e. 13 per thousand)	93/3056 (i.e. 30 per thousand)				

*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.

[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).

BACKGROUND

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 (formulation 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 neurones 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 (Pälvimäki 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 enhances 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 SRRI 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. W e 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.

- Death
- Adverse events including gastrointestinal (GI) side effects, bleeding, seizures, and any other side effect. For this update, there were sufficient data on fractures to include this as an additional analysis, and so we included this as an additional Forest plot.
- Cognition-this could include self report or directly measured cognition. We would have prioritised directly measured cognition if these data had been available. In the previous update no trials reported this-but the new trials included in this update did include cognition.
- Leaving the trial early (for reasons other than death).

We anticipated that most studies would assess these at the end of treatment and possibly at one or more time points. We did not stipulate a minimum follow-up time. We did not stipulate in advance precisely how multiple time points would be handled (if they had been found).

In the previous update we stated that we would also analyse change in depression scores over time. For this update, we made the decision just to analyse depression score at the end of the studies, as change in scores were not reported by the new included trials.

Search methods for identification of studies

See the methods for the Cochrane Stroke Group Specialised register. We searched for studies in all languages and arranged for the translation of trials where necessary.

Electronic searches

We developed the MEDLINE search strategy with the help of the Cochrane Stroke Group Information Specialist and adapted it for the other databases.

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)
- US National Institutes of Health ongoing Trials Register ClinicalTrials.gov (www.ClinicalTrials.gov) (7 January 2021)
- 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

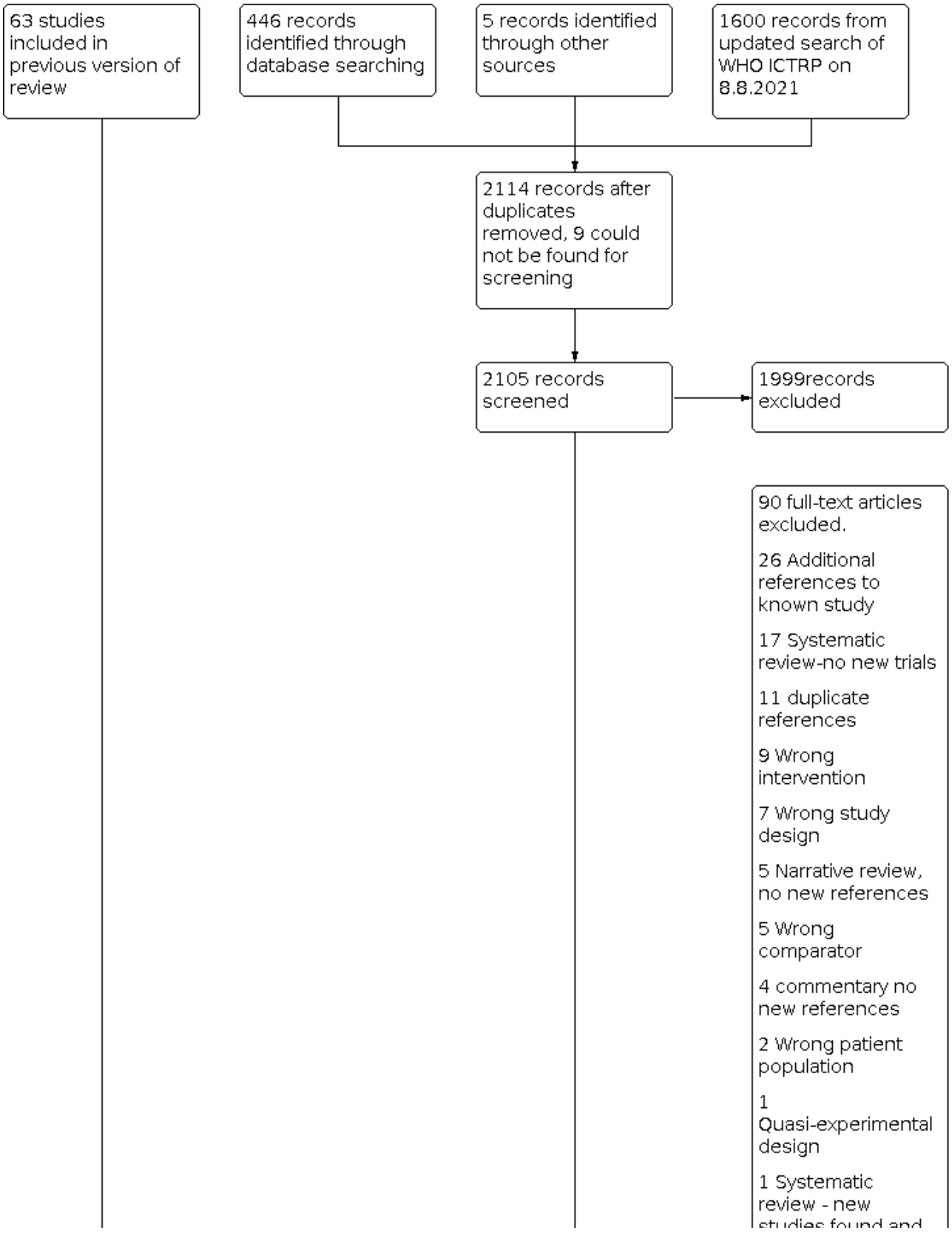
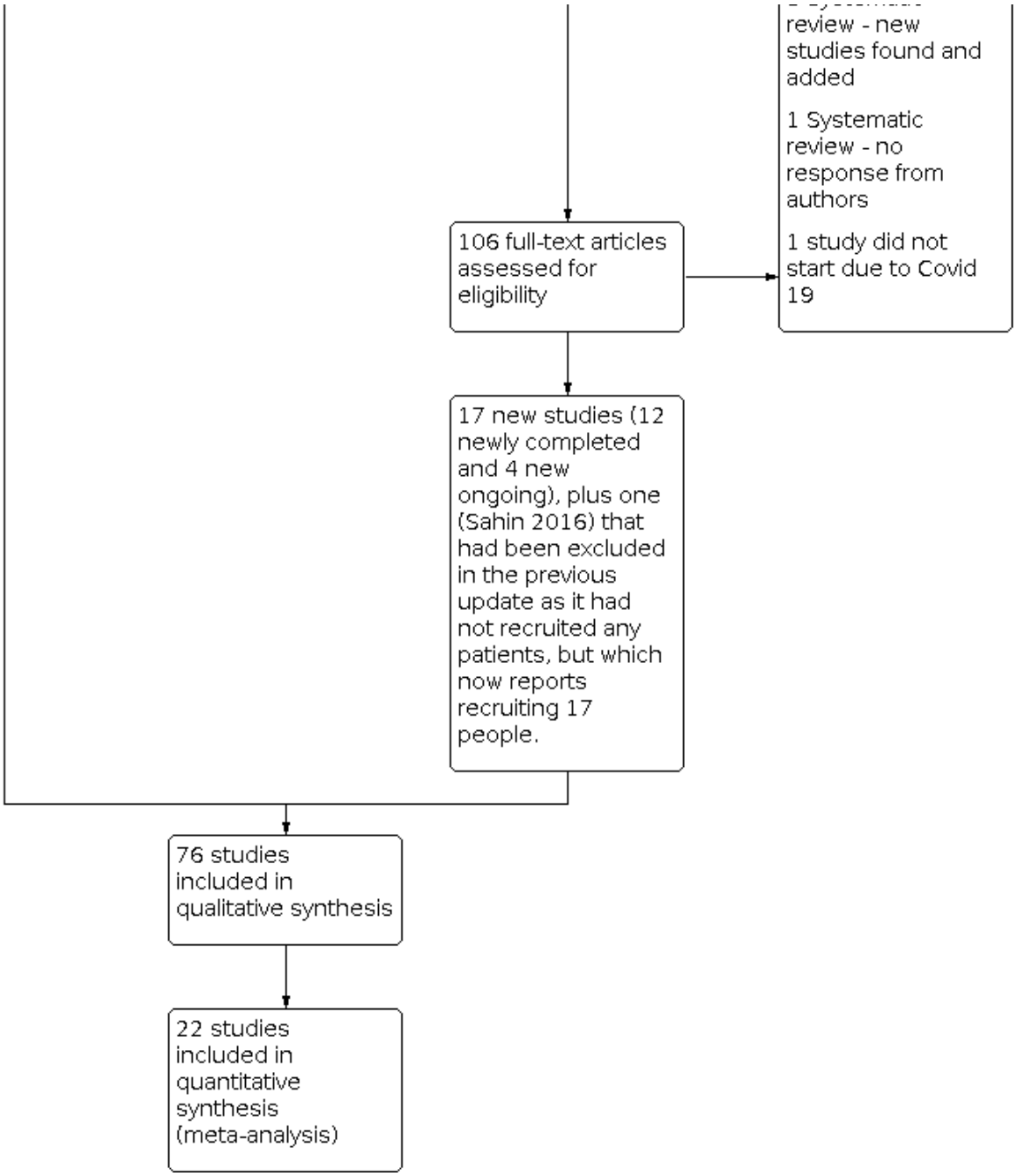


Figure 1. (Continued)



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 Funtional Independence Measure (FIM) for disability score, the Beck Depression Inventory (BDI) or the Hamilton Rating Scale for Depression (HAMD) 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 I^2 statistic. We assessed statistical heterogeneity by visually examining forest plots. Thresholds for the interpretation of the I^2 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 ; IRCT201112228490N1; 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.

- Five of these previously ongoing studies are still ongoing: EudraCT 2005-005266-37, NCT02767999, NCT02865642, NCT03448159, NCT03826875.
- 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; Birchenall 2019; Brown 1998; Chen 2001; Cheng 2003; Chollet 2011; Dam 1996; Dike 2019; EFFECTS 2020; Feng 2004; FOCUS 2019; 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

2001; Razazian 2014; Restifo 2001; Robinson 2000a; Robinson 2000b; Shah 2016; Song 2006; Wang 2003; Wen 2006; Wiart 2000; Xu 2001; Zhao 2011; Zhou 2008);

- eight studies used sertraline (Almeida 2006; Burns 1999; Guo 2009; Meara 1998; Murray 2005; NCT00177424; Rasmussen 2003; Xie 2005);
- 13 studies used paroxetine (Chen 2002; Chen 2005b; GlaxoSmithKline 1998; He 2005; Lai 2006; Li 2005; Li 2007; Pan 2018; Wang 2009; 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; Bembenek 2020; Birchenall 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 2016; 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; Feng 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 2008; Li 2017; Liu 2006; Meara 1998; Miao 2004; Murray 2005; Robinson 2000a; Song 2006; Wang 2003; 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; Bembenek 2020; Birchenall 2019; Brown 1998; Burns 1999; 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; NCT00177424; 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; Anderson 2002; Anonymous 2012a; Anonymous 2012b; Berends 2009; Chen 2019; Choi Kwon 2008; Finkenzeller 2009; Foster 2019; Bonin Pinto 2019; Gourab 2015; Graffagnino 2002; Ji 2000; Kitago 2020; Li 2002; Liang 2003; Liu 2004; Liu 2020; Mosarrezaii 2018; NCT01963832; Robinson 2011; Sitzer 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; Kitago 2020; Liu 2020; Mosarrezaii 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; IRCT201112228490N1; IRCT2012101011062N1; IRCT2017041720258N37; IRCT20210307050617N1; 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;

Jurcau 2016; NCT00967408). See Characteristics of studies awaiting classification.

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.

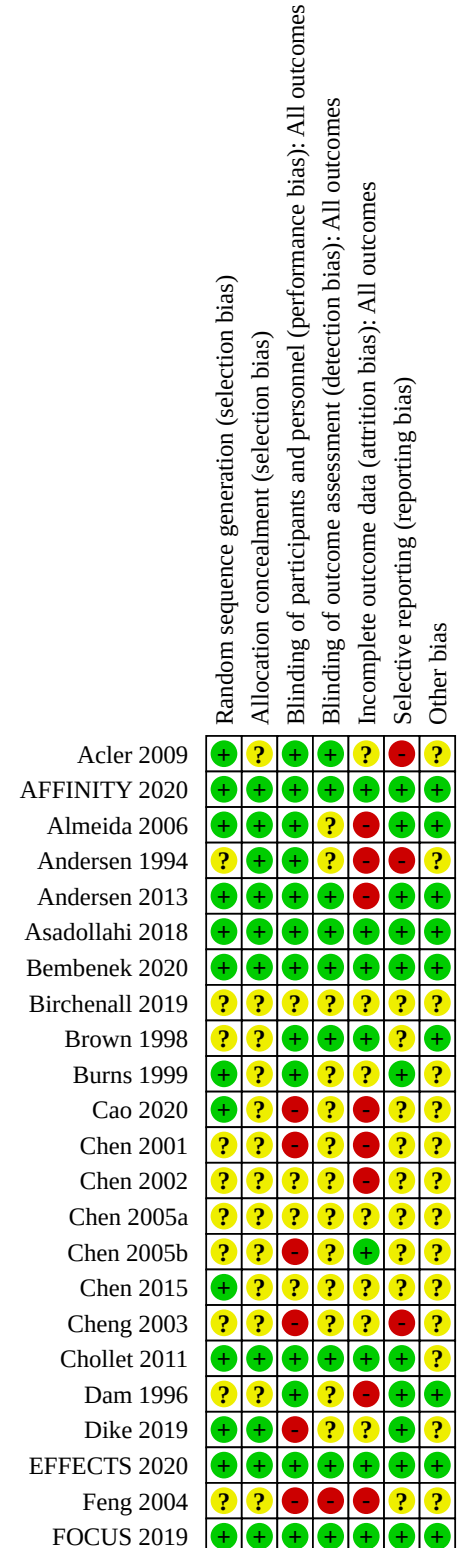


Figure 2. (Continued)

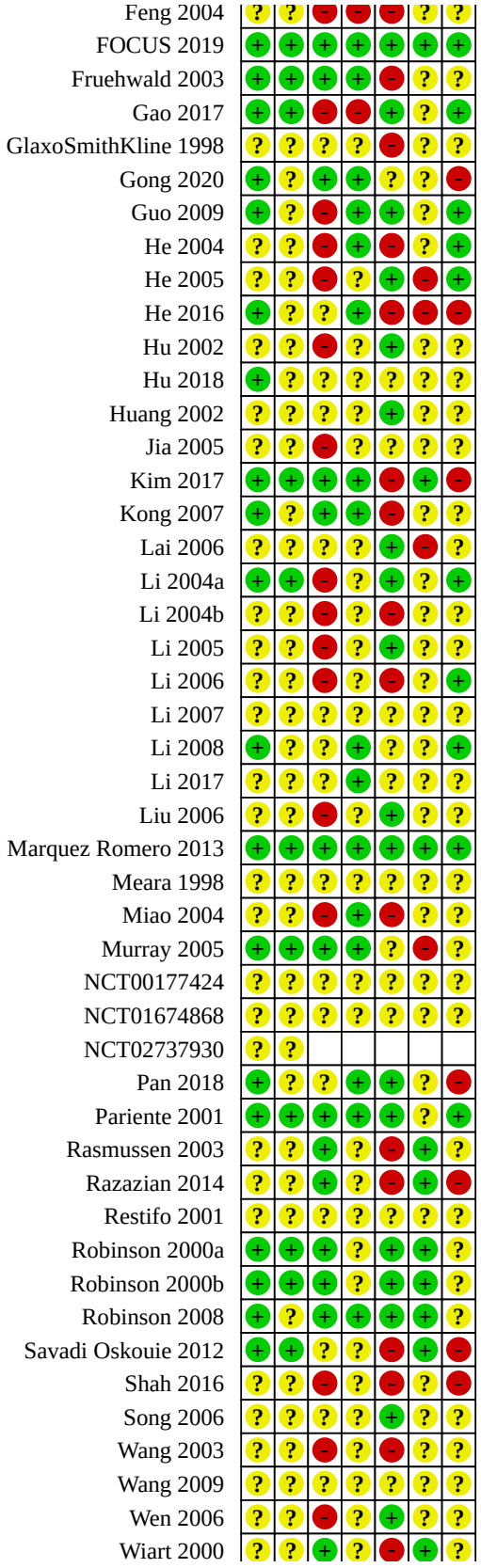


Figure 2. (Continued)

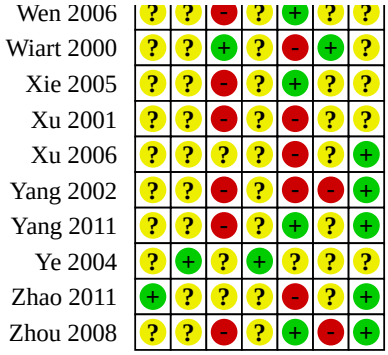
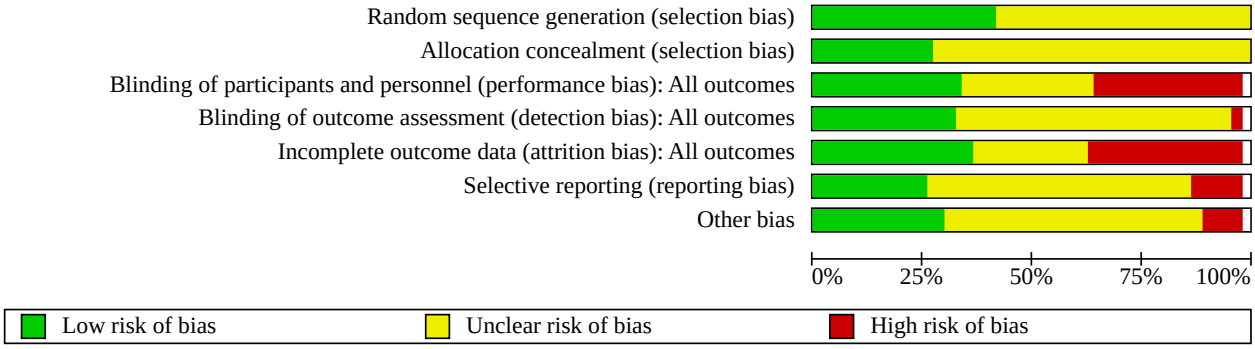


Figure 3. 'Risk of bias' graph: review authors' judgements about each 'risk of bias' item presented as percentages across all included studies.



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 a 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

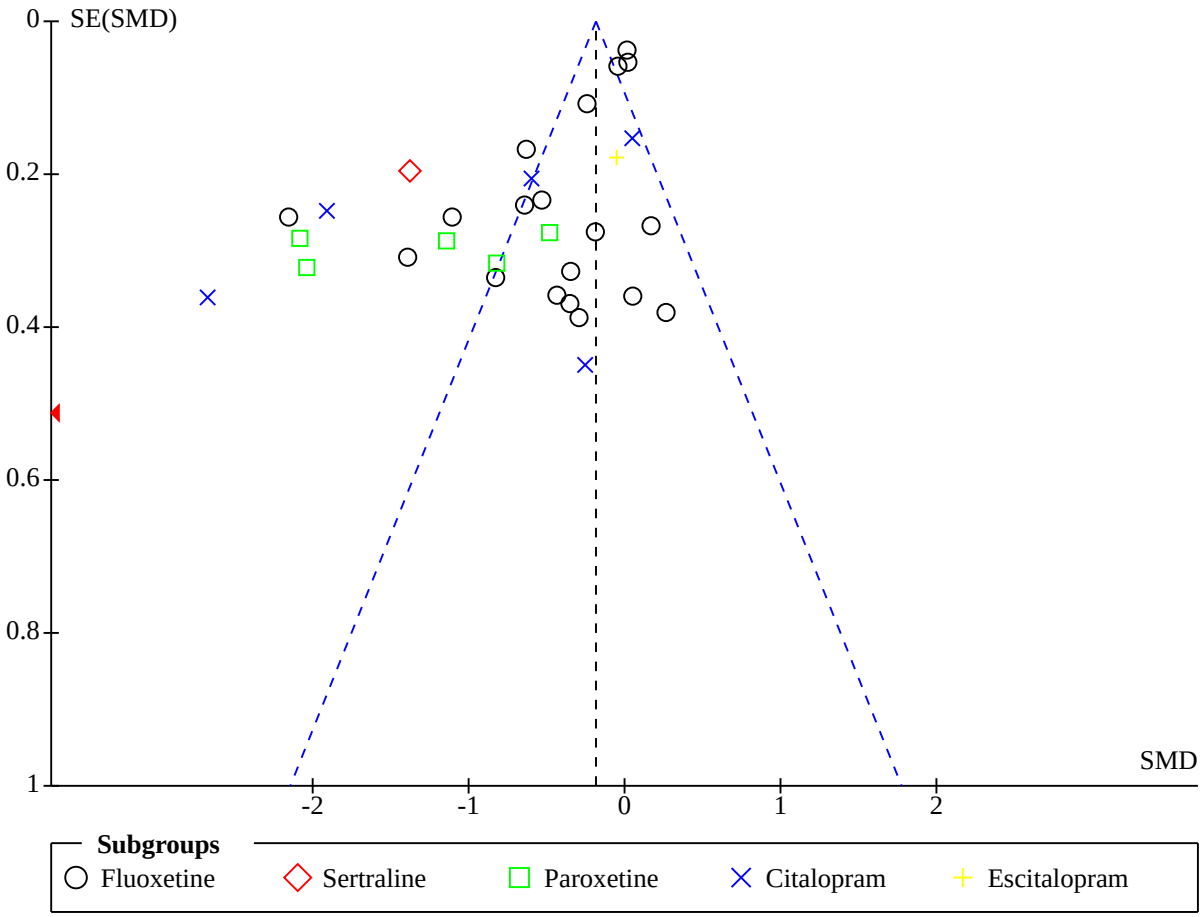
Six trials were at low risk of bias across all domains (AFFINITY 2020; Asadollahi 2018; Bembenek 2020; EFFECTS 2020; FOCUS 2019; Marquez Romero 2013) (Figure 2; Figure 3). For two of these trials, the final judgement was made after obtaining further information from the trialists (Asadollahi 2018; Bembenek 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 (I^2 = 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 I^2 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, I^2 = 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 (I^2 = 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 (I^2 = 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 (I^2 = 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 (I^2 = 45%) (Analysis 1.8).

Gastrointestinal side effects at end of treatment

One study (30 participants) of 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 I^2 = 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, I^2 = 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; Bembenek 2020; EFFECTS 2020; FOCUS 2019). MD was -1.22 (95% CI -2.37 to -0.07) in favour of control, 4 trials, 5373 participants, I^2 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; I^2 = 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; Bembenek 2020; FOCUS 2019). The mean difference between groups was -0.06 (95% CI -1.24 to 1.11; 5524 participants, P = 0.92, I^2 = 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 ; I^2 = 0, no important heterogeneity, high -quality of 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 (I^2 = 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, I^2 = 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 SSRI 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.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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		
Bias	**Authors' judgement**	**Support for judgement**

Acler 2009 *(Continued)*

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

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: fluoxetine = 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%)

AFFINITY 2020 *(Continued)*

	• 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	ACTRN12611000774921Recruitment 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.

AFFINITY 2020 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: " 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."
Allocation concealment (selection bias)	Low risk	Quote: " 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."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "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."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 5% dropped out or died and there is no compelling evidence of a difference between the 2 groups
Selective reporting (reporting bias)	Low risk	All outcomes in protocol were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Almeida 2006

Study characteristics

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)

Almeida 2006 *(Continued)*

	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
Interventions	Treatment: sertraline 50 mg daily (night) Control: matched placebo Duration: treatment continued for 24 weeks Duration of follow-up (post-treatment to study end): 28 weeks
Outcomes	Depression: change in scores from baseline to end of treatment on HDRS, proportion depressed Change in MMSE scores mRS Death Leaving the trial early Check list of possible AEs read out to participant by a research nurse
Funding source	Funded by an unrestricted grant from Rotary Health Research Fund
Notes	Recruitment June 2004 to June 2006 Conflicts of interest not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Centralised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated in paper, matched placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated in paper
Incomplete outcome data (attrition bias) All outcomes	High risk	Performed last observation carried forward
Selective reporting (reporting bias)	Low risk	Trial protocol published on www.strokecentre.org/trials . This weblink is no longer available so we have been unable to check whether all the outcomes

Almeida 2006 *(Continued)*

		were reported. We have contacted the author to check this-who confirm that all endpoints were reported
Other bias	Low risk	No other obvious biases

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)*

	Unable to use: BI, Social Activities Index, MMSE (data not presented)
Funding source	Funded by Lundbeck Foundation, Medical Research Foundation for North Jutland County, The Aalgorg 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

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

Methods	Multicentre Study type: interventional (clinical trial) Intervention model: parallel assignment Primary purpose: treatment
Participants	642 participants Country: Denmark Setting: inpatient

Andersen 2013 *(Continued)*

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 m^2)
- 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated randomization code was used to randomize patients in blocks of 10."
Allocation concealment (selection bias)	Low risk	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."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participant, care provider, and investigator assured and unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessor assured and unlikely that the blinding could have been broken
Incomplete outcome data (attrition bias) All outcomes	High risk	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 < 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 < 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)
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 to the review have been reported in the prespecified way
Other bias	Low risk	The study appears to be free of other sources of bias

Asadollahi 2018

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)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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)."
Allocation concealment (selection bias)	Low risk	Computer-generated schedule confirmed with authors
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All of the drugs for each group of subjects were over-encapsulated by a pharmacist."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Three evaluators were used in our study, namely, neurology residents who were blind to the interventions."
Incomplete outcome data (attrition bias) All outcomes	Low risk	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: "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.")
Selective reporting (reporting bias)	Low risk	There was just one outcome measure planned (see reference on Iranian clinical trials register) and this was reported
Other bias	Low risk	The study appears to be free of other sources of bias

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

Bembenek 2020 *(Continued)*

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 ay 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 201 8. Authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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
Allocation concealment (selection bias)	Low risk	Allocation was concealed (further information obtained from the study author Jan Bembenek to confirm this)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "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."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Clinicians involved in randomisation and outcome assessments, the patients, and their families, were all masked so as to be unaware of treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	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
Selective reporting (reporting bias)	Low risk	Trial was registered and all outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

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

Birchenall 2019 *(Continued)*

	Inclusion criteria • Age 18 to 80 years • Social security affiliation • Day 3 to day 15 after stroke or brain haemorrhage • Hemiparesia 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
Risk of bias	

Birchenall 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available
Allocation concealment (selection bias)	Unclear risk	No information available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available
Selective reporting (reporting bias)	Unclear risk	No information available
Other bias	Unclear risk	No information available

Brown 1998

Study characteristics	
Methods	Parallel design Analysis: per protocol: 1 withdrawn (treatment), excluded from analysis
Participants	Diagnosis: stroke, time from stroke to randomisation not reported Randomised 10 to treatment and 10 to control Treatment: 9 completed treatment, mean ± SD age 61.4 ± 8.6 years, 55% men Control: 10 people completed placebo, mean ± SD age 63.7 ± 5.4 years, 60% men 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 Exclusion criteria: cognitive impairment, dysphasia, major depressive disorder
Interventions	Treatment: fluoxetine 20 mg daily Control: matched placebo Duration: 10 days Duration of follow-up: (end of treatment to end of study) 0
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

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

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

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

Cao 2020

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

Cao 2020 *(Continued)*

Funding source	
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	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
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control group did not receive a placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	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
Incomplete outcome data (attrition bias) All outcomes	High risk	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
Selective reporting (reporting bias)	Unclear risk	No protocol is available
Other bias	Unclear risk	The authors did not reply to questions and so we have graded this as unclear

Chen 2001

Study characteristics

Methods	Randomised trial Aim: 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
Participants	Country: China Setting: not described Participants: internal carotid system cerebral infarction or haemorrhage within previous 2 months Fluoxetine: 19 people, mean age 61.71 ± 8.13 years, 8 men Control: 18 people, mean age 62.85 ± 7.32 years, 7 men

Chen 2001 *(Continued)*

	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

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

Chen 2002

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		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process available to permit a judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described to allow a definite judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information available to permit a judgement of 'low risk' or 'high risk'

Chen 2002 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about blinding of outcome assessment available to permit a judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts: 4 in placebo and 0 in paroxetine
Selective reporting (reporting bias)	Unclear risk	Insufficient information available to permit a judgement of 'low risk' or 'high risk'
Other bias	Unclear risk	Demographic data not provided, so we cannot determine whether the baseline was balanced

Chen 2005a

Study characteristics	
Methods	To observe the changes of neurotransmitter in people with post-stroke depression by using encephalofluctuography technology, and observe the effect of antidepression treatment on the activity of neurotransmitter
Participants	48 participants with post-stroke depression
Interventions	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
Outcomes	Encephalofluctuography technology Level of sympathin and 5-hydroxytryptamine at 4 weeks and 3 months after treatment started
Funding source	Not stated
Notes	No data from our endpoints of interest, so data not included in a meta-analysis Recruitment March 2001 to December 2001 Conflicts of interest not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	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'
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described or not described in sufficient detail to allow a definite judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias)	Unclear risk	Not described

Chen 2005a *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Unclear

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

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) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts: none
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	No obvious risks, baseline similar

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)*

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

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

Cheng 2003 *(Continued)*

	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

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) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	59 participants were diagnosed to have depression by symptoms but only 57 were included in the results table
Selective reporting (reporting bias)	High risk	No protocol, no report of the results of the self-rating anxiety scale
Other bias	Unclear risk	No clear description of differences between the treatment and control group

Chollet 2011

Study characteristics

Methods	Randomised parallel-group trial
Participants	Location: France

Chollet 2011 *(Continued)*

	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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Balanced by centre with an allocation based on a block size of 4 generated with a computer random-number generator
Allocation concealment (selection bias)	Low risk	Sequentially-numbered opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical capsules for control arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study site investigators and all investigators were masked to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts: 2 participants died (1 in each group) and 3 dropped out; not stated how missing outcome data were dealt with
Selective reporting (reporting bias)	Low risk	Trial protocol published on www.strokecentre.org/trials, all outcomes were reported

Chollet 2011 *(Continued)*

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)*

Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Examining neurologists blind to treatment". 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
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above
Incomplete outcome data (attrition bias) All outcomes	High risk	2/35 dropouts (5.7%), per-protocol analysis
Selective reporting (reporting bias)	Low risk	Trial available, including results on www.strokecentre.org/trials: all specified outcome measures were reported
Other bias	Low risk	Baseline characteristics similar in the 2 groups

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

Dike 2019 *(Continued)*

	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	N o funding
Notes	PACTR201412000967245. Recruitment between January 2015 and May 2016. All authors declare no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Block randomization was used in the assignment of study participants. Permuted 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."
Allocation concealment (selection bias)	Low risk	Quote: "Allocation concealment was done using sequentially numbered envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	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
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	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

Dike 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	All the prespecified outcomes were reported
Other bias	Unclear risk	Insufficient information to to assess whether an important risk of bias exists

EFFECTS 2020

Study characteristics	
Methods	Multicentre RCT Study type: interventional (clinical trial) Allocation: randomised Intervention model: parallel assignment Masking: quadruple (participant, care provider, investigator, outcomes assessor) Primary purpose: treatment
Participants	1500 participants Country: Sweden Setting: inpatient At randomisation number allocated: N = 1500: fluoxetine (n = 750); placebo (n = 750) % male: fluoxetine (62%); placebo (62%) Age: mean age: fluoxetine = 70.6 ± 11.3; placebo = 71.0± 10.5 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

EFFECTS 2020 *(Continued)*

- History of epileptic seizures
- History of allergy or contraindications to fluoxetine
- Pregnant or breastfeeding
- Previous drug overdose or attempted suicide
- Already enrolled into a CTIMP
- Current or recent (within the last month) depression requiring treatment with an SSRI antidepressant
- Current use of medications which have serious interactions with fluoxetine
- Use of any MAOI during the last 5 weeks

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	clinicaltrials.gov/ct2/show/NCT02683213. Recruitment between Oct 20, 2014, and June 28, 2019 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 inthe 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

Bias	Authors' judgement	Support for judgement
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

EFFECTS 2020 *(Continued)*

		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) All outcomes	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) All outcomes	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) All outcomes	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)*

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	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)
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	Baseline balanced

FOCUS 2019

Study characteristics

Methods	Multicentre RCT

FOCUS 2019 *(Continued)*

	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
- Euroquol 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

Funding source	MHRA approval granted. Start-up phase funded by The Stroke Association. Main phase funded by NIHR
Notes	ISRCTN83290762. Recruitment 10 September 2012 to 31 March 2017. Authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned in a 1:1 ratio to receive fluoxetine or placebo, by use of a centralised randomization system."
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly assigned in a 1:1 ratio to receive fluoxetine or placebo, by use of a centralised randomization system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	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."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	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%)
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

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

Fruehwald 2003 *(Continued)*

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 Decmeber 1998. Conflicts of interest not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation, using random permutated block design
Allocation concealment (selection bias)	Low risk	Centralised concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States blinded, used matching placebo

Fruehwald 2003 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	States blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	4/54, per protocol analysis
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	Baseline balanced All participants were randomly assigned to either fluoxetine or placebo treatment by the drug company independently of the research teams and the study centres

Gao 2017

Study characteristics	
Methods	Study type: interventional (clinical trial) Primary purpose: treatment
Participants	274 participants Country: China Setting: outpatient At randomisation number allocated: N = 274, citalopram (n = 91); placebo (n = 91); cognitive behavioural therapy (n = 92) % male: 51.8% Age: 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) Subtype of stroke: not available Severity of stroke: not available Time since stroke onset: acute ischaemic stroke within the previous 7 days 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

Gao 2017 *(Continued)*

Interventions	Experimental: citalopram 20 mg per day for a minimum of 3 months + general discussions Comparator 1: placebo + general discussions Comparator 2: placebo + cognitive behavioural therapy
Outcomes	• Depressive symptoms (17-item HAMD), 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization into one of three intervention groups was undertaken by an independent researcher using computer-generated random number sequences ..."
Allocation concealment (selection bias)	Low risk	Quote: "... that were prepared in advance and placed in consecutively numbered, sealed, opaque envelopes."
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-

Gao 2017 *(Continued)*

		pram + general discussions], persistent side-effects from the drugs led five patients to leave the study (two owing to orthostatic dizziness, one owing to palpitation, 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
Selective reporting (reporting bias)	Unclear risk	There is no study protocol available. Therefore insufficient information to judge high or low
Other bias	Low risk	The study appears to be free from other sources of bias

GlaxoSmithKline 1998

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 paroxetine 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-Global 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	Study period 29 August 1998 to 15 October 1999. Conflicts of interest not stated. Study number PAR625. Date updated: 11 March 2005

Risk of bias

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

Gong 2020

Study characteristics

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

Gong 2020 *(Continued)*

	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 (rtPA) 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 trila 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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"
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment is not described to allow a definite judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "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."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Three neurology residents who were blinded to the interventions served as eva- luators in the study. The evaluators obtained the patients' FMMS 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."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	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
Selective reporting (reporting bias)	Unclear risk	No published protocol to cross check for selective reporting
Other bias	High risk	Non-standard analysis of outcomes

Guo 2009

Study characteristics

Methods	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 Aim: to treat depression Analysis: according to allocated treatment
Participants	Country: China Setting: unknown Stroke criteria: first ever stroke, clinical diagnosis plus relevant lesion on imaging, age ≥ 60 years old Depression criteria: HAMD score ≥ 8, no depression prior to stroke Treatment: 40 people, mean age 67.6 ± 12.43 years, 23 men Control: 40 people, mean age 64.5 ± 12.07 years, 22 men

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random-number table
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	Outcome assessor blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts, analysed by allocated treatment
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	No obvious risk, balance baseline

He 2004

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

Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Balanced baseline, no obvious risks

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

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) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts, analysed according to treatment group
Selective reporting (reporting bias)	High risk	No protocol, the authors mentioned using the SDS and the SAS for evaluation but they did not report the results
Other bias	Low risk	Balanced baseline

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

He 2016 *(Continued)*

	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 benzodiapines 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
Interventions	Experimental: 20 mg of fluoxetine a day for 90 days and conventional therapy Comparator: conventional therapy
Outcomes	Primary outcome at days 15, 90 and 180 • NIHSS score Secondary outcome at days 90 and 180 • BI score

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Insufficient information on method of allocation concealment to judge high or low
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of high or low
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The evaluator was banned from participation in the treatment or from querying of the randomisation data."
Incomplete outcome data (attrition bias) All outcomes	High risk	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 > 5% lost to follow-up
Selective reporting (reporting bias)	High risk	The trial registration number/protocol does not match the study design presented, but rather matches ChiCTR-IPR - 15007658
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

Hu 2002

Study characteristics

Hu 2002 *(Continued)*

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method 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	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	No dropouts

Hu 2002 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	Balanced baseline, no other obvious risks

Hu 2018

Study characteristics	
Methods	Aim: to explore the effect of escitalopram on the neural function and cognitive function of patients with post-stroke depression RCT
Participants	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 > 18 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
Interventions	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
Outcomes	HAMD score NIHSS score MMSE score FIM score
Funding source	Scientific research program of Shandong Provincial Department of Health (Funding number: 2012ws1783)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table method
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described

Hu 2018 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No protocol available to check
Other bias	Unclear risk	Not described

Huang 2002

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo used, but unclear if identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts, analysed according to treatment group
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	No description of the differences between treatment and control group in baseline characteristics

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	HAMD Extent of neurological damage Recurrent stroke Death Did not report AEs
Funding source	Source of funding not stated
Notes	–

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	Unclear risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts: 6 in treatment group (2 refused allocation), 4 in control group (2 refused allocation)
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	Balanced baseline

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

Kim 2017 *(Continued)*

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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"
Allocation concealment (selection bias)	Low risk	Quote: "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"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The placebo was identical in appearance to escitalopram" 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 (detection bias) All outcomes	Low risk	Quote: "All investigators including interviewers and assessors of the outcome, participants, and care providers were masked to treatment assignment

Kim 2017 *(Continued)*

		throughout the study. The code could be unblinded only with the approval of the steering committee."
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated table of random digits
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical capsules, participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States that researchers were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	17/90 dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	Balanced baseline

Lai 2006

Study characteristics

Methods	Parallel design Analysis: analysed according to allocated treatment groups

Lai 2006 *(Continued)*

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo used, not stated if matching
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated

Lai 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No participant dropped out
Selective reporting (reporting bias)	High risk	No protocol, stated that they would evaluate side effects but these were not reported
Other bias	Unclear risk	Demographic details at baseline not described

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		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer random numbers

Li 2004a *(Continued)*

Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Balanced baseline

Li 2004b

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

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

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

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 Participaients 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated whether blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysed according to allocated treatment group, no participant dropped out
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	No description of differences between treatment and control group

Li 2006

Study characteristics	
Methods	Parallel group
Participants	All pathological types of stroke, CT or MRI needed for diagnosis 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 Treatment: 52 people, mean ± SD age 61.12 ± 10.25, 32 men Control: 53 people, mean ± SD age 60.89 ± 9.12, 35 men
Interventions	Treatment: citalopram 20 mg daily plus usual care Control: usual care Duration of treatment: 12 weeks Duration of follow-up (end of treatment to end of study): 0
Outcomes	HDRS (also known as HAMD) BI CSS MMSE Side effects reported according to the participant's complaints and observation, no description of who recorded AEs; and reported only for the treatment group
Funding source	Source of funding not stated
Notes	–

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description
Incomplete outcome data (attrition bias) All outcomes	High risk	2 dropouts in treatment group, 4 in control group. 1 in treatment group died, and 2 in the control group died (i.e. > 5%)

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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided

Li 2007 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	No information provided

Li 2008

Study characteristics	
Methods	Parallel trial, 3 (fluoxetine versus "free and easy wandering" versus placebo), we are using the fluoxetine versus placebo comparison in this review
Participants	Country: China Setting: unclear Stroke criteria: by neuroimaging, ischaemic or PICH Depression diagnosis: "each patient was evaluated by a psychiatrist", HAMD > 20 included Fluoxetine group: 60 people, mean age 69.2 ± 3.5 years, men 41.6% Control: 30 people, mean age 67.8 ± 3.9 years, men 56.7% Excluded psychiatric illness other than depression, antidepressants within previous 2 weeks, MMSE < 23, severe aphasia
Interventions	Treatment: fluoxetine 20 to 40 mg daily Control: placebo Duration of treatment: 8 weeks Duration of follow-up (treatment end to study end): 0
Outcomes	HAMD BI Description of why participants left the trial early AEs (reported by participant or observed/elicited by physician at each visit)
Funding source	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
Notes	Note twice as many in fluoxetine as in control group 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers

Li 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Paper states blinded, used placebo (though unclear if matching, thus unclear (had a matching placebo been used then it would have been low)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4/90 dropped out (< 5%)
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Balanced baseline

Li 2017

Study characteristics	
Methods	Aim: to investigate the effect of escitalopram oxalate in the early treatment of post-stroke depression, cognition and neurological function
Participants	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
Interventions	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
Outcomes	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
Funding source	Unclear
Notes	
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Li 2017 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessed by 2 neurologist and 2 pyschiatrists unaware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

Liu 2006

Study characteristics	
Methods	Parallel design Aim: to study effect of citalopram on post-stroke depression and neurological functional rehabilitation
Participants	Country: China Setting: inpatient Stroke criteria: stroke during "recovery phase" at 6 to 9 months, NIHSS score ≥ 13, HAMD score ≥ 17 60 people randomised, of whom 38 were men, mean age 60.7 ± 8.6 years. Demographics for treatment and control groups were not provided Treatment: 30 people, age and gender not stated Control: 30 people, age and gender not stated Exclusion criteria: previous psychiatric disorder, dementia, aphasia, consciousness disturbance
Interventions	Treatment: citalopram 20 mg daily plus routine stroke care Control: routine stroke care Duration of treatment: 6 weeks Duration of follow-up (treatment end to study end): 0
Outcomes	HAMD NIHSS

Liu 2006 *(Continued)*

	BI Death
Funding source	Source of funding not stated
Notes	AEs not reported

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) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	Baseline balance reported by authors

Marquez Romero 2013

Study characteristics

Methods	Multicentre Study type: interventional (clinical trial) Primary purpose: supportive care
Participants	32 participants Country: Mexico Setting: inpatient At randomisation number allocated: N = 32: fluoxetine (n = 15); placebo (n = 17) % men: 50% Age: mean age 55.1 ± 12.2

Marquez Romero 2013 *(Continued)*

	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

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 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)*

Bias	Authors' judgement	Support for judgement
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) All outcomes	Low risk	Quote: "Fluoxetine and placebo tablets will be identical in form, color, odor and packaging." "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) All outcomes	Low risk	Blinding of participants and key study personnel ensured, and unlikely that blinding could have been broken
Incomplete outcome data (attrition bias) All outcomes	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 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 Comment: report includes data from 30 participants (14 participants in the fluoxetine group and 16 in the placebo 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	
Methods	Parallel design Analysis: unclear
Participants	Location: Wales, UK Setting: inpatient Treatment: unclear

Meara 1998 *(Continued)*

	Control: unclear Stroke criteria: ischaemic stroke > 11 weeks prior to randomisation Depression criteria: GDS (15-item) score > 4 Other entry criteria: not stated Exclusion criteria: moderate to severe dementia, severe aphasia, communication difficulties, poorly controlled epilepsy
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

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) All outcomes	Unclear risk	Double-blind reported, those who were blind not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind reported, those who were blind not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Insufficient data to make a judgement

Meara 1998 *(Continued)*

Other bias	Unclear risk	Insufficient data to make a judgement

Miao 2004

Study characteristics	
Methods	Parallel group 9 not allocated (5 in treatment group refused allocation, 4 in the control group refused allocation)
Participants	Country: China Setting: mixed inpatient and outpatient 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 Mood: depression after stroke onset, HAMD score ≥ 20 Participants: 90 randomised, 34 in each group at treatment end Treatment: 34 people, age 58.16 ± 8.49 years, 19 men Control: 34 people, age 62.45 ± 8.24 years, 18 men Exclusion criteria: other organic brain disorders and other aetiologies-related depression
Interventions	Treatment: citalopram 20 mg daily plus usual stroke care Control: usual stroke care Duration of treatment: 6 weeks Duration of follow-up (treatment end to study end): 0
Outcomes	HAMD SDS Efficacy Death AEs (only in the citalopram group) Method of recording AEs was not stated
Funding source	Source of funding not stated
Notes	–

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Simple random sampling" Comment: no further description given

Miao 2004 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation 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	Blinding described
Incomplete outcome data (attrition bias) All outcomes	High risk	9 not allocated after randomisation, 13 dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	Baseline balanced

Murray 2005

Study characteristics	
Methods	Parallel design 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
Participants	Location: Sweden Setting: mixed Treatment: 62 people, mean ± SD age 71 ± 10 years, 52% men Control: 61 people, mean ± SD age 71 ± 10 years, 44% men Stroke criteria: all subtypes, diagnosis by WHO criteria and CT (100%); stroke 3 to 367 days prior to randomisation (average time 128 days) Depression criteria: psychiatric interview (DSM-IV, major and minor) and MADRS > 9 Other entry criteria: > 17 years of age, stroke within the previous 12 months Comparability of treatment groups: significant trend towards more left-hemisphere lesion strokes in treatment group 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 Participants with < 20% reduction in MADRS score at 6 weeks were excluded
Interventions	Treatment: sertraline 50 mg daily; possible dose escalation to 100 mg after 4 weeks Control: matching placebo

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

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

NCT00177424

Study characteristics

Methods	Study type: interventional (clinical trial)

NCT00177424 *(Continued)*

	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 27 2014

Risk of bias

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

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

NCT01674868 *(Continued)*

	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 to10 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Withdrawn: unable to find patients meeting inclusion/exclusion criteria
Allocation concealment (selection bias)	Unclear risk	Withdrawn: unable to find patients meeting inclusion/exclusion criteria

NCT01674868 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Withdrawn: unable to find patients meeting inclusion/exclusion criteria
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Withdrawn: unable to find patients meeting inclusion/exclusion criteria
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawn: unable to find patients meeting inclusion/exclusion criteria
Selective reporting (reporting bias)	Unclear risk	Withdrawn: unable to find patients meeting inclusion/exclusion criteria
Other bias	Unclear risk	Withdrawn: unable to find patients meeting inclusion/exclusion criteria

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
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

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

Pan 2018 *(Continued)*

- 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random number table"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge high or low
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to judge high or low
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All scale evaluators were trained and tested by the main investigator and were blind to the group assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	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) < 5% overall loss to follow-up
Selective reporting (reporting bias)	Unclear risk	There is no study protocol/trial register reference, so insufficient information to judge high or low
Other bias	High risk	The authors state that one of the inclusion criteria is Montreal Cognitive Assessment (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 experi-

Pan 2018 *(Continued)*

	mental group have improved on the MoCA between days 0 and 15. The results 'Comparison of MoCA scores' and table 3 suggests otherwise

Pariente 2001

Study characteristics	
Methods	Prospective double-blind cross-over placebo-controlled study of 8 people with pure motor hemiparesis
Participants	Lacunar ischaemic stroke, assessed by brain CT Quote: "Early phase of recovery"
Interventions	Single dose of fluoxetine
Outcomes	fMRI (raw data provided) Finger tapping (presented as a graph, no raw data) NIHSS, motricity index, BI, trunk control test, Ashworth Scale, somatosensory scale (no data)
Funding source	Source of funding not stated
Notes	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 Dates of recruitment not given. Conflicts not stated

Risk of bias

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

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		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated

Rasmussen 2003 *(Continued)*

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

Razazian 2014

Study characteristics	
Methods	Study type: interventional (clinical trial) Primary purpose: treatment
Participants	172 participants Country: Iran (Islamic Republic of) Setting: inpatient At randomisation number allocated: fluoxetine n = 86; placebo n = 86 % male: unclear Age: fluoxetine group = unclear; placebo = unclear Subtype of stroke: not available Severity of stroke: not available Time since stroke onset: not available Inclusion criteria • Middle cerebral artery stroke (documented with imaging) • Hemiplegia, monoplegia or paresis • No coma • Consent • Suitable for discharge • Not admitted to Intensive care unit Exclusion criteria • Death from any cause during study

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

Bias	Authors' judgement	Support for judgement
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)*

Selective reporting (reporting bias)	Low risk	Protocol available and all the study's prespecified outcomes that are of interest to the review have been reported in a prespecified way
Other bias	High risk	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

Restifo 2001

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Random allocation"; method not described
Allocation concealment (selection bias)	Unclear risk	Quote: "Random allocation"; method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	A placebo was used, not clear if it was matching
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear from abstract
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear from abstract
Selective reporting (reporting bias)	Unclear risk	Unclear from abstract

Restifo 2001 *(Continued)*

Other bias	Unclear risk	Unclear from abstract

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 Fundacion 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		
Bias	**Authors' judgement**	**Support for judgement**

Robinson 2000a *(Continued)*

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

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
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 Fundacion Perez Companc. Eli Lilly and company supplied the fluoxetine and placebo
Notes	Note difference in time since stroke between groups Dates of recruitment not stated. Conflicts of interest not stated

Risk of bias

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

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

Robinson 2008 *(Continued)*

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 Neuropyschological 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 RO1MH-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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised blocks of 3, 6, and 9
Allocation concealment (selection bias)	Unclear risk	Not described

Robinson 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analyses, all participants used in analysis Dropouts: 5 in placebo and 7 drop-outs in escitalopram
Selective reporting (reporting bias)	Low risk	All specified outcome data reported. Trial published on www.strokecentre.org/trials
Other bias	Unclear risk	There was more diabetes in the escitalopram group than placebo group

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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."
Allocation concealment (selection bias)	Low risk	Quote: "Allocation was concealed using the sequentially numbered black envelopes."
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 =

Savadi Oskouie 2012 *(Continued)*

		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 t0 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of high or low
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the method of allocation concealment to permit judgement of high or low
Blinding of participants and personnel (performance bias) All outcomes	High risk	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
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	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
Selective reporting (reporting bias)	Unclear risk	No study protocol available. Insufficient information to permit judgement of high or low
Other bias	High risk	The use of matching suggests a matched case control design rather than an RCT design

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)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Balanced baseline

Wang 2003

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 *(Continued)*

Funding source	Source of funding not stated
Notes	–

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) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	13 dropped out of fluoxetine group, and 9 dropped out of control group
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	Baseline appeared balanced but no statistical comparison between groups

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)*

	AEs
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	No information provided

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	Treatment: fluoxetine 20 mg daily plus routine stroke care Control: routine stroke care Duration of treatment: 8 weeks Duration of follow-up (end of treatment to end of study): 0
Outcomes	HAMD MESSS AEs (method of obtaining data not stated) Death
Funding source	Source of funding not stated
Notes	–

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) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysed according to treatment group, no dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	Balanced baseline

Wiart 2000

Study characteristics

Methods	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)
Participants	Location: France Setting: unclear Treatment: 16 people, mean ± SD age 66 ± 7 years, 65% men Control: 15 people, mean ± SD age 66 ± 12 years, 40% men 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) Depression criteria: psychiatric interview (ICD-10 criteria) and MADRS score > 19 Other entry criteria: all antidepressant or neuroleptic drugs stopped 10 days prior to enrolment Comparability of treatment groups: balanced Exclusion criteria: severe psychiatric problems which required hospitalisation, severe aphasia, previous stroke, severe cognitive impairment, chronic alcoholism, chronic associated handicapping pathology, contraindication to fluoxetine
Interventions	Treatment: fluoxetine 20 mg daily Control: matched placebo Duration of treatment: 45 days Duration of follow-up (treatment end to study end): 0
Outcomes	Depression: change in scores from baseline to end of treatment of MADRS, 50% reduction in MADRS score Additional: FIMs MMSE Motricity Index Leaving the study early Death AEs ("evaluated qualitatively and quantitatively". Complete blood count, liver test and renal function test were carried out at each assessment visit)
Funding source	Lilly France Laboratory provided methodological and financial support
Notes	Dates of recruitment not stated. Conflicts of interest not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated

Wiart 2000 *(Continued)*

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

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 Recruitedquote: "clinically stable stroke patients with post-stroke depression" No other inclusion and exclusion criteria given 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	–

Xie 2005 *(Continued)*

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) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	No clear description between treatment and control

Xu 2001

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)*

	Duration of follow-up (treatment end to study end): 0
Outcomes	Zung SDS ADL (BI) Neural function deficient Death AEs not reported
Funding source	Source of funding not stated
Notes	–

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) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	10/62 dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	No clear description of stroke criteria and imaging

Xu 2006

Study characteristics

Methods	Parallel group Aim: to test whether early prophylactic antidepressant treatment by paroxetine has any beneficial influence on the rate of post-stroke depression and rehabilitation
Participants	Country: China Setting: inpatient

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

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

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		
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) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Yang 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	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)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Case sequence" randomisation
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	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	No difference in baseline

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)*

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Used "number table", but unclear if this was a random number table
Allocation concealment (selection bias)	Low risk	The study designer was not involved in assessment and treatment, the assessors did not know the allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The participants were blinded. Not clear if those delivering the treatment were blind, but no placebo used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only 1 dropped out in paroxetine group
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	Different numbers reported to have been recruited and randomised, baseline similar

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participants were randomised into 2 groups (with fluoxetine or without fluoxetine) according to the sequence number and a block randomisation table
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of high or low
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of high or low
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	Attrition rate of fluoxetine group vs control group was 4/41 (9.8%) vs 7/41 (17.1%) > 5% loss to follow-up

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Not described

Zhou 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts, analysed according to allocated treatment group
Selective reporting (reporting bias)	High risk	No protocol, no raw data provided for several of the outcomes
Other bias	Low risk	Baseline similar

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
HAMA: 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

mRS: modified Rankin score
NIHSS: National Institutes of Health Stroke Scale
PASE: Physical Activity Scale for the Elderly
PICH: primary intracerebral haemorrhage
RCT: randomised controlled trial
RS: Rankin score
SAH: subarachnoid haemorrhage
SAS: Zung Self-rating Anxiety Scale
SD: standard deviation
SDS: Zung Self-rating Depression Scale
SF-36: Short Form-36
SIS: Stroke Impact Scale
SSRI: selective serotonin reuptake inhibitors
SSS: Scandinavian Stroke Scale
TESS: Treatment Emergent Symptom Scale
TIA: transient ischaemic attack
VAS: visual analogue scale
WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12619000573156	Trial abandoned prior to initiating recruitment due to COVID-19 pandemic
Andersen 1993	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
Andersen 2012	The trial never started
Anderson 2002	The trial never started
Anonymous 2012a	Unable to find publication after extensive searching
Anonymous 2012b	Unable to find publication after extensive searching
Berends 2009	Mean time from stroke onset to fluoxetine was 39.1 months
Bonin Pinto 2019	Participants were recruited within 2 years (not 1 year) of stroke
Chen 2019	Tandospirone + escitalopram (combination therapy) and escitalopram (monotherapy) in people with vascular depression
Choi Kwon 2008	Participants more than 1 year post-stroke
Finkenzeller 2009	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
Foster 2019	2 arms: 1 with SSRI plus exercise and 1 arm with placebo plus exercise
Gourab 2015	Time of stroke onset > 12 months
Graffagnino 2002	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

Study	Reason for exclusion
Ji 2000	SSRI plus active intervention versus active treatment alone
Kitago 2020	Combined intervention
Li 2002	There is no random component in the sequence generation process
Liang 2003	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
Liu 2004	SSRI plus active intervention versus active treatment alone
Liu 2020	Wrong comparator
Mosarrezaii 2018	Qu0te: "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." Allocation concealment procedure was inadequately concealed
NCT01963832	Study withdrawn (not funded)
Robinson 2011	Ineligible outcomes: prevention of generalised anxiety disorder
Sitzer 2002	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
Sun 2015	Mean time since onset 19.2 ± 3.5 months. No placebo or usual-care control group (Prozac, acupuncture, and prozac plus acupuncture)
Vogel 2020	Open-label single-group study
Xu 2007	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
Zhou 2003	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

SSRI: selective serotonin reuptake inhibitor

Characteristics of studies awaiting classification *[ordered by study ID]*

Guo 2016

Methods	Study type: interventional (clinical trial) Actual enrolment: 300 Allocation: randomised Intervention model: parallel assignment Masking: single (outcomes assessor) Primary purpose: prevention

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 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 > 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

Guo 2016 *(Continued)*

	• Withdrawal from the study
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

He 2018 *(Continued)*

	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, hyperlipids 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

Jurcau 2016 *(Continued)*

	At randomisation numbers allocated: N = 89 Experimental group: escitalopram = 43 Comparator group: ?secondary preventive treatment = 46 % male: unclear Age: unclear Subtype of stroke: unclear Severity of stroke: unclear Time since stroke onset: unclear Inclusion criteria: unclear Exclusion criteria: unclear withdrawal criteria: unclear
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

ChiCTR1800019467 *(Continued)*

	Masking: unclear Primary purpose: treatment
Participants	China Inclusion criteria • Age 30 to 80 years • First-time acute (in the past 72 hours) ischaemic stroke • Diagnosis of stroke confirmed by imaging • Consent Exclusion criteria • Haemorrhagic stroke • Coma • Massive cerebral infarction • Poor coordination of transcranial doppler ultrasonography • Currently participating or have participated in other clinical trials within 3 months
Interventions	Experimental: 20 mg of fluoxetine daily for 90 days Comparator: conventional therapy
Outcomes	Baseline, 30 days after treatment, 90 days after treatment, 180 days after treatment Automatic regulation of cerebral blood flow
Starting date	
Contact information	
Notes	

CTRI/2018/12/016568

Study name	An interventional study to look at efficacy of fluoxetine in patients with post-stroke anxiety
Methods	Study type: interventional (clinical trial) Estimated enrolment: 60 participants Allocation: randomised Intervention model: parallel assignment Masking: triple (participant, investigator and outcome assessor) Primary purpose: treatment
Participants	Country: India Setting: inpatient Inclusion criteria • Age 18 years to 99 years • Ischaemic stroke, haemorrhagic stroke and TIA

CTRI/2018/12/016568 *(Continued)*

	• Able to understand English or Hindi Exclusion criteria • Known psychiatric disorder • Moderate to severe depression (HAM-D > 13) • Aphasia • Severe cognitive deficit • Refusal to participate in study
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	

EudraCT 2005-005266-37

Study name	Influence of escitalopram on the incidence of depression and dementia following acute middle cerebral artery territory infarction. A randomised, placebo-controlled, double-blind study
Methods	Study type: interventional (clinical trial) Estimated enrolment: 60 participants Allocation: randomised Intervention model: parallel assignment Masking: double (detail unclear) Primary purpose: prevention
Participants	Country: Germany Setting: inpatient Inclusion criteria • Acute MCA territory infarction • Aiming to recruit 60 over 3 years • Within 7 days of stroke onset • Prepared to and considered able to follow the whole trial period

EudraCT 2005-005266-37 *(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 www.clinicaltrialsregister.eu/ctr-search/trial/2005-005266-37/DE

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 epilepsy • "No history of cerebral haemorrhage and heart of cerebral stroke" [sic] • No history of systemic diseases of other organs, including liver failure and kidney • No cardiac pace maker, 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

IRCT2012101011062N1

Study name	A study of sertraline effect on quality of life in stroke inpatients
Methods	Study type: interventional (clinical trial) Estimated enrolment: 80 participants Allocation: randomised Intervention model: parallel assignment Masking: unclear Primary purpose: prevention
Participants	Iran (Islamic Republic of Iran) Inclusion criteria • 55 years old to 75 years old • First-ever stroke Exclusion criteria • History of stroke • Renal failure • Hepatic failure • Cardiac failure • Substance related disorders Aiming to recruit 80 participants
Interventions	Experimental: 3 weeks after stroke sertraline 50 mg a day for 12 months versus Comparator: 3 weeks after stroke a placebo tablet every day
Outcomes	Primary outcomes collected at 3 months, 6 months, 9 months • Quality of life (NHP) Secondary outcomes collected at 3 months, 6 months, 9 months • Depression (BDI)
Starting date	28 November 2012. Contacted author for an update on 4 May 2021 but no response received
Contact information	Reza Pirzeh, Tabriz University of Medical Sciences, Iran (Islamic Republic of) pirzehr@tbzmed.ac.ir
Notes	IRCT2012101011062N1

IRCT2017041720258N37

Study name	Evaluation of fluoxetine and standard treatment efficacy on change to side effect of stroke of ischaemic strokes in both hemispheres in anterior circulation
Methods	Study type: interventional (clinical trial) Estimated enrolment: 60 participants

IRCT20170417202580N37 *(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 stoke 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

IRCT20210307050617N1 *(Continued)*

Outcomes	Rate of improvement in motor function
Starting date	22 August 2020
Contact information	sepanta1968@yahoo.com
Notes	

NCT02386475

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)*

Starting date	1 January 2015. Study completed 31 October 2019. No results available-contacted author on 4 May 2021
Contact information	Dolores Cocho mailto:dcocho%40fhag.es?subject=NCT02386475, SELEIS, Effect of Serotonin and Levodopa in Ischemic Stroke
Notes	NCT02386475

NCT02767999

Study name	Resting state MRI connectivity in acute ischemic stroke: serotonin selective reuptake Inhibitor (SSRI) in enhancing motor recovery: a placebo controlled study
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

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	Virginie Sattler, Dr: sattler.v@chu-toulouse.fr François 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)

NCT02865642 *(Continued)*

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.pastore-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

NCT03448159 *(Continued)*

	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

NCT03448159 *(Continued)*

	mailto:farrell%40canadianstroke.ca?subject=NCT03448159, 17-5134.0, Fluoxetine Opens Window to Improve Motor Recovery After Stroke
Notes	NCT03448159

NCT03826875

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

Study name	Randomized controlled trial of fluoxetine or placebo on quality of life after acute ischemic stroke
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 Lorwatanapongsa: sirikanyalor@yahoo.com
Notes	TCTR20181216001

BDI: Beck Depression Inventory;
BDNF: brain-derived neurotrophic factor;

BI: Barthel Index;
CTIMP: Clinical Trial of an Investigational Medicinal Product;
DWI: diffusion-weighted imaging;
FLAIR: fluid-attenuated inversion recovery;
FMMS: Fugl Meyr Motor Score;
fMRI: functional magnetic resonance imaging;
HAM-A:Hamilton Anxiety Rating Scale;
HAM-D: Hamilton Depression Rating Scale;
JTT: Jebsen Taylor Test;
MADRS: Montgomery-Åsberg Depression Rating Scale;
MAOI: mono-amino-oxidase inhibitor;
MCA: middle cerebral artery;
MHRA: Medicines and Healthcare products Regulatory Agency
MRA: magnetic resonance angiography;
MRI: magnetic resonance imaging;
mRS: modified Rankin score;
NHP: Nottingham Health Profile;
NIHSS: National Institute of Health Stroke Scale
NPI: Neuropsychiatric Inventory Scale;
PHQ-9: Patient Health Questionnaire;
QoL: quality of life;
RCT: randomised controlled trial;
rTMS: repetitive transcranial magnetic stimulation;
SF-36: Short Form-36;
smRSq: simplified modified Rankin Scale questionnaire;
SSRI: selective serotonin reuptake inhibitor;
TCD: transcranial Doppler;
TIA: transient ischaemic attack;

DATA AND ANALYSES

Comparison 1. SSRI versus control at end of treatment, by SSRI

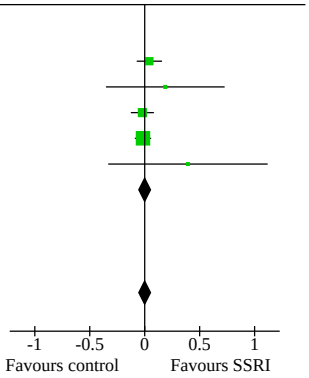
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Disability (primary outcome). Studies at low risk of bias	5	5436	Std. Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.05, 0.05]
1.1.1 Fluoxetine	5	5436	Std. Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.05, 0.05]
1.2 Independent on modified Rankin score (mRS 0 to 2) (primary outcome). Studies at low risk of bias	5	5926	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.93, 1.03]
1.3 Neurological deficit score (studies at low risk of bias)	1	30	Std. Mean Difference (IV, Fixed, 95% CI)	-0.39 [-1.12, 0.33]
1.3.1 Fluoxetine	1	30	Std. Mean Difference (IV, Fixed, 95% CI)	-0.39 [-1.12, 0.33]
1.4 Motor deficits (studies at low risk of bias)	6	5518	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.02, 0.08]
1.4.1 Fluoxetine	6	5518	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.02, 0.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Depression, continuous data (studies at low risk of bias)	4	5356	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.19, -0.08]
1.5.1 Fluoxetine	4	5356	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.19, -0.08]
1.6 Depression, dichotomous data (studies at low risk of bias)	3	5907	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.65, 0.86]
1.6.1 Fluoxetine	3	5907	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.65, 0.86]
1.7 Death (trials at low risk of bias)	6	6090	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.82, 1.24]
1.7.1 Fluoxetine	6	6090	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.82, 1.24]
1.8 Seizures (studies at low risk of bias)	6	6080	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.00, 1.98]
1.8.1 Fluoxetine	6	6080	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.00, 1.98]
1.9 Gastrointestinal side effects (studies at low risk of bias)	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.33, 8.83]
1.9.1 Fluoxetine	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.33, 8.83]
1.10 Bleeding (studies at low risk of bias)	6	6088	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.69, 1.70]
1.10.1 Fluoxetine (except for Asadollahi 2018)	6	6088	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.69, 1.70]
1.11 Fractures (studies at low risk of only)	6	6080	Odds Ratio (M-H, Fixed, 95% CI)	2.35 [1.62, 3.41]
1.12 Cognition (trials at low risk of bias)	4	5373	Mean Difference (IV, Fixed, 95% CI)	-1.22 [-2.37, -0.07]
1.13 Leaving the study before the end of scheduled follow-up for reasons other than death (trials at low risk of bias)	6	6090	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.03, 2.40]
1.13.1 Fluoxetine	6	6090	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.03, 2.40]
1.14 Fatigue at end of treatment (studies at low risk of bias only)	4	5524	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-1.24, 1.11]
1.15 Quality of life at end of treatment (studies at low risk of bias)	3	5482	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.02, 0.02]
1.16 Disability (all studies regardless of risk of bias)	32	7667	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.23, -0.14]
1.16.1 Fluoxetine	19	6590	Std. Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.13, -0.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.16.2 Sertraline	1	130	Std. Mean Difference (IV, Fixed, 95% CI)	-1.38 [-1.76, -0.99]
1.16.3 Paroxetine	5	293	Std. Mean Difference (IV, Fixed, 95% CI)	-1.29 [-1.55, -1.03]
1.16.4 Citalopram	5	446	Std. Mean Difference (IV, Fixed, 95% CI)	-0.68 [-0.88, -0.48]
1.16.5 Escitalopram	2	208	Std. Mean Difference (IV, Fixed, 95% CI)	-0.67 [-1.00, -0.34]
1.17 Independent on modified Rankin score (mRS 0 to 2) (all studies regardless of risk of bias)	8	6792	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.93, 1.01]
1.17.1 Fluoxetine	6	6039	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.94, 1.03]
1.17.2 Sertraline	1	111	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.97, 1.04]
1.17.3 Citalopram	1	642	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.82, 0.98]

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

Study or Subgroup	SSRI Mean	SSRI SD	SSRI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.1.1 Fluoxetine								
AFFINITY 2020	81.3	23.4	569	80.3	23.5	591	21.3%	0.04 [-0.07 , 0.16]
Bembenek 2020	78.75	23.42	26	74.07	25.71	27	1.0%	0.19 [-0.35 , 0.73]
EFFECTS 2020 (1)	79.3	23.8	697	79.8	23.1	697	25.7%	-0.02 [-0.13 , 0.08]
FOCUS 2019	59.66	31.16	1402	60.15	31.5	1397	51.5%	-0.02 [-0.09 , 0.06]
Marquez Romero 2013 (2)	65	11.85	14	45	66.67	16	0.5%	0.39 [-0.33 , 1.12]
Subtotal (95% CI)			**2708**			**2728**	**100.0%**	**-0.00 [-0.05 , 0.05]**
Heterogeneity: Chi² = 2.45, df = 4 (P = 0.65); I² = 0%								
Test for overall effect: Z = 0.02 (P = 0.99)								
Total (95% CI)			**2708**			**2728**	**100.0%**	**-0.00 [-0.05 , 0.05]**
Heterogeneity: Chi² = 2.45, df = 4 (P = 0.65); I² = 0%								
Test for overall effect: Z = 0.02 (P = 0.99)								
Test for subgroup differences: Not applicable								



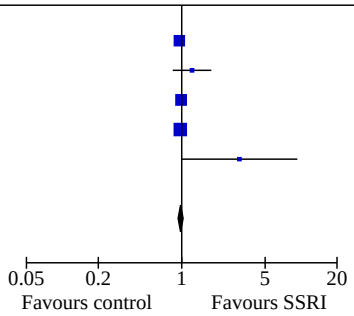
Footnotes

(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

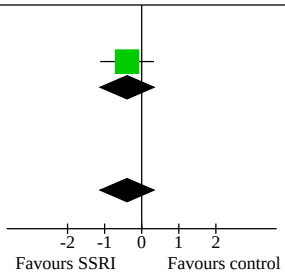
Analysis 1.2. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 2: Independent on modified Rankin score (mRS 0 to 2) (primary outcome). Studies at low risk of bias

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFFINITY 2020	432	624	458	632	29.6%	0.96 [0.89 , 1.03]
Bembenek 2020	20	27	17	28	1.1%	1.22 [0.84 , 1.77]
EFFECTS 2020	466	737	475	742	30.8%	0.99 [0.91 , 1.07]
FOCUS 2019	572	1553	588	1553	38.3%	0.97 [0.89 , 1.07]
Marquez Romero 2013	8	14	3	16	0.2%	3.05 [1.00 , 9.31]
Total (95% CI)		**2955**		**2971**	**100.0%**	**0.98 [0.93 , 1.03]**
Total events:	1498		1541			
Heterogeneity: Chi² = 5.84, df = 4 (P = 0.21); I² = 32%						
Test for overall effect: Z = 0.89 (P = 0.37)						
Test for subgroup differences: Not applicable						



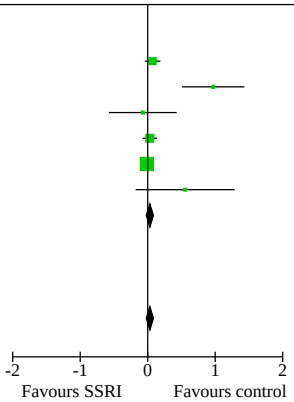
Analysis 1.3. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 3: Neurological deficit score (studies at low risk of bias)

Study or Subgroup	SSRI Mean	SSRI SD	SSRI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.3.1 Fluoxetine								
Marquez Romero 2013	8.5	3.29	14	12	11.38	16	100.0%	-0.39 [-1.12 , 0.33]
Subtotal (95% CI)			**14**			**16**	**100.0%**	**-0.39 [-1.12 , 0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.07 (P = 0.29)								
Total (95% CI)			**14**			**16**	**100.0%**	**-0.39 [-1.12 , 0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.07 (P = 0.29)								
Test for subgroup differences: Not applicable								



Analysis 1.4. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 4: Motor deficits (studies at low risk of bias)

Study or Subgroup	SSRI Mean	SSRI SD	SSRI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.4.1 Fluoxetine								
AFFINITY 2020	72.3	24.1	570	70.5	25.3	591	21.1%	0.07 [-0.04 , 0.19]
Asadollahi 2018	51.65	26.49	60	27.96	18.71	30	1.3%	0.97 [0.51 , 1.43]
Bembenek 2020	27.16	28.5	30	29.17	25.71	31	1.1%	-0.07 [-0.58 , 0.43]
EFFECTS 2020	69.4	24.7	694	68.6	25.9	689	25.2%	0.03 [-0.07 , 0.14]
FOCUS 2019 (1)	57.05	29.6	1398	57.4	29.47	1395	50.8%	-0.01 [-0.09 , 0.06]
Marquez Romero 2013	75.5	32.95	14	48.5	56.9	16	0.5%	0.56 [-0.18 , 1.29]
Subtotal (95% CI)			**2766**			**2752**	**100.0%**	**0.03 [-0.02 , 0.08]**
Heterogeneity: Chi² = 19.83, df = 5 (P = 0.001); I² = 75%								
Test for overall effect: Z = 1.19 (P = 0.23)								
Total (95% CI)			**2766**			**2752**	**100.0%**	**0.03 [-0.02 , 0.08]**
Heterogeneity: Chi² = 19.83, df = 5 (P = 0.001); I² = 75%								
Test for overall effect: Z = 1.19 (P = 0.23)								
Test for subgroup differences: Not applicable								

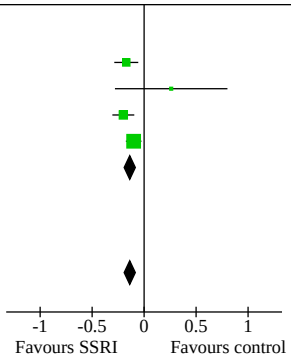


Footnotes

(1) For FOCUS, AFFINITY, EFFECTS and Benbenek 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)

Study or Subgroup	SSRI Mean	SSRI SD	SSRI Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.5.1 Fluoxetine								
AFFINITY 2020	-77.8	15.2	570	-75.2	15.1	591	21.7%	-0.17 [-0.29 , -0.06]
Bembenek 2020	-67.41	19.04	26	-72.43	18.93	27	1.0%	0.26 [-0.28 , 0.80]
EFFECTS 2020	-78.7	15.7	695	-75.5	16.3	696	25.9%	-0.20 [-0.31 , -0.09]
FOCUS 2019 (1)	11.98	5.24	1372	12.52	5.47	1379	51.4%	-0.10 [-0.18 , -0.03]
Subtotal (95% CI)			**2663**			**2693**	**100.0%**	**-0.14 [-0.19 , -0.08]**
Heterogeneity: Chi² = 4.68, df = 3 (P = 0.20); I² = 36%								
Test for overall effect: Z = 5.05 (P < 0.00001)								
Total (95% CI)			**2663**			**2693**	**100.0%**	**-0.14 [-0.19 , -0.08]**
Heterogeneity: Chi² = 4.68, df = 3 (P = 0.20); I² = 36%								
Test for overall effect: Z = 5.05 (P < 0.00001)								
Test for subgroup differences: Not applicable								

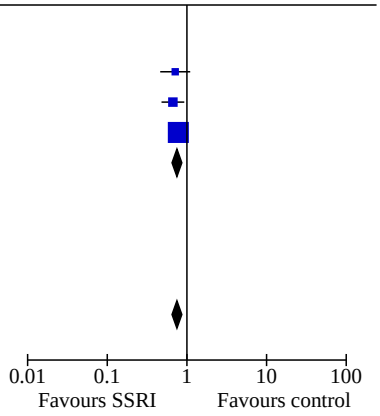


Footnotes

(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 w

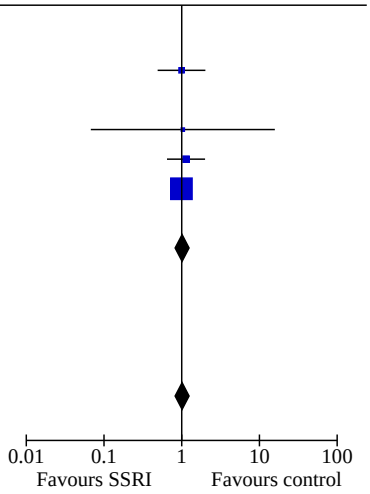
Analysis 1.6. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 6: Depression, dichotomous data (studies at low risk of bias)

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Fluoxetine						
AFFINITY 2020	33	642	46	638	11.6%	0.71 [0.46 , 1.10]
EFFECTS 2020	54	750	81	750	20.4%	0.67 [0.48 , 0.93]
FOCUS 2019	210	1564	269	1563	67.9%	0.78 [0.66 , 0.92]
Subtotal (95% CI)		**2956**		**2951**	**100.0%**	**0.75 [0.65 , 0.86]**
Total events:	297		396			
Heterogeneity: Chi² = 0.76, df = 2 (P = 0.68); I² = 0%						
Test for overall effect: Z = 4.03 (P < 0.0001)						
Total (95% CI)		**2956**		**2951**	**100.0%**	**0.75 [0.65 , 0.86]**
Total events:	297		396			
Heterogeneity: Chi² = 0.76, df = 2 (P = 0.68); I² = 0%						
Test for overall effect: Z = 4.03 (P < 0.0001)						
Test for subgroup differences: Not applicable						



Analysis 1.7. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 7: Death (trials at low risk of bias)

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 Fluoxetine						
AFFINITY 2020	15	642	15	638	9.0%	0.99 [0.49 , 2.02]
Asadollahi 2018	0	60	0	30		Not estimable
Bembenek 2020	1	30	1	31	0.6%	1.03 [0.07 , 15.78]
EFFECTS 2020	25	750	22	750	13.1%	1.14 [0.65 , 2.00]
FOCUS 2019 (1)	129	1564	130	1563	77.4%	0.99 [0.79 , 1.25]
Marquez Romero 2013	0	15	0	17		Not estimable
Subtotal (95% CI)		**3061**		**3029**	**100.0%**	**1.01 [0.82 , 1.24]**
Total events:	170		168			
Heterogeneity: Chi² = 0.19, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Total (95% CI)		**3061**		**3029**	**100.0%**	**1.01 [0.82 , 1.24]**
Total events:	170		168			
Heterogeneity: Chi² = 0.19, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Test for subgroup differences: Not applicable						

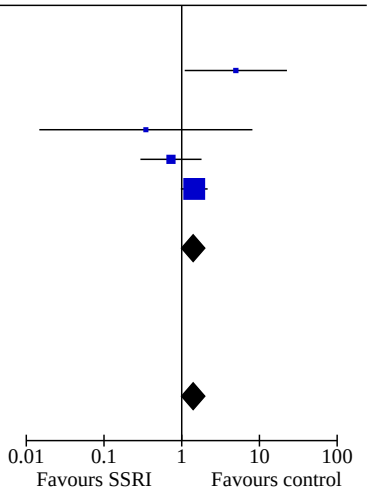


Footnotes

(1) We used the number randomised as the denominator

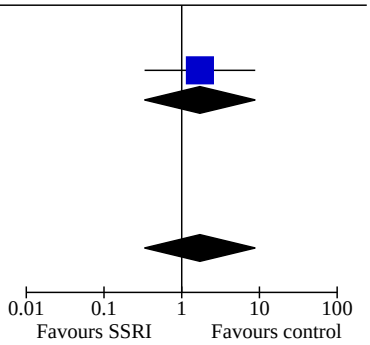
Analysis 1.8. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 8: Seizures (studies at low risk of bias)

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Fluoxetine						
AFFINITY 2020	10	642	2	638	3.7%	4.97 [1.09 , 22.59]
Asadollahi 2018	0	60	0	30		Not estimable
Bembenek 2020	0	26	1	27	2.7%	0.35 [0.01 , 8.12]
EFFECTS 2020	8	750	11	750	20.2%	0.73 [0.29 , 1.80]
FOCUS 2019	58	1564	40	1563	73.4%	1.45 [0.97 , 2.15]
Marquez Romero 2013	0	14	0	16		Not estimable
Subtotal (95% CI)		**3056**		**3024**	**100.0%**	**1.40 [1.00 , 1.98]**
Total events:	76		54			
Heterogeneity: Chi² = 5.49, df = 3 (P = 0.14); I² = 45%						
Test for overall effect: Z = 1.93 (P = 0.05)						
Total (95% CI)		**3056**		**3024**	**100.0%**	**1.40 [1.00 , 1.98]**
Total events:	76		54			
Heterogeneity: Chi² = 5.49, df = 3 (P = 0.14); I² = 45%						
Test for overall effect: Z = 1.93 (P = 0.05)						
Test for subgroup differences: Not applicable						



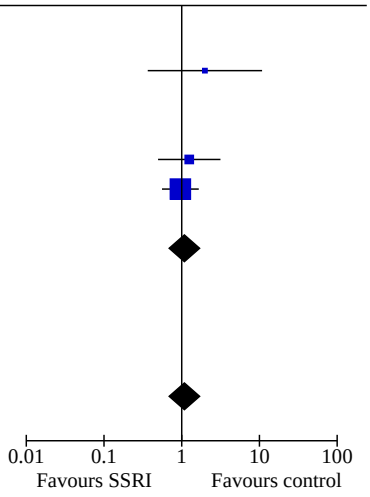
Analysis 1.9. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 9: Gastrointestinal side effects (studies at low risk of bias)

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.9.1 Fluoxetine						
Marquez Romero 2013	3	14	2	16	100.0%	1.71 [0.33 , 8.83]
Subtotal (95% CI)		**14**		**16**	**100.0%**	**1.71 [0.33 , 8.83]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Total (95% CI)		**14**		**16**	**100.0%**	**1.71 [0.33 , 8.83]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Not applicable						



Analysis 1.10. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 10: Bleeding (studies at low risk of bias)

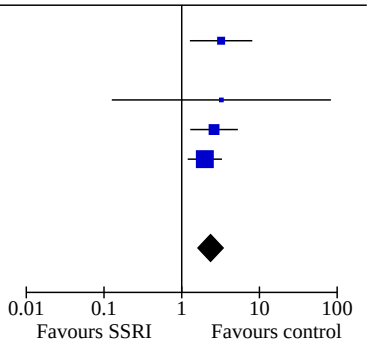
Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 Fluoxetine (except for Asadollahi 2018)						
AFFINITY 2020	4	642	2	638	5.6%	1.99 [0.37 , 10.81]
Asadollahi 2018	0	60	0	30		Not estimable
Bembenek 2020	0	30	0	31		Not estimable
EFFECTS 2020	10	750	8	750	22.2%	1.25 [0.50 , 3.15]
FOCUS 2019	25	1564	26	1563	72.2%	0.96 [0.56 , 1.66]
Marquez Romero 2013	0	14	0	16		Not estimable
Subtotal (95% CI)		**3060**		**3028**	**100.0%**	**1.08 [0.69 , 1.70]**
Total events:	39		36			
Heterogeneity: Chi² = 0.77, df = 2 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.34 (P = 0.73)						
Total (95% CI)		**3060**		**3028**	**100.0%**	**1.08 [0.69 , 1.70]**
Total events:	39		36			
Heterogeneity: Chi² = 0.77, df = 2 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.34 (P = 0.73)						
Test for subgroup differences: Not applicable						



Analysis 1.11. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 11: Fractures (studies at low risk of only)

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AFFINITY 2020	19	642	6	638	14.9%	3.21 [1.27 , 8.10]
Asadollahi 2018	0	60	0	30		Not estimable
Bembenek 2020 (1)	1	26	0	27	1.2%	3.24 [0.13 , 83.08]
EFFECTS 2020	28	750	11	750	27.0%	2.61 [1.29 , 5.27]
FOCUS 2019	45	1564	23	1563	56.9%	1.98 [1.19 , 3.29]
Marquez Romero 2013	0	14	0	16		Not estimable
Total (95% CI)		**3056**		**3024**	**100.0%**	**2.35 [1.62 , 3.41]**
Total events:	93		40			

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



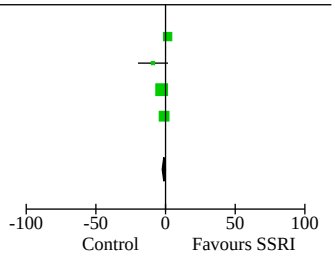
Footnotes

(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)

Study or Subgroup	SSRI Mean	SSRI SD	SSRI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
AFFINITY 2020 (1)	84.6	19.3	570	83.1	20.4	591	25.2%	1.50 [-0.78 , 3.78]
Bembenek 2020	84.89	17.15	26	93.92	22.56	27	1.1%	-9.03 [-19.79 , 1.73]
EFFECTS 2020	84.7	18.3	696	87.5	15.5	698	41.5%	-2.80 [-4.58 , -1.02]
FOCUS 2019	72.89	27.43	1378	73.93	26.83	1387	32.2%	-1.04 [-3.06 , 0.98]
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

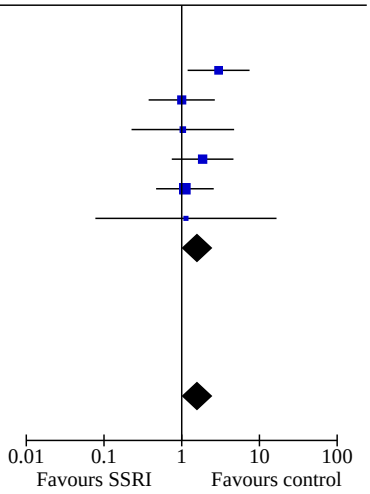


Footnotes

(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)

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.13.1 Fluoxetine						
AFFINITY 2020	18	642	6	638	17.9%	2.98 [1.19 , 7.46]
Asadollahi 2018	10	60	5	30	19.9%	1.00 [0.38 , 2.66]
Bembenek 2020 (1)	3	30	3	31	8.8%	1.03 [0.23 , 4.72]
EFFECTS 2020	13	750	7	750	20.8%	1.86 [0.75 , 4.63]
FOCUS 2019	11	1564	10	1563	29.8%	1.10 [0.47 , 2.58]
Marquez Romero 2013	1	15	1	17	2.8%	1.13 [0.08 , 16.59]
Subtotal (95% CI)		**3061**		**3029**	**100.0%**	**1.57 [1.03 , 2.40]**
Total events:	56		32			
Heterogeneity: Chi² = 3.84, df = 5 (P = 0.57); I² = 0%						
Test for overall effect: Z = 2.09 (P = 0.04)						
Total (95% CI)		**3061**		**3029**	**100.0%**	**1.57 [1.03 , 2.40]**
Total events:	56		32			
Heterogeneity: Chi² = 3.84, df = 5 (P = 0.57); I² = 0%						
Test for overall effect: Z = 2.09 (P = 0.04)						
Test for subgroup differences: Not applicable						

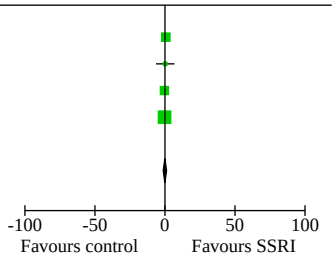


Footnotes

(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 confir

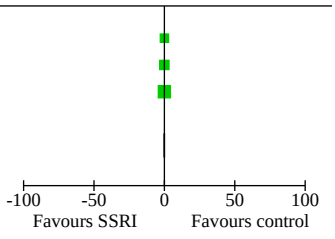
Analysis 1.14. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 14: Fatigue at end of treatment (studies at low risk of bias only)

Study or Subgroup	SSRI Mean	SSRI SD	SSRI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
AFFINITY 2020	68.11	21.54	642	67.48	20.39	638	26.1%	0.63 [-1.67 , 2.93]
Bembenek 2020	49.52	12.36	26	49.31	12.18	27	3.2%	0.21 [-6.40 , 6.82]
EFFECTS 2020	55.5	21.8	692	55.9	22.5	692	25.3%	-0.40 [-2.73 , 1.93]
FOCUS 2019	56.54	23.54	1405	56.83	23.59	1402	45.4%	-0.29 [-2.03 , 1.45]
Total (95% CI)			**2765**			**2759**	**100.0%**	**-0.06 [-1.24 , 1.11]**
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								



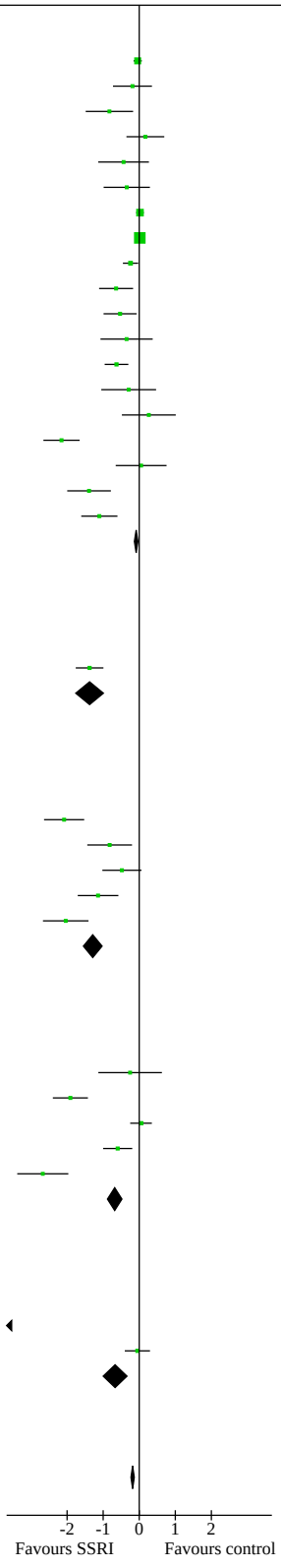
Analysis 1.15. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 15: Quality of life at end of treatment (studies at low risk of bias)

Study or Subgroup	SSRI Mean	SSRI SD	SSRI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
AFFINITY 2020	0.73	0.32	642	0.71	0.31	638	25.8%	0.02 [-0.01 , 0.05]
EFFECTS 2020	0.65	0.29	687	0.65	0.31	684	30.5%	0.00 [-0.03 , 0.03]
FOCUS 2019	0.47	0.36	1412	0.48	0.36	1419	43.7%	-0.01 [-0.04 , 0.02]
Total (95% CI)			**2741**			**2741**	**100.0%**	**0.00 [-0.02 , 0.02]**
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								



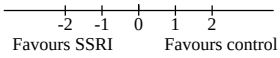
Analysis 1.16. Comparison 1: SSRI versus control at end of treatment, by SSRI, Outcome 16: Disability (all studies regardless of risk of bias)

Study or Subgroup	Control Mean	Control SD	Control Total	SSRI Mean	SSRI SD	SSRI Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.16.1 Fluoxetine								
AFFINITY 2020	80.3	23.5	591	81.3	23.4	569	15.8%	-0.04 [-0.16 , 0.07]
Bembenek 2020	74.07	25.71	27	78.75	23.42	26	0.7%	-0.19 [-0.73 , 0.35]
Chen 2001 (1)	71.56	9.41	20	79.31	8.94	19	0.5%	-0.83 [-1.48 , -0.17]
Cheng 2003	-26.38	14.2	25	-29.15	17.38	32	0.8%	0.17 [-0.35 , 0.69]
Dam 1996	54.1	21.1	16	61.9	13	16	0.4%	-0.43 [-1.14 , 0.27]
Dike 2019	46	25	19	55	26	19	0.5%	-0.35 [-0.99 , 0.30]
EFFECTS 2020	79.8	23.1	697	79.3	23.8	697	19.0%	0.02 [-0.08 , 0.13]
FOCUS 2019	60.15	31.16	1410	59.66	31.16	1413	38.4%	0.02 [-0.06 , 0.09]
He 2016	84.74	18.85	170	88.81	14.69	177	4.7%	-0.24 [-0.45 , -0.03]
Kong 2007	52.3	12.5	36	60.4	12.5	37	0.9%	-0.64 [-1.11 , -0.17]
Li 2008	38.4	5.8	28	40.8	3.7	58	1.0%	-0.53 [-0.99 , -0.07]
Marquez Romero 2013	45	73.15	16	65	21.42	14	0.4%	-0.35 [-1.07 , 0.37]
Razazian 2014	14.26	1.8	75	15.68	2.61	75	1.9%	-0.63 [-0.96 , -0.30]
Robinson 2000a	56.2	7.8	13	59.2	11.6	14	0.4%	-0.29 [-1.05 , 0.47]
Robinson 2000b	63.1	8.2	15	60.5	10.8	13	0.4%	0.27 [-0.48 , 1.01]
Wang 2003	59	4	47	69	5.1	51	0.8%	-2.15 [-2.66 , -1.65]
Wiart 2000	88.7	25.3	15	87.4	22.8	16	0.4%	0.05 [-0.65 , 0.76]
Xu 2001	67	4.1	27	73	4.4	26	0.6%	-1.39 [-2.00 , -0.79]
Zhao 2011	-34.6	5.2	34	-27.6	7.1	37	0.8%	-1.11 [-1.61 , -0.60]
Subtotal (95% CI)			**3281**			**3309**	**88.4%**	**-0.09 [-0.13 , -0.04]**
Heterogeneity: Chi² = 141.73, df = 18 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 3.44 (P = 0.0006)								
1.16.2 Sertraline								
Xie 2005	79.8	4.5	65	88.7	7.9	65	1.4%	-1.38 [-1.76 , -0.99]
Subtotal (95% CI)			**65**			**65**	**1.4%**	**-1.38 [-1.76 , -0.99]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.03 (P < 0.00001)								
1.16.3 Paroxetine								
Chen 2005b	51.76	7.32	38	65.72	5.92	40	0.7%	-2.08 [-2.64 , -1.53]
Chen 2002	51.5	10.3	20	61	12.2	24	0.5%	-0.82 [-1.44 , -0.20]
He 2005	78.33	15.01	27	84.26	8.41	27	0.7%	-0.48 [-1.02 , 0.06]
Xu 2006	-32.81	4.13	29	-27.63	4.81	28	0.7%	-1.14 [-1.70 , -0.58]
Ye 2004	50.26	13.4	30	78.75	14.19	30	0.5%	-2.04 [-2.67 , -1.41]
Subtotal (95% CI)			**144**			**149**	**3.1%**	**-1.29 [-1.55 , -1.03]**
Heterogeneity: Chi² = 24.24, df = 4 (P < 0.0001); I² = 83%								
Test for overall effect: Z = 9.75 (P < 0.00001)								
1.16.4 Citalopram								
Acler 2009	75	25	10	82	28	10	0.3%	-0.25 [-1.13 , 0.63]
Chen 2015	57.2	8.9	48	79.2	13.5	48	0.9%	-1.91 [-2.39 , -1.42]
Gao 2017	72.3	15.9	86	71.5	16.2	85	2.3%	0.05 [-0.25 , 0.35]
Li 2006	59.17	9.02	49	64.36	8.23	50	1.3%	-0.60 [-1.00 , -0.19]
Liu 2006	35.4	9.1	30	64.4	12.1	30	0.4%	-2.67 [-3.38 , -1.97]
Subtotal (95% CI)			**223**			**223**	**5.2%**	**-0.68 [-0.88 , -0.48]**
Heterogeneity: Chi² = 78.86, df = 4 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 6.64 (P < 0.00001)								
1.16.5 Escitalopram								
Hu 2018	58.2	4.18	41	88.48	6.04	41	0.2%	-5.78 [-6.78 , -4.77]
Li 2017	56.32	2.43	62	56.45	2.63	64	1.7%	-0.05 [-0.40 , 0.30]
Subtotal (95% CI)			**103**			**105**	**1.9%**	**-0.67 [-1.00 , -0.34]**
Heterogeneity: Chi² = 111.38, df = 1 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 3.97 (P < 0.0001)								
Total (95% CI)			**3816**			**3851**	**100.0%**	**-0.18 [-0.23 , -0.14]**
Heterogeneity: Chi² = 510.83, df = 31 (P < 0.00001); I² = 94%								
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%								



Analysis 1.16. (Continued)

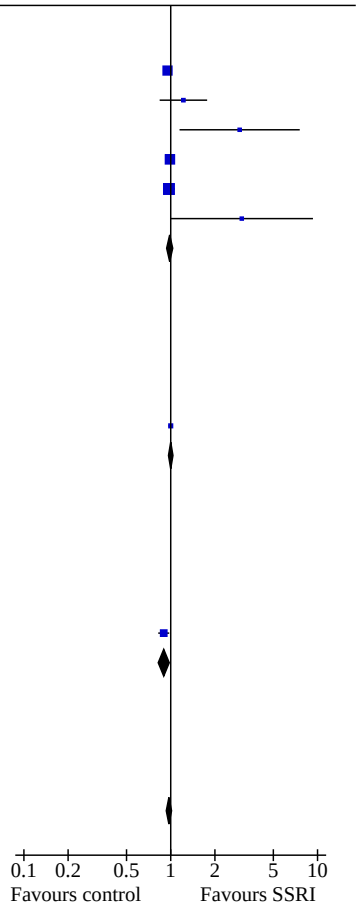
Test for overall effect: Z = 7.85 (P < 0.00001)
Test for subgroup differences: Chi² = 154.62, df = 4 (P < 0.00001), I² = 97.4%



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)

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.17.1 Fluoxetine						
AFFINITY 2020	430	624	458	632	24.5%	0.95 [0.89 , 1.02]
Bembenek 2020	20	27	17	28	0.9%	1.22 [0.84 , 1.77]
Chollet 2011	15	57	5	56	0.3%	2.95 [1.15 , 7.56]
EFFECTS 2020	466	737	475	742	25.5%	0.99 [0.91 , 1.07]
FOCUS 2019	572	1553	588	1553	31.7%	0.97 [0.89 , 1.07]
Marquez Romero 2013	8	14	3	16	0.2%	3.05 [1.00 , 9.31]
Subtotal (95% CI)		**3012**		**3027**	**83.0%**	**0.98 [0.94 , 1.03]**
Total events:	1511		1546			
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	56	56	3.0%	1.00 [0.97 , 1.04]
Subtotal (95% CI)		**55**		**56**	**3.0%**	**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	261	323	14.0%	0.90 [0.82 , 0.98]
Subtotal (95% CI)		**319**		**323**	**14.0%**	**0.90 [0.82 , 0.98]**
Total events:	231		261			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.50 (P = 0.01)						
Total (95% CI)		**3386**		**3406**	**100.0%**	**0.97 [0.93 , 1.01]**
Total events:	1797		1863			
Heterogeneity: Chi² = 17.27, df = 7 (P = 0.02); I² = 59%						
Test for overall effect: Z = 1.35 (P = 0.18)						
Test for subgroup differences: Chi² = 5.35, df = 2 (P = 0.07), I² = 62.6%						



Comparison 2. SSRI versus control at end of follow up, by SSRI

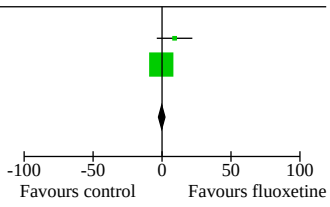
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Disability (studies at low risk of bias only)	2	2591	Mean Difference (IV, Fixed, 95% CI)	-0.24 [-2.59, 2.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Independent on modified rankin score (0-2) (studies at low risk of bias only)	2	3137	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.89, 1.19]
2.3 Depression, continuous data (studies at low risk of bias only)	2	2684	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.36, 0.44]
2.4 Depression, dichotomous (studies at low risk of bias only)	1	3083	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.73, 1.04]
2.5 Motor deficits (studies at low risk of bias only)	2	2688	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-3.00, 1.46]
2.6 Cognition (studies at low risk of bias only)	2	2689	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-2.32, 1.62]
2.7 Death (studies at low risk of bias only)	2	3144	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.12]
2.8 Leaving the trial before the end of follow-up, for reasons other than death (studies at low risk of bias)	2	3188	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.54, 1.51]
2.9 Disability, all studies irrespective of risk of bias	2	2691	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-2.56, 2.06]
2.10 Independent on mRS (0-2) all studies irrespective of risk of bias	2	3134	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.89, 1.19]

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)

Study or Subgroup	SSRI Mean	SSRI SD	SSRI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Bembenek 2020	83.33	19.83	24	74.25	26.94	27	3.3%	9.08 [-3.81 , 21.97]
FOCUS 2019 (1)	61.63	30.7	1227	62.19	30.78	1313	96.7%	-0.56 [-2.95 , 1.83]
Total (95% CI)			**1251**			**1340**	**100.0%**	**-0.24 [-2.59 , 2.11]**

Heterogeneity: Chi² = 2.08, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable

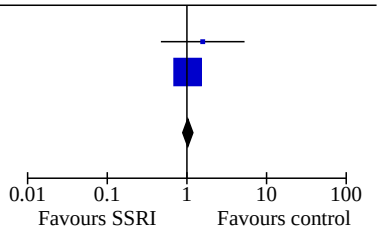


Footnotes
(1) Used the daily activities from the Stroke Impact Scale from FOCUS and Bembenek

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)

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bembenek 2020	20	26	19	28	1.2%	1.58 [0.47 , 5.29]
FOCUS 2019 (1)	562	1539	557	1544	98.8%	1.02 [0.88 , 1.18]
Total (95% CI)		**1565**		**1572**	**100.0%**	**1.03 [0.89 , 1.19]**
Total events:	582		576			

Heterogeneity: Chi² = 0.50, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Not applicable



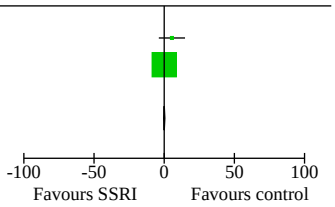
Footnotes

(1) mRS at 12 months for all four trials are included, denonomiator 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)

Study or Subgroup	SSRI Mean	SSRI SD	SSRI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Bembenek 2020 (1)	73.5	16.3	24	68	17.7	27	0.2%	5.50 [-3.83 , 14.83]
FOCUS 2019 (2)	12.36	5.21	1323	12.33	5.31	1310	99.8%	0.03 [-0.37 , 0.43]
Total (95% CI)			**1347**			**1337**	**100.0%**	**0.04 [-0.36 , 0.44]**

Heterogeneity: Chi² = 1.32, df = 1 (P = 0.25); I² = 24%
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable



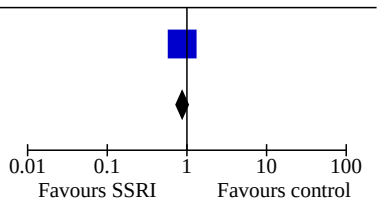
Footnotes

(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)

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
FOCUS 2019	292	1539	327	1544	100.0%	0.87 [0.73 , 1.04]
Total (95% CI)		**1539**		**1544**	**100.0%**	**0.87 [0.73 , 1.04]**
Total events:	292		327			

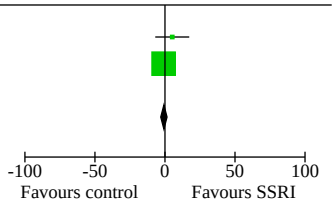
Heterogeneity: Not applicable
Test for overall effect: Z = 1.53 (P = 0.13)
Test for subgroup differences: Not applicable



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)

Study or Subgroup	SSRI Mean	SSRI SD	SSRI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Bembenek 2020	83.3	20.2	24	78.1	23.97	27	3.4%	5.20 [-6.93 , 17.33]
FOCUS 2019	55.73	29.76	1322	56.71	29.65	1315	96.6%	-0.98 [-3.25 , 1.29]
Total (95% CI)			**1346**			**1342**	**100.0%**	**-0.77 [-3.00 , 1.46]**

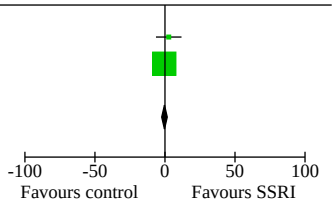
Heterogeneity: Chi² = 0.96, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



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)

Study or Subgroup	SSRI Mean	SSRI SD	SSRI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Bembenek 2020	88.54	15.76	24	85.85	17.43	27	4.7%	2.69 [-6.42 , 11.80]
FOCUS 2019	73.26	26.33	1324	73.76	26.55	1314	95.3%	-0.50 [-2.52 , 1.52]
Total (95% CI)			**1348**			**1341**	**100.0%**	**-0.35 [-2.32 , 1.62]**

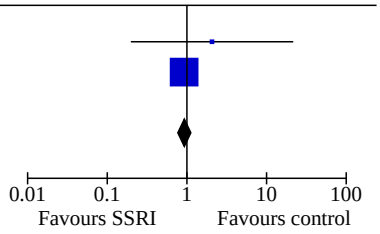
Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable



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)

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bembenek 2020	2	30	1	31	0.5%	2.07 [0.20 , 21.61]
FOCUS 2019	182	1539	198	1544	99.5%	0.92 [0.76 , 1.11]
Total (95% CI)		**1569**		**1575**	**100.0%**	**0.93 [0.77 , 1.12]**
Total events:	184		199			

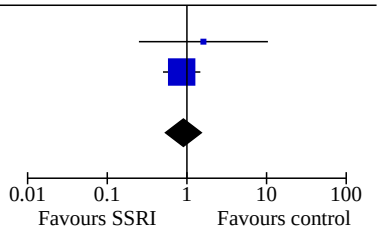
Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.78 (P = 0.43)
Test for subgroup differences: Not applicable



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)

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bembenek 2020 (1)	3	30	2	31	5.8%	1.61 [0.25 , 10.39]
FOCUS 2019 (2)	25	1564	29	1563	94.2%	0.86 [0.50 , 1.47]
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



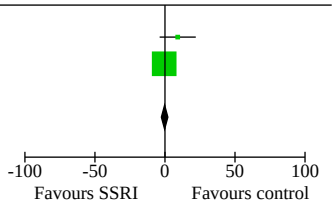
Footnotes

(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

Study or Subgroup	SSRI Mean	SSRI SD	SSRI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Bembenek 2020	83.3	19.83	24	74.2	26.94	27	3.2%	9.10 [-3.79 , 21.99]
FOCUS 2019 (1)	61.63	30.7	1327	62.19	30.78	1313	96.8%	-0.56 [-2.91 , 1.79]
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



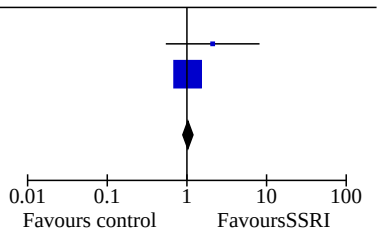
Footnotes

(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

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bembenek 2020	20	24	19	27	0.8%	2.11 [0.54 , 8.16]
FOCUS 2019	562	1539	557	1544	99.2%	1.02 [0.88 , 1.18]
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



ADDITIONAL TABLES

Table 1. Sensitivity analysis for co-primary outcomes depending on the method of analysis

	mRS (RR and 95% CI)	Disability (SMD and 95% CI)
Fixed-effect	0.98 (0.93, 1.03)	-0.0 (-0.05, 0.05)
Random-effects	0.98 (0.92, 1.04)	-0.00 (-0.05, 0.05)

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 hematoma* or bleed*)):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 inhib*):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 dapoxetin* or etoperidon* or escitalopram or femoxetin* or fenfluramin* or fluoxetin* or fluvoxamin* or nonfenfluramin* or paroxetin* or sertralin$ or trazodone or vilazodone or zimelidine):ti,ab,kw (Word variations have been searched)
#23 (Celexa or Cipramil or Cipram or Recital or Emocal or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Esertia or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Fluctin or fluox or Lovan or Luvox or Fevarin or Faverin or Favoxil or Movox or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Zoloft or Lustral or Serlain or Asentra):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.

4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. hemiplegia/ or exp paresis/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. exp Gait Disorders, Neurologic/
8. or/1-7
9. exp Serotonin Uptake Inhibitors/
10. ((serotonin or 5-HT or 5 HT or 5-hydroxytryptamine or 5 hydroxytryptamine) adj5 (uptake or reuptake or re-uptake) adj5 inhib$).tw.
11. SSRI$1.tw.
12. (alaproclat$ or cericlamin$ or citalopram or dapoxetin$ or escitalopram or femoxetin$ or fluoxetin$ or fluvoxamin$ or paroxetin$ or sertralin$ or trazodone or vilazodone or zimelidine).tw,nm.
13. (Celexa or Cipramil or Cipram or Recital or Emocal or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Esertia or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Fluctin or fluox or Lovan or Luvox or Fevarin or Faverin or Favoxil or Movox or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Zoloft or Lustral or Serlain or Asentra).tw,nm.
14. 9 or 10 or 11 or 12 or 13
15. 8 and 14
16. exp animals/ not humans.sh.
17. 15 not 16
18. Randomized Controlled Trials as Topic/
19. random allocation/
20. Controlled Clinical Trials as Topic/
21. control groups/
22. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
23. Clinical Trials Data Monitoring Committees/
24. double-blind method/
25. single-blind method/
26. Placebos/
27. placebo effect/
28. cross-over studies/
29. Multicenter Studies as Topic/
30. Therapies, Investigational/
31. Drug Evaluation/
32. Research Design/
33. Program Evaluation/
34. evaluation studies as topic/
35. randomized controlled trial.pt.
36. controlled clinical trial.pt.
37. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
38. multicenter study.pt.
39. (evaluation studies or comparative study).pt.
40. meta analysis.pt.
41. meta-analysis as topic/
42. random$.tw.
43. (controlled adj5 (trial$ or stud$)).tw.
44. (clinical$ adj5 trial$).tw.
45. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
46. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
47. ((multicenter or multicentre or therapeutic) adj5 (trial$ or stud$)).tw.
48. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
49. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
50. (coin adj5 (flip or flipped or toss$)).tw.
51. latin square.tw.
52. versus.tw.
53. (cross-over or cross over or crossover).tw.
54. placebo$.tw.
55. sham.tw.
56. (assign$ or alternate or allocat$ or counterbalance$ or multiple baseline).tw.
57. controls.tw.
58. (treatment$ adj6 order).tw.
59. (meta-analy$ or metaanaly$ or meta analy$ or systematic review or systematic overview).tw.

60. or/18-59
61. 17 and 60

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 cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
5. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
6. hemiparesis/ or hemiplegia/ or paresis/
7. (hemipleg$ or hemipar$ or paresis or paretic).tw.
8. or/1-7
9. exp serotonin uptake inhibitor/
10. ((serotonin or 5-HT or 5 HT or 5-hydroxytryptamine or 5 hydroxytryptamine) adj5 (uptake or reuptake or re-uptake) adj5 inhib$).tw.
11. SSRI$1.tw.
12. (alaproclat$ or cericlamin$ or citalopram or dapoxetin$ or escitalopram or femoxetin$ or fluoxetin$ or fluvoxamin$ or paroxetin$ or sertralin$ or trazodone or vilazodone or zimelidine).tw.
13. (Celexa or Cipramil or Cipram or Recital or Emocal or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Esertia or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Fluctin or fluox or Lovan or Luvox or Fevarin or Faverin or Favoxil or Movox or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Zoloft or Lustral or Serlain or Asentra).tw,tn.
14. 9 or 10 or 11 or 12 or 13
15. 8 and 14
16. limit 15 to human
17. Randomized Controlled Trial/
18. Randomization/
19. Controlled Study/
20. control group/
21. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/
22. Double Blind Procedure/
23. Single Blind Procedure/ or triple blind procedure/
24. placebo/
25. "types of study"/
26. research subject/
27. random$.tw.
28. (controlled adj5 (trial$ or stud$)).tw.
29. (clinical$ adj5 trial$).tw.
30. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
31. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
32. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
33. (coin adj5 (flip or flipped or toss$)).tw.
34. versus.tw.
35. placebo$.tw.
36. controls.tw.
37. or/17-36
38. 16 and 37

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

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

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

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 cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. (hemipleg$ or hemipar$ or paresis or paretic).tw.
6. hemiparesis/ or hemiplegia/
7. or/1-6
8. exp serotonin reuptake inhibitors/

9. ((serotonin or 5-HT or 5 HT or 5-hydroxytryptamine or 5 hydroxytryptamine) adj5 (uptake or reuptake or re-uptake) adj5 inhib$).tw.
10. SSRI$1.tw.
11. (alaproclat$ or cericlamin$ or citalopram or dapoxetin$ or escitalopram or femoxetin$ or fluoxetin$ or fluvoxamin$ or paroxetin$ or sertralin$ or trazodone or vilazodone or zimelidine).tw.
12. (Celexa or Cipramil or Cipram or Recital or Emocal or Dalsan or Sepram or Seropram or Citox or Priligy or Lexapro or Cipralex or Seroplex or Esertia or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Fluctin or fluox or Lovan or Luvox or Fevarin or Faverin or Favoxil or Movox or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Zoloft or Lustral or Serlain or Asentra).tw.
13. 8 or 9 or 10 or 11 or 12
14. 7 and 13

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 alaproclate OR CEREBR* AND cericlamine OR CEREBR* AND citalopram OR CEREBR* AND clomipramine OR CEREBR* AND dapoxetine 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 alaproclate OR STROKE AND cericlamine OR STROKE AND citalopram OR STROKE AND clomipramine OR STROKE AND dapoxetine 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 alaproclate OR cericlamine OR citalopram OR clomipramine OR dapoxetine 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

Date	Event	Description
7 January 2021	New citation required and conclusions have changed	The conclusions are now more certain than in the previous version.
7 January 2021	New search has been performed	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.

HISTORY

Protocol first published: Issue 11, 2011
Review first published: Issue 11, 2012

Date	Event	Description
14 March 2019	New citation required and conclusions have changed	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.
14 March 2019	New search has been performed	We have clarified that there are 2 primary outcomes: independence and disability.

Date	Event	Description
		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 I^2 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;

Date	Event	Description
		(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 Drottning Victorias 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.

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- 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; Anxiety Disorders; Fluoxetine [adverse effects]; *Serotonin Uptake Inhibitors [adverse effects]; *Stroke [drug therapy]

MeSH check words

Humans