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

Mead GE, Hsieh CF, Lee R, Kutlubaev MA, Claxton A, Hankey GJ, Hackett ML



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[Intervention Review]

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery

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ABSTRACT

Background

Stroke is the major cause of adult disability. Selective serotonin reuptake inhibitors (SSRIs) have been used for many years to manage depression. Recently, small trials have demonstrated that SSRIs might improve recovery after stroke, even in people who are not depressed. Systematic reviews and meta-analyses are the least biased way to bring together data from several trials. Given the promising effect of SSRIs on stroke recovery seen in small trials, a systematic review and meta-analysis is needed.

Objectives

To determine whether SSRIs improve recovery after stroke, and whether treatment with SSRIs was associated with adverse effects.

Search methods

We searched the Cochrane Stroke Group Trials Register (August 2011), Cochrane Depression Anxiety and Neurosis Group Trials Register (November 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 8), MEDLINE (from 1948 to August 2011), EMBASE (from 1980 to August 2011), CINAHL (from 1982 to August 2011), AMED (Allied and Complementary Medicine) (from 1985 to August 2011), PsycINFO (from 1967 to August 2011) and PsycBITE (Pyschological Database for Brain Impairment Treatment Efficacy) (March 2012). To identify further published, unpublished and ongoing trials we searched trials registers, pharmaceutical websites, reference lists, contacted experts and performed citation tracking of included studies.

Selection criteria

We included randomised controlled trials that recruited stroke survivors (ischaemic or haemorrhagic) at any time within the first year. The intervention was any SSRI, given at any dose, for any period. We excluded drugs with mixed pharmacological effects. The comparator was usual care or placebo. In order to be included, trials had to collect data on at least one of our primary (dependence and disability) or secondary (impairments, depression, anxiety, quality of life, fatigue, healthcare cost, death, adverse events and leaving the trial early) outcomes.

Data collection and analysis

We extracted data on demographics, type of stroke, time since stroke, our primary and secondary outcomes, and sources of bias. For trials in English, two review authors independently extracted data. For Chinese papers, one review author extracted data. We used standardised mean differences (SMD) to estimate treatment effects for continuous variables, and risk ratios (RR) for dichotomous effects, with their 95% confidence intervals (CIs).

Main results

We identified 56 completed trials of SSRI versus control, of which 52 trials (4060 participants) provided data for meta-analysis. There were statistically significant benefits of SSRI on both of the primary outcomes: RR for reducing dependency at the end of treatment was 0.81 (95% CI 0.68 to 0.97) based on one trial, and for disability score, the SMD was 0.92 (95% CI 0.62 to 1.23) (22 trials involving 1310 participants) with high heterogeneity between trials ($I^2 = 85\%$; P < 0.0001). For neurological deficit, depression and anxiety, there were statistically significant benefits of SSRIs. For neurological deficit score, the SMD was -1.00 (95% CI -1.26 to -0.75) (29 trials involving 2011 participants) with high heterogeneity between trials ($I^2 = 86\%$; P < 0.00001). For dichotomous depression scores, the RR was 0.43 (95% CI 0.24 to 0.77) (eight trials involving 771 participants) with high heterogeneity between trials ($I^2 = 77\%$; P < 0.0001). For continuous depression scores, the SMD was -1.91 (95% CI -2.34 to -1.48) (39 trials involving 2728 participants) with high heterogeneity between trials ($I^2 = 95\%$; P < 0.00001). For anxiety, the SMD was -0.77 (95% CI -1.52 to -0.02) (eight trials involving 413 participants) with high heterogeneity between trials ($I^2 = 92\%$; P < 0.00001). There was no statistically significant benefit of SSRI on cognition, death, motor deficits and leaving the trial early. For cognition, the SMD was 0.32 (95% CI -0.23 to 0.86), (seven trials involving 425 participants) with high heterogeneity between trials ($I^2 = 86\%$; P < 0.00001). The RR for death was 0.76 (95% CI 0.34 to 1.70) (46 trials involving 3344 participants) with no heterogeneity between trials ($I^2 = 0\%$; P = 0.85). For motor deficits, the SMD was -0.33 (95% CI -1.22 to 0.56) (two trials involving 145 participants). The RR for leaving the trial early was 1.02 (95% CI 0.86 to 1.21) in favour of control, with no heterogeneity between trials. There was a non-significant excess of seizures (RR 2.67; 95% CI 0.61 to 11.63) (seven trials involving 444 participants), a non-significant excess of gastrointestinal side effects (RR 1.90; 95% CI 0.94 to 3.85) (14 trials involving 902 participants) and a non-significant excess of bleeding (RR 1.63; 95% CI 0.20 to 13.05) (two trials involving 249 participants) in those allocated SSRIs. Data were not available on quality of life, fatigue or healthcare costs.

There was no clear evidence from subgroup analyses that one SSRI was consistently superior to another, or that time since stroke or depression at baseline had a major influence on effect sizes. Sensitivity analyses suggested that effect sizes were smaller when we excluded trials at high or unclear risk of bias.

Only eight trials provided data on outcomes after treatment had been completed; the effect sizes were generally in favour of SSRIs but CIs were wide.

Authors' conclusions

SSRIs appeared to improve dependence, disability, neurological impairment, anxiety and depression after stroke, but there was heterogeneity between trials and methodological limitations in a substantial proportion of the trials. Large, well-designed trials are now needed to determine whether SSRIs should be given routinely to patients with stroke.

PLAIN LANGUAGE SUMMARY

Selective serotonin reuptake inhibitors for stroke recovery

Selective serotonin reuptake inhibitors (SSRIs) are a class of drugs that have been in use for many years, mainly for the treatment of mood disorders such as depression. Animal studies have shown that SSRIs may have other direct effects on the brain, such as encouraging the development of new brain cells. If this also occurs in humans, recovery from stroke may be improved. This review brought together the results of 52 trials (4060 participants) of SSRIs in people who had had a stroke in the previous year, to find out whether SSRIs might reduce dependency and disability. The review found promising evidence that SSRIs might improve recovery after stroke, even in patients who were not depressed. Large trials are now needed to confirm or refute these findings, and to determine whether SSRIs increase the risk of side effects such as seizures. If effective, SSRIs would be a low-cost, simple and widely applicable treatment for patients with stroke.

BACKGROUND

Description of the condition

Each year, stroke affects about 16 million people for the first time and causes about 5.7 million deaths (Strong 2007). Moreover, survivors of stroke account for about 51 million disability-adjusted life years (DALYs). This is because recovery of functional independence after stroke only occurs in about half of all survivors of stroke, and mainly during the first six months after a stroke (Hankey 2007a; Hankey 2007b). Although major advances in the early reperfusion of ischaemic stroke have been realised in recent years (e.g. by intravenous thrombolysis and prevention of early 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 a class of drug that have been available for many years. Their main use in clinical practice is for mood disorders, particularly depression. They are sometimes used in stroke to manage emotionalism (Hackett 2010) (i.e. emotional behaviour that the patient reports as being outside normal control and that occurs in situations that previously would not have provoked such behaviour). Small trials have suggested that fluoxetine, one of the SSRIs, might have a favourable effect on motor recovery after stroke (Chollet 2011; Yi 2010). The recently published 'Fluoxetine on Motor Rehabilitation after Ischemic Stroke' (FLAME) trial reported that 15 (26%) of 56 acute stroke patients allocated to receive fluoxetine and five (9%) of 54 allocated to placebo had a modified Rankin score (mRS) of 0 to 2 (no dependency on other people) at three months, and an odds ratio (OR) of 3.8 (95% confidence interval (CI) 1.2 to 10.7) (Chollet 2011).

How the intervention might work

In animal studies, multiple, potentially beneficial effects of SS-RIs 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 patients 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, for example, 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 upregulation (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 (Palvimaki 1994).

In healthy humans, functional magnetic resonance imaging (fMRI) studies have demonstrated that fluoxetine can modulate cerebral motor activity (Loubinoux 1999). Zittel et al investigated the effects of a single dose of citalopram 40 mg in eight chronic stroke patients and reported that dexterity was significantly improved (Zittel 2008).

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

It is rare for treatments for neurological diseases such as stroke to have a dramatically favourable effect, such as that of fluoxetine on recovery after stroke as suggested by the FLAME trial (Chollet 2011). Treatments for stroke are far more likely to have a modest treatment effect, at best, which can nevertheless be clinically worthwhile. If modest but worthwhile treatment effects are to be reliably detected or refuted, then any errors in the evaluation of their effectiveness need to be much smaller than the effect of the treatment itself, otherwise the errors may nullify the effect of the treatment and lead to a false-negative result. Similarly, if the treatment is not effective, substantial errors could lead to a false-positive result, or an exaggerated positive result.

The common sources of error in trials of interventions are systematic error (bias) and random error. Systematic errors can be minimised by proper randomisation, analysis by allocated treatment, evaluation of outcome evaluation blinded to the allocated treatment, emphasis on the overall primary results, and publication of all studies irrespective of the results; whereas random error can really only be minimised by studying the effect of the treatment compared with a control on a large number of major outcomes, and therefore in all trials. It is therefore important to systemat-

ically review all the relevant trials that have evaluated the effect of SSRIs on recovery after stroke (published and unpublished) to minimise systematic and random error in our estimates of the potential effects of SSRIs on recovery after stroke. Although a review of fluoxetine in stroke has already been undertaken and published (Yi 2010), the searches were done in 2009 and so the review did not include the FLAME trial (Chollet 2011). The review was limited to fluoxetine rather than all SSRIs (Yi 2010). Furthermore, although the authors of the existing review considered some important aspects of study quality, the Cochrane 'Risk of bias' tool was not used, so the review authors may have missed some sources of bias. Thus, there is a need to produce an updated, methodologically robust systematic review incorporating all the relevant trials that have examined the role of all SSRIs for stroke recovery.

If a simple, inexpensive drug such as one of the SSRIs is shown to improve stroke recovery, this would have major implications for patients, carers, health services, social care services and the economy.

There are two previous Cochrane reviews of interventions to treat and prevent depression after stroke (Hackett 2008a; Hackett 2008b). These two reviews focused on depression and included physical measures as secondary outcomes. However, the reviews excluded studies in which there was no placebo. Thus, we decided that a new review focusing on SSRIs for recovery after stroke was needed.

OBJECTIVES

Our objective was to determine whether SSRIs improve recovery after stroke, and whether treatment with SSRIs was associated with adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

The review was restricted to all relevant randomised controlled trials (RCTs) in patients with a clinical diagnosis of stroke (Hatano 1976) where an SSRI had been given within the first year of stroke onset. Initially we decided to include trials that recruited patients within three months of stroke onset, but for some relevant trials, the study authors did not state the time since stroke. If we had excluded these studies, we would have lost a large amount of potentially relevant information. Thus, we changed our inclusion criteria to include trials (1) that stipulated that patients had to be

recruited within 12 months of stroke onset, and (2) trials where the mean (or median) time since stroke was less than 12 months. The searches identified several trials 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 arm.

We excluded trials using a cross-over design. We also excluded trials in which two or more active interventions were compared against each other rather than a placebo or standard care group. We included trials in all languages. There was no restriction on the eligibility of RCTs on the basis of sample size or duration of follow-up. We considered unpublished reports, abstracts, brief and preliminary reports for inclusion on the same basis as published reports.

We included published trials that fulfilled our inclusion criteria, even if they provided no data that we could use in our metaanalysis.

We categorised as 'studies awaiting classification' trials for which we identified a protocol, but no published results, and no clear evidence that they were still ongoing (e.g. no response from study author).

We categorised ongoing trials as 'ongoing' if we received confirmation from the author that they were still recruiting or analysing the results.

Types of participants

We included trials 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). Trials had to recruit participants within 12 months of stroke onset or the mean time since stroke had to be less than 12 months. We intended to include trials that recruited patients with subarachnoid haemorrhage and perform subgroup analyses of this type of stroke, though we did not find any such trials. We intended to exclude trials that included mixed populations (such as stroke and head injury or other central nervous system disorders) unless separate results for patients with stroke were available, but we found no such trials.

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 fluoxetine was compared with another

active intervention (e.g. another type of drug or herb or acupuncture).

Types of outcome measures

Primary outcomes

Disability and dependence at the end of treatment or at the end of follow-up.

We anticipated that disability would be measured by the Barthel Index and Functional Independence Measure (FIM). However, if disability was measured using other scales, we included these data too.

We anticipated that dependency would be measured by the mRS. If other scales were used, we included these data too.

Secondary outcomes

Impairments, depression, anxiety, quality of life, fatigue, healthcare cost, death, adverse events, leaving the trial early (for any reason, including death). After publication of the protocol for this review, we stipulated that we were particularly interested in gastrointestinal (GI) side effects, bleeding and seizures, as these side effects are either common or potentially serious after stroke, and are known side effects of SSRIs.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We searched for relevant trials in all languages and arranged for translation of trial reports published in languages other than English.

Electronic searches

We searched the following electronic bibliographic databases:

• Cochrane Stroke Group Trials Register (August 2011);

• Cochrane Depression Anxiety and Neurosis Group Trials Register (November 2011);

Cochrane Central Register of Controlled Trials

(CENTRAL) (*The Cochrane Library* 2011, Issue 8) (Appendix 1);
MEDLINE (from 1948 to August 2011) (Appendix 2);

- EMBASE (from 1980 to August 2011) (Appendix 3);
- CINAHL (from 1982 to August 2011) (Appendix 4);

• AMED (Allied and Complementary Medicine) (from 1985 to August 2011) (Appendix 5);

• PsycINFO (from 1967 to August 2011) (Appendix 6);

• PsycBITE Pyschological Database for Brain Impairment Treatment Efficacy (www.psycbite.com/) (March 2012).

We developed the MEDLINE search strategy with the help of the Cochrane Stroke Group Trials Search Co-ordinator and adapted it for the other databases. For www.psycbite.com, we used the search terms on the 'drop down' menu (Stroke/CVA (cerebrovascular accident) and RCT and > 18 years). In addition, we searched:

• the online Clinical Trial Results and Clinical Trial Registries for Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Novartis, Pfizer, Roche, and Lundbeck (August 2011);

• the following ongoing trials registers:

 Stroke Trials Registry (www.strokecenter.org/trials) (September 2011);

 ClinicalTrials.gov (www.ClinicalTrials.gov) (September 2011);

 Current Controlled Trials (www.controlled-trials.com) (January 2012);

EU Clinical Trials Register (

www.clinicaltrialsregister.eu) (January 2012).

Searching other resources

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

• searched reference lists of included trials and relevant reviews when full texts were retrieved for detailed scrutiny;

• used Science Citation Index Cited Reference Search for forwards tracking of the included trials that were listed on Web of Science (February 2012);

• contacted researchers in the field.

Data collection and analysis

Selection of studies

Brenda Thomas, the Cochrane Stroke Group Trials Search Coordinator, ran the searches of CENTRAL, MEDLINE, EMBASE, CINAHL, AMED and PsycINFO and downloaded the resulting references into Reference Manager. At this point some duplicate references were removed automatically. Further scrutiny of each citation enabled Maureen Harding (who provided administrative support) to remove further duplicates.

One review author (GM) then scrutinised the resulting titles and abstracts and excluded obviously irrelevant reports. The same review author (GM) obtained the full text of the remaining studies and applied the inclusion and exclusion criteria. When there were uncertainties, she sought the views of a second review author. We had intended that two review authors would independently scrutinise all the citations but this was not possible owing to the large number of studies identified from the searches.

Two review authors (GM and RL) independently scrutinised the titles and abstracts (when available) from the electronic searches of Cochrane Depression Anxiety and Neurosis Group Trials Register. Two review authors (GM and MK) independently scrutinised

the titles and abstracts (when available) from searches of Cochrane Stroke Group Trials Register. The review authors excluded obviously irrelevant studies and obtained the full text of all remaining trials.

We had planned that one experienced review author (GM or MH or GH) and one less experienced review author (MK, RL or MB) would independently scrutinise each full-text article and decide whether they fulfilled inclusion criteria. Owing to the large number of studies that were obtained as full texts, this was not possible, and so one experienced review author (GM) applied the inclusion criteria to the full texts for all the papers written in English, and one Chinese speaking review author (C-F H) applied the inclusion criteria to the potentially eligible papers written in Chinese. We had planned to ask a third review author should any disagreements arose, but this was not necessary.

One review author (AC) searched the clinical trial databases, then sent a list of potentially eligible trials to GM for further scrutiny and agreement about whether the trials should be obtained in full text. AC and GM then decided whether these trials should be included.

We included a study flow diagram (Figure 1) that includes the number of unique references identified by the searches, the number of records excluded after preliminary screening of titles and abstracts, and the number of records retrieved in full text. We took appropriate notes during the search process and created an Excel spreadsheet listing the publications that were obtained as full text, thus ensuring that the flow diagram could be completed correctly.



Figure I. Study flow diagram.

Data extraction and management

We developed a paper data extraction form based on the one used for previous Cochrane reviews in depression (Hackett 2008a; Hackett 2008b). It was piloted on three papers and we made minor modifications. We had planned that two review authors (an experienced one and a less experienced one) would independently extract data from each study, including risk of bias. We did this for all papers written in English, and for the single paper written in German, but for papers written in Chinese, only one review author (C-F H) extracted data.

We extracted the following data:

- 1. the report: author, year and source of publication;
- 2. the study: sample characteristics, social demography;

3. 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 lesion, particularly for patients with minor strokes;

4. the research design and features: adherence, non-response and length of follow-up;

5. the intervention: type, duration, dose, timing and mode of delivery;

6. the effect size: sample size, nature of outcome, estimate and standard deviation (SD) (or standard error (SE)).

We stored the data extraction sheets electronically as Word documents.

Assessment of risk of bias in included studies

We assessed risk of bias using The Cochrane Collaboration's risk of bias tool. For each study, we determined whether there was allocation concealment; how randomisation was performed (including how sequences were generated); whether there was blinding of patient, personnel and outcome assessors; whether there were incomplete outcome data and whether there was selective outcome data reporting. We were guided by the *Cochrane Handbook for Systematic Reviews of Interventions* when making these judgements (Higgins 2011).

We also recorded whether there was an imbalance in baseline characteristics. We also noted whether there was minimisation or stratification based on baseline variables, and early stopping of the intervention.

For randomisation, we categorised the trials as low risk of bias if there was computer-generated random numbers, or the use of

a random number table. We categorised other methods of randomisation (e.g. 'flicking a coin', use of 'number tables') as 'unclear risk'. If a patient was allocated according to other criteria (e.g. sequence of admission) we categorised this as 'high risk'. If the randomisation method was not described, we categorised the random sequence generation as 'unclear risk'.

For allocation concealment, we categorised trials as 'low risk' if an opaque envelope was used, or if the allocation was performed by a computer. If the method was not described, we categorised this as 'unclear risk'. If other methods were used, we categorised them as 'high risk'.

For blinding of personnel and patients, we categorised studies as 'low risk' if a matching placebo was used. If a placebo was used but it was not described as matching, we categorised this as 'unclear risk'.

For blinding of outcome assessor, we categorised as 'low risk' if the outcome assessor was described as being blind. If the outcome assessor was not blind, we categorised as 'high risk'; for all other we categorised as 'unclear risk'. We did this at the level of a study rather than for individual outcomes, for example if there was blinding for the majority of outcomes (e.g. activities of daily living (ADL), neurological score and disability) but one outcome was by selfreport (e.g. depression), we categorised the study as 'low risk'.

For incomplete outcome data, if the authors stated 'intention-totreat' analysis (and they undertook it) and stated the method they used to impute missing values (e.g. last value carried forward, best and worst outcome/sensitivity, bootstrapping, etc) we categorised the study as 'low risk' of bias. If per-protocol analyses were presented only, we categorised as 'low risk' if the drop-outs were small (small was defined as less than 5%). If per-protocol analyses were presented only and drop-outs were greater than 5%, then risk of bias was 'high'.

For selective reporting, we categorised as 'low risk' those trials in which there was a published protocol (either as a full journal article or abstract), or a description of the trial design on a trial database prior to publication of the trial results, and when the outcome measures listed in the trial protocol were reported in the results. We defined as 'high risk' any trial that described an outcome measure in the methods but did not provide results. All other trials were categorised as 'unclear risk'.

Following editorial review, 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'.

Following editorial review, we also extracted data on how adverse effects were recorded, and listed these in the descriptions of the studies.

Measures of treatment effect

We carried out statistical analyses using the Review Manager software, RevMan 5.1 (RevMan 2011). We calculated a summary statistic for each outcome measure used to describe the observed treatment effect. All summary statistics reported in this review referred to effects at either: (1) the end of intervention, or (2) the end of follow-up.

Unit of analysis issues

Prior to commencing the review, we anticipated that most of the trials would have a simple parallel group design where each individual was randomised to one of two treatment groups. We had planned to perform subgroup analyses should a trial have three (or more) arms, two of which were different doses of SSRIs. In fact, we did not find any such trials, but we did identify several trials with three arms: a control arm and two active arms (including the SSRI arm). For these trials, we included data only from the control arm and the SSRI arm.

Dealing with missing data

We had intended to approach primary investigators for missing data, but this was not possible owing to the larger than expected number of trials. We did, however, contact authors of studies published in abstract form to enquire whether they had been subsequently published as full-text articles.

Assessment of heterogeneity

Tests of heterogeneity seek to determine whether there are genuine differences underlying the results of the studies (heterogeneity), or whether the variation in findings is compatible with chance alone (homogeneity) (Higgins 2003). P values are obtained by comparing the statistic with a χ^2 distribution with k-1 degrees of freedom (where k is the number of studies). However, the test is known to be poor at detecting true heterogeneity among studies as significant. Thus, the I² statistic was developed to quantify the effect of heterogeneity, providing a measure of the degree of inconsistency in the studies' results (Higgins 2003). I² describes the percentage of total variation across studies that is because of heterogeneity rather than chance. In this review, we investigated statistical heterogeneity using the I² statistic available in RevMan (RevMan 2011).

We used I² as a measure of heterogeneity between trials and also between our pre-defined subgroups. We interpreted the amount of heterogeneity as low, moderate and high to I² values of 25%, 50% and 75%, respectively (Higgins 2003). We also stated whether the I² value was statistically significant, based on the P value.

Assessment of reporting biases

We assessed publication bias by a funnel plot, using disability as this was one of our primary outcomes.

We tried to avoid language bias by including all trials, irrespective of language: we sought translation where needed. Owing to the large number of papers written in Chinese, an additional review author (C-F H), who is fluent in Chinese, joined the team. He translated and extracted data from these papers.

We checked for selective reporting of results 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.

Data synthesis

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 RevMan are means and SDs. When extracting continuous data from the study reports, we checked whether trials reported SD or SE. We had planned to use SE or 95% CI to compute 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 (SMD) because different scales were used for the same outcomes (e.g. Barthel Index and FIM for disability, the Beck Depression inventory (BDI) or the Hamilton Rating Scale for Depression (HAMD) for depression). It should be noted that the SMD does not correct for differences in the direction of the scale. As some scales increased with disease severity and others decreased, we multiplied the mean value from one set of trials by -1. An example of this is the National Institute of Health Stroke Scale (where a low score indicates a less severe stroke) and the Scandinavian Stroke Scale (SSS) (where a low score indicates a more severe stroke).

We used the random-effects model for all our analyses.

Subgroup analysis and investigation of heterogeneity

We performed the following subgroup analyses.

1. Type of SSRI.

2. Trials that stated that depression had to be present at recruitment and trials that did not have depression as an inclusion criterion.

3. Time since stroke at recruitment. We categorised these as less than three months, three to six months, six to nine months, nine to 12 months; where less than three months was equivalent to 0 to 90 days, three to six months was equivalent to 91 to 180

days, six to nine months was equivalent to 181 to 271 days and nine to 12 months was equivalent to 272 to 365 days.

We had intended to perform a subgroup analysis for motor or non-motor deficits at entry and for brand of drug, but there was insufficient information in the trial reports. Dose of drug was reported but most trials used the same dose for each individual SSRI, so we decided that there were insufficient data to explore the influence of dose of drug on outcome.

Sensitivity analysis

We performed sensitivity analyses to explore the influence of the key aspects of trial quality that we identified during our assessment of risk of bias (i.e. randomisation, allocation concealment, blinding, incomplete outcome data, selective reporting). We did this by excluding the trials that were categorised as 'high risk' and 'unclear' risk, and repeating the previous analyses on only those studies at low risk of bias.

We reported the effect sizes as being larger, similar or smaller than if all trials had been included, accepting that there was some degree of subjective assessment in making decisions about 'larger', 'similar' or 'smaller'. We also reported whether results were still statistically significant when only those at low risk of bias were included.

RESULTS

Description of studies

Results of the search

Figure 1 shows the flow diagram for the selection of studies. The searches by Brenda Thomas identified the 2673 citations (after electronic removal of 102 duplicates when importing into Reference Manager): 249 from MEDLINE, 1803 from EMBASE, 197 from CENTRAL, 170 from CINAHL, 20 from AMED and 234 from PsycINFO. We removed a further 405 duplicates by visual scrutiny of the searches. The remaining 2268 titles and abstracts (when available) were scrutinised by GM. We identified a further 27 citations relating to the same study, by the same author team. We retrieved 143 full texts for detailed scrutiny.

The search of the Cochrane Stroke Trials Register identified 32 citations, of which 11 were duplicates; we retrieved 24 full texts. The search of the Cochrane Depression and Anxiety Group Trials register identified 47 citations, of which 13 were duplicates; we retrieved 21 full texts.

The search of www.pyscbite.com by GM identified 310 citations. We retrieved the full text for one of these, which had already been identified by other searches. The searches of clinical trials registers identified 138 citations. Of these, we retrieved 27 citations for detailed scrutiny by two review authors (AC and GM).

The searches of the pharmaceutical websites identified 541 citations. We retrieved full texts for eight of these, of which one trial was eligible for inclusion.

One review author (RL) performed a cited reference search (5 February 2012) of 32 trials that were listed on Web of Science (Acler 2009; Almeida 2006; Andersen 1994; Brown 1998; Burns 1999; Chollet 2011; Dam 1996; Fruehwald 2003; He 2004; Ji 2000; Jia 2005; Kong 2007; Lai 2006; Li 2004a; Li 2004b; Li 2008; Liang 2003; Meara 1998; Miao 2004; Murray 2005; Rasmussen 2003; Robinson 2000a; Robinson 2000b; Robinson 2008; Sitzer 2002; Wiart 2000; Xie 2005; Xu 2001; Xu 2006; Yang 2002; Ye 2004; Zhou 2003) and identified 828 citations. These were all screened for relevance. No trials were identified that had not been identified previously.

We identified two trials that appeared to fulfil our inclusion criteria (Sitzer 2002; Whyte 2005). However, we could find no published results and when we sought further information from the authors, we received no responses. One of these trials is listed on www.clinicaltrials.gov as 'terminated because recruitment goals could not be met' (Whyte 2005). We have listed these two trials as 'awaiting assessment'.

We identified five ongoing trials that appeared to fulfil our inclusion criteria (2005-005266-37; AFFINITY 2011; Carda 2009; EMOTION 2011; FOCUS 2011).

Included studies

We identified four trials that fulfilled our inclusion criteria, but that did not provide data that we could use in a meta-analysis (Chen KN 2005; Meara 1998; Pariente 2001; Restifo 2001).

We identified a total of 51 completed trials that fulfilled our inclusion criteria and that provided data that we could use in the meta-analysis. Two of these studies (He 2005: Ye 2004) were each published twice in different journals.

Of the 51 trials that provided data that we included in our metaanalysis, one trial (Robinson 2000a/Robinson 2000b) reported data separately for depressed and non-depressed people, so we have split this study into two.

Thus, we have 52 trials. Together these 52 trials randomised a total of 4060 patients to SSRI or control.

Of the 52 trials that we could use in our meta-analysis:

• 28 trials used fluoxetine (Brown 1998; Chen 2001; Cheng 2003; Chollet 2011; Dam 1996; Feng 2004; Fruehwald 2003; He 2004; Hu 2002; Huang 2002; Ji 2000; Kong 2007; Li 2002; Li 2004a; Li 2004b; Li 2008; Liang 2003; Liu 2004; Robinson 2000a; Robinson 2000b; Song 2006; Wang 2003; Wen 2006; Wiart 2000; Xu 2001; Xu 2007; Zhou 2003; Zhou 2008);

seven trials used sertraline (Almeida 2006; Burns 1999;
 Finkenzeller 2009; Guo 2009; Murray 2005; Rasmussen 2003;

Xie 2005);

• 10 used paroxetine (Chen 2002; Chen T 2005;

GlaxoSmithKline 1998; He 2005; Lai 2006; Li 2005; Xu 2006; Yang 2002; Yang 2011; Ye 2004);

• five used citalopram (Acler 2009; Andersen 1994; Li 2006; Liu 2006; Miao 2004);

- one used escitalopram (Robinson 2008);
- one used either sertraline or fluoxetine (Jia 2005).

Patient characteristics

Of the 52 trials that provided data for meta-analysis, the mean age of patients ranged from 55 years (Liu 2004) to 77 years (Finkenzeller 2009), with most trials recruiting patients in their 60s. The included trials generally excluded patients who could not consent for themselves, patients with dementia, patients with communication difficulties and those with contraindications to SSRIs. Some trials recruited patients with either haemorrhagic or ischaemic stroke, and some restricted entry only to those with ischaemic stroke (see Characteristics of included studies). Some recruited people with depression and some recruited people without depression (see 'Depression as an inclusion criterion' below).

Mean time since stroke

Of the trials included in our meta-analysis, the mean time since stroke was zero to three months for 31 trials (Acler 2009; Andersen 1994; Almeida 2006; Chen 2001 Chen T 2005; Cheng 2003; Chollet 2011; Feng 2004; Fruehwald 2003; Finkenzeller 2009; He 2004; Hu 2002; Huang 2002; Kong 2007; Li 2004a; Li 2004b; Li 2008; Liang 2003; Liu 2004; Rasmussen 2003; Robinson 2008; Song 2006; Wiart 2000; Yang 2011; Ye 2004; Wen 2006; Xie 2005; Xu 2001; Xu 2006; Zhou 2003; Zhou 2008).

A further three trials (He 2005; Lai 2006; Li 2006) described participants as having an 'acute stroke' - we assumed this meant zero to three months, so included these in the zero- to three-month group. The mean time since stroke was between five and 16 weeks in two studies, so we included these in the zero- to three-month group (Robinson 2000a; Robinson 2000b).

We included four trials in the three- to six-months category: 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 trials recruited between six and nine months (Guo 2009; Liu 2006).

No trials reported recruiting patients between nine and 12 months after stroke.

The time was not reported for 10 trials (Brown 1998; Burns 1999; Chen 2002; GlaxoSmithKline 1998 (less than 12 months); Ji 2000; Jia 2005; Li 2002 (at least two weeks after stroke onset); Li 2005; Xu 2007 and Wang 2003).

Depression as an inclusion criterion

In 17 of these 52 trials, a diagnosis of depression (however made) was not one of the inclusion criteria: Acler 2009; Almeida 2006; Brown 1998; Burns 1999; Chollet 2011; Dam 1996; He 2004; Kong 2007; Li 2004a; Liu 2004; Rasmussen 2003; Robinson 2000b; Robinson 2008; Wen 2006; Xu 2006; Zhou 2003 and Zhou 2008. In the remaining trials that had data that we could use in the meta-analysis, participants had to have depression (though criteria for diagnosing depression varied between trials).

Excluded studies

We listed as excluded studies non-randomised comparisons of SSRIs and control, studies that compared two active treatments (rather than SSRI versus control), and studies that recruited patients more than one year after stroke onset. Those that were obviously irrelevant (e.g. not an SSRI) or those that had been already been excluded from previous reviews (Hackett 2008a; Hackett 2008b) were excluded on the basis of an abstract only; we excluded the remaining studies only after we had scrutinised the full texts. In total, there were 48 excluded studies.

Risk of bias in included studies

Risk of bias is summarised in Figure 2 and Figure 3. The figures include all included studies, irrespective of whether they provided data that we could use in our meta-analysis.

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'risk of bias' item presented as percentages across all included studies.



Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



In the text below, we have listed only the studies that did provide data for meta-analysis.

Allocation

Of the trials that provided data for meta-analysis, there was low risk of bias for random sequence generation for 14 trials (Acler 2009; Almeida 2006; Burns 1999; Chollet 2011; Fruehwald 2003; Guo 2009; Kong 2007; Li 2004a; Li 2008; Liu 2004; Murray 2005; Robinson 2000a; Robinson 2000b; Robinson 2008). The risk of bias in the other trials was either uncertain or high.

Of the trials that provided data for meta-analysis, there was low risk of bias for allocation concealment for nine trials (Almeida 2006; Andersen 1994; Chollet 2011; Fruehwald 2003; Li 2004a; Murray 2005; Robinson 2000a; Robinson 2000b; Ye 2004).

Blinding

For blinding of participants and personnel (performance bias), there was low risk of bias for 16 trials (Acler 2009; Almeida 2006; Andersen 1994; Brown 1998; Burns 1999; Chollet 2011; Dam 1996; Fruehwald 2003; Kong 2007; Li 2008; Murray 2005; Rasmussen 2003; Robinson 2000a; Robinson 2000b; Robinson 2008; Wiart 2000). The risk of bias in the other trials was either uncertain or high.

For blinding of outcome assessor (detection bias), there was low risk of bias for 11 trials (Acler 2009; Brown 1998; Chollet 2011; Fruehwald 2003; Guo 2009; He 2004; Kong 2007; Li 2008; Murray 2005; Robinson 2008; Ye 2004). The risk of bias in the other trials was either uncertain or high.

Incomplete outcome data

There was low risk of bias for incomplete outcome data (attrition bias) for 30 trials (Almeida 2006; Andersen 1994; Brown 1998; Burns 1999; Chen T 2005; Chollet 2011; Guo 2009; He 2005; Hu 2002; Huang 2002; Ji 2000; Lai 2006 Li 2002; Li 2004a; Li 2005; Liang 2003; Liu 2004; Liu 2006; Murray 2005; Pariente 2001; Rasmussen 2003; Robinson 2000a; Robinson 2000b; Robinson 2008; Song 2006; Wen 2006; Wiart 2000; Xie 2005; Yang 2011; Zhou 2008).

Selective reporting

There was sufficient information provided to assess that risk of bias was low in 10 trials (Almeida 2006; Andersen 1994; Burns 1999; Chollet 2011; Dam 1996; Rasmussen 2003; Robinson 2000a; Robinson 2000b; Robinson 2008; Wiart 2000). We classified the remaining trials as unclear because we could not determine from the information available whether all planned outcomes were reported. Several trials were reported as high risk as not all outcomes listed in the methods were reported in the results.

Other potential sources of bias

We checked for differences in baseline characteristics and other sources of bias. If there were differences in baseline characteristics, we made a judgement as to whether these differences would have introduced bias.

Following editorial review, the sources of funding and information on drug company involvement were extracted by GM from the papers written in English and from papers written in Chinese by CF-H. If the funding source was not stated, we categorised the study as 'unclear risk'.

Effects of interventions

Dependency at the end of treatment

Two trials reported data on dependency using the mRS (Almeida 2006; Chollet 2011) (Analysis 1.1). RR for reducing dependency at the end of treatment was 0.81 (95% CI 0.68 to 0.97); this analysis was based on one trial (Chollet 2011) because the RR was not estimable for the other trial (Almeida 2006).

GlaxoSmithKline 1998 provided data on the change in mRS but did not provide the SD of the change, so we could not use these data in the meta-analyses.

With the inclusion of only two trials, there were insufficient data to comment on effects in the different subgroups, that is type of SSRI (Analysis 1.1), time since stroke (Analysis 3.1) and depression at randomisation (Analysis 4.1).

Disability at the end of treatment

Several disability scales were used including the Barthel, modified Barthel, FIM, or 'ADL score'.

Several Chinese papers used an 'ADL score' but did not reference this (Cheng 2003; Feng 2004; Xie 2005; Yang 2002; Zhou 2008). Of these, one trial (Cheng 2003) did not provide a reference for the ADL score, but stated that a lower score was better (so we were able to use the data in our meta-analysis). One trial used an ADL score and did not reference it, but stated that a score of 100 meant independent, and a score of 0 to 20 very severe functional disability (Xie 2005); thus we used these data in our meta-analysis. We could not determine the direction of the ADL score in three trials (Feng 2004; Yang 2002; Zhou 2008), so we did not use these data in the meta-analysis.

For scales in which a higher score meant better function (e.g. Barthel), we entered the mean score as a positive number. For scales in which a higher score meant worse function, we multiplied the mean ADL score by -1 to correct for differences in direction of the score.

We were unable to use other disability data in the meta-analysis for the following reasons: GlaxoSmithKline 1998 provided data on change in Barthel score but no SD; Li 2004b reported a dichotomous Barthel (not continuous); Finkenzeller 2009 provided data on median and interquartile range (IQR) (not means and SD); Guo 2009 reported only FIM cognition and FIM mobility (so we could not include these data as a global measure of disability) and Robinson 2008 reported that FIM data improved over time, but did not provide raw data. Murray 2005 did not report the ADL data although the paper stated that they had collected these data. This left continuous data on disability from 22 trials (1310 participants) that could be used in the meta-analysis (Analysis 1.2). The SMD was 0.92 (95% CI 0.62 to 1.23) in favour of SSRI. There was high heterogeneity between trials (I² = 85%; P < 0.00001).

Subgroup: type of SSRI (Analysis 1.2)

Of these 22 trials, 13 used fluoxetine (Chen 2001; Cheng 2003; Dam 1996; Kong 2007; Li 2008; Liu 2004; Robinson 2000a; Robinson 2000b; Wang 2003; Wiart 2000; Xu 2001; Xu 2007; Zhou 2003), three used citalopram (Acler 2009; Li 2006; Liu 2006), one used sertraline (Xie 2005) and five used paroxetine (Chen 2002; Chen T 2005; He 2005; Xu 2006; Ye 2004). There was moderate heterogeneity between the subgroups ($I^2 = 58\%$; P = 0.07) (Higgins 2002; Higgins 2003) (Analysis 1.2).

Subgroup: time since stroke (Analysis 3.2)

There was evidence of high heterogeneity between subgroups ($I^2 = 89\%$; P < 0.00001). The largest effect size was observed in trials in which the time since stroke was not reported and the smallest effect size in trials that recruited patients between three and six months after stroke onset (Analysis 3.2).

Subgroup: depression had to be present at diagnosis (Analysis 4.2)

There was evidence of high heterogeneity between subgroups ($1^2 = 79\%$; P = 0.03). The larger effect size was observed in those trials that stipulated that patients had to have depression at recruitment (Analysis 4.2).

Neurological deficit score at end of treatment

A number of different neurological deficit scores were reported including the Scandinavian neurological stroke scale (high score = better function, range 0 to 48), the Modified Scandinavian Edinburgh stroke scale (MESSS) (high score = worse function; total 45: 0 to 15: mild; 16 to 30: moderate; 31 to 45: severe), Chinese Stroke Scale (CSS), National Institutes of Health Stroke Score (NIHSS) (higher score = worse deficit), Canadian neurological scale, Neurological function defect scale (rated as recovery, obviously improved, improved no effect or deteriorated) and the Hemiplegic Stroke Scale (HSS) (0 to 100, higher score = greater deficit).

In the papers from China, different names were given to the neurological impairment scale used. We believe that this scale was originally proposed in 1995 at the Fourth National Science Meeting on Cerebral Vascular Disease in China (Chen 1996). Thus, the SSS, MESSS, CSS, Chinese neurological impairment scale (CNS) (Ye 2004), neurological function damage (Jia 2005), neurological function defect scale (Li 2002) and neurological function impairment (Wang 2003) were all the same scale.

Although some of the Chinese papers stated that they used the SSS, we believe that they are referring to the MESSS according to the references cited in their papers. The score range of the MESSS is from 0 to 45 points with severity degree (mild: 0 to 15; moderate: 16 to 30: severe: 31 to 45), lower is better. This applies to Cheng 2003; He 2004; He 2005 and Li 2005 (and fits with their description of effects, i.e. improvement in neurological function in the SSRI group).

Data from several trials could not be used in the meta-analysis: Hu 2002 (because the paper quoted values for MESS above certain decrement levels rather than the mean and SD at the end of treatment), Li 2004b (continuous data for CSS not given), Zhou 2008 (no raw data on MESS), Murray 2005 (did not provide raw data on SSS at follow-up) and Yang 2002 (stated that they would report the CSS but no data were reported).

In our meta-analysis, we included data from 29 trials (2011 participants) that reported a neurological deficit score at the end of treatment (Analysis 1.3). The SMD was -1.00 (95% CI -1.26 to -0.75) in favour of SSRI. There was high heterogeneity between trials ($I^2 = 86\%$; P < 0.00001).

Subgroup: type of SSRI

There was moderate heterogeneity between subgroups ($I^2 = 61\%$; P = 0.04) (Analysis 1.3). The largest effect size was for citalopram (though this was based on only three trials) and the smallest effect size for sertraline (though this was based only on two trials).

Subgroup: time since stroke (Analysis 3.3)

There was heterogeneity between subgroups ($I^2 = 26\%$) but it was not statistically significant (P = 0.26) (Analysis 3.3).

Subgroup: patients had to have depression at the time of recruitment (Analysis 4.3)

There was evidence of high heterogeneity between subgroups ($I^2 = 76.9\%$; P = 0.04), with the larger effect in patients who had to have depression at recruitment (Analysis 4.3).

Depression at end of treatment

If trials reported several outcomes (e.g. change in scores between baseline and follow-up, dichotomous data for depression scales, or continuous data at end of treatment or follow-up, or both), we decided, after having performed data extraction, to use the absolute depression score at the end of treatment (mean and SD). If those data were not available, we used dichotomous data (e.g. depressed/not depressed). If trials used both the HAMD and BDI, we used the HAMD.

We noted that for all the depression measures used (HAMD, BDI, Montgomery-Åsberg Depression Rating Scale (MADRS), Zung), a higher score means more severe depression. Song 2006 used a self-rated depression scale, we assumed that a higher score meant more severe depression, as this fits with the description of the benefit of fluoxetine.

For some trials, we could not use data in the meta-analysis. Brown 1998 quoted median (not mean) Hamilton Depression Rating Scale (HDRS), Hu 2002 reported HAMD as the 'proportion with a number of different decrement levels', Zhou 2008 and Yang 2002 provided no raw data, and Burns 1999 did not report depression scores at the end of treatment.

Continuous depression scores

For continuous depression scores (Analysis 1.4), there were 39 trials (2728 participants). The SMD was -1.91 (95% CI -2.34 to -1.48), a statistically significant effect in favour of SSRI. There was high heterogeneity between trials ($I^2 = 95\%$; P < 0.00001).

Subgroup: type of SSRI (Analysis 1.4)

There was high heterogeneity between subgroups ($I^2 = 78\%$; P = 0.001), with the largest effect seen for paroxetine and the smallest for sertraline (Analysis 1.4).

Subgroup: time since stroke (Analysis 3.4)

There was no heterogeneity between subgroups ($I^2 = 0\%$; P = 0.66) (Analysis 3.4).

Subgroup: had to have depression at recruitment (Analysis 4.4)

There was heterogeneity between subgroups ($I^2 = 35.5\%$) that was not statistically significant (P = 0.21) (Analysis 4.4).

Dichotomous depression scores

For dichotomous depression scores, we included eight trials (771 participants) in the meta-analysis (Analysis 1.5). The RR was 0.43 (95% CI 0.24 to 0.77), a statistically significant effect in favour of SSRI. There was high heterogeneity between trials ($I^2 = 77\%$; P < 0.0001).

Subgroup: type of SSRI (Analysis 1.5)

There was no heterogeneity between subgroups of SSRIs ($I^2 = 0\%$; P = 0.59) (Analysis 1.5).

Subgroup: time since stroke (Analysis 3.5)

There was high heterogeneity ($I^2 = 93\%$; P = 0.00001), with the larger effect size seen in the trials that recruited patients within the first three months of stroke onset (Analysis 3.5).

Subgroup: depression at recruitment (Analysis 4.5)

There was low heterogeneity ($I^2 = 25\%$, P = 0.31) (Analysis 4.5). There was a smaller effect size for trials in which patients had to have depression at recruitment.

Anxiety at end of treatment

No trials reported dichotomous anxiety data.

Lai 2006 provided a 'self-rating anxiety scale', for which a lower score was better, so we included these data in the meta-analysis. We included eight trials (413 participants) reporting continuous data for anxiety in the meta-analysis (Analysis 1.6). The SMD was -0.77 (95% CI -1.52 to -0.02). There was high heterogeneity between trials ($I^2 = 92\%$; P < 0.00001).

Subgroup: type of SSRI (Analysis 1.6)

There was moderate heterogeneity between subgroups ($I^2 = 70.6\%$; P = 0.03), with the largest effect seen for paroxetine (Analysis 1.6).

Subgroup: time since stroke (Analysis 3.7)

All trials included recruited patients between zero and three months, so there were no data available for this subgroup analysis (Analysis 3.7).

Subgroup: depression at recruitment (Analysis 4.6)

There was low heterogeneity ($I^2 = 29.7\%$, P = 0.23) (Analysis 4.6).

Cognition at end of treatment

We could not use the cognition data from Almeida 2006 in the meta-analysis because the changes in scores between baseline and end of treatment were reported (there was no difference between placebo and sertraline group). Li 2004b reported that 20/31 in the fluoxetine group had a Mini-Mental State Examination (MMSE) score ≥ 24 compared with only 14/32 in the control group. It is not generally possible to combine dichotomous data with the continuous data in a meta-analysis. For resource reasons, we were unable to contact the authors to obtain raw data.

We included seven trials (425 participants) that reported continuous data in the meta-analysis (Analysis 1.8). The SMD was 0.32 (95% CI -0.23 to 0.86). There was high heterogeneity between trials (I² = 86%; P < 0.00001). This analysis included data from the Iowa subgroup of a larger trial (Robinson 2008). The scores at the end of treatment were similar in the two groups, but there had been a larger improvement in scores from baseline to end of treatment in those allocated an SSRI (Robinson 2008).

Subgroup: type of SSRI (Analysis 1.8)

There was high heterogeneity between subgroups ($I^2 = 92.6\%$; P < 0.00001) with the largest effect size for citalopram, although this was based on a single trial (Analysis 1.8).

Subgroup: time since stroke (Analysis 3.8)

There was no heterogeneity ($I^2 = 0\%$; P = 0.64) (Analysis 3.8).

Subgroup: depression at recruitment (Analysis 4.8)

There was moderate heterogeneity between subgroups ($I^2 = 49.8\%$) but this was not statistically significant (P = 0.16) (Analysis 4.8).

Motor deficits

The FLAME trial reported the Fugl Myer total motor score (Chollet 2011) and Dam 1996 reported the HSS motor component. We combined these data using SMD (Analysis 1.16). The SMD was -0.33 (95% CI -1.22 to 0.56), a non-significant difference. There was high heterogeneity in relation to time since stroke ($I^2 = 80\%$; P = 0.02) (Analysis 3.14). Both trials recruited people without depression, so we could not perform subgroup analyses for depression at onset.

Death at end of treatment

Five trials did not report deaths, and the number randomised did not equal the number at end of treatment, so we do not know how many patients had died (Chen 2002; GlaxoSmithKline 1998; Kong 2007; Rasmussen 2003; Wang 2003). One trial did not state the number randomised or the number who died (Finkenzeller 2009).

This left data from 46 trials (3344 participants) providing data for meta-analysis. RR for death was 0.76 (95% CI 0.34 to 1.70) (Analysis 1.9). There was no heterogeneity between trials ($I^2 = 0\%$; P = 0.85).

Subgroup: type of SSRI (Analysis 1.9)

There was no heterogeneity between SSRIs ($I^2 = 0\%$; P = 0.69) (Analysis 1.9).

Subgroup: time since stroke (Analysis 3.9)

There was no heterogeneity according to time since stroke ($I^2 = 0\%$; P = 0.56) (Analysis 3.9).

Subgroup: depression at onset (Analysis 4.9)

There was no heterogeneity between subgroups ($I^2 = 2.1\%$; P = 0.31) (Analysis 4.9).

Side effects at end of treatment

Side effects were reported in only some of the trials, and for the majority of these trials, it was unclear whether these had been collected systematically. Furthermore, when a particular side effect was not reported (e.g. seizures), we do not know whether this was because the side effect had not occurred or whether seizures had occurred but had not been reported.

Side effects: seizures at end of treatment

We decided that we would include data only if the trials specifically reported either seizures or no seizures. Thus, we did not include trials that listed adverse effects but did not mention either the presence or absence of seizures in the analyses. Therefore, we included data from the following seven trials (744 participants): Andersen 1994; Chollet 2011; Dam 1996; He 2004; Liang 2003; Wiart 2000 and Ye 2004. The RR was 2.67 (95% CI 0.61 to 11.63) (Analysis 1.10). There was no heterogeneity between trials.

Subgroups

There was no significant heterogeneity between subgroups of SSRI (Analysis 1.10), subgroups according to time since stroke at randomisation (Analysis 3.10) or according to depression at recruitment (Analysis 4.10).

Side effect: gastrointestinal side effects at end of treatment

Some trials split GI side effects into different symptoms and reported them in such a way that we do not know whether the side effects relate to 'events' or to 'patients'. If we were uncertain whether the trials reported 'events' or 'patients', we elected not to include them in our meta-analyses (Higgins 2011). This applied to Almeida 2006; GlaxoSmithKline 1998; Murray 2005; Rasmussen 2003; Robinson 2008. In two of these trials, GI side effects were more common (GlaxoSmithKline 1998; Murray 2005) and in the other three trials, there was no difference between groups (Almeida 2006; Rasmussen 2003; Robinson 2008).

One trial (Kong 2007) reported 'somatic side effects' as a reason for withdrawing from the trial, but did not stipulate what these side effects were. We did not include these data in the meta-analysis.

Two trials reported GI side effects for the treatment but not the control group (Wang 2003; Xie 2005) so could not be included in the meta-analysis.

We included 14 trials (902 participants) in the meta-analysis; the RR was 1.90 (95% CI 0.94 to 3.85) (Analysis 1.11).

There was no significant heterogeneity between trials ($I^2 = 31\%$; P = 0.14) (Analysis 1.11).

Subgroup analyses

There was moderate heterogeneity between subgroups of SSRI ($I^2 = 48.9\%$) that was not statistically significant (P = 0.14) (Analysis 1.11). There was no heterogeneity between the other subgroups (time since stroke: $I^2 = 0\%$; P = 0.85 (Analysis 3.11); depression at onset: $I^2 = 0\%$; P = 0.57 (Analysis 4.11)).

Side effect: bleeding at end of treatment

Two trials reported bleeding as a side effect (GlaxoSmithKline 1998; Robinson 2008). The RR was 1.63 (95% CI 0.20 to 13.05) in favour of control (Analysis 1.12). There was no significant heterogeneity ($I^2 = 0\%$; P = 0.59).

Change in cognition

Only one trial reported change in cognition and found no difference between groups (Analysis 1.14).

Leaving the study early (before the follow-up at the end of treatment)

Finkenzeller 2009 did not report drop-outs, Song 2006 did not report drop-outs from each group (though total drop outs were reported) and, in one trial, there were inconsistencies in reporting data (Xu 2007).

We included data from 49 trials (3851 participants) (Analysis 1.15). The RR was 1.02 (95% CI 0.86 to 1.21) in favour of control. There was no significant heterogeneity between trials. There was no significant heterogeneity between SSRIs (Analysis 1.15) or the other subgroups (Analysis 3.12; Analysis 4.12).

Follow-up beyond treatment end

Only eight trials (Almeida 2006; Burns 1999; Cheng 2003; Fruehwald 2003; Guo 2009; Robinson 2000a; Robinson 2000b; Wang 2003) followed up participants beyond the treatment period, although Burns 1999 did not provide any long-term data. Note that in one trial, the duration of antidepressant treatment ranged from three to six months, so some patients followed up beyond three months were still taking the antidepressant (Wang 2003).

Of these, only one trial reported dependence (Almeida 2006), two disability (Almeida 2006; Wang 2003) (note that although Guo

2009 reported FIM cognition and mobility, these data could not be used because the total FIM score was not provided), five reported depression (Almeida 2006; Cheng 2003; Fruehwald 2003; Guo 2009; Wang 2003), two reported cognition (Almeida 2006; Guo 2009) and four reported neurological impairment (Cheng 2003; Fruehwald 2003; Guo 2009; Wang 2003). Three reported deaths (Cheng 2003; Guo 2009; Wang 2003). Two reported nine-year mortality (Robinson 2000a; Robinson 2000b); although these data could not be used in the meta-analysis, the trialists reported that those allocated an antidepressant (either nortriptyline or fluoxetine) were more likely to be alive at nine years.

For disability (two trials, 155 participants) (Analysis 2.2), there was a non-significant effect for SSRI. For neurological impairment scales (four trials, 275 participants (Analysis 2.3) there was a non-significant effect in favour of SSRI. For continuous depression scores, there was a significant benefit for SSRI (four trials, 275 participants) (Analysis 2.4) but for dichotomous depression scores (one trial, 99 participants) (Analysis 2.5) the benefit was not statistically significant. There were no statistically significant differences between SSRI and control for dependence (Analysis 2.1) and cognition (Analysis 2.6; Analysis 2.7). Note that the numbers of participants were small and CIs were wide.

Sensitivity analyses

We excluded trials with unclear or high risk of bias for each characteristic and repeated the same analyses for each outcome at the end of treatment, including only trials at low risk of bias (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.6; Analysis 1.7; Analysis 1.8; Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.13; Analysis 1.14; Analysis 1.15). We described the effect sizes (after exclusion of the trials at unclear or high risk of bias) as smaller, similar or bigger, in order to help the reader interpret the data. This was a subjective judgement by the review author (GM) performing the analyses.

Low risk of bias for randomisation

When only those trials with low risk of bias were included, the effect sizes for dependence was the same (although this was based only on two trials) (Analysis 5.1), the effect size for disability (Analysis 5.2), neurological deficit (Analysis 5.3), depression (Analysis 5.4; Analysis 5.5) and anxiety (Analysis 4.6; Analysis 3.8; Analysis 3.9) were all smaller, although still in favour of SSRI, but some of the effects were not statistically significant: depression (Analysis 5.4), anxiety (Analysis 5.6) and death (Analysis 5.9). The rate of seizures, GI side effects and leaving the trial early remained similar (Analysis 5.10; Analysis 5.11; Analysis 5.15, respectively) though the difference between SSRI and control for GI side effects did not reach statistical significance.

Low risk of allocation concealment

When only those trials with low risk of bias were included, the effect size for dependence was the same (although based only on two trials) (Analysis 6.1), the effect size for disability (Analysis 6.2), depression (continuous) (Analysis 6.4), neurological deficit (Analysis 6.3), anxiety (Analysis 6.6) and death (Analysis 6.9) were smaller and not significant for disability (Analysis 6.2), depression (Analysis 6.4; Analysis 6.5) and anxiety (Analysis 6.6). There was no significant difference in the rate of seizures between groups (Analysis 6.10).

Low risk of bias for patient/personnel blinding

When only those trials with low risk of bias were included, the effect size of dependence was the same (Analysis 7.1): the effect sizes for disability (Analysis 7.2), neurological deficit (Analysis 7.3), depression (Analysis 7.4; Analysis 7.5), anxiety (Analysis 7.6) and cognition (Analysis 7.8) were all smaller, and for cognition (Analysis 7.8) and anxiety (Analysis 7.6) were not statistically significant. The rate of seizures remained similar (Analysis 7.10) (but was not significantly different between SSRI and control) and the rate of GI side effect was lower and not significantly different between SSRI and control (Analysis 7.11).

Low risk of bias for blinding of outcome assessor

When only those trials with low risk of bias were included, the effect size of dependence was the same (Analysis 8.1): the effect sizes for disability were similar (Analysis 8.2), the effect sizes for neurological deficit (Analysis 8.3) and depression (Analysis 8.4; Analysis 8.5) were smaller. Cognition could not be estimated (

Analysis 7.8). The effect on anxiety (Analysis 8.6) was larger and statistically significant. The rate of seizures and GI side effects were not statistically different between groups (Analysis 8.10; Analysis 8.11).

Low risk of bias for outcome data reporting

When only those trials with low risk of bias were included, the effect size for dependence was the same (Analysis 9.1), the effect sizes for disability (Analysis 9.2) and depression (dichotomous) (Analysis 9.5) were similar and statistically significant. The effect sizes for neurological deficit and continuous depression scores were larger and statistically significant (Analysis 9.3; Analysis 9.4). The effect sizes for death (Analysis 9.9), seizures (Analysis 9.10) and GI side effects (Analysis 9.11) were similar and not statistically different between SSRI and control.

Low risk of bias for selective reporting

When only those trials with low risk of bias were included, the effect size for dependence was the same (Analysis 10.1), the effect sizes for disability (Analysis 10.2), neurological deficit score (Analysis 10.3), depression (continuous) (Analysis 10.4), anxiety (Analysis 10.6) and cognition (Analysis 10.8) were all smaller and not significant. The rate of seizures remained similar though not significantly different between groups (Analysis 10.10) and the rate of GI side effects was lower and not significantly different between groups (Analysis 10.11).

The funnel plot for one of our primary outcomes (disability at the end of treatment) appeared to be asymmetric on visual inspection (Figure 4), although note that the interpretation is uncertain (Higgins 2011 Section 10.4.3.1.).





DISCUSSION

Summary of main results

We identified 56 completed trials comparing an SSRI with control, but four of these did not provide data that could be used in the meta-analysis (Chen KN 2005; Meara 1998; Pariente 2001; Restifo 2001). This left 52 trials with data that could be used in a meta-analysis. These trials were from all over the world, including China. They mostly recruited inpatients. Fluoxetine was the most commonly used SSRI. Most trials that reported time since stroke randomised patients who were within three months of stroke onset. Some trials stipulated that patients had to have depression, while some did not require that patients had to have depression at entry. Most of the trials excluded patients who could not consent for themselves (e.g. those with cognitive impairment and those with aphasia).

The duration of treatment varied from weeks to months. Only eight trials followed people up after treatment had been completed.

There were insufficient data to determine whether withdrawal effects were experienced, because adverse events were not reported in the first few weeks after the SSRI had been discontinued.

There were beneficial effects of SSRIs on our two primary outcomes (dependence and disability) and some of our secondary outcomes (neurological deficit, mood, anxiety) at the end of treatment. There was substantial heterogeneity between trials. None of the trials reported fatigue, which is a common and distressing post-stroke problem, for which there is no treatment. None of the trials reported healthcare costs. The number of deaths was lower in the group allocated SSRI, but this difference was not statistically significant, and there was no heterogeneity between trials. There was a non-significant excess of seizures, GI side effects and bleeding in those allocated an SSRI. There was no difference between SSRI and control in the number leaving the trial early. The trials that followed up patients beyond the period of treatment reported beneficial effects of SSRI on disability, neurological deficit and depression, though CIs were wide.

A subgroup analysis did not identify any type of SSRI that had consistently better effects than the other SSRIs. Note that most of the data related to fluoxetine.

For the subgroup of time since stroke, there was no heterogeneity

between these subgroups less than three months after stroke and more than three months after stroke, though not all trials reported time since stroke.

There was statistically significant heterogeneity between trials that recruited those with depression at onset for disability (Analysis 4.2), and dichotomous depression scores (Analysis 4.5), with larger effect sizes seen in the trials that recruited patients with depression. These data suggest that SSRIs might be of more benefit in people with depression - although importantly, benefits were also observed in patients without depression.

Our sensitivity analyses, in which we excluded trials with high or unclear risk of bias, demonstrated that the effect sizes were generally smaller and, for some outcomes, were no longer significant. The number of adverse events remained similar after excluding trials at high or unclear risk of bias.

Overall completeness and applicability of evidence

We performed extensive searches and we identified many more trials than we had been anticipating based on our knowledge of previous systematic reviews, suggesting that other reviews may have missed relevant trials. Our review question was deliberately broad (including all SSRIs, given for any reason and at any time within the first year after stroke) to ensure that we identified all trials that were relevant to the question about whether SSRIs might be of benefit in stroke. We did not search Chinese databases and so we may have missed some papers that had titles and abstracts written only in Chinese. However, we did scrutinise relevant systematic reviews from Chinese authors who had searched the Chinese databases (Chen 2006; Chen 2007; Yi 2010). Our searches also identified papers written in Chinese that had English abstracts and we included these papers in our review.

The funnel plot appeared asymmetric on visual inspection, which would be consistent with publication bias - although note that there are many other causes of funnel plot asymmetry besides publication bias (Higgins 2011).

How do these data apply to 'real' patients? In these trials, the patients recruited were younger than patients with stroke (mean age generally in the 60s). Most trials excluded patients unable to consent for themselves (e.g. those with aphasia and those with cognitive impairment). This is an important limitation of the existing data. It is important to include these people in trials, because the risks and benefits may be different from other patients (e.g. an SSRI may be of more harm in patients who cannot report adverse effects, or may be of more benefit if undiagnosed depression is treated). Most trials recruited patients within three months of stroke, and so we cannot be certain about the effect of an SSRI initiated after this time.

Most trials included patients with both haemorrhagic and ischaemic stroke, and no trial reported data separately for these two pathological subtypes of stroke. We cannot be sure whether the apparent benefits are because SSRIs might speed up the rate of recovery or influence the ultimate level of disability. This would need data from multiple time points and a repeated measures analysis. There were insufficient data to perform these analyses.

Quality of the evidence

The trials were generally small; the largest one recruited only 229 patients (GlaxoSmithKline 1998). There were multiple different sources of bias in most of the trials that we identified (Figure 2; Figure 3). Some trials did not report in detail important methodological aspects of the trials (including sequence generation, allocation concealment, blinding, incomplete outcome reporting, selective reporting), making it difficult to determine the risk of bias. When there was sufficient information to make judgements about sources of bias, we identified multiple sources of bias in many of the trials. The funding source was not reported for a substantial proportion of the trials. When funding was declared, there were frequently links with the pharmaceutical industry (e.g. provision of the drug and placebo, payment of honoraria and expenses). Only some of the trials reported side effects, and of those that did,

only some explained how side effects were collected. When we performed sensitivity analyses including only those trials at low risk of bias, the effect sizes were smaller, suggesting that methodological limitations of the trials may have led to overestimation of effect sizes.

Potential biases in the review process

Only one author extracted data from studies written in Chinese. This author checked the data extraction carefully. The majority of Chinese papers had English abstracts, and so a second author was able to check data provided in the English abstract. We cannot be certain that there were no mistakes in data extraction, but if these did occur, it is unlikely that this would have led to a systematic overestimation or a systemic underestimation of effect sizes.

Only one author (GM) screened titles and abstracts for the MED-LINE and EMBASE searches. There is a small possibility that this single author might have missed trials, but there is no reason to suspect that any missed trials would have been systematically different (e.g. in relation to risk of bias, size of effects) than the trials that we identified.

We did not systematically search the Chinese databases. Of the Chinese papers that we did identify, there were frequently multiple sources of bias, so if we had identified additional Chinese publications, inclusion of such trials may have led to an overestimate of the true effects of treatment.

The database searches were performed in August 2011. It is possible that we have missed trials published since then, but our cited reference searches in February 2012 did not identify any new trials. When we update the review, we will search the databases from

September 2011 onwards.

Agreements and disagreements with other studies or reviews

One of the key limitation of previous reviews is that their research question was narrow (e.g. effect of SSRI on treating or preventing depression after stroke, effect of SSRI on motor recovery, or reviewing a single SSRI). By contrast, our review had broad inclusion criteria, providing a more complete picture of the evidence for SSRIs in stroke. Furthermore, we rigorously assessed risk of bias, performed sensitivity analyses and also performed subgroup analyses to determine the impact of depression at randomisation, the type of SSRI and the time since stroke at randomisation. We identified some studies that had not been included in previous systematic reviews.

A previous systematic review of fluoxetine (Yi 2010) found that it reduced disability and dependency and reduced the risk of poststroke depression but the review (Yi 2010) did not explore the effect of all possible types of bias on the estimate of effect and did not include the FLAME Trial (Chollet 2011). Another review found only three RCTs of antidepressants and could not perform a meta-analysis (Bhogal 2005). One systematic review published in 2007 identified only 10 trials recruiting 703 non-depressed patients, and concluded that antidepressants given prophylactically reduced the rate of developing depression (Chen 2007), but other outcomes were not reported. One review of antidepressants for the treatment of post-stroke depression by the same authors (Chen 2006) found only 16 trials and concluded that antidepressants were of benefit for depression and other outcomes. In one review published in 2009 of six trials of any drug that might influence neurotransmitters, with motor function as the outcome of interest (Berends 2009b), the authors concluded that there was insufficient information to draw conclusions on the effect of SSRIs on motor recovery (Berends 2009b). One review of pharmacological interventions for post-stroke depression published in 2003 identified only 10 trials, and concluded that the SSRIs may be effective for treating post-stroke depression (Van de Meent 2003). One nonsystematic review of antidepressants in the treatment of stroke suggested that antidepressants might be of benefit (Burns 2010).

In two reviews of interventions to treat and prevent depression after stroke (Hackett 2008a; Hackett 2008b) the authors pooled data from randomised placebo-controlled trials of all antidepressants. There were insufficient trials of adequate quality to perform subgroup analyses by antidepressant subtype. The authors concluded that there was evidence that antidepressants did not prevent depression after stroke and recommended that the evidence of benefit of antidepressants as a treatment strategy had to be weighed against the evidence of associated increased risk (adverse events). An explanation for these less supportive recommendations for antidepressant use lies in the differing inclusion criteria. Of the 32 trials contributing continuous depression data in this current review, only five trials (Andersen 1994; Fruehwald 2003; Murray 2005; Robinson 2000a; Wiart 2000) used matching placebo control arms and were included in the Hackett (Hackett 2008a; Hackett 2008b) reviews. The six trials that stated placebo was used (with uncertainty regarding matching Chen 2002; GlaxoSmithKline 1998; Huang 2002; Lai 2006; Li 2008; Song 2006) were not included. Seven (Acler 2009; Brown 1998; Burns 1999; Chollet 2011; Dam 1996; Kong 2007; Robinson 2000b) of the 10 trials contributing dichotomous data to the current review used matching placebo control arms; however, two (Acler 2009; Chollet 2011) of these were published after the Hackett reviews (Hackett 2008a; Hackett 2008b) and one (Kong 2007) was not identified in the searches performed for the Hackett reviews, presumably because it had not been indexed by the time of the searches.

Our searches also identified commentaries on our included trials, in particular on the more recently published, larger trials from high impact journals written in English. For example, there are multiple commentaries and letters (e.g. Anonymous 2011; Berends 2011; Friedman 2011; Robinson 2011) on the FLAME trial (Chollet 2011), and on the trial by Robinson 2008 and colleagues, in which cognitive outcomes for a subset of patients were published after the main trial results had been published (e.g. Anonymous 2010; Formulary Staff 2010). The message from these commentaries is that SSRIs are a promising intervention for stroke; and the general view is that further larger trials are needed.

AUTHORS' CONCLUSIONS

Implications for practice

Review data provide evidence of benefit of SSRI for reducing disability and neurological impairment scores in people with stroke. However, the extent of the benefit is uncertain, as our sensitivity analyses demonstrated that effect sizes were generally smaller when only methodologically robust trials were included. Furthermore, there was a statistically non-significant increase in risk of adverse effects in people given an SSRI, although data on adverse effects are limited. There is insufficient evidence from this review to make recommendations about which is the most effective SSRI, which has the fewest side effects, for how long it should be given and at what dose.

Current practice is often to give an antidepressant (often an SSRI) to stroke survivors with depression, in whom it is possible to assess for depressive symptoms. The results of this review demonstrate large effect sizes for mood scores at the end of treatment and appear to provide support for this practice, but these data predominantly come from comparison of an active drug with usual care, and data on adverse effects are limited, although generally in favour of the control arm. We suggest that the evidence tentatively supports the use of prescription antidepressants to treat depression in people after stroke, but this must be considered in the light of evidence of an associated increase in harm and we recommend patients are well monitored for adverse effects. There are insufficient data to make recommendations about the risk of bleeding, which is of particular relevance to patients with haemorrhagic stroke who develop depression, and to patients with ischaemic stroke who are prescribed antiplatelet or anticoagulant drugs.

Patients with aphasia were generally excluded from the trials in this review, so we do not know whether SSRIs are effective in patients whose mood cannot be formally assessed. In clinical practice, if depression is suspected in patients with aphasia, a trial of antidepressants is often given. This review cannot confirm whether or not this practice should continue. This is an area where further research is needed.

Implications for research

Currently, SSRIs are not generally prescribed with the aim of improving neurological recovery or to prevent depression after stroke. Our review provided tantalising evidence of benefits of SSRIs in patients who did not have to have depression to enter the trial. These benefits included improvements in dependence, disability, neurological impairment scores and depressive symptoms. However, given the methodological limitations of a large proportion of the trials, and the wide CIs for effect sizes when only methodological sound trials are included, we cannot be sure whether these effects are real. If these effects are real, and if the risk of side effects is sufficiently low, then SSRIs would become an important (and low cost) treatment for patients with stroke. Thus, there is a need for a larger trial of SSRI in stroke (excluding those with depression) to determine the effect on both the rate of recovery and the ultimate level of disability and dependency. It is crucial that such a trial is methodologically sound with a low risk of bias. Furthermore, long-term follow-up, after treatment has been completed, is crucial to determine whether any benefits are sustained. Given that most of the evidence from this review relates to fluoxetine, this would seem the drug of choice to test in a big trial. Citalopram and escitalopram may lead to prolongation of the QT interval, and because a large proportion of stroke survivors have underlying coronary artery disease, these two drugs are not, in our view, the best choice of drugs to test in a future trial. It is important that patients with aphasia and cognitive impairment are included. There

is a need to systematically report adverse events, including seizures and bleeding. It is important to ensure that follow-up data are as complete as possible, and that there is a method for dealing with any missing data. There should be subgroup analyses for patients with ischaemic and haemorrhagic stroke, to explore whether SS-RIs might increase the risk of recurrent intracranial bleeding in patients with intracerebral haemorrhage, and whether there is a higher risk of haemorrhagic transformation of infarct when SSRIs are given to patients with ischaemic stroke who are also taking anticoagulants. Finally, protocols for trials should be published in advance to allow readers to determine whether or not there has been selective reporting of outcome assessments.

We identified five ongoing trials, including two large trials (AFFINITY 2011; FOCUS 2011) that aim to recruit 1580 patients and 3000 patients, respectively. Both of these large trials will start recruiting in 2012.

It will clearly be important to update this review with the results of ongoing trials. Furthermore, an individual patient meta-analysis would also be worthwhile; this would allow us to investigate the influence of covariates on heterogeneity of treatment effects fully, both within and between trials (Simmonds 2005).

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

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Acler 2009

| Methods | Parallel design Randomisation: computer generated, individual Allocation concealment: not described Blinding: patients, outcome assessors and physiotherapists all blinded Analysis: not stated whether ITT | |
|---|--|-----------------------------------|
| Participants | Location: Italy Setting: inpatient Inclusion criteria: first-ever ischaemic stroke, CT or MRI documenting a single mono- hemispheric lesion, age below 80 years, within 3 months of onset 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 | |
| Notes | Exclusion criteria: major affective disorders, alcohol abuse and dementia leading to unco- operative behaviour, pacemakers, metal in the head, concomitant neuropathies, systemic vasculopathies, major affective disorders | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Computer-generated random numbers |

Allocation concealment (selection bias)Unclear riskMethod of allocation concealment not
statedIncomplete outcome data (attrition bias)
All outcomesUnclear riskIt is not stated whether data from all re-
cruited patients are reported

Acler 2009 (Continued)

| Selective reporting (reporting bias) | Unclear risk | Side effects were not reported though they were assessed |
|--|--------------|---|
| Other bias | Unclear risk | Source of funding not stated; unclear whether or not a drug company was in- volved in the study |
| 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 |

Almeida 2006

| Methods | Parallel design Randomisation: computer-generated random list of numbers Allocation concealment: centralised Blinding: double blind: participants: yes; investigators: yes; outcome assessors: unknown Analysis: ITT (last observation carried forward), withdrawn owing to becoming de- pressed, AE, treating practitioner started antidepressant, medical advice, no reason given, not contactable - numbers not included |
|---------------|--|
| Participants | Location: Australia Setting: inpatient Treatment: 55 people, mean ± SD age 68 ± 13 years, 67% men Control: 56 people, mean ± SD age 67 ± 13 years, 62% men Stroke criteria: acute ischaemic or haemorrhagic stroke, diagnosis by clinical signs (ICD- 10) and CT (100% imaged, 10/111 CT scan did not show acute ischaemia); stroke on average < 2 weeks prior to randomisation Not depressed (HADS-D had to be over 7) Other entry criteria: not stated Comparability of treatment groups: more participants in treatment group with previous heart attack and stroke, also higher levels of hypertension |
| 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 |

Almeida 2006 (Continued)

| | Check list of possible AEs read out to patient by a research nurse |
|-------|--|
| Notes | 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 |

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 |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Performed last observation carried forward |
| Selective reporting (reporting bias) | Low risk | Trial protocol published on www.strokecentre.org/trials |
| Other bias | Low risk | No other obvious biases Funded by an unrestricted grant from Ro- tary Health Research Fund |
| 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 |

Andersen 1994

| Methods | Parallel design Randomisation: blocks of 4 used Allocation concealment: centralised opaque envelopes Blinding: double blind reported, those blinded not stated 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%) |

Andersen 1994 (Continued)

| | ; 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 |
|---------------|---|
| Interventions | Treatment: citalopram 10 mg in participants > 66 years, 20 mg in participants < 67 years daily; dose doubled if no response to treatment within 3 weeks Control: 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/trialsstates 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) Unable to use: BI, Social Activities Index, MMSE (data not presented) |
| Notes | Exclusion criteria: depression within last year, receiving current treatment for depression, severe dementia or communication problems, degenerative or expansive neurological disease, decreased consciousness |

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 |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Although there were drop-outs, analysis performed both per protocol and using last observation carried forward |
| Selective reporting (reporting bias) | Low risk | Trial published on www.strokecentre.org/ trials The primary outcome was reported |
| Other bias | Unclear risk | Funded by Lundbeck Foundation, Medi- cal Research Foundation for North Jutland County, The Aalgorg Diocese Research |

Andersen 1994 (Continued)

| | | Foundation, Consultant Otorhinolaryn- gologist Kopp's Foundation and Stine and Martinus Sorensen's Foundation. Lund- beck Pharma A/S provided the citalopram and placebo; thus we have classified this as 'unclear risk' |
|--|--------------|---|
| 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 |

Brown 1998

| Methods | Parallel design Randomisation: unclear Allocation concealment: randomised by an independent statistician Blinding: double-blind participants: yes; nursing staff: yes; rating clinicians: yes 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 |
| 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 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 |
| Notes | Exclusion criteria: cognitive impairment, dysphasia, major depressive disorder |
| Risk of bias | |

Brown 1998 (Continued)

| 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 |
| 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 judge- ment |
| Other bias | Unclear risk | No other obvious biases, baseline balanced Funder not stated |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | States blinding, matched placebo |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | States blinding |

Burns 1999

| Methods | Parallel design Randomisation: blocks of 4 using list produced by medical statistics department Allocation concealment: unclear Blinding: run-in was single blind and run-out was single blind; treatment phase reported as double blind, those blinded not stated 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 |
| 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: 1. improved score on lability scale |

Burns 1999 (Continued)

| | 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) |
|-------|---|
| Notes | Exclusion criteria: less than 1 month since stroke, depression or dementia using the DSM III-R criteria |

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 |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Analysis: ITT, last observation carried for- ward |
| 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 influ- ence on bias Funded by an unrestricted personal grant from Pfizer, the manufacturers of sertraline Statistical analysis was carried out indepen- dently by the Applied Statistics Research Unit in Canterbury |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Matched placebo |
| 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 |

Chen 2001

| Methods | used the fluoxetine plus usual care versus us Aim: to observe effects of integrative Chi depressive symptoms and rehabilitation of post-stroke depression Randomisation: by computer Allocation concealment: unclear Blinding: not described | nese herb YuLeShu and fluoxetine on the neurological impairment in patients with xetine group, 1 dropped out of the YuLeShu |
|---|--|---|
| Participants | Country: China Setting: not described Patients: 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 Depression: diagnosis of depression according to DSM-IV Inclusion criteria: HDRS ≥ 20 but < 35 and/or Zung SDS ≥ 41 Exclusion criteria: HDRS > 35 | |
| 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 | |
| Notes | Excluded: previous depression, aphasia, severe cardiac, pulmonary, hepatic and renal diseases, previous stroke | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear risk | States 'using a computer' but method not described |

| Allocation concealment (selection bias) | Unclear risk | Not described |
|--|--------------|------------------------|
| Incomplete outcome data (attrition bias) All outcomes | High risk | 4/37 drop-outs |
| Selective reporting (reporting bias) | Unclear risk | Protocol not published |

| Other bias | Unclear risk | Reported that of the people who completed the tests, there were no differences in base- line No comment on whether there were differ- ences in baseline for the entire group Funded by a local scientific academic fund, drug company not involved |
|--|--------------|--|
| 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 |

Chen 2002

| 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 Randomisation: not described Allocation concealment: not described Blinding: not described Drop-outs: 4 in placebo and 0 in paroxetine |
|---------------|--|
| 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 |
| Interventions | Treatment: paroxetine 20 mg daily Control: placebo guvitamine 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 |

| Notes | Exclusion: pre-stroke mental disease, cognition disorder (MMSE < 24), marked deteri- |
|-------|--|
| | oration in depression during treatment (HAMD > 24) or suicide mood, intolerance to |
| | drug |
| | Paroxetine given 3 times per day while placebo given once a day |

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 |
| Incomplete outcome data (attrition bias) All outcomes | High risk | 4/48 drop-outs |
| Selective reporting (reporting bias) | Unclear risk | No protocol available |
| Other bias | Unclear risk | Demographic data not provided, so we can- not determine whether the baseline was balanced Funder not stated, unclear if there was drug company involvement |
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk | Placebo was used, but unclear if this was matching |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Not described |

Chen KN 2005

| Methods | Aim: to observe the changes of neurotransmitter in patients with post-stroke depression by using Encephalofluctuography Technology, and observe the effect of antidepression treatment on the activity of neurotransmitter |
|---------------|--|
| Participants | 48 patients 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 |

Chen KN 2005 (Continued)

Notes

No data from our endpoints of interest, so data not included in a meta-analysis

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|--|--------------------|--|
| Random sequence generation (selection bias) | Unclear risk | 'Randomly divided' but method not stated |
| Allocation concealment (selection bias) | Unclear risk | Method not stated |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Not described |
| Selective reporting (reporting bias) | Unclear risk | Unclear |
| Other bias | Unclear risk | Unclear |
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk | Not described |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Not described |

Chen T 2005

| Methods | Parallel group Randomisation: no description of method Allocation concealment: not described Blinding: not described Analysis: according to allocated treatment group Drop-outs: none |
|--------------|--|
| 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 |

Chen T 2005 (Continued)

| 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 rehabili- tation Duration of treatment: 12 weeks Duration of follow-up (post-treatment to study end): 0 weeks |
|---------------|---|
| Outcomes | HAMD BI Death Number completing the trial |
| Notes | Excluded: severe cardiac, hepatic and renal organic diseases, psychiatric disorders 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 |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop-outs |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | No obvious risks, baseline similar No description of funding |
| 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 |

Cheng 2003

| Methods | Parallel design Aim: to treat depression and augment rehabilitation Randomisation: not stated Allocation concealment: not described Blinding: not described Analysis: according to allocated treatment group Drop-outs: none |
|---------------|--|
| 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 |
| Interventions | Treatment: fluoxetine 20 mg daily Control: no fluoxetine Duration of treatment: 6 months Duration of follow-up (post-treatment to study end): 6 months |
| Outcomes | SSS ADL HAMD Zung SDS Zung SAS No deaths, none left trial early No data on AEs |
| Notes | Excluded: major psychological trauma history in previous 1 year, severe mental retar- dation, severe impairment of lingual expression or comprehension, major complicated medical event in previous 1 year |
| | |

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 |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | 59 patients were diagnosed to have depres- sion by symptoms but only 57 were in- cluded in the results table |

Cheng 2003 (Continued)

| 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. No de- scription of funding |
| 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 |

Chollet 2011

| Methods | Randomised parallel group trial Randomisation: balanced by centre with an allocation based on a block size of 4 generated with a computer random-number generator Allocation concealment: sequentially numbered opaque envelopes Blinding: participants, those delivering the interventions and those assessing outcome Drop-outs: 2 patients died (1 in each group) and 3 dropped out - not stated how missing outcome data were dealt with |
|---------------|--|
| Participants | Location: France Setting: stroke units Inclusion criteria: aged 18 to 85 years with FMMS of 55 or less, acute ischaemic stroke with hemiparesis or hemiplegia, 5 to 10 days after stroke onset, unclear if there had to be a visible lesion on brain imaging Treatment: 59 people, mean ± SD age 66.4 ± 11.7 years; 63% men Control: 59 people, mean ± SD age 62.9 ± 13.4 years; 59% men Comparability of treatment groups: total FMMS score fluoxetine 17.1 compared with 13.4 in placebo Previous stroke more common in the fluoxetine group; fluoxetine group had more dia- betes |
| 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 |
| Notes | Exclusions: clinical depression or treatment with antidepressants, MADRS > 19, aphasia severe enough to mask detection/assessment of depression, pregnancy, patient on neu- |

Chollet 2011 (Continued)

roleptics/benzodiazepines, owing to undergo carotid endarterectomy, other major diseases that would prevent follow-up

Risk of bias Bias Authors' judgement Support for judgement Balanced by centre with an allocation based Random sequence generation (selection Low risk on a block size of 4 generated with a combias) puter random-number generator Allocation concealment (selection bias) Low risk Sequentially numbered opaque envelopes Low risk 5/188 drop-outs, which is less than 5% Incomplete outcome data (attrition bias) All outcomes protocol Selective reporting (reporting bias) Low risk Trial published on www.strokecentre.org/trials, all outcomes were reported Other bias Unclear risk Note difference in baseline: it is not clear what effect this had on results, so we have classified this as 'unclear risk' 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 Blinding of participants and personnel Low risk Identical capsules for control arm (performance bias) All outcomes Blinding of outcome assessment (detection Low risk All study site investigators and all investibias) gators were masked to treatment allocation All outcomes

Dam 1996

| Methods | Parallel design Randomisation: unclear Allocation concealment: unclear Blinding: double blind reported - participants: unclear; examining neurologists: yes 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 |

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

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| | 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 entry criteria: unable to walk Comparability of treatment groups: balanced |
|---------------|---|
| 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 |
| Notes | 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 |

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 |
| Incomplete outcome data (attrition bias) All outcomes | High risk | 2/35 drop-outs, 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 | Unclear risk | Baseline characteristics similar in the 2 groups. Funding source not stated (so cat- egorised as unclear risk) |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | "Examining neurologists blind to treat- ment". Unclear if this refers to outcome as- sessors or the neurologist caring for the pa- tient. However, placebo was 'matched' so this is low risk |

| Blinding of outcome assessment (detection | Unclear risk | See above |
|---|--------------|-----------|
| bias) | | |
| All outcomes | | |
| | | |

Feng 2004

| Bias | Authors' judgement | Support for judgement | |
|--------------------|--|---|--|
| Notes Risk of bias | Excluded: previous stroke, previo and renal diseases | Excluded: previous stroke, previous depression, and severe cardiac, pulmonary, hepatic and renal diseases | |
| Outcomes | MESSS Reported side effects in fluoxeting Unclear how side effects were col | ADL - although score not referenced, so not used in analysis | |
| Interventions | Control: usual stroke care Duration of treatment: 60 days | | |
| Participants | Stroke criteria: ischaemic stroke v confirmation by imaging. Did no diagnosis Depression: psychiatric interview Included those with no previous 54 patients with post-stroke depr 18 received fluoxetine plus usual Huoxue decoction | Setting: mixed inpatient and outpatient Stroke criteria: ischaemic stroke within 1 month of stroke onset, clinical diagnosis plu confirmation by imaging. Did not state whether a visible lesion was needed to make diagnosis Depression: psychiatric interview using DSM IV, Zung SDS ≥ 41 Included those with no previous psychiatric history 54 patients with post-stroke depression were randomised 18 received fluoxetine plus usual care, 18 received usual care only and 18 received Jiey | |
| Methods | in people with depression, usual of We are using data from 'fluoxet' depression' Aim: to study the influence of Jiey depression after cerebral infarctio Randomisation: method not state Allocation concealment: no descr Blinding: no description Drop-outs: 8 participants dropped | Aim: to study the influence of Jieyu Huoxue decoction on rehabilitation of patients with depression after cerebral infarction Randomisation: method not stated Allocation concealment: no description | |

Feng 2004 (Continued)

| Random sequence generation (selection bias) | Unclear risk | Method not stated |
|--|--------------|---|
| Allocation concealment (selection bias) | Unclear risk | No description |
| 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. Funding source not stated, so categorised as 'unclear risk' |
| 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 |

Finkenzeller 2009

| Methods | 3-arm trial: sertraline plus psychotherapy versus psychotherapy alone versus sertraline alone. We are using the sertraline plus psychotherapy versus psychotherapy alone com- parison Randomisation: by 'flicking a coin' Allocation concealment: not described Blinding: not described |
|---------------|---|
| Participants | Country: Germany Stroke diagnosis: ICD-9 or 10 (ischaemic cerebral infarction or haemorrhage) Mood: HAMD > 14 on 17-point version Treatment: 25 people, age 71.7 ± 7.1 years; 50% men Control: 27 people, age 65.8 ± 12.6 years; 41% men Time since stroke (days): 25.5 ± 12.2 in sertraline plus psychotherapy and 28.0 ± 16.6 in sertraline alone |
| Interventions | Treatment: sertraline 50 mg or 100 mg for 4 to 8 weeks (unclear how dose was decided) plus psychotherapy Control: psychotherapy alone Duration of treatment: 4 to 8 weeks Duration of follow-up (end of treatment to study end): 0 |

Finkenzeller 2009 (Continued)

| Outcomes | Change in 17-item HDRS Change in HADS BI Extended BI |
|----------|---|
| Notes | Excluded: current or previous psychiatric history excluded including patients with sub- stance abuse, personality disorders, higher levels of cognitive disorders including demen- tia, aphasia, acute suicidal ideation, delirium or renal failure excluded (creatinine > 2 mg/dL or urea > 40 mg/dL) |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|--|--------------------|---|
| Random sequence generation (selection bias) | Unclear risk | Randomised by flicking a coin |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Not described |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Low risk | Baseline balanced. Funded by an indepen- dent research grant from Pfizer Pharma GmbH, Karlsruhe (we have categorised this as low risk as the grant was 'indepen- dent') |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | No placebo used |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Not described |

Fruehwald 2003

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

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|---|
| Random sequence generation (selection bias) | Low risk | Computerised randomisation, using ran- dom permutated block design |
| Allocation concealment (selection bias) | Low risk | Centralised concealment |

Fruehwald 2003 (Continued)

| 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 The medication was supplied by Lannacher Heilmittel, Lannach, Austria All patients were randomly assigned to ei- ther fluoxetine or placebo treatment by the drug company independently of the re- search teams and the study centres |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | States blinded, used matching placebo |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | States blinded |

GlaxoSmithKline 1998

| Methods | Parallel group Randomisation: not stated Allocation concealment: not described Blinding: not described 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 |
| 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 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) |

GlaxoSmithKline 1998 (Continued)

| | score (score of < 4) at endpoint GI side effects reported, but unclear whether these are 'events' or 'patients', so we cannot use these data. It is not clear how the side effects were collected Withdrawal from study |
|-------|---|
| Notes | 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 |

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 |
| 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. Source of funding not stated, but we assume it was funded by Glaxo- SmithKline |
| 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 |

Guo 2009

| 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 Randomisation: random number table Allocation concealment: not described Blinding: blinding of outcome assessors Analysis: according to allocated treatment Drop-outs: none |
|---------------|---|
| Participants | Country: China Setting: unknown Stroke criteria: first ever stroke, clinical diagnosis plus relevant lesion on imaging, age \geq 60 years old Depression criteria: HAMD score \geq 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 |
| Interventions | Treatment: sertraline 50 mg daily plus stroke care (acute, secondary prevention, rehabil- itation 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 |
| Notes | Exclusions: psychiatric disorders or family psychiatric disorders, severe cognitive im- pairment, 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 |
| 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 |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop-outs, analysed by allocated treat- ment |
| Selective reporting (reporting bias) | Unclear risk | No protocol |

Guo 2009 (Continued)

| Other bias | Low risk | No obvious risk, balance baseline. Funded by a Local scientific academic fund |
|--|--|--|
| 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 |
| He 2004 | | |
| Methods | Parallel group Randomisation: 'according to recruitment sequence' Allocation concealment: not described Blinding: of participants: not described; of those delivering intervention: no; of outcome assessors: yes Analysis: according to treatment allocation Drop-outs: 13 dropped out after randomisation | |
| 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 de- pression at recruitment Treatment: 36 people, mean age 70.8 \pm 6.7 years, 25 men Control: 35 people, mean age 70.4 \pm 6.8 years, 23 men | |
| 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 | |
| Notes | Exclusion: psychiatric disorders, dysphasia, consciousness disturbance, agnosia, severe dementia 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 |

He 2004 (Continued)

| Random sequence generation (selection bias) | Unclear risk | Not described |
|--|--------------|--|
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Incomplete outcome data (attrition bias) All outcomes | High risk | 13 dropped out after randomisation |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Low risk | Balanced baseline, no obvious risks. Funded by Local scientific academic fund |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | No placebo |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | "Outcome assessors blind" |

He 2005

| Methods | Parallel design. 3 groups: paroxetine, paroxetine plus psychotherapy, control. We are using paroxetine and control data in this review Randomisation: "according to age, sex, stroke type, neurological function deficit", and level of depression/anxiety Allocation concealment: unknown Blinded: unclear Analysis: according to treatment group Drop-outs: none |
|---------------|---|
| Participants | Location: China Setting: inpatient Stroke criteria: first ever stroke; ischaemic and haemorrhagic, timing: "acute", clinical diagnosis plus confirmation by imaging (though not clear that 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 |
| 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 |

He 2005 (Continued)

| 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 |
|----------|---|
| Notes | 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 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 |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop-outs, analysed according to treat- ment 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. Funded by a local scien- tific academic fund |
| 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 |

| Hu 2002 | |
|---------------|---|
| Methods | Parallel design Aim: to study effect of antidepressants on depressive symptoms and nervous function Randomisation: stated, but method not described Allocation concealment: not described Blinding: not described Drop-outs: none |
| Participants | Country: China Setting: inpatient Stroke criteria: all pathological stroke types, clinical diagnosis plus confirmation by imag- ing (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 |
| 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 |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop-outs |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | Balanced baseline, no other obvious risks. Source of funding not stated |

Hu 2002 (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 |

Huang 2002

| Methods | Parallel design Aim: efficacy and tolerance of fluoxetine in Randomisation: method not stated Allocation concealment: not described Blinding: not described Analysis: according to treatment group Drop-outs: none | early post-stroke depression |
|---|--|------------------------------|
| 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 Patients 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 | |
| Notes | No obvious AEs were found, but they did not specifically report seizures | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear risk | Method not stated |

Huang 2002 (Continued)

| Allocation concealment (selection bias) | Unclear risk | Method not stated |
|--|--------------|--|
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop-outs, analysed according to treat- ment group |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | No description of the differences between treatment and control group in base- line characteristics. Source of funding 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 |

Ji 2000

| Methods | Parallel design Aim: to study effect of fluoxetine in treatment of depression after stroke Randomisation: method not described Allocation concealment: not described Blinding: not described Drop-outs: none |
|---------------|---|
| Participants | Country: China Setting: outpatient Stroke: clinical diagnosis plus confirmation of relevant lesion on imaging Depression: severe depression criteria of CCMD-II-R and HAMD score > 20 Other inclusion/exclusion criteria not stated Treatment: 20 people, age and gender not described Control: 20 people, age and gender not described |
| Interventions | Treatment: fluoxetine 20 mg daily, plus routine treatment and supportive psychotherapy Control: routine treatment and supportive psychotherapy Duration of treatment: 8 weeks Duration of follow-up (end of treatment to study end): 0 |
| Outcomes | HAMD Did not report side effects No drop-outs, no deaths |
| Notes | - |

Risk of bias

| KISR OJ DIAS | | |
|--|--------------------|---|
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear risk | Method not described |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop outs |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | Balanced baseline Source of funding not stated |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | No placebo |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Not described |

Jia 2005

| Methods | Parallel design Aim: to determine the effect of early intervention for post stroke depression on movement after 3 months of stroke Randomisation: method not stated Allocation concealment: not stated Blinding: none Drop-outs: 6 in treatment group (2 refused allocation), 4 in control group (2 refused allocation) |
|--------------|--|
| 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 |

Jia 2005 (Continued)

| Interventions | Treatment: either fluoxetine or sertraline (given sertraline if also had anxiety) plus routine stroke care 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 |
| Notes | Excluded: organic psychiatric disorders such as Alzheimer's disease or degenerative dis- ease, functional disorders such as schizophrenia and affective disorders |

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 |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | 10/184 (5.4%) |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | Balanced baseline Source of funding not stated |
| 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 |

Kong 2007

| Methods | Parallel Aim: to study whether fluoxetine could prevent post-stroke depression and improve neurological function Randomisation: computer-generated table of random digits Allocation concealment: not described Blinding: all blind Drop-outs: 17 |
|---------------|---|
| 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 |
| 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 |
| Notes | Exclusion: major depression, current antidepressants, allergy to fluoxetine, substance abuse, bipolar disorder, schizophrenia, MMSE $\leq 23/30$, substance abuse, obvious liver and renal deficit |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|--|--------------------|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated table of random dig- its |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Incomplete outcome data (attrition bias) All outcomes | High risk | 17/90 drop-outs |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | Balanced baseline Source of funding not stated. Fluoxetine |

| | | and placebo were supplied by Lilly Phar- maceutical Company |
|--|----------|--|
| 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 |

| Lai 2006 | | | |
|---------------|---|--|--|
| Methods | Parallel design Randomisation: randomised stated, metho Allocation concealment: unclear Blinding: unclear Analysis: analysed according to allocated tr Drop-outs: none | | |
| Participants | clear that stroke lesion had to be present), | ung SDS > 53, but no clear description about | |
| Interventions | | | |
| Outcomes | Additional: Zung SAS (abnormal is the sco Death | 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 | |
| Notes | Exclusion criteria: unclear | Exclusion criteria: unclear | |
| Risk of bias | | | |
| Bias | Authors' judgement | Support for judgement | |

Lai 2006 (Continued)

| Random sequence generation (selection bias) | Unclear risk | Method not stated |
|--|--------------|--|
| Allocation concealment (selection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No patient dropped out |
| Selective reporting (reporting bias) | High risk | No protocol, stated that they would evalu- ate side effects but these were not reported |
| Other bias | Unclear risk | Demographic details at baseline not de- scribed. Source of funding 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 |

Li 2002

| Methods | Parallel trial Randomisation: according to the case sequence (odd number was paroxetine group, and even number was control group) Allocation concealment: unclear Blinding: unclear Analysis: according to allocated treatment group Drop-outs: none |
|---------------|--|
| Participants | Location: China Setting: not stated Treatment: 46 people, mean age 66 ± 5 years, 22 men Control: 46 people, mean age 64 ± 5 years, 20 men Stroke criteria: ischaemic stroke, clinical diagnosis plus brain imaging (though not clear that stroke lesion had to be present) Depression diagnosis: DSM III-R criteria diagnosed 2 weeks after stroke onset |
| Interventions | Treatment: fluoxetine 20 mg plus usual care Control: usual care (note, no placebo) Duration of treatment: 1 month Duration of follow-up (treatment end to study end): 0 |
| Outcomes | Neurological function defect scale (this is the same as the CSS) HDRS Cerebral blood flow |
Li 2002 (Continued)

| | EEG No deaths or AEs reported | | |
|--|---|---|--|
| Notes | Excluded previous stroke and previous TIA | Excluded previous stroke and previous TIA | |
| Risk of bias | | | |
| Bias | Authors' judgement | Support for judgement | |
| Random sequence generation (selection bias) | High risk | "According to case sequence" | |
| Allocation concealment (selection bias) | High risk | "According to case sequence"; researchers would be able to predict treatment alloca- tion | |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop-outs | |
| Selective reporting (reporting bias) | Unclear risk | No protocol | |
| Other bias | Unclear risk | Baseline balanced Source of funding not stated | |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | No placebo | |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Unknown | |

Li 2004a

| Methods | Parallel group Aim: to study effects of fluoxetine on neurological impairment and post-stroke depression Randomisation: computer random numbers Allocation concealment: opaque, sealed up, serial numbered envelopes Blinding: not described Drop-outs: none |
|--------------|---|
| 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 |

Li 2004a (Continued)

| 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) |
| Notes | Excluded severe psychiatric disorders, severe cardiac, pulmonary, hepatic and renal disease |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|--|--------------------|---|
| Random sequence generation (selection bias) | Low risk | Computer random numbers |
| Allocation concealment (selection bias) | Low risk | Opaque sealed envelopes |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop-outs |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | Balanced baseline Source of funding not stated |
| 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 |

Li 2004b

| Methods | Parallel design Aim: to treat depression Randomisation: not stated |
|---------|--|
| | Allocation concealment: not described Blinding: not stated |
| | Drop-outs: 6 in treatment and 4 in control group |

Li 2004b (Continued)

| 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 |
|---------------|--|
| 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) BI (reported as a dichotomous variable) Data for continuous variables not provided Death reported Side effects in only treatment group reported, not control group. Method of reporting side effects not stated |
| Notes | Exclusion: previous depression or psychiatric interview, dementia (according to MMSE scores), aphasia, severe cardiac, pulmonary, hepatic, renal function impairment, consciousness disturbance 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 |
| Incomplete outcome data (attrition bias) All outcomes | High risk | 10/73 dropped out |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | Baseline balanced. Source of funding not stated |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | No placebo |

Li 2004b (Continued)

| Blinding of outcome assessment (detection | Unclear risk | Not stated |
|---|--------------|------------|
| bias) | | |
| All outcomes | | |

Li 2005

| Methods | Parallel design Improvement of post-stroke depression and augmentation of rehabilitation Randomisation: not described Allocation concealment: unknown Blinding: unclear |
|---------------|--|
| 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 Treatment: 74 patients Control: 74 patients Patients 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 |
| 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 |
| Notes | Excluded: previous psychiatric disorders, severe dementia, aphasia, consciousness disturbance |

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 |
| 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 |

Li 2005 (Continued)

| Other bias | Unclear risk | No description of differences between treatment and control group Source of funding not stated |
|--|--------------|--|
| 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 |

Li 2006

| LI 2000 | |
|---------------|--|
| Methods | Parallel group Randomisation: not described Blinding: unclear Drop-outs: 2 in treatment group, 4 in control 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 \geq 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 patient's complaints and observation, no description of who recorded AEs; and reported only for the treatment group |
| Notes | - |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|-----------------------|
| Random sequence generation (selection bias) | Unclear risk | No description |

Li 2006 (Continued)

| Allocation concealment (selection bias) | Unclear risk | No description |
|--|--|--|
| Incomplete outcome data (attrition bias) All outcomes | High risk | 2 drop-outs in treatment group, 4 in con- trol group. 1 in treatment group died, and 2 in the control group died (i.e. > 5%) |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | Baseline balanced Source of funding not stated |
| 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 |
| Li 2008 | | |
| Methods | Parallel trial, 3 (fluoxetine versus "free and easy wandering" versus placebo), we are using the fluoxetine versus placebo comparison in this review Randomisation: computer-generated randomisation Allocation concealment: not described Blinding: participants, those delivering the intervention and outcome assessors Drop-outs: 2 in fluoxetine group, 2 in placebo group | |
| Participants | Country: China Setting: unclear Stroke criteria: by neuroimaging, ischaemic or PICH Depression diagnosis: "each patient was evaluated by a psychiatrist", HAMD > 20 in- cluded 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% | |
| 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 patients left the trial early AEs (reported by patient or observed/elicited by physician at each visit) | |

Li 2008 (Continued)

| Notes | Excluded psychiatric illness other than depression, antidepressants within previous 2 |
|-------|---|
| | weeks, MMSE < 23, severe aphasia |
| | Note twice as many in fluoxetine than control group |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|--|--------------------|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated random numbers |
| Allocation concealment (selection bias) | Unclear risk | Unclear |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | 4/90 dropped out (< 5%) |
| Selective reporting (reporting bias) | Unclear risk | No placebo |
| Other bias | Low risk | Balanced baseline. Funded by the Natural Science Foundation of Shandong Province, People's Republic of China. None of au- thors had financial ties with the companies producing the medications in this study |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Paper states blinded, used placebo (though unclear if matching) |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Blinded |

Liang 2003

| Methods | Parallel group Aim: treat depression and augment rehabilitation Randomisation: according to admission sequence Allocation concealment: not described Blinding: not described Dropouts: none |
|--------------|--|
| Participants | Country: China Setting: inpatient Stroke: clinical diagnosis plus confirmation by imaging (though not clear that a stroke lesion had to be present), MESSS ≥ 16 , stroke onset in previous month, age ≤ 80 years old, absence of aphasia Depression: depression lasts for ≥ 2 weeks, DSM III-R depression, HAMD scale score ≥ 13 |

Liang 2003 (Continued)

| | Treatment: 42 people, mean age 59.5 ± 7.9 years, 17 men Control: 21 people, mean age 61.8 ± 7.8 years, 10 men | |
|--|---|---|
| Interventions | Treatment: fluoxetine 20 mg daily plus routine stroke care Control: routine stroke care Duration of treatment: 4 weeks Duration of follow-up (treatment end to study end): 0 | |
| Outcomes | HAMD MESSS Described AEs; no mention of seizures. Method of recording side effects not stated | |
| Notes | Note twice as many in treatment compared | d with control group |
| Risk of bias | | |
| Bias | Authors' judgement Support for judgement | |
| Random sequence generation (selection bias) | High risk | Randomisation "according to admission se- quence" |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop-outs |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | Note twice as many in treatment compared with control group - unclear if this was in- tentional. Source of funding not stated |
| 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 |

| Methods | Parallel design Randomisation: random number table, minimisation on age, gender and clinical con- dition Allocation concealment: not stated Blinding: states double-blind, but those who are blinded are not stated Analysis: according to allocated treatment group. Drop-outs: none |
|---------------|---|
| Participants | Location: China Setting: inpatient Treatment: 30 people, mean age 53 \pm 10 years, 20 men Control: 30 people, mean age 58 \pm 10 years, 18 men Stroke criteria: hemispheric stroke (infarct or haemorrhage). Clinical diagnosis of stroke plus confirmation by imaging. Did not state whether a visible lesion had to be present Around 2 weeks after stroke onset Anxiety criteria: HAMA \geq 14 Other entry criteria: > 40 years, clear consciousness Comparability of treatment groups: no difference between treatment and control in age, sex, stroke type and level of clinical condition |
| Interventions | Treatment: fluoxetine 20 mg daily and alprazolam 0.2 mg 3 times a day for 60 days, plus usual stroke care Control: alprazolam 0.2 mg 3 times a day for 60 days, plus usual stroke care Duration of treatment: 60 days Duration of follow-up (treatment end to study end): 0 |
| Outcomes | HAMA BI Modified SSS AEs reported, but not stated how data were collected |
| Notes | Exclusion criteria: personal or family history of psychiatric disorders, accompanied by psychiatric disorders other than depression and anxiety, severe cognitive impairment, obvious aphasia including partial motor aphasia without sensory aphasia, severe heart failure, respiratory failure, lung cancer or other severe physical diseases preventing the participants from coming to examinations |
| Pick of him | |

| 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 stated |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop-outs |

Liu 2004 (Continued)

| Selective reporting (reporting bias) | Unclear risk | No protocol |
|--|--------------|---|
| Other bias | Unclear risk | Baseline balanced. Source of funding not stated |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Stated double blind, but those who were blinded were not stated, no placebo used |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Stated double blind, but those who were blinded were not stated |

| Liu 2006 | | | |
|---------------|---|--|--|
| Methods | Parallel design Aim: to study effect of citalopram on po rehabilitation Randomisation: method not described Allocation concealment: not described Blinding: not stated | Aim: to study effect of citalopram on post-stroke depression and neurological functional rehabilitation Randomisation: method not described Allocation concealment: not described | |
| Participants | HAMD score ≥ 17 60 people randomised, of whom 38 wer for treatment and control groups were Treatment: 30 people, age and gender r | Setting: inpatient Stroke criteria: stroke during "recovery phase" at 6 to 9 months, NIHSS score ≥ 13 , | |
| Interventions | Control: routine stroke care Duration of treatment: 6 weeks | | |
| Outcomes | HAMD NIHSS BI Death | NIHSS BI | |
| Notes | Exclusion criteria: previous psychiatric turbance. AEs not reported | Exclusion criteria: previous psychiatric disorder, dementia, aphasia, consciousness dis- turbance. AEs not reported | |
| Risk of bias | | | |
| Bias | Authors' judgement | Support for judgement | |

Liu 2006 (Continued)

| Random sequence generation (selection bias) | Unclear risk | Method not described |
|--|---|---|
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop-outs |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | Baseline balance reported by authors. Source of funding not stated |
| 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 |
| Meara 1998 | | |
| Methods | Parallel design Randomisation: unclear Allocation concealment: unclear Blinding: reported as double-blind but those not blinded were not stated Analysis: unclear | |
| Participants | Location: Wales, UK Setting: inpatient Treatment: unclear Control: unclear Stroke criteria: ischaemic stroke > 11 weeks prior to randomisation Depression criteria: GDS (15-item) score > 4 Other entry criteria not stated | |
| 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 | |

Meara 1998 (Continued)

| Notes | Exclusion criteria: moderate to severe dementia, severe aphasia, communication difficul- ties, poorly controlled epilepsy Contacted author for more details but no response |
|-------|---|
| | We could not use the data in our meta-analysis |

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 |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Not described |
| Selective reporting (reporting bias) | Unclear risk | Insufficient data to make a judgement |
| Other bias | Unclear risk | Insufficient data to make a judgement. Source of funding not stated |
| 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 |

Miao 2004

| Methods | Parallel group Randomisation: "simple random sampling" Allocation concealment: not described Outcome assessors: stated that they are blinded 9 not allocated (5 in treatment group refused allocation, 4 in the control group refused allocation) Drop-outs: 6 in treatment group, 7 in control group |
|--------------|---|
| Participants | Country: China Setting: mixed inpatient and outpatient All stroke pathological types, clinical diagnosis plus confirmation by imaging that a rele- vant 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 Patients: 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 |
|---------------|---|
| 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 |
| Notes | Exclusion criteria: other organic brain disorders and other aetiologies-related depression |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|--|--------------------|--|
| Random sequence generation (selection bias) | Unclear risk | "Simple random sampling" - no further de- scription given |
| Allocation concealment (selection bias) | Unclear risk | Allocation not described |
| Incomplete outcome data (attrition bias) All outcomes | High risk | 9 not allocated after randomisation, 13 drop-outs |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | Baseline balanced. Source of funding not stated |
| 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 |

Murray 2005

| Methods | Parallel design Randomisation: block Allocation concealment: centralised Blinding: double blind; participants: yes; relatives: yes; clinical examiners: yes; nursing staff: yes 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 | |
| Interventions | Treatment: sertraline 50 mg daily; possible dose escalation to 100 mg after 4 weeks Control: matching placebo 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, Ex- amination social performance, treatment costs, mortality, relative's situation, neuropsy- chological performance, neurological recovery (data not presented) AEs (selected data presented) using a modified version of the Udvalg for Kliniske Un- dersogelser side effect rating scale | |
| Notes | 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 less than 20% reduction in MADRS score at 6 weeks were excluded | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |

Murray 2005 (Continued)

| Random sequence generation (selection bias) | Low risk | Block randomisation |
|--|--|---|
| Allocation concealment (selection bias) | Low risk | Centralised randomisation |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | ITT as well as per protocol |
| 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 patients had left hemisphere brain lesion in sertra- line group than in placebo group (statisti- cally significant) Funded by an unrestricted grant, study drug and placebo from Pfizer AG Sweden and grants from the AFA Insurances and Marianne and Marcus Wallenberg Founda- tion |
| 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 |
| Pariente 2001 | | |
| Methods | Prospective double-blind cross-over placebo controlled study of 8 patients with pure motor hemiparesis | |
| Participants | Lacunar ischaemic stroke, assessed by brain CT "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) | |
| Notes | We could not use these data in our meta-analyses. The authors reported that fluoxetine led to hyperactivation in the ipsi-lesional (that is on the same side as the stroke lesion) | |

primary motor cortex during a motor task; moreover, fluoxetine significantly improved

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

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Pariente 2001 (Continued)

motor skills of the affected side (Pariente 2001)

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 |
| 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 re- ported |
| Other bias | Unclear risk | Balanced baseline. Source of funding not stated |
| 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 |

Rasmussen 2003

| Methods | Parallel design Randomisation: unclear Allocation concealment: unclear Blinding: double blind reported, those blinded not stated Analysis: ITT (last observation carried forward) and per-protocol: details of those ex- cluded 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 |

Rasmussen 2003 (Continued)

| 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 Underso- gelser Side Effect Rating Scale Did not report death |
| 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 | Method not stated |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Used ITT analysis and last observation car- ried 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 intro- duce bias. There was no significant differ- ence between groups 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 |
| 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 |

Restifo 2001

| 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 reor- ganisation |
| Notes | Abstract only, full paper could not be found by our searches |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|--|--------------------|---|
| Random sequence generation (selection bias) | Unclear risk | "Random allocation" method not described |
| Allocation concealment (selection bias) | Unclear risk | "Random allocation", method not described |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Unclear from abstract |
| Selective reporting (reporting bias) | Unclear risk | Unclear from abstract |
| Other bias | Unclear risk | Unclear from abstract. Source of funding not stated |
| 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 |

| Methods | Parallel design Comparison on fluoxetine, nortriptyline and placebo. We are using the fluoxetine and placebo data Randomisation: random number table Allocation concealment: held by independent person Blinding: unclear 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 |
| 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) |
| Notes | 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 an- tidepressant for a 2-week washout period Note difference in time since stroke between treatment groups |

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 |
| 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 |

Robinson 2000a (Continued)

| Other bias | Unclear risk | Imbalance in treatment groups for time since stroke and gender Funded by NIMH grants and grants from the Raul Carrea Institute of Neurological Research and Fundacion Perez Companc. Eli Lilly and company supplied the fluoxe- tine and placebo |
|--|--------------|--|
| 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 |

Robinson 2000b

| Methods | Parallel design Comparison on fluoxetine, nortriptyline and placebo. We are using the fluoxetine and placebo data Randomisation: random number table Allocation concealment: held by independent person Blinding: unclear 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 |
| 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) |

Robinson 2000b (Continued)

| Notes | 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 an- |
| | tidepressant for a 2-week washout period |
| | Note difference in time since stroke between groups |
| | с . |

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 |
| 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. 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 |
| 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 |

Robinson 2008

| Methods | Parallel group, 3-arm (escitalopram, placebo, problem-solving therapy group). We a using the escitalopram versus placebo arm in this review Randomisation: randomised, blocks of 3, 6 and 9 within each block assigned 1 of the | |
|---------|---|--|
| | treatments | |
| | Allocation concealment: unclear | |
| | Blinding: placebo and escitalopram: identical pills, outcome assessors blind | |
| | Analysis: ITT | |
| | Drop-outs: 5 in placebo and 7 drop-outs in escitalopram - all patients included in analysis | |

Robinson 2008 (Continued)

| Participants | Country: USA Setting: mixed: neurology department and newspaper advertisements Stroke criteria: ischaemic or haemorrhagic stroke not because of complications of in- tracranial 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 |
|---------------|---|
| Interventions | Treatment: escitalopram 5 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 Patients, 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 |
| Notes | The escitalopram group had significantly more diabetes than the placebo group Exclusion: acute coronary syndrome, neurodegenerative disorders, DSM IV criteria for alcohol or substance abuse |

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 |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | ITT analyses, all patients used in analysis |
| 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 escitalo- pram group than placebo group The initial report states that "This work was supported solely by National Institute of Mental Health Grant RO1MH-65134. |

Robinson 2008 (Continued)

| Blinding of participants and personnel | Low risk | All the study medications were purchased using NIMH grant funds." In a subsequent letter to the Journal, the authors disclosed honoraria and expenses from pharmaceu- tical 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 in- put from Forest Laboratories Identical placebo |
|--|----------|--|
| 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 blind |

Song 2006

| Methods | Aim: to evaluate changes in depression and cognitive impairment in patients with post- stroke depression treated with fluoxetine Parallel trial Randomisation: not stated Allocation concealment: not described Blinding: not described Drop-outs: none |
|---------------|--|
| 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 |
| 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 |

Song 2006 (Continued)

| Notes | Excluded: previous mental disorders, previous "neurological disorder", if other psychi- |
|-------|---|
| | atric drugs had been taken, these had to be stopped for 1 week before fluoxetine was |
| | administered |

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 |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop-outs |
| Selective reporting (reporting bias) | Unclear risk | Unclear |
| Other bias | Unclear risk | Balanced baseline. Source of funding not stated |
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk | Placebo - but not clear whether identical |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Not described |

Wang 2003

| Methods | Parallel design 3-arm trial: routine care, fluoxetine plus routine care, amitriptyline plus routine care. We are using the routine care and fluoxetine plus routine care in this analysis Aim: to observe effects of antidepressant therapy on post-stroke and neurological reha- bilitation in the elderly Randomisation: not described Allocation concealment: not described Blinding: not described |
|--------------|---|
| Participants | Country: China Setting: inpatient Stroke criteria: ischaemic stroke, clinical diagnosis plus confirmation by imaging (al- though not clear whether a stroke lesion had to be present) Depression diagnosed according to CCMD-II-R diagnostic criteria, HAMD \geq 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 |

Wang 2003 (Continued)

| Interventions | Treatment: fluoxetine 20 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 |
| Notes | Excluded: psychiatric disorder history, severe cardiac, pulmonary, hepatic and renal dis- eases |

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 |
| 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 statisti- cal comparison between groups. Source of funding not stated |
| 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 |

| Wen 2006 | |
|---------------|---|
| Methods | Parallel trial Aim: to explore effects of prophylactic antidepression therapy on nerve functional reha- bilitation after stroke Randomisation: not described Allocation concealment: not described Blinding: not described Analysis: according to treatment group Drop-outs: none |
| Participants | Country: China Setting: inpatient Stroke criteria: acute stroke of all pathological subtypes, clinical diagnosis plus confir- mation 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 |
| 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 |
| Notes | 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 |

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 |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Analysed according to treatment group, no drop-outs |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | Balanced baseline. Source of funding not stated |

Wen 2006 (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 |
| Wiart 2000 | | |
| Methods | placebo were "identical white tablets" - so administering the treatment were blind | nd not stated. However, the treatment and o reasonable to assume patients and those rard), withdrawn owing to AE (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 | |
| Interventions | Treatment: fluoxetine 20 mg daily Control: matched placebo Duration of treatment: 45 days Duration of follow-up (treatment end to str | udy end): 0 |
| Outcomes | tion in MADRS score Additional: FIMs MMSE Motricity Index Leaving the study early Death | to end of treatment of MADRS, 50% reduc- ively". Complete blood count, liver test and assessment visit) |

Wiart 2000 (Continued)

| Notes | Exclusion criteria: severe psychiatric problems which required hospitalisation, severe |
|-------|--|
| | aphasia, previous stroke, severe cognitive impairment, chronic alcoholism, chronic asso- |
| | ciated handicapping pathology, contraindication to fluoxetine |

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 |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Used last observation carried forward |
| Selective reporting (reporting bias) | Low risk | Trial published on www.strokecentre.org/ trials. The primary outcome was reported |
| Other bias | Unclear risk | Baseline balanced. Lilly France Labora- tory provided methodological and financial support |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | "Identical white capsules" given |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Method of blinding not stated |

Xie 2005

| Methods | Aim: to study the effect of treatment with sertraline in elderly patients with post-stroke depression Parallel study Randomisation: yes although method not stated Allocation concealment: not described Blinding: not described Drop-outs: none |
|--------------|--|
| Participants | Country: China Setting: unclear Recruited "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 |

Xie 2005 (Continued)

| | 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 |
| NI . | |

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 |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop-outs |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | No clear description between treatment and control. Local scientific academic fund funded the study |
| 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 |

| Methods | Parallel Aim: to study the effect of fluoxetine on depression in early recovery stage of cerebral infarction Randomisation: no description of method Allocation concealment: not described Blinding: not described Drop-outs: 6 in treatment group, 4 in control group |
|---------------|--|
| 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 patient characteristics) |
| 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 | Zung SDS ADL (BI) Neural function deficient Death AEs not reported |
| Notes | Excluded if previous antidepressants |

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 |
| Incomplete outcome data (attrition bias) All outcomes | High risk | 10/62 drop outs |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Unclear risk | No clear description of stroke criteria and imaging. Source of funding not stated |

Xu 2001 (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 |
| Xu 2006 | | |
| 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 Randomisation: "sequence numbers" Allocation concealment: not described Blinding: not described Drop-outs: 7 | |
| Participants | Country: China Setting: inpatient 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 | |
| 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 | |
| Notes | Exclusion: no severe hepatic or renal impairment, DSM IV depression not stated as an inclusion, but none met criteria for depression initially 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 | Unclear risk | "Sequence numbers" - risk unclear |

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

bias)

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Xu 2006 (Continued)

| Allocation concealment (selection bias) | Unclear risk | Not described |
|--|--------------|---|
| Incomplete outcome data (attrition bias) All outcomes | High risk | 7 patients dropped out |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Low risk | Baseline balance. Study funded by local sci- entific academic fund |
| 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 |

Xu 2007

| Methods | 3-arm trial: "fluoxetine plus usual care" versus "Wuling capsule plus usual care" versus "fluoxetine plus usual care plus Wuling capsule" We are using the "fluoxetine plus Wuling capsule plus usual care" versus "Wuling capsule and usual care" comparison Aim: to evaluate the efficacy of Wuling capsule in treating patients with post-stroke depression Randomisation: "according to the number table" Allocation concealment: not described Blinding: not described Drop-outs: 2 in fluoxetine group, 2 in combined group |
|---------------|--|
| Participants | Country: China Setting: unclear Stroke criteria: stroke plus CT or MR for definitive diagnosis. Did not state that visible lesion was needed to make the diagnosis, no previous psychiatric disorder history, first acute stroke, available for follow-up and able to give informed consent Depression criteria: CCMD-3 depression diagnostic criteria, first ever depression, HAMD score > 17 Number randomised in each group was 36 Demographic data provided for fluoxetine plus Wuling capsule plus usual care: 36 people, mean age 61.1 ± 10.2 years, 19 men Wuling capsule plus usual care: 36 people, mean age 65.2 ± 14.2 years, 18 men This does not correspond to the 2 drop-outs in the combined group |
| Interventions | "Fluoxetine 20 mg daily plus usual care" versus "Wuling capsule plus usual care" versus "fluoxetine 20 mg daily plus usual care plus Wuling capsule" We are using the "fluoxetine plus Wuling capsule plus usual care" versus "Wuling capsule and usual care" |

| | Duration of treatment: 3 months Duration of follow-up (treatment end to study end): 0 |
|----------|---|
| Outcomes | HAMD MMSE MESSS BI Death Nausea Used Asberg Rating Scale for Side Effect. Recorded according to the patient's complaints and observation, no description of who recorded AEs |
| Notes | Excluded: no previous organic brain diseases. Note inconsistency in number of dropouts |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|--|--------------------|---|
| Random sequence generation (selection bias) | Unclear risk | Unclear - states "number table" but not clear if this was a random number table |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | 2 patients in the combined "Wulung capsule plus fluoxetine plus usual care" dropped out. The authors did not report any drop-outs in the "Wulung capsule plus usual care" group |
| Selective reporting (reporting bias) | Unclear risk | Unclear |
| Other bias | Unclear risk | Note inconsistencies in relation to number of drop outs. Source of funding not stated |
| 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

| Methods | Parallel group Aim: to study effects of antidepressant in treatment of patients with post-stroke depres- sion Randomisation: not described Allocation concealment: not described Blinding: not described Drop-outs: 11; 4 in treatment group, 7 in control group |
|---------------|--|
| 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 |
| 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 |
| Incomplete outcome data (attrition bias) All outcomes | High risk | 11/121 (9%) drop-outs |
| 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 | Unclear risk | No baseline differences between groups, no other obvious source of bias. Source of funding not reported |

Yang 2002 (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 |

Yang 2011

| no previous psychiatric and psychological disorders, age < 75 years old, st < 72 hours, NIHSS score: 4 to 19 Mood: HAMD \geq 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 | roke onset time | |
|--|--|--|
| Control: usual stroke care Duration of treatment: at least 3 months Duration of follow-up: 0OutcomesHAMD score, IL-1 β and IL-6 level Death | 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 \geq 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 | |
| Death | Control: usual stroke care Duration of treatment: at least 3 months | |
| | Death | |
| and addictive substance induced psychiatric disorders, infectious disease, impairment to affect communication, severe aphasia to affect commu | 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 dis- ease such as brain tumour, or symptomatic stroke, encephalitis | |
| Risk of bias | | |
| Bias Authors' judgement Support for judgement | | |

Yang 2011 (Continued)

| Random sequence generation (selection bias) | Unclear risk | "Case sequence" randomisation |
|--|--------------|---|
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop-outs |
| Selective reporting (reporting bias) | Unclear risk | No protocol |
| Other bias | Low risk | No difference in baseline. Source of fund- ing: local scientific academic fund |
| 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 |

Ye 2004

| Methods | Aim: to investigate whether antidepressive therapy is needed for patients 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 Randomisation: number table Allocation concealment and blinding: "the study designer did not involve in assessment and treatment, the assessors did not know the allocation" Blinding of those delivering the treatment: unclear Drop-outs: 1 in paroxetine group, none in control group |
|---------------|--|
| 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 |
| 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 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 |
|----------|---|
| Notes | Exclusion criteria: severe cardiac, hepatic and renal diseases, multiple infarcts or haem- orrhage 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 did not involve in as- sessment and treatment, the assessors did not know the allocation |
| 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. Source of funding not stated |
| 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 |

| Zhou 2 | 2003 |
|--------|------|
|--------|------|

| Bias | Authors' judgement | Support for judgement | |
|---------------|--|--|--|
| Risk of bias | | | |
| Notes | Exclusion criteria: severe psychiatric impairment, severe cognitive impairment, unable to complete the test, aphasia, severe cardiac, hepatic, pulmonary, and renal disorders, previous stroke Inclusion criteria: at least 1 limb with muscle power \leq grade 3 | | |
| Outcomes | HAMD HAMA MESSS ADL AEs (in fluoxetine group only) | | |
| Interventions | Treatment: fluoxetine 20 mg plus usual stroke care Control: usual stroke care Duration of treatment: 60 days Duration of follow-up (end of treatment to end of study): 0 | | |
| Participants | Country: China Setting: inpatient Stroke: all pathological types, clinica not clear that stroke lesion had to be Onset to recruitment time was 13 to 34 days in the control group Mood: HAMD \leq 7 and HAMA \leq 7 Exclusion criteria: HAMD \geq 17 or 1 Age \leq 80 years Treatment: 30 people, mean age 65 = | Country: China Setting: inpatient Stroke: all pathological types, clinical diagnosis plus confirmation on imaging (though not clear that stroke lesion had to be present) Onset to recruitment time was 13 to 34 days in the treatment group of stroke and 13 to 34 days in the control group Mood: HAMD \leq 7 and HAMA \leq 7 Exclusion criteria: HAMD \geq 17 or HAMA \geq 17 'during observation' | |
| Methods | Parallel study Aim: effect of fluoxetine on function Randomisation: according to admiss Allocation concealment: not describe Blinding: not described Drop-outs: 6 | ion date | |

| Dias | Authors Judgement | Support for Judgement |
|--|-------------------|-------------------------------|
| Random sequence generation (selection bias) | High risk | "According to admission date" |
| Allocation concealment (selection bias) | Unclear risk | Unclear |
| Incomplete outcome data (attrition bias) All outcomes | High risk | 6/60 (10%) drop-outs |
| Selective reporting (reporting bias) | Unclear risk | No protocol |

Zhou 2003 (Continued)

| Other bias | Low risk | Baseline characteristics balanced. Funded by local scientific academic fund |
|--|---|--|
| 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 |
| Zhou 2008 | | |
| Methods | Aim: to study effect of early paroxetine on post-stroke depression and rehabilitation Parallel design Randomisation: not described Allocation concealment: not described Blinding: not stated Analysis: according to treatment groups Drop-outs | |
| 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 | |
| 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 | |
| Notes | Excluded: previous psychiatric disorders, severe hepatic and renal impairment, taking agents with obvious interaction with fluoxetine in recent 1 month | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear risk | Method not described |

Zhou 2008 (Continued)

| Allocation concealment (selection bias) | Unclear risk | Not described |
|--|--------------|--|
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No drop-outs, analysed according to allo- cated treatment group |
| Selective reporting (reporting bias) | High risk | No protocol, no raw data provided for sev- eral of the outcomes |
| Other bias | Low risk | Baseline similar. Source of funding not stated |
| 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 |

ADL: activities of daily livingAE: adverse events 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 EEG: electroencephalogram 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 IL: interleukin ITT: intention-to-treat JHFI: Johns Hopkins Functioning Inventory MADRS: Montgomery-Åsberg Depression Rating Scale MCA: middle cerebral artery MESSS: Modified Edinburgh-Scandinavian Stroke Scale MMSE: Mini-Mental State Examination MRI: magnetic resonance imaging

mRS: modified Rankin score NIHSS: National Institutes of Health Stroke Scale PICH: primary intracerebral haemorrhage RS: Rankin score SAS: Zung Self-rating Anxiety Scale SD: standard deviation SDS: Zung Self-rating Depression Scale SF-36: Short Form-36 SSS: Scandinavian Stroke Scale TESS: Treatment Emergent Symptom Scale TIA: transient ischaemic attack WHO: World Health Organization

Characteristics of excluded studies [ordered by study ID]

| Study | Reason for exclusion |
|---------------------------|--|
| Berends 2009a | Mean time from stroke onset to fluoxetine was 39.1 months. Also listed as flu2006 (EudraCT 2008-003349-97) |
| Bian 2006 | Meclofenoxate plus fluoxetine versus fluoxetine alone |
| Chen SD 2005 | Comparison of fluoxetine and clomipramine |
| Choi-Kwon 2008 | Patients > 1 year post stroke |
| Cui 2001 | Abstract, no data, unclear if randomised |
| Ding 2005 | Combination of paroxetine and psychotherapy versus paroxetine alone |
| Erfurth 2001 | Open trial |
| Fedin 2004 | Coaxil is not an SSRI |
| Flu 2008 | A clinical trial that ended prematurely because 3 patients had been recruited by 6 months (information from Professor MJ IJzerman) |
| Gao 2005 | Not randomised - patients allocated according to their order of admission |
| Gekht 2002 | Milnacipran is an SNRI, not a SSRI |
| Gonzalez-Torrecillas 1995 | Not randomised |
| Havle 2010 | All given citalopram, no control |
| He 2001 | Some patients were > 1 year post stroke |

(Continued)

| He 2010 | Patients with depression were given fluoxetine, measured 5HT and event-related potentials. not ran- domised, no clinical data |
|----------------|--|
| He Y 2004 | Comparison of paroxetine and amitriptyline |
| Hong 2004 | Comparison of the curative effects of yuxingchangzhi tang and fluoxetine |
| Horvath 2006 | Open label phase IV study |
| Hu 2004 | Comparison of fluoxetine and psychotherapy |
| Kimura 2002 | Milnacipran, not a SSRI |
| Li W 1999 | Comparison of 2 types of fluoxetine |
| Liang 2005 | Used fluoxetine or clomipramine in the treatment group |
| Liu G 2006 | Clinical control study of citalopram and amitriptyline in the treatment of post-stroke depression |
| Liu X 2004 | Citalopram versus amitriptyline, no control group |
| Loubinoux 2002 | A study of paroxetine in healthy individuals |
| Luo 2006 | Comparison of amitriptyline and fluoxetine |
| Marko 1994 | Comparison of mobeclamid and nortriptyline |
| Mei 2001 | A controlled trial comparing paroxetine versus fluoxetine in the treatment of post stroke depression |
| Mitchell 2008 | Combination of psychological intervention plus antidepressants |
| Miyai 1998 | Comparison of 3 different antidepressants, no control |
| Mo 2004 | Comparison of Saint John's Wort extract with fluoxetine in the treatment of post-stroke depression |
| Ooboshi 2008 | Comparison of paroxetine and sulpiride |
| Rampello 2004 | Comparison of citalopram and reboxetine |
| Ruddell 2007 | 1 patient randomised |
| Sato 2006 | RCT of milnacipran, which is not an SSRI |
| Shan 2001 | Onset to recruitment was more than 1 year in some patients |
| Simis 2006 | Patients not randomised |

(Continued)

| Spalletta 2003 | Open study of sertraline |
|------------------|--|
| Stamenkovic 1996 | Sertraline given to 10 patients, no control group |
| Wu 2010 | Comparison of acupuncture and medication for post-stroke depression |
| Yuan 2004 | Comparison of paroxetine and amitriptyline |
| Zhang 2005 | Comparison of acupuncture and fluoxetine |
| Zhao 1999 | Compared fluoxetine and psychotherapy with fluoxetine, no placebo or standard care group |
| Zhao 2005 | Comparison of citalopram and amitriptyline |
| Zhao F-T 2005 | Citalopram versus venlafaxine |
| Zheng 2006 | Paroxetine plus psychotherapy |
| Zifko 2002 | Open trial |
| Zittel 2008 | 8 chronic stroke, mean duration of hemiparesis 36 months |

RCT: randomised controlled trial SNR: serotonin-norepinephrine reuptake inhibitor SSRI: selective serotonin reuptake inhibitor

Characteristics of studies awaiting assessment [ordered by study ID]

Sitzer 2002

| Methods | Double blind, randomised placebo controlled trial |
|---------------|--|
| Participants | Patients will be within the first 6 days after hospital admission |
| Interventions | Randomised to 50 mg/day sertraline or placebo Aim to recruit 300 participants from 10 centres |
| Outcomes | Depressive symptoms will be assessed using the Hospital Anxiety and Depression Scale, the Montgomery-Asberg Depression Rating Scale, and the International Diagnosis Checklist for International Classification of Diseases-10 at baseline, 4 weeks, 12 weeks, and 24 weeks. Functional outcome will be determined by the European Stroke Scale, the modified Rankin score, and the Barthel Index. Cognitive performance will be assessed by the Mini-Mental State Examination and the Digit Span Test. Quality of life will be determined at 12 and 24 weeks using the SF-36. Treatment and follow-up are scheduled to continue for 6 months with follow-up visits after 4 weeks, 3 months and 6 months |

Sitzer 2002 (Continued)

| Notes | Listed as a major ongoing trial in Stroke (see citation). Randomisation and follow-ups August 2001 through to January 2003 |
|-------|---|
| | Author did not respond to emails requesting more information Pre-dis is listed on the author's web page (www.zafes.com/institutes/neurology/index-sitzer.html) but there are no publications associated with this |

Whyte 2005

| Methods | Placebo-controlled trial of sertraline to prevent depression |
|---------------|---|
| Participants | Ischaemic stroke, within 3 months, > 40 years, speaks English Exclusion: major depression, current antidepressant treatment, severe language impairment, history of another central nervous system disorder, pregnant or breastfeeding, medical unstable, other medical contraindications |
| Interventions | Treatment: sertraline in doses increasing to 75 mg daily Control: placebo (matching) 10-month treatment period, 2-month naturalistic continuation phase |
| Outcomes | Primary outcome: major depression |
| Notes | Contacted author twice, no response. Website www.clinicaltrials.gov states that study was terminated as recruitment goals could not be met. No published data available through our searches |

Characteristics of ongoing studies [ordered by study ID]

2005-005266-37

| Trial name or title | 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 | Randomised, placebo controlled |
| Participants | 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 Exclusions: 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 |
| Interventions | Escitalopram or placebo Duration of treatment: not stated |
| Outcomes | Depression (MADRS) after 180 days Incidence of dementia after 180 days (Clinical Dementia Rating scale) Severity of dementia |

2005-005266-37 (Continued)

| | 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 |

AFFINITY 2011

| Trial name or title | Assessment oF FluoxetINe In sTroke recoverY (AFFINITY) trial |
|---------------------|---|
| Methods | Fluoxetine (20 mg once daily) for 6 months via oral capsule or enteral tube |
| Participants | Men or women aged 18 years or more with: clinical diagnosis of stroke 2 to 15 days previously, and 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 Aiming to recruit 1580 patients |
| Interventions | Fluoxetine 20 mg daily or matching placebo for 6 months |
| Outcomes | mRS, Stroke impact scale, depression (PHQ-9), vitality component of SF-36, Euroquol 5D, healthcare utilisation (data linkage to patient medical records and patient diary recording hospital admissions/visits and general practitioner/specialist visits), adverse events, social functioning (FAI), adherence to trial medication (patient self report of medication compliance and tablet counting), cognition (TICSm), Outcomes collected at 6 months and 12 months |
| Starting date | July 2012 |
| Contact information | graeme.hankey@health.wa.gov.au |
| Notes | ACTRN12611000774921 |

Carda 2009

| Trial name or title | Effects on clinical and functional outcome of escitalopram in adult stroke patients |
|---------------------|---|
| Methods | Randomised, parallel assignment, double blind study. |
| Participants | > 18 years First ischaemic or haemorrhagic stroke Exclusions: unstable medical conditions, unable to understand study aims and procedures, severe aphasia, other progressive neurological disease, previous or concomitant psychiatric illness, patients not willing to participate |
| Interventions | Experimental: escitalopram and rehabilitation. Escitalopram given 5 mg od for the first week, 10 mg od from the second to fourth week, and 20 mg daily until the 6th month Comparator: placebo and rehabilitation |
| Outcomes | Not stated |
| Starting date | July 2009. Aiming to recruit 200 |
| Contact information | stefano.carda@virgilio.it cisari@tin.it |
| Notes | Contacted author Prof Cisari; response received; data being analysed |

EMOTION 2011

| Trial name or title | The preventative effect of escitalopram on depression and related emotional disorders in acute stroke patients |
|---------------------|--|
| Methods | Multicentre, randomised, parallel assignment, double-blind trial to prevent depression |
| Participants | Acute stroke, within 21 days of onset. Both haemorrhagic and ischaemic, $mRS \ge 2$ on screening, without definite history of depression, without serious communication problem, those who agree to participate Long list of exclusion criteria |
| Interventions | Experimental: escitalopram: first week 5 mg, 2nd week ~ 12 week: 10 mg Placebo: "sugar pill". First week 5 mg, 2nd week ~ 12 week: 10 mg Stopped at 14 weeks At follow-up at 24 weeks, assessment for post-stroke depression and related symptoms |
| Outcomes | Not listed |
| Starting date | January 2011. Aiming to enrol 444 participants. Estimated primary completion date: December 2013 |
| Contact information | jongskim@amc.seoul.kr |
| Notes | - |

FOCUS 2011

| Trial name or title | Fluoxetine or control under supervision |
|---------------------|--|
| Methods | Randomised placebo-controlled, blinded trial |
| Participants | Men or women aged 18 years or more with: clinical diagnosis of stroke 2 to 15 days previously, and 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 Aiming to recruit 3000 patients |
| Interventions | Fluoxetine 20 mg daily or matching placebo for 6 months |
| Outcomes | mRS, Stroke Impact Scale, Mental Health Inventory 5, vitality component of SF-36, Euroquol 5D, resource use, adverse events. Outcomes collected at 6 and 12 months |
| Starting date | July 2012 |
| Contact information | gmead@staffmail.ed.ac.uk |
| Notes | MHRA approval granted. Start up phase funded by The Stroke Association |

CT: computerised tomography FAI: Frenchay Activities Index MADRS: Montgomery-Åsberg Depression Rating Scale MCA: middle cerebral artery MHRA: M edicines and Healthcare products Regulatory Agency mRS: modified Rankin score NPI: Neuropsychiatric Inventory Scale od: once daily PHQ-9: Patient Health Questionnaire SF-36: Short Form-36 TICSm: telephone interview for cognitive status - modified

DATA AND ANALYSES

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---------------------------------|-------------------|------------------------|---|----------------------|
| 1 Dependent on modified Rankin | 2 | 223 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] |
| score (mRS 3 to 5) | | | | |
| 1.1 Fluoxetine | 1 | 112 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] |
| 1.2 Sertraline | 1 | 111 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Disability | 22 | 1310 | Std. Mean Difference (IV, Random, 95% CI) | 0.92 [0.62, 1.23] |
| 2.1 Fluoxetine | 13 | 708 | Std. Mean Difference (IV, Random, 95% CI) | 0.68 [0.31, 1.06] |
| 2.2 Sertraline | 1 | 130 | Std. Mean Difference (IV, Random, 95% CI) | 1.38 [0.99, 1.76] |
| 2.3 Citalopram | 3 | 179 | Std. Mean Difference (IV, Random, 95% CI) | 1.18 [-0.22, 2.58] |
| 2.4 Paroxetine | 5 | 293 | Std. Mean Difference (IV, Random, 95% CI) | 1.31 [0.67, 1.95] |
| 2.5 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| 2.6 Sertraline or fluoxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| 3 Neurological deficit score | 29 | 2011 | Std. Mean Difference (IV, Random, 95% CI) | -1.00 [-1.26, -0.75] |
| 3.1 Fluoxetine | 17 | 1095 | Std. Mean Difference (IV, Random, 95% CI) | -0.93 [-1.29, -0.57] |
| 3.2 Sertraline | 2 | 108 | Std. Mean Difference (IV, Random, 95% CI) | -0.26 [-0.96, 0.45] |
| 3.3 Citalopram | 3 | 179 | Std. Mean Difference (IV, Random, 95% CI) | -1.43 [-2.25, -0.60] |
| 3.4 Paroxetine | 6 | 455 | Std. Mean Difference (IV, Random, 95% CI) | -1.21 [-1.68, -0.74] |
| 3.5 Fluoxetine or sertraline | 1 | 174 | Std. Mean Difference (IV, Random, 95% CI) | -1.40 [-1.73, -1.06] |
| 4 Depression (continuous data) | 39 | 2728 | Std. Mean Difference (IV, Random, 95% CI) | -1.91 [-2.34, -1.48] |
| 4.1 Fluoxetine | 21 | 1260 | Std. Mean Difference (IV, Random, 95% CI) | -1.97 [-2.63, -1.32] |
| 4.2 Sertraline | 4 | 383 | Std. Mean Difference (IV, Random, 95% CI) | -0.13 [-1.11, 0.85] |
| 4.3 Citalopram | 5 | 313 | Std. Mean Difference (IV, Random, 95% CI) | -1.92 [-3.08, -0.75] |
| 4.4 Paroxetine | 8 | 598 | Std. Mean Difference (IV, Random, 95% CI) | -2.81 [-3.66, -1.96] |
| 4.5 Fluoxetine or sertraline | 1 | 174 | Std. Mean Difference (IV, Random, 95% CI) | -1.50 [-1.84, -1.16] |
| 4.6 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Depression (dichotomous data) | 8 | 771 | Risk Ratio (M-H, Random, 95% CI) | 0.43 [0.24, 0.77] |
| 5.1 Fluoxetine | 3 | 206 | Risk Ratio (M-H, Random, 95% CI) | 0.31 [0.17, 0.57] |
| 5.2 Sertraline | 2 | 166 | Risk Ratio (M-H, Random, 95% CI) | 0.59 [0.28, 1.25] |
| 5.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.4 Paroxetine | 2 | 282 | Risk Ratio (M-H, Random, 95% CI) | 0.53 [0.15, 1.92] |
| 5.5 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.14, 0.99] |
| 6 Anxiety (continuous data) | 8 | 413 | Std. Mean Difference (IV, Random, 95% CI) | -0.77 [-1.52, -0.02] |
| 6.1 Fluoxetine | 4 | 169 | Std. Mean Difference (IV, Random, 95% CI) | -0.23 [-0.67, 0.21] |
| 6.2 Sertraline | 1 | 50 | Std. Mean Difference (IV, Random, 95% CI) | 0.36 [-0.20, 0.92] |
| 6.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 6.4 Paroxetine | 3 | 194 | Std. Mean Difference (IV, Random, 95% CI) | -1.97 [-3.81, -0.12] |
| 6.5 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 7 Anxiety (dichotomous data) | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 8 Cognition (continuous scores | 7 | 425 | Std. Mean Difference (IV, Random, 95% CI) | 0.32 [-0.23, 0.86] |
| end of treatment) | | | | |
| 8.1 Fluoxetine | 4 | 158 | Std. Mean Difference (IV, Random, 95% CI) | 0.04 [-0.27, 0.35] |
| 8.2 Sertraline | 1 | 80 | Std. Mean Difference (IV, Random, 95% CI) | 0.53 [0.08, 0.98] |
| 8.3 Citalopram | 1 | 99 | Std. Mean Difference (IV, Random, 95% CI) | 1.69 [1.23, 2.16] |
| 8.4 Escitalopram | 1 | 88 | Std. Mean Difference (IV, Random, 95% CI) | -0.07 [-0.49, 0.35] |

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

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

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| 9 Death | 46 | 3344 | Risk Ratio (M-H, Random, 95% CI) | 0.76 [0.34, 1.70] |
|-------------------------------------|----|------|---|---------------------|
| 9.1 Fluoxetine | 25 | 1502 | Risk Ratio (M-H, Random, 95% CI) | 0.78 [0.14, 4.39] |
| 9.2 Sertraline | 5 | 461 | Risk Ratio (M-H, Random, 95% CI) | 0.91 [0.20, 4.19] |
| 9.3 Citalopram | 5 | 341 | Risk Ratio (M-H, Random, 95% CI) | 0.77 [0.17, 3.38] |
| 9.4 Paroxetine | 9 | 739 | Risk Ratio (M-H, Random, 95% CI) | 0.2 [0.01, 4.01] |
| 9.5 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 4.92 [0.24, 100.25] |
| 9.6 Sertraline or fluoxetine | 1 | 184 | Risk Ratio (M-H, Random, 95% CI) | 0.2 [0.01, 4.11] |
| 10 Seizures | 7 | 444 | Risk Ratio (M-H, Random, 95% CI) | 2.67 [0.61, 11.63] |
| 10.1 Fluoxetine | 5 | 318 | Risk Ratio (M-H, Random, 95% CI) | 2.19 [0.41, 11.85] |
| 10.2 Sertraline | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.3 Citalopram | 1 | 66 | Risk Ratio (M-H, Random, 95% CI) | 5.0 [0.25, 100.32] |
| 10.4 Paroxetine | 1 | 60 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 11 Gastrointestinal side effects | 14 | 902 | Risk Ratio (M-H, Random, 95% CI) | 1.90 [0.94, 3.85] |
| 11.1 Fluoxetine | 11 | 760 | Risk Ratio (M-H, Random, 95% CI) | 1.68 [0.82, 3.42] |
| 11.2 Sertraline | 1 | 28 | Risk Ratio (M-H, Random, 95% CI) | 0.33 [0.01, 7.55] |
| 11.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 11.4 Paroxetine | 2 | 114 | Risk Ratio (M-H, Random, 95% CI) | 10.21 [1.32, 78.77] |
| 11.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 11.6 Sertraline and paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12 Bleeding | 2 | 347 | Risk Ratio (M-H, Random, 95% CI) | 1.63 [0.20, 13.05] |
| 12.1 Fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.2 Sertraline | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.4 Paroxetine | 1 | 229 | Risk Ratio (M-H, Random, 95% CI) | 3.13 [0.13, 76.10] |
| 12.5 Escitalopram | 1 | 118 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.06, 15.61] |
| 12.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 13 Change in depression scores | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| between baseline and follow-up | | | | |
| 13.1 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 14 Change in cognition between | 1 | 99 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [-0.39, 0.39] |
| baseline and end of treatment | | | | |
| 14.1 Sertraline | 1 | 99 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [-0.39, 0.39] |
| 15 Leaving the trial before the end | 49 | 3851 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.86, 1.21] |
| of scheduled follow-up | | | | |
| 15.1 Fluoxetine | 25 | 1585 | Risk Ratio (M-H, Random, 95% CI) | 1.21 [0.87, 1.67] |
| 15.2 Sertraline | 6 | 609 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.69, 1.32] |
| 15.3 Citalopram | 5 | 339 | Risk Ratio (M-H, Random, 95% CI) | 1.20 [0.41, 3.47] |
| 15.4 Paroxetine | 11 | 1017 | Risk Ratio (M-H, Random, 95% CI) | 0.88 [0.51, 1.52] |
| 15.5 Sertraline or fluoxetine | 1 | 184 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.26, 3.88] |
| 15.6 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 1.38 [0.46, 4.09] |
| 16 Motor deficits | 2 | 145 | Std. Mean Difference (IV, Random, 95% CI) | -0.33 [-1.22, 0.56] |
| 16.1 Fluoxetine | 2 | 145 | Std. Mean Difference (IV, Random, 95% CI) | -0.33 [-1.22, 0.56] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|--|-------------------|------------------------|---|----------------------|
| 1 Dependent on modified Rankin score | 1 | 94 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.02, 9.04] |
| 1.1 Sertraline | 1 | 94 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.02, 9.04] |
| 1.2 Fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Disability | 2 | 155 | Std. Mean Difference (IV, Random, 95% CI) | 1.78 [-1.01, 4.57] |
| 3 Neurological deficit score (higher score: worse outcome) | 4 | 275 | Std. Mean Difference (IV, Random, 95% CI) | -0.63 [-1.30, 0.04] |
| 3.1 Fluoxetine | 3 | 195 | Std. Mean Difference (IV, Random, 95% CI) | -0.77 [-1.61, 0.08] |
| 3.2 Sertraline | 1 | 80 | Std. Mean Difference (IV, Random, 95% CI) | -0.25 [-0.69, 0.19] |
| 4 Depression (continuous data) | 4 | 275 | Std. Mean Difference (IV, Random, 95% CI) | -1.10 [-2.16, -0.04] |
| 4.1 Fluoxetine | 3 | 195 | Std. Mean Difference (IV, Random, 95% CI) | -1.32 [-2.74, 0.11] |
| 4.2 Sertraline | 1 | 80 | Std. Mean Difference (IV, Random, 95% CI) | -0.47 [-0.91, -0.03] |
| 5 Depression (dichotomous data) | 1 | 99 | Risk Ratio (M-H, Random, 95% CI) | 0.77 [0.34, 1.76] |
| 5.1 Sertraline | 1 | 99 | Risk Ratio (M-H, Random, 95% CI) | 0.77 [0.34, 1.76] |
| 6 Cognition (higher score is better) | 1 | 80 | Std. Mean Difference (IV, Random, 95% CI) | 0.26 [-0.18, 0.70] |
| 6.1 Sertraline | 1 | 80 | Std. Mean Difference (IV, Random, 95% CI) | 0.26 [-0.18, 0.70] |
| 7 Change in cognition between | 1 | 99 | Std. Mean Difference (IV, Random, 95% CI) | 0.02 [-0.37, 0.42] |
| baseline and follow-up | | | | |
| 7.1 Sertraline | 1 | 99 | Std. Mean Difference (IV, Random, 95% CI) | 0.02 [-0.37, 0.42] |
| 8 Death | 3 | 257 | Risk Ratio (M-H, Random, 95% CI) | 0.08 [0.00, 1.41] |

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

Comparison 3. SSRI versus control (according to time since stroke when recruited)

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|--|-------------------|------------------------|---|-------------------|
| 1 Dependent on modified Rankin score | 2 | 223 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] |
| 1.1 Mean time since stroke < 2 weeks | 2 | 223 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] |
| 1.2 Mean time since stroke 2 weeks to 3 months at randomisation | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.3 Mean time since stroke 3 to 6 months at randomisation | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.4 Mean time since stroke > 6 months and < 9 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.5 Mean time since stroke at randomisation 9 to 12 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.6 Mean time since stroke not known | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Disability | 22 | 1310 | Std. Mean Difference (IV, Random, 95% CI) | 0.92 [0.62, 1.23] |

| 2.1 Mean time since stroke < 3 months | 17 | 1004 | Std. Mean Difference (IV, Random, 95% CI) | 0.77 [0.47, 1.06] |
|--|----|------|---|----------------------|
| 2.2 Mean time since stroke 3 to 6 months at randomisation | 1 | 32 | Std. Mean Difference (IV, Random, 95% CI) | 0.43 [-0.27, 1.14] |
| 2.3 Mean time since stroke > 6 months and < 9 months | 1 | 60 | Std. Mean Difference (IV, Random, 95% CI) | 2.67 [1.97, 3.38] |
| 2.4 Mean time since stroke 9 | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| to 12 months 2.5 Mean time since stroke | 3 | 214 | Std. Mean Difference (IV, Random, 95% CI) | 1.43 [0.40, 2.45] |
| not known 3 Neurological deficit score | 29 | 2011 | Std. Mean Difference (IV, Random, 95% CI) | -1.00 [-1.26, -0.75] |
| 3.1 Mean time since stroke < | 19 | 1183 | Std. Mean Difference (IV, Random, 95% CI) | -1.01 [-1.31, -0.72] |
| 3 months | | 1100 | | 1101 [1131, 01, 2] |
| 3.2 Mean time since stroke 3 to 6 months | 1 | 32 | Std. Mean Difference (IV, Random, 95% CI) | -0.27 [-0.97, 0.42] |
| 3.3 Mean time since stroke 6 to 9 months | 2 | 140 | Std. Mean Difference (IV, Random, 95% CI) | -1.40 [-3.08, 0.28] |
| 3.4 Mean time since stroke 9 to 12 months | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.5 Mean time since stroke not known | 7 | 656 | Std. Mean Difference (IV, Random, 95% CI) | -0.96 [-1.56, -0.36] |
| 4 Depression (continuous) | 39 | 2728 | Std. Mean Difference (IV, Random, 95% CI) | -1.91 [-2.34, -1.48] |
| 4.1 Time since stroke < 3 months | 27 | 1697 | Std. Mean Difference (IV, Random, 95% CI) | -1.96 [-2.54, -1.37] |
| 4.2 Time since stroke 3 to 6 months | 3 | 223 | Std. Mean Difference (IV, Random, 95% CI) | -1.16 [-2.97, 0.65] |
| 4.3 Time since stroke 6 to 9 months | 2 | 140 | Std. Mean Difference (IV, Random, 95% CI) | -1.56 [-3.99, 0.86] |
| 4.4 Time since stroke 9 to 12 months | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.5 Time since stroke not known | 7 | 668 | Std. Mean Difference (IV, Random, 95% CI) | -2.19 [-2.62, -1.76] |
| 5 Depression (dichotomous) | 8 | 771 | Risk Ratio (M-H, Random, 95% CI) | 0.43 [0.24, 0.77] |
| 5.1 Time since stroke < 3 months | 7 | 546 | Risk Ratio (M-H, Random, 95% CI) | 0.39 [0.26, 0.57] |
| 5.2 Time since stroke 3 to 6 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.3 Time since stroke 6 to 9 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.4 Time since stroke 9 to 12 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.5 Time since stroke unknown | 1 | 225 | Risk Ratio (M-H, Random, 95% CI) | 0.87 [0.76, 0.99] |
| 6 Anxiety (dichotomous) | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 6.1 Time since stroke < 3 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 6.2 Time since stroke 3 to 6 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 6.3 Time since stroke 6 to 9 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| | | | | |

| 6.4 Time since stroke 9 to 12 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
|---|----|------|--|----------------------|
| 6.5 Time from stroke onset | 0 | 0 | Did Datis (M II Data data 050/ CI) | |
| unknown | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 7 Anxiety (continuous) | 8 | 413 | Std. Mean Difference (IV, Random, 95% CI) | -0.77 [-1.52, -0.02] |
| 7.1 Time since stroke < 3 | 8 | 413 | Std. Mean Difference (IV, Random, 95% CI) | -0.77 [-1.52, -0.02] |
| months | U | 115 | | 0.77 [1.92, 0.02] |
| 7.2 Time since stroke 3 to 6 | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| months | | | | |
| 7.3 Time since stroke 6 to 9 | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| months | | | | |
| 7.4 Time since stroke 9 to 12 | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| months | | | | |
| 7.5 Time since stroke | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| unknown | | | | |
| 8 Cognition | 7 | 425 | Std. Mean Difference (IV, Random, 95% CI) | 0.32 [-0.23, 0.86] |
| 8.1 Time since stroke < 3 | 5 | 273 | Std. Mean Difference (IV, Random, 95% CI) | 0.28 [-0.57, 1.13] |
| months | | | | |
| 8.2 Time since stroke 3 to 6 | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| months | 1 | 00 | | 0.52 [0.00, 0.00] |
| 8.3 Time since stroke 6 to 9 months | 1 | 80 | Std. Mean Difference (IV, Random, 95% CI) | 0.53 [0.08, 0.98] |
| 8.4 Time since stroke 9 to 12 | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | |
| months | 0 | 0 | Std. Mean Difference (IV, Kandolli, 95% CI) | 0.0 [0.0, 0.0] |
| 8.5 Time since stroke | 1 | 72 | Std. Mean Difference (IV, Random, 95% CI) | 0.23 [-0.23, 0.69] |
| unknown | 1 | 72 | otd. Wear Difference (17, Randolli, 9976 Ci) | 0.25 [0.25, 0.05] |
| 9 Death | 46 | 3404 | Risk Ratio (M-H, Random, 95% CI) | 0.76 [0.34, 1.70] |
| 9.1 Time since stroke < 3 | 34 | 2311 | Risk Ratio (M-H, Random, 95% CI) | 0.94 [0.38, 2.36] |
| months | | | | |
| 9.2 Time since stroke 3 to 6 | 4 | 369 | Risk Ratio (M-H, Random, 95% CI) | 0.20 [0.01, 4.02] |
| months | | | | |
| 9.3 Time since stroke 6 to 9 | 2 | 140 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| months | | | | |
| 9.4 Time since stroke 9 to 12 | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| months | | | | |
| 9.5 Time since stroke | 7 | 584 | Risk Ratio (M-H, Random, 95% CI) | 0.49 [0.07, 3.65] |
| unknown | - | | | |
| 10 Seizure | 7 | 444 | Risk Ratio (M-H, Random, 95% CI) | 2.67 [0.61, 11.63] |
| 10.1 Time since stroke < 3 | 6 | 409 | Risk Ratio (M-H, Random, 95% CI) | 2.22 [0.41, 12.06] |
| months 10.2 Time since stroke 3 to 6 | 1 | 25 | Disk Datio (MH Dandam 0504 CI) | 474 [0 24 02 07] |
| months | 1 | 35 | Risk Ratio (M-H, Random, 95% CI) | 4.74 [0.24, 92.07] |
| 10.3 Time since stroke 6 to 9 | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| months | 0 | 0 | | 0.0 [0.0, 0.0] |
| 10.4 Time since stroke 9 to | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12 months | Ũ | 0 | | 0.0 [0.0, 0.0] |
| 10.5 Time since stroke | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| unknown | | | | 4 |
| 11 Gastrointestinal side effects | 14 | 902 | Risk Ratio (M-H, Random, 95% CI) | 1.90 [0.94, 3.85] |
| 11.1 Time since stroke < 3 | 11 | 767 | Risk Ratio (M-H, Random, 95% CI) | 1.92 [0.83, 4.45] |
| months | | | | |
| | | | | |

| 11.2 Time since stroke 3 to 6 | 1 | 35 | Risk Ratio (M-H, Random, 95% CI) | 4.74 [0.24, 92.07] |
|-----------------------------------|----|------|---|----------------------|
| months | | | | |
| 11.3 Time since stroke 6 to 9 | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| months | | | | |
| 11.4 Time since stroke 9 to | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12 months | | | | |
| 11.5 Time since stroke unknown | 2 | 100 | Risk Ratio (M-H, Random, 95% CI) | 1.51 [0.14, 16.29] |
| 12 Leaving the trial early | 49 | 3851 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.86, 1.21] |
| 12.1 Time since stroke < 3 | 34 | 2435 | Risk Ratio (M-H, Random, 95% CI) | 1.12 [0.90, 1.40] |
| months | | | | |
| 12.2 Time since stroke 3 to 6 | 3 | 246 | Risk Ratio (M-H, Random, 95% CI) | 0.83 [0.59, 1.19] |
| months | | | | |
| 12.3 Time since stroke 6 to 9 | 2 | 140 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| months | | | | |
| 12.4 Time since stroke 9 to | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12 months | | | | |
| 12.5 Time since stroke not | 10 | 1030 | Risk Ratio (M-H, Random, 95% CI) | 0.97 [0.62, 1.51] |
| known | | | | |
| 13 Bleeding | 2 | 347 | Risk Ratio (M-H, Random, 95% CI) | 1.63 [0.20, 13.05] |
| 13.1 Time since stroke < 3 | 1 | 118 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.06, 15.61] |
| months | | | | |
| 13.2 Time since stroke not | 1 | 229 | Risk Ratio (M-H, Random, 95% CI) | 3.13 [0.13, 76.10] |
| known | | | | |
| 14 Motor deficits | 2 | 145 | Std. Mean Difference (IV, Random, 95% CI) | -0.33 [-1.22, 0.56] |
| 14.1 < 3 months | 1 | 113 | Std. Mean Difference (IV, Random, 95% CI) | -0.74 [-1.12, -0.35] |
| 14.2 3 to 6 months | 1 | 32 | Std. Mean Difference (IV, Random, 95% CI) | 0.18 [-0.52, 0.87] |

Comparison 4. SSRI versus control according to depression at time of recruitment

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|--|-------------------|------------------------|---|----------------------|
| 1 Modified Rankin score | 2 | 223 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] |
| 1.1 Had to have depression at recruitment | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.2 Did not have to have depression at recruitment | 2 | 223 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] |
| 2 Disability | 22 | 1310 | Std. Mean Difference (IV, Random, 95% CI) | 0.92 [0.62, 1.23] |
| 2.1 Had to have depression at recruitment | 15 | 986 | Std. Mean Difference (IV, Random, 95% CI) | 1.11 [0.71, 1.51] |
| 2.2 Did not have to have depression at onset | 7 | 324 | Std. Mean Difference (IV, Random, 95% CI) | 0.55 [0.27, 0.84] |
| 3 Neurological deficit score | 29 | 2011 | Std. Mean Difference (IV, Random, 95% CI) | -1.00 [-1.26, -0.75] |
| 3.1 Had to have depression at recruitment | 19 | 1420 | Std. Mean Difference (IV, Random, 95% CI) | -1.19 [-1.47, -0.91] |
| 3.2 Did not have to have depression at recruitment | 10 | 591 | Std. Mean Difference (IV, Random, 95% CI) | -0.63 [-1.08, -0.17] |
| 4 Depression (continuous) | 39 | 2728 | Std. Mean Difference (IV, Random, 95% CI) | -1.91 [-2.34, -1.48] |

| 4.1 Had to have depression at recruitment | 31 | 2256 | Std. Mean Difference (IV, Random, 95% CI) | -2.06 [-2.54, -1.58] |
|---|---|------------|--|---|
| 4.2 Did not have to have | 8 | 472 | Std. Mean Difference (IV, Random, 95% CI) | -1.35 [-2.35, -0.36] |
| depression at recruitment | 0 | 4/2 | Std. Mean Difference (17, Kandolli, 9970 CI) | -1.5) [-2.5), -0.50] |
| 5 Depression (dichotomous) | 8 | 771 | Risk Ratio (M-H, Random, 95% CI) | 0.43 [0.24, 0.77] |
| 5.1 Had to have depression at | 2 | 288 | Risk Ratio (M-H, Random, 95% CI) | 0.66 [0.30, 1.46] |
| recruitment | 2 | 200 | | 0.00 [0.30, 1.10] |
| 5.2 Did not have to have | 6 | 483 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.25, 0.59] |
| depression at recruitment | , i i i i i i i i i i i i i i i i i i i | | | |
| 6 Anxiety (continuous) | 8 | 413 | Std. Mean Difference (IV, Random, 95% CI) | -0.77 [-1.52, -0.02] |
| 6.1 Had to have depression at | 5 | 271 | Std. Mean Difference (IV, Random, 95% CI) | -1.10 [-2.32, 0.12] |
| recruitment | | | | |
| 6.2 Did not have to have | 3 | 142 | Std. Mean Difference (IV, Random, 95% CI) | -0.28 [-0.85, 0.29] |
| depression at recruitment | | | | |
| 7 Anxiety (dichotomous) | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 7.1 Had to have depression at | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| recruitment | | | | |
| 7.2 Did not have to have | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| depression at baseline | | | | |
| 8 Cognition | 7 | 425 | Std. Mean Difference (IV, Random, 95% CI) | 0.32 [-0.23, 0.86] |
| 8.1 Had to have depression at | 5 | 309 | Std. Mean Difference (IV, Random, 95% CI) | 0.48 [-0.21, 1.17] |
| recruitment | | | | |
| 8.2 Did not have to have | 2 | 116 | Std. Mean Difference (IV, Random, 95% CI) | -0.08 [-0.45, 0.28] |
| depression at recruitment | | | | |
| 9 Death | 46 | 3344 | Risk Ratio (M-H, Random, 95% CI) | 0.76 [0.34, 1.70] |
| 9.1 Had to have depression at recruitment | 32 | 2468 | Risk Ratio (M-H, Random, 95% CI) | 0.53 [0.18, 1.54] |
| 9.2 Did not have to have | 14 | 876 | Risk Ratio (M-H, Random, 95% CI) | 1.22 [0.36, 4.13] |
| depression at recruitment | | | | |
| 10 Seizures | 7 | 444 | Risk Ratio (M-H, Random, 95% CI) | 2.67 [0.61, 11.63] |
| 10.1 Had to have depression at recruitment | 4 | 220 | Risk Ratio (M-H, Random, 95% CI) | 1.97 [0.27, 14.55] |
| 10.2 Did not have to have | 3 | 224 | Risk Ratio (M-H, Random, 95% CI) | 3.83 [0.44, 33.53] |
| depression at recruitment | | | | |
| 11 Gastrointestinal side effects | 14 | 902 | Risk Ratio (M-H, Random, 95% CI) | 1.90 [0.94, 3.85] |
| 11.1 Had to have depression | 8 | 523 | Risk Ratio (M-H, Random, 95% CI) | 1.72 [0.58, 5.12] |
| at recruitment | | | | |
| 11.2 Did not have to have | 6 | 379 | Risk Ratio (M-H, Random, 95% CI) | 2.53 [1.18, 5.42] |
| depression at recruitment | 10 | | | |
| 12 Leaving the trial early | 49 | 3851 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.86, 1.21] |
| 12.1 Had to have depression | 35 | 2860 | Risk Ratio (M-H, Random, 95% CI) | 0.97 [0.77, 1.21] |
| at recruitment | | | | |
| 12.2 Did not have to have | 14 | 991 | Risk Ratio (M-H, Random, 95% CI) | 1.10 [0.84, 1.44] |
| depression at entry | 2 | 2/7 | | 1 (2 [0 20 12 05] |
| 13 Bleeding | 2 | 347 | Risk Ratio (M-H, Random, 95% CI) | 1.63 [0.20, 13.05] |
| 13.1 Depression at onset 13.2 No depression at onset | 1 1 | 229 118 | Risk Ratio (M-H, Random, 95% CI) Risk Ratio (M-H, Random, 95% CI) | 3.13 [0.13, 76.10] 1.0 [0.06, 15.61] |
| 14 Motor deficits | 2 | 118 145 | Std. Mean Difference (IV, Random, 95% CI) | -0.33 [-1.22, 0.56] |
| 14.1 No depression at onset | 2 | 145 | Std. Mean Difference (IV, Random, 95% CI) | -0.33 [-1.22, 0.56] |
| 14.2 Depression at onset | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| . 1.2 Depression at onset | 5 | v | sta. mean Emerence (17, Nandoni, 77/0 CI) | 0.0 [0.0, 0.0] |

| Comparison 5. | SSRI versus control, | end of treatment, | , randomisation: | low risk of bias |
|---------------|----------------------|-------------------|------------------|------------------|
|---------------|----------------------|-------------------|------------------|------------------|

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|----------------------------------|-------------------|------------------------|--|--|
| 1 Dependent on modified Rankin | 2 | 223 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] |
| score (mRS 3 to 5) | | | | |
| 1.1 Fluoxetine | 1 | 112 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] |
| 1.2 Sertraline | 1 | 111 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Disability | 7 | 325 | Std. Mean Difference (IV, Random, 95% CI) | 0.39 [0.15, 0.63] |
| 2.1 Fluoxetine | 6 | 305 | Std. Mean Difference (IV, Random, 95% CI) | 0.38 [0.11, 0.66] |
| 2.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.3 Citalopram | 1 | 20 | Std. Mean Difference (IV, Random, 95% CI) | 0.25 [-0.63, 1.13] |
| 2.4 Paroxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.5 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.6 Sertraline or fluoxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Neurological deficit score | 10 | 649 | Std. Mean Difference (IV, Random, 95% CI) | -0.72 [-1.11, -0.33] |
| 3.1 Fluoxetine | 5 | 362 | Std. Mean Difference (IV, Random, 95% CI) | -0.52 [-0.89, -0.15] |
| 3.2 Sertraline | 2 | 108 | Std. Mean Difference (IV, Random, 95% CI) | -0.26 [-0.96, 0.45] |
| 3.3 Citalopram | 3 | 179 | Std. Mean Difference (IV, Random, 95% CI) | -1.43 [-2.25, -0.60] |
| 3.4 Paroxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.5 Fluoxetine or sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Depression (continuous data) | 10 | 647 | Std. Mean Difference (IV, Random, 95% CI) | -0.17 [-0.61, 0.28] |
| 4.1 Fluoxetine | 6 | 374 | Std. Mean Difference (IV, Random, 95% CI) | -0.38 [-0.91, 0.16] |
| 4.2 Sertraline | 3 | 253 | Std. Mean Difference (IV, Random, 95% CI) | 0.28 [-0.63, 1.20] |
| 4.3 Citalopram | 1 | 20 | Std. Mean Difference (IV, Random, 95% CI) | -0.40 [-1.29, 0.48] |
| 4.4 Paroxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.5 Fluoxetine or sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Depression (dichotomous data) | 3 | 283 | Risk Ratio (M-H, Random, 95% CI) | 0.50 [0.27, 0.92] |
| 5.1 Fluoxetine | 1 | 67 | Risk Ratio (M-H, Random, 95% CI) | 0.26 [0.06, 1.12] |
| 5.2 Sertraline | 1 | 99 | Risk Ratio (M-H, Random, 95% CI) | 0.77 [0.34, 1.76] |
| 5.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.5 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.14, 0.99] |
| 6 Anxiety (continuous data) | 3 | 115 | Std. Mean Difference (IV, Random, 95% CI) | -0.40 [-0.85, 0.05] |
| 6.1 Fluoxetine | 3 | 115 | Std. Mean Difference (IV, Random, 95% CI) | -0.40 [-0.85, 0.05] |
| 6.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 6.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 6.4 Paroxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 6.5 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 7 Anxiety (dichotomous data) | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 8 Cognition (continuous scores | 4 | 223 | Std. Mean Difference (IV, Random, 95% CI) | 0.16 [-0.18, 0.49] |
| end of treatment) | 4 | 223 | Std. Mean Difference (1V, Randolli, 9970 CI) | 0.10 [-0.18, 0.49] |
| 8.1 Fluoxetine | 2 | 55 | Std. Mean Difference (IV, Random, 95% CI) | 0.03 [-0.50, 0.56] |
| 8.2 Sertraline | 1 | 80 | Std. Mean Difference (IV, Random, 95% CI) Std. Mean Difference (IV, Random, 95% CI) | 0.53 [0.08, 0.98] |
| 8.3 Citalopram | 0 | 80 0 | Std. Mean Difference (IV, Random, 95% CI) Std. Mean Difference (IV, Random, 95% CI) | 0.05 [0.08, 0.98] |
| 8.4 Escitalopram | 0 | 88 | Std. Mean Difference (IV, Random, 95% CI) Std. Mean Difference (IV, Random, 95% CI) | -0.07 [-0.49, 0.35] |
| 9 Death | 13 | 88 920 | Risk Ratio (M-H, Random, 95% CI) | 1.06 [0.36, 3.09] |
| 9.1 Fluoxetine | 13 7 | 920 452 | Risk Ratio (M-H, Random, 95% CI) Risk Ratio (M-H, Random, 95% CI) | 0.78 [0.14, 4.39] |
| 9.1 Fluoxetine 9.2 Sertraline | 4 | 432 331 | Risk Ratio (M-H, Random, 95% CI) Risk Ratio (M-H, Random, 95% CI) | 0.78 [0.14, 4.59] 0.91 [0.20, 4.19] |
| 9.2 Sertraine 9.3 Citalopram | 4 | 20 | Risk Ratio (M-H, Random, 95% CI) Risk Ratio (M-H, Random, 95% CI) | 0.91 [0.20, 4.19] |
| 9.4 Paroxetine | | | | |
| 7.4 l'aroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |

| 9.5 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 4.92 [0.24, 100.25] |
|-------------------------------------|----|------|---|---------------------|
| 9.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10 Seizures | 1 | 118 | Risk Ratio (M-H, Random, 95% CI) | 3.0 [0.12, 72.18] |
| 10.1 Fluoxetine | 1 | 118 | Risk Ratio (M-H, Random, 95% CI) | 3.0 [0.12, 72.18] |
| 10.2 Sertraline | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 11 Gastrointestinal side effects | 5 | 363 | Risk Ratio (M-H, Random, 95% CI) | 1.92 [0.98, 3.77] |
| 11.1 Fluoxetine | 4 | 335 | Risk Ratio (M-H, Random, 95% CI) | 2.09 [1.05, 4.18] |
| 11.2 Sertraline | 1 | 28 | Risk Ratio (M-H, Random, 95% CI) | 0.33 [0.01, 7.55] |
| 11.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 11.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 11.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 11.6 Sertraline and paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12 Bleeding | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.1 Fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.2 Sertraline | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 13 Change in depression scores | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| between baseline and follow-up | | | | |
| 13.1 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 14 Change in cognition between | 1 | 99 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [-0.39, 0.39] |
| baseline and end of treatment | | | | |
| 14.1 Sertraline | 1 | 99 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [-0.39, 0.39] |
| 15 Leaving the trial before the end | 15 | 1168 | Risk Ratio (M-H, Random, 95% CI) | 0.99 [0.80, 1.23] |
| of scheduled follow-up | - | | | |
| 15.1 Fluoxetine | 8 | 552 | Risk Ratio (M-H, Random, 95% CI) | 1.16 [0.72, 1.89] |
| 15.2 Sertraline | 5 | 479 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.69, 1.32] |
| 15.3 Citalopram | 1 | 20 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 15.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 15.5 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 15.6 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 1.38 [0.46, 4.09] |
| 16 Bleeding | 1 | 118 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.06, 15.61] |

Comparison 6. SSRI versus control at end of treatment, concealment of allocation: low risk

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|--|-------------------|------------------------|---|--------------------|
| 1 Dependent on modified Rankin score (mRS 3 to 5) | 2 | 223 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] |
| 1.1 Fluoxetine | 1 | 112 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] |
| 1.2 Sertraline | 1 | 111 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Disability | 3 | 115 | Std. Mean Difference (IV, Random, 95% CI) | 0.70 [-0.73, 2.13] |
| 2.1 Fluoxetine | 2 | 55 | Std. Mean Difference (IV, Random, 95% CI) | 0.01 [-0.54, 0.56] |

| 2.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
|----------------------------------|---|-----|---|----------------------|
| 2.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.4 Paroxetine | 1 | 60 | Std. Mean Difference (IV, Random, 95% CI) | 2.04 [1.41, 2.67] |
| 2.5 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.6 Sertraline or fluoxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Neurological deficit score | 4 | 289 | Std. Mean Difference (IV, Random, 95% CI) | -0.94 [-1.63, -0.26] |
| 3.1 Fluoxetine | 3 | 229 | Std. Mean Difference (IV, Random, 95% CI) | -0.68 [-1.30, -0.06] |
| 3.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.4 Paroxetine | 1 | 60 | Std. Mean Difference (IV, Random, 95% CI) | -1.76 [-2.36, -1.15] |
| 3.5 Fluoxetine or sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Depression (continuous data) | 7 | 464 | Std. Mean Difference (IV, Random, 95% CI) | -0.72 [-1.52, 0.07] |
| 4.1 Fluoxetine | 4 | 215 | Std. Mean Difference (IV, Random, 95% CI) | -0.01 [-0.54, 0.53] |
| 4.2 Sertraline | 1 | 123 | Std. Mean Difference (IV, Random, 95% CI) | -0.16 [-0.52, 0.19] |
| 4.3 Citalopram | 1 | 66 | Std. Mean Difference (IV, Random, 95% CI) | -0.54 [-1.04, -0.05] |
| 4.4 Paroxetine | 1 | 60 | Std. Mean Difference (IV, Random, 95% CI) | -5.32 [-6.43, -4.21] |
| 4.5 Fluoxetine or sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Depression (dichotomous data) | 2 | 166 | Risk Ratio (M-H, Random, 95% CI) | 0.53 [0.19, 1.49] |
| 5.1 Fluoxetine | 1 | 67 | Risk Ratio (M-H, Random, 95% CI) | 0.26 [0.06, 1.12] |
| 5.2 Sertraline | 1 | 99 | Risk Ratio (M-H, Random, 95% CI) | 0.77 [0.34, 1.76] |
| 5.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 6 Anxiety (continuous data) | 3 | 115 | Std. Mean Difference (IV, Random, 95% CI) | -0.66 [-1.74, 0.42] |
| 6.1 Fluoxetine | 2 | 55 | Std. Mean Difference (IV, Random, 95% CI) | -0.13 [-0.66, 0.40] |
| 6.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 6.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 6.4 Paroxetine | 1 | 60 | Std. Mean Difference (IV, Random, 95% CI) | -1.67 [-2.26, -1.08] |
| 6.5 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 7 Anxiety (dichotomous data) | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 8 Cognition (continuous scores | 2 | 55 | Std. Mean Difference (IV, Random, 95% CI) | 0.03 [-0.50, 0.56] |
| end of treatment) | | | | |
| 8.1 Fluoxetine | 2 | 55 | Std. Mean Difference (IV, Random, 95% CI) | 0.03 [-0.50, 0.56] |
| 8.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 8.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 8.4 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| 9 Death | 9 | 651 | Risk Ratio (M-H, Random, 95% CI) | 0.87 [0.30, 2.50] |
| 9.1 Fluoxetine | 5 | 302 | Risk Ratio (M-H, Random, 95% CI) | 0.78 [0.14, 4.39] |
| 9.2 Sertraline | 2 | 223 | Risk Ratio (M-H, Random, 95% CI) | 0.79 [0.08, 8.19] |
| 9.3 Citalopram | 1 | 66 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.15, 6.68] |
| 9.4 Paroxetine | 1 | 60 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 9.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 9.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10 Seizures | 3 | 244 | Risk Ratio (M-H, Random, 95% CI) | 3.93 [0.44, 34.85] |
| 10.1 Fluoxetine | 1 | 118 | Risk Ratio (M-H, Random, 95% CI) | 3.0 [0.12, 72.18] |
| 10.2 Sertraline | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 10.3 Citalopram | 1 | 66 | Risk Ratio (M-H, Random, 95% CI) | 5.0 [0.25, 100.32] |
| 10.4 Paroxetine | 1 | 60 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 11 Gastrointestinal side effects | 2 | 178 | Risk Ratio (M-H, Random, 95% CI) | 2.48 [1.06, 5.80] |
| 11.1 Fluoxetine | 1 | 118 | Risk Ratio (M-H, Random, 95% CI) | 2.33 [0.96, 5.66] |
| | | | | |

| 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
|---|--|--|---|
| 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1 | 60 | Risk Ratio (M-H, Random, 95% CI) | 5.0 [0.25, 99.95] |
| 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| | | | |
| 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1 | 99 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [-0.39, 0.39] |
| | | | |
| 1 | 99 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [-0.39, 0.39] |
| 9 | 673 | Risk Ratio (M-H, Random, 95% CI) | 1.21 [0.75, 1.95] |
| | | | |
| 5 | 312 | Risk Ratio (M-H, Random, 95% CI) | 1.11 [0.58, 2.11] |
| 2 | 234 | Risk Ratio (M-H, Random, 95% CI) | 1.10 [0.47, 2.54] |
| 1 | 66 | Risk Ratio (M-H, Random, 95% CI) | 6.00 [0.76, 47.14] |
| 1 | 61 | Risk Ratio (M-H, Random, 95% CI) | 3.10 [0.13, 73.16] |
| 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| | $ \begin{array}{c} 0\\ 1\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 1\\ 1\\ 9\\ 5\\ 2\\ 1\\ 1\\ 0\\ 0\\ 0 \end{array} $ | $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 0 0 Risk Ratio (M-H, Random, 95% CI) 1 60 Risk Ratio (M-H, Random, 95% CI) 0 0 Std. Mean Difference (IV, Random, 95% CI) 1 99 Std. Mean Difference (IV, Random, 95% CI) 1 99 Std. Mean Difference (IV, Random, 95% CI) 2 234 Risk Ratio (M-H, Random, 95% CI) 5 312 Risk Ratio (M-H, Random, 95% CI) 1 66 Risk Ratio (M-H, Random, |

Comparison 7. SSRI versus control at end of treatment, patient/personnel blind: low risk of bias

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|--|-------------------|------------------------|---|----------------------|
| 1 Dependent on modified Rankin score (mRS 3 to 5) | 2 | 223 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] |
| 1.1 Fluoxetine | 1 | 112 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] |
| 1.2 Sertraline | 1 | 111 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Disability | 7 | 297 | Std. Mean Difference (IV, Random, 95% CI) | 0.36 [0.12, 0.59] |
| 2.1 Fluoxetine | 6 | 277 | Std. Mean Difference (IV, Random, 95% CI) | 0.35 [0.08, 0.61] |
| 2.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.3 Citalopram | 1 | 20 | Std. Mean Difference (IV, Random, 95% CI) | 0.25 [-0.63, 1.13] |
| 2.4 Paroxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.5 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.6 Sertraline or fluoxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Neurological deficit score | 6 | 315 | Std. Mean Difference (IV, Random, 95% CI) | -0.32 [-0.55, -0.10] |
| 3.1 Fluoxetine | 4 | 267 | Std. Mean Difference (IV, Random, 95% CI) | -0.35 [-0.59, -0.11] |
| 3.2 Sertraline | 1 | 28 | Std. Mean Difference (IV, Random, 95% CI) | 0.17 [-0.57, 0.91] |
| 3.3 Citalopram | 1 | 20 | Std. Mean Difference (IV, Random, 95% CI) | -0.68 [-1.59, 0.23] |
| 3.4 Paroxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| 3.5 Fluoxetine or sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |

| 4 Depression (continuous data) | 11 | 646 | Std. Mean Difference (IV, Random, 95% CI) | -0.40 [-0.71, -0.09] |
|----------------------------------|-----|-----|--|----------------------|
| 4.1 Fluoxetine | 8 | 437 | Std. Mean Difference (IV, Random, 95% CI) | -0.40 [-0.71, -0.09] |
| 4.2 Sertraline | 1 | 123 | Std. Mean Difference (IV, Random, 95% CI) | -0.16 [-0.52, 0.19] |
| 4.3 Citalopram | 2 | 86 | Std. Mean Difference (IV, Random, 95% CI) | -0.51 [-0.94, -0.08] |
| 4.4 Paroxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.5 Fluoxetine or sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Depression (dichotomous data) | 3 | 283 | Risk Ratio (M-H, Random, 95% CI) | 0.52 [0.30, 0.90] |
| 5.1 Fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.2 Sertraline | 2 | 166 | Risk Ratio (M-H, Random, 95% CI) | 0.59 [0.28, 1.25] |
| 5.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.5 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.14, 0.99] |
| 6 Anxiety (continuous data) | 2 | 55 | Std. Mean Difference (IV, Random, 95% CI) | -0.13 [-0.66, 0.40] |
| 6.1 Fluoxetine | 2 | 55 | Std. Mean Difference (IV, Random, 95% CI) Std. Mean Difference (IV, Random, 95% CI) | |
| 6.2 Sertraline | 2 0 | 0 | | -0.13 [-0.66, 0.40] |
| | 0 | | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 6.3 Citalopram 6.4 Paroxetine | | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 6.5 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 7 Anxiety (dichotomous data) | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 8 Cognition (continuous scores | 4 | 174 | Std. Mean Difference (IV, Random, 95% CI) | -0.10 [-0.39, 0.20] |
| end of treatment) | | 26 | | |
| 8.1 Fluoxetine | 3 | 86 | Std. Mean Difference (IV, Random, 95% CI) | -0.12 [-0.55, 0.30] |
| 8.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 8.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 8.4 Escitalopram | 1 | 88 | Std. Mean Difference (IV, Random, 95% CI) | -0.07 [-0.49, 0.35] |
| 9 Death | 14 | 865 | Risk Ratio (M-H, Random, 95% CI) | 1.05 [0.41, 2.66] |
| 9.1 Fluoxetine | 8 | 411 | Risk Ratio (M-H, Random, 95% CI) | 0.78 [0.14, 4.39] |
| 9.2 Sertraline | 3 | 251 | Risk Ratio (M-H, Random, 95% CI) | 0.91 [0.20, 4.19] |
| 9.3 Citalopram | 2 | 86 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.15, 6.68] |
| 9.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 9.5 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 4.92 [0.24, 100.25] |
| 9.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10 Seizures | 4 | 250 | Risk Ratio (M-H, Random, 95% CI) | 2.67 [0.61, 11.63] |
| 10.1 Fluoxetine | 3 | 184 | Risk Ratio (M-H, Random, 95% CI) | 2.19 [0.41, 11.85] |
| 10.2 Sertraline | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 10.3 Citalopram | 1 | 66 | Risk Ratio (M-H, Random, 95% CI) | 5.0 [0.25, 100.32] |
| 10.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 10.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 10.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 11 Gastrointestinal side effects | 5 | 303 | Risk Ratio (M-H, Random, 95% CI) | 1.37 [0.63, 2.98] |
| 11.1 Fluoxetine | 4 | 275 | Risk Ratio (M-H, Random, 95% CI) | 1.48 [0.65, 3.39] |
| 11.2 Sertraline | 1 | 28 | Risk Ratio (M-H, Random, 95% CI) | 0.33 [0.01, 7.55] |
| 11.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 11.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 11.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 11.6 Sertraline and paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 12 Bleeding | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 12.1 Fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 12.2 Sertraline | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 12.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| 12.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| | | | | |

| 12.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
|-------------------------------------|----|------|---|----------------------|
| 13 Change in depression scores | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| between baseline and follow-up | | | | |
| 13.1 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| 14 Change in cognition between | 1 | 99 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [-0.39, 0.39] |
| baseline and end of treatment | | | | |
| 14.1 Sertraline | 1 | 99 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [-0.39, 0.39] |
| 15 Leaving the trial before the end | 16 | 1111 | Risk Ratio (M-H, Random, 95% CI) | 1.05 [0.82, 1.36] |
| of scheduled follow-up | | | | |
| 15.1 Fluoxetine | 9 | 509 | Risk Ratio (M-H, Random, 95% CI) | 1.19 [0.74, 1.92] |
| 15.2 Sertraline | 4 | 399 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.69, 1.32] |
| 15.3 Citalopram | 2 | 86 | Risk Ratio (M-H, Random, 95% CI) | 6.00 [0.76, 47.14] |
| 15.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| 15.5 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| 15.6 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 1.38 [0.46, 4.09] |

Comparison 8. SSRI versus control at end of treatment, outcome assessor blind: low risk of bias

| No. ofOutcome or subgroup titlestudies | | No. of participants | Statistical method | Effect size |
|--|----|------------------------|---|----------------------|
| 1 Dependent on modified Rankin | 2 | 223 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] |
| score (mRS 3 to 5) | | | | |
| 1.1 Fluoxetine | 1 | 112 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] |
| 1.2 Sertraline | 1 | 111 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Disability | 4 | 239 | Std. Mean Difference (IV, Random, 95% CI) | 0.87 [0.16, 1.58] |
| 2.1 Fluoxetine | 2 | 159 | Std. Mean Difference (IV, Random, 95% CI) | 0.57 [0.24, 0.90] |
| 2.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.3 Citalopram | 1 | 20 | Std. Mean Difference (IV, Random, 95% CI) | 0.25 [-0.63, 1.13] |
| 2.4 Paroxetine | 1 | 60 | Std. Mean Difference (IV, Random, 95% CI) | 2.04 [1.41, 2.67] |
| 2.5 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.6 Sertraline or fluoxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Neurological deficit score | 8 | 640 | Std. Mean Difference (IV, Random, 95% CI) | -0.76 [-1.15, -0.38] |
| 3.1 Fluoxetine | 4 | 306 | Std. Mean Difference (IV, Random, 95% CI) | -0.41 [-0.63, -0.18] |
| 3.2 Sertraline | 1 | 80 | Std. Mean Difference (IV, Random, 95% CI) | -0.56 [-1.01, -0.11] |
| 3.3 Citalopram | 1 | 20 | Std. Mean Difference (IV, Random, 95% CI) | -0.68 [-1.59, 0.23] |
| 3.4 Paroxetine | 1 | 60 | Std. Mean Difference (IV, Random, 95% CI) | -1.76 [-2.36, -1.15] |
| 3.5 Fluoxetine or sertraline | 1 | 174 | Std. Mean Difference (IV, Random, 95% CI) | -1.40 [-1.73, -1.06] |
| 4 Depression (continuous data) | 10 | 741 | Std. Mean Difference (IV, Random, 95% CI) | -1.39 [-2.10, -0.68] |
| 4.1 Fluoxetine | 5 | 390 | Std. Mean Difference (IV, Random, 95% CI) | -1.01 [-1.69, -0.34] |
| 4.2 Sertraline | 2 | 203 | Std. Mean Difference (IV, Random, 95% CI) | -0.23 [-0.51, 0.04] |
| 4.3 Citalopram | 2 | 88 | Std. Mean Difference (IV, Random, 95% CI) | -1.85 [-4.65, 0.96] |
| 4.4 Paroxetine | 1 | 60 | Std. Mean Difference (IV, Random, 95% CI) | -5.32 [-6.43, -4.21] |
| 4.5 Fluoxetine or sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Depression (dichotomous data) | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.14, 0.99] |
| 5.1 Fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 5.2 Sertraline | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.5 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.14, 0.99] |

| 6 Anxiety (continuous data) | 1 | 60 | Std. Mean Difference (IV, Random, 95% CI) | -1.67 [-2.26, -1.08] |
|--|----|-----|--|----------------------|
| 6.1 Fluoxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 6.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| 6.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| 6.4 Paroxetine | 1 | 60 | Std. Mean Difference (IV, Random, 95% CI) | -1.67 [-2.26, -1.08] |
| 6.5 escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 7 Anxiety (dichotomous data) | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| 8 Cognition (continuous scores | 2 | 168 | Std. Mean Difference (IV, Random, 95% CI) | 0.21 [-0.36, 0.78] |
| end of treatment) | | | | |
| 8.1 Fluoxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| 8.2 Sertraline | 1 | 80 | Std. Mean Difference (IV, Random, 95% CI) | 0.51 [0.06, 0.95] |
| 8.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 8.4 Escitalopram | 1 | 88 | Std. Mean Difference (IV, Random, 95% CI) | -0.07 [-0.49, 0.35] |
| 9 Death | 11 | 833 | Risk Ratio (M-H, Random, 95% CI) | 1.13 [0.25, 4.97] |
| 9.1 Fluoxetine | 5 | 343 | Risk Ratio (M-H, Random, 95% CI) | 1.28 [0.16, 10.11] |
| 9.2 Sertraline | 2 | 203 | Risk Ratio (M-H, Random, 95% CI) | 0.20 [0.01, 4.02] |
| 9.3 Citalopram | 2 | 110 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| 9.4 Paroxetine | 1 | 60 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 9.5 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 4.92 [0.24, 100.25] |
| 9.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10 Seizures | 3 | 249 | Risk Ratio (M-H, Random, 95% CI) | 3.0 [0.12, 72.18] |
| 10.1 Fluoxetine | 2 | 189 | Risk Ratio (M-H, Random, 95% CI) | 3.0 [0.12, 72.18] |
| 10.2 Sertraline | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.4 Paroxetine | 1 | 60 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 11 Gastrointestinal side effects | 5 | 367 | Risk Ratio (M-H, Random, 95% CI) | 1.74 [0.87, 3.49] |
| 11.1 Fluoxetine | 3 | 279 | Risk Ratio (M-H, Random, 95% CI) | 1.77 [0.81, 3.85] |
| 11.2 Sertraline | 1 | 28 | Risk Ratio (M-H, Random, 95% CI) | 0.33 [0.01, 7.55] |
| 11.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 11.4 Paroxetine | 1 | 60 | Risk Ratio (M-H, Random, 95% CI) | 5.0 [0.25, 99.95] |
| 11.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 11.6 Sertraline and paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12 Bleeding | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.1 Fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.2 Sertraline | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.2 Sertraine 12.3 Citalopram | 0 | 0 | | 0.0 [0.0, 0.0] |
| 12.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 12.5 Escitalopram 12.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| | | | | |
| 13 Change in depression scores | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| between baseline and follow-up | 0 | 0 | | 0.0.[0.0.0.0] |
| 13.1 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 14 Change in cognition between | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| baseline and end of treatment | | | | |
| 14.1 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 15 Leaving the trial before the end | 12 | 947 | Risk Ratio (M-H, Random, 95% CI) | 0.94 [0.71, 1.24] |
| of scheduled follow-up | | | | |
| 15.1 Fluoxetine | 6 | 456 | Risk Ratio (M-H, Random, 95% CI) | 1.07 [0.65, 1.76] |
| 15.2 Sertraline | 2 | 203 | Risk Ratio (M-H, Random, 95% CI) | 0.79 [0.53, 1.18] |
| 15.3 Citalopram | 2 | 110 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.48, 2.07] |
| | | | | |

| 15.4 Paroxetine | 1 | 61 | Risk Ratio (M-H, Random, 95% CI) | 3.10 [0.13, 73.16] |
|-------------------------------|---|-----|----------------------------------|--------------------|
| 15.5 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 15.6 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 1.38 [0.46, 4.09] |

Comparison 9. SSRI versus control at end of treatment, incomplete outcome data: low risk of bias

| Outcome or subgroup title | | | Statistical method | Effect size | |
|---------------------------------|----|------|---|----------------------|--|
| 1 Dependent on modified Rankin | | | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] | |
| score (mRS 3 to 5) | | | | | |
| 1.1 Fluoxetine | 1 | 112 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] | |
| 1.2 Sertraline | 1 | 111 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 2 Disability | 10 | 598 | Std. Mean Difference (IV, Random, 95% CI) | 0.77 [0.22, 1.33] | |
| 2.1 Fluoxetine | 6 | 276 | Std. Mean Difference (IV, Random, 95% CI) | 0.22 [-0.12, 0.55] | |
| 2.2 Sertraline | 1 | 130 | Std. Mean Difference (IV, Random, 95% CI) | 1.38 [0.99, 1.76] | |
| 2.3 Citalopram | 1 | 60 | Std. Mean Difference (IV, Random, 95% CI) | 2.67 [1.97, 3.38] | |
| 2.4 Paroxetine | 2 | 132 | Std. Mean Difference (IV, Random, 95% CI) | 1.28 [-0.29, 2.86] | |
| 2.5 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 2.6 Sertraline or fluoxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 3 Neurological deficit score | 13 | 999 | Std. Mean Difference (IV, Random, 95% CI) | -1.12 [-1.55, -0.68] | |
| 3.1 Fluoxetine | 7 | 537 | Std. Mean Difference (IV, Random, 95% CI) | -1.14 [-1.78, -0.49] | |
| 3.2 Sertraline | 2 | 108 | Std. Mean Difference (IV, Random, 95% CI) | -0.26 [-0.96, 0.45] | |
| 3.3 Citalopram | 1 | 60 | Std. Mean Difference (IV, Random, 95% CI) | -2.27 [-2.93, -1.61] | |
| 3.4 Paroxetine | 3 | 294 | Std. Mean Difference (IV, Random, 95% CI) | -1.29 [-2.09, -0.49] | |
| 3.5 Fluoxetine or sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 4 Depression (continuous data) | 20 | 1590 | Std. Mean Difference (IV, Random, 95% CI) | -2.16 [-2.77, -1.55] | |
| 4.1 Fluoxetine | 10 | 637 | Std. Mean Difference (IV, Random, 95% CI) | -2.65 [-3.88, -1.41] | |
| 4.2 Sertraline | 3 | 333 | Std. Mean Difference (IV, Random, 95% CI) | -0.64 [-1.41, 0.14] | |
| 4.3 Citalopram | 2 | 126 | Std. Mean Difference (IV, Random, 95% CI) | -1.67 [-3.89, 0.56] | |
| 4.4 Paroxetine | 6 | 494 | Std. Mean Difference (IV, Random, 95% CI) | -2.50 [-3.37, -1.63] | |
| 4.5 Fluoxetine or sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 5 Depression (dichotomous data) | 6 | 486 | Risk Ratio (M-H, Random, 95% CI) | 0.41 [0.26, 0.65] | |
| 5.1 Fluoxetine | 3 | 203 | Risk Ratio (M-H, Random, 95% CI) | 0.25 [0.11, 0.57] | |
| 5.2 Sertraline | 2 | 166 | Risk Ratio (M-H, Random, 95% CI) | 0.59 [0.28, 1.25] | |
| 5.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 5.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 5.5 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.14, 0.99] | |
| 6 Anxiety (continuous data) | 5 | 249 | Std. Mean Difference (IV, Random, 95% CI) | -1.03 [-2.09, 0.04] | |
| 6.1 Fluoxetine | 3 | 115 | Std. Mean Difference (IV, Random, 95% CI) | -0.40 [-0.85, 0.05] | |
| 6.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 6.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 6.4 Paroxetine | 2 | 134 | Std. Mean Difference (IV, Random, 95% CI) | -2.16 [-5.83, 1.51] | |
| 6.5 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 7 Anxiety (dichotomous data) | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 8 Cognition (continuous scores | 5 | 254 | Std. Mean Difference (IV, Random, 95% CI) | 0.07 [-0.26, 0.40] | |
| end of treatment) | | | | | |
| 8.1 Fluoxetine | 3 | 86 | Std. Mean Difference (IV, Random, 95% CI) | -0.12 [-0.55, 0.30] | |
| 8.2 Sertraline | 1 | 80 | Std. Mean Difference (IV, Random, 95% CI) | 0.53 [0.08, 0.98] | |
| 8.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |

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

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| 8.4 Escitalopram | 1 | 88 | Std. Mean Difference (IV, Random, 95% CI) | -0.07 [-0.49, 0.35] |
|-------------------------------------|----|------|---|----------------------|
| 9 Death | 28 | 2156 | Risk Ratio (M-H, Random, 95% CI) | 0.99 [0.37, 2.64] |
| 9.1 Fluoxetine | 15 | 958 | Risk Ratio (M-H, Random, 95% CI) | 0.55 [0.07, 4.34] |
| 9.2 Sertraline | 5 | 461 | Risk Ratio (M-H, Random, 95% CI) | 0.91 [0.20, 4.19] |
| 9.3 Citalopram | 2 | 126 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.15, 6.68] |
| 9.4 Paroxetine | 6 | 494 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 9.5 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 4.92 [0.24, 100.25] |
| 9.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 10 Seizures | 5 | 332 | Risk Ratio (M-H, Random, 95% CI) | 2.22 [0.41, 12.06] |
| 10.1 Fluoxetine | 3 | 212 | Risk Ratio (M-H, Random, 95% CI) | 1.52 [0.20, 11.80] |
| 10.2 Sertraline | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| 10.3 Citalopram | 1 | 66 | Risk Ratio (M-H, Random, 95% CI) | 5.0 [0.25, 100.32] |
| 10.4 Paroxetine | 1 | 54 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| 10.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| 10.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| 11 Gastrointestinal side effects | 8 | 507 | Risk Ratio (M-H, Random, 95% CI) | 1.67 [0.56, 4.97] |
| 11.1 Fluoxetine | 6 | 425 | Risk Ratio (M-H, Random, 95% CI) | 1.43 [0.47, 4.36] |
| 11.2 Sertraline | 1 | 28 | Risk Ratio (M-H, Random, 95% CI) | 0.33 [0.01, 7.55] |
| 11.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| 11.4 Paroxetine | 1 | 54 | Risk Ratio (M-H, Random, 95% CI) | 19.00 [1.16, 310.94] |
| 11.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 11.6 Sertraline and paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 12 Bleeding | 1 | 54 | Risk Ratio (M-H, Random, 95% CI) | 19.00 [1.16, 310.94] |
| 12.1 Fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| 12.2 Sertraline | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| 12.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 12.4 Paroxetine | 1 | 54 | Risk Ratio (M-H, Random, 95% CI) | 19.00 [1.16, 310.94] |
| 12.5 Escitalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 12.6 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 13 Change in depression scores | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \ [0.0, \ 0.0]$ |
| between baseline and follow-up | | | | |
| 13.1 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| 14 Change in cognition between | 1 | 99 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [-0.39, 0.39] |
| baseline and end of treatment | | | | |
| 14.1 Sertraline | 1 | 99 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [-0.39, 0.39] |
| 15 Leaving the trial before the end | 28 | 2130 | Risk Ratio (M-H, Random, 95% CI) | 1.51 [1.02, 2.23] |
| of scheduled follow-up | | | | |
| 15.1 Fluoxetine | 13 | 784 | Risk Ratio (M-H, Random, 95% CI) | 1.62 [0.75, 3.51] |
| 15.2 Sertraline | 6 | 609 | Risk Ratio (M-H, Random, 95% CI) | 1.46 [0.79, 2.72] |
| 15.3 Citalopram | 2 | 126 | Risk Ratio (M-H, Random, 95% CI) | 6.00 [0.76, 47.14] |
| 15.4 Paroxetine | 6 | 494 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \ [0.0, 0.0]$ |
| 15.5 Sertraline or fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ |
| 15.6 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 1.38 [0.46, 4.09] |

| C · 10 | CODI | 1 . 1 6 | 1 | 1 • 1 |
|----------------|--------------------|------------------------|----------------------|-------------|
| Comparison 10. | SSKI versus contro | l at end of treatment, | selective reporting | low risk |
| 001110011 101 | | | bereet, e reporting. | 10.00 11011 |

| Outcome or subgroup title | No. of No. of studies participants | | Statistical method | Effect size | |
|---------------------------------|---------------------------------------|-----|---|----------------------|--|
| 1 Dependent on modified Rankin | 2 | 223 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] | |
| score (mRS 3 to 5) | | | | | |
| 1.1 Fluoxetine | 1 | 112 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.68, 0.97] | |
| 1.2 Sertraline | 1 | 111 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 2 Disability | 4 | 118 | Std. Mean Difference (IV, Random, 95% CI) | 0.11 [-0.26, 0.47] | |
| 2.1 Fluoxetine | 4 | 118 | Std. Mean Difference (IV, Random, 95% CI) | 0.11 [-0.26, 0.47] | |
| 2.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ | |
| 2.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 2.4 Paroxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 2.5 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 2.6 Sertraline or fluoxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 3 Neurological deficit score | 3 | 172 | Std. Mean Difference (IV, Random, 95% CI) | -0.20 [-0.50, 0.10] | |
| 3.1 Fluoxetine | 2 | 144 | Std. Mean Difference (IV, Random, 95% CI) | -0.27 [-0.60, 0.06] | |
| 3.2 Sertraline | 1 | 28 | Std. Mean Difference (IV, Random, 95% CI) | 0.17 [-0.57, 0.91] | |
| 3.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 3.4 Paroxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 3.5 Fluoxetine or sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 4 Depression (continuous data) | 6 | 294 | Std. Mean Difference (IV, Random, 95% CI) | -0.22 [-0.63, 0.18] | |
| 4.1 Fluoxetine | 5 | 228 | Std. Mean Difference (IV, Random, 95% CI) | -0.13 [-0.64, 0.37] | |
| 4.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 4.3 Citalopram | 1 | 66 | Std. Mean Difference (IV, Random, 95% CI) | -0.54 [-1.04, -0.05] | |
| 4.4 Paroxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 4.5 Fluoxetine or sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ | |
| 5 Depression (dichotomous data) | 3 | 283 | Risk Ratio (M-H, Random, 95% CI) | 0.52 [0.30, 0.90] | |
| 5.1 Fluoxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ | |
| 5.2 Sertraline | 2 | 166 | Risk Ratio (M-H, Random, 95% CI) | 0.59 [0.28, 1.25] | |
| 5.3 Citalopram | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 5.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 5.5 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.14, 0.99] | |
| 6 Anxiety (continuous data) | 2 | 55 | Std. Mean Difference (IV, Random, 95% CI) | -0.13 [-0.66, 0.40] | |
| 6.1 Fluoxetine | 2 | 55 | Std. Mean Difference (IV, Random, 95% CI) | -0.13 [-0.66, 0.40] | |
| 6.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ | |
| 6.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 6.4 Paroxetine | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 6.5 Escitalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 7 Anxiety (dichotomous data) | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | $0.0 \; [0.0, 0.0]$ | |
| 8 Cognition (continuous scores | 3 | 86 | Std. Mean Difference (IV, Random, 95% CI) | -0.12 [-0.55, 0.30] | |
| end of treatment) | | | | | |
| 8.1 Fluoxetine | 3 | 86 | Std. Mean Difference (IV, Random, 95% CI) | -0.12 [-0.55, 0.30] | |
| 8.2 Sertraline | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 8.3 Citalopram | 0 | 0 | Std. Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 9 Death | 9 | 568 | Risk Ratio (M-H, Random, 95% CI) | 1.20 [0.43, 3.37] | |
| 9.1 Fluoxetine | 5 | 257 | Risk Ratio (M-H, Random, 95% CI) | 0.55 [0.07, 4.34] | |
| 9.2 Sertraline | 2 | 128 | Risk Ratio (M-H, Random, 95% CI) | 1.54 [0.26, 9.07] | |
| 9.3 Citalopram | 1 | 66 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.15, 6.68] | |
| 9.4 Paroxetine | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] | |
| 9.5 Escitalopram | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 4.92 [0.24, 100.25] | |

| $\begin{array}{c} 0.0 \ [0.0, 0.0] \\ 2.67 \ [0.61, 11.63] \\ 2.19 \ [0.41, 11.85] \\ 0.0 \ [0.0, 0.0] \\ 5.0 \ [0.25, 100.32] \\ 0.0 \ [0.0, 0.0] \\ 0.0 \ [0.0, 0.0] \\ 0.0 \ [0.0, 0.0] \\ 1.35 \ [0.42, 4.29] \\ 1.60 \ [0.44, 5.77] \end{array}$ |
|---|
| $\begin{array}{c} 2.19 \ [0.41, 11.85] \\ 0.0 \ [0.0, 0.0] \\ 5.0 \ [0.25, 100.32] \\ 0.0 \ [0.0, 0.0] \\ 0.0 \ [0.0, 0.0] \\ 0.0 \ [0.0, 0.0] \\ 1.35 \ [0.42, 4.29] \end{array}$ |
| $\begin{array}{c} 0.0 \; [0.0, 0.0] \\ 5.0 \; [0.25, 100.32] \\ 0.0 \; [0.0, 0.0] \\ 0.0 \; [0.0, 0.0] \\ 0.0 \; [0.0, 0.0] \\ 1.35 \; [0.42, 4.29] \end{array}$ |
| 5.0 [0.25, 100.32] 0.0 [0.0, 0.0] 0.0 [0.0, 0.0] 0.0 [0.0, 0.0] 1.35 [0.42, 4.29] |
| 0.0 [0.0, 0.0] 0.0 [0.0, 0.0] 0.0 [0.0, 0.0] 1.35 [0.42, 4.29] |
| 0.0 [0.0, 0.0] 0.0 [0.0, 0.0] 1.35 [0.42, 4.29] |
| 0.0 [0.0, 0.0] 1.35 [0.42, 4.29] |
| 1.35 [0.42, 4.29] |
| |
| 1 60 [0 44 5 77] |
| |
| 0.33 [0.01, 7.55] |
| $0.0 \ [0.0, 0.0]$ |
| $0.0 \ [0.0, \ 0.0]$ |
| $0.0 \ [0.0, \ 0.0]$ |
| $0.0 \ [0.0, \ 0.0]$ |
| 0.0 [0.0, 0.0] |
| 0.0 [0.0, 0.0] |
| 0.0 [0.0, 0.0] |
| 0.0 [0.0, 0.0] |
| 0.0 [0.0, 0.0] |
| 0.0 [0.0, 0.0] |
| 0.0 [0.0, 0.0] |
| CI) 0.0 [0.0, 0.0] |
| |
| CI) 0.0 [0.0, 0.0] |
| CI) 0.0 [-0.39, 0.39] |
| |
| CI) 0.0 [-0.39, 0.39] |
| 1.32 [0.87, 1.99] |
| |
| 1.55 [0.70, 3.45] |
| 1.17 [0.63, 2.16] |
| 6.00 [0.76, 47.14] |
| 0.0 [0.0, 0.0] |
| 0.0 [0.0, 0.0] |
| 1.38 [0.46, 4.09] |
| • |

Analysis I.I. Comparison I SSRI versus control at end of treatment, by SSRI, Outcome I Dependent on modified Rankin score (mRS 3 to 5).

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

Comparison: I SSRI versus control at end of treatment, by SSRI

Outcome: I Dependent on modified Rankin score (mRS 3 to 5)

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|---|---------------------------|---------|--------------------|---------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| I Fluoxetine | | | | |
| Chollet 2011 | 42/57 | 50/55 | + | 0.81 [0.68, 0.97] |
| Subtotal (95% CI) | 57 | 55 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Contr | ol) | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 2.34$ (P | = 0.019) | | | |
| 2 Sertraline | | | | |
| Almeida 2006 | 0/55 | 0/56 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 55 | 56 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.0$ (P \cdot | < 0.00001) | | | |
| Total (95% CI) | 112 | 111 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Contro | ol) | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = | = 0.0, df = 0 (P = 1.00); | 2 =0.0% | | |
| Test for overall effect: $Z = 2.34$ (P | = 0.019) | | | |
| Test for subgroup differences: Not | t applicable | | | |
| | | | <u> </u> | |
| | | | 0.01 0.1 10 100 | |

0.01 0.1 I Favours SSRI

Favours control

Analysis I.2. Comparison I SSRI versus control at end of treatment, by SSRI, Outcome 2 Disability.

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

Comparison: I SSRI versus control at end of treatment, by SSRI

Outcome: 2 Disability

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Sto Meai Difference |
|--|------------------------|----------------------|--------------------------------|--------------------|-----------------------------|---------------|---------------------------|
| | N | Mean(SD) | Ν | Mean(SD) | IV,Random,95% CI | | IV,Random,95% C |
| Fluoxetine Chen 2001 | 19 | 79.31 (8.94) | 18 | 71.56 (9.41) | | 4.3 % | 0.83 [0.15, 1.50 |
| Cheng 2003 | 25 | -26.38 (14.2) | 32 | -29.15 (17.38) | | 4.7 % | 0.17 [-0.35, 0.69 |
| Dam 1996 | 16 | 61.9 (13) | 16 | 54.1 (21.1) | - + + | 4.3 % | 0.43 [-0.27, 1.14 |
| Kong 2007 | 37 | 60.4 (12.5) | 36 | 52.3 (13.5) | | 4.9 % | 0.62 [0.15, 1.09 |
| Li 2008 | 58 | 40.8 (3.7) | 28 | 38.4 (5.8) | | 4.9 % | 0.53 [0.07, 0.99 |
| Liu 2004 | 30 | 70.33 (10.74) | 30 | 64.33 (7.7) | | 4.7 % | 0.63 [0.11, 1.15 |
| Robinson 2000a | 14 | 59.2 (11.6) | 13 | 56.2 (7.74) | | 4.1 % | 0.29 [-0.47, 1.05 |
| Robinson 2000b | 13 | 60.5 (10.8) | 15 | 63.1 (8.2) | | 4.1 % | -0.27 [-1.01, 0.48 |
| Wang 2003 | 51 | 75 (4.2) | 47 | 61 (6.9) | F | 4.7 % | 2.46 [1.93, 2.98 |
| Wiart 2000 | 16 | 87.4 (22.8) | 15 | 88.7 (25.3) | | 4.3 % | -0.05 [-0.76, 0.65 |
| Xu 2001 | 26 | 73 (4.4) | 27 | 67 (4.1) | | 4.5 % | 1.39 [0.79, 2.00 |
| Xu 2007 | 36 | 64.4 (8.23) | 36 | 56.9 (6.68) | | 4.8 % | 0.99 [0.50, 1.48 |
| Zhou 2003 | 28 | -27.8 (7.1) | 26 | -32.5 (7.8) | | 4.7 % | 0.62 [0.07, 1.17 |
| Subtotal (95% CI) | 369 | | 339 | | • | 59.0 % | 0.68 [0.31, 1.06 |
| Heterogeneity: Tau ² = 0.38 Test for overall effect: Z = 2 2 Sertraline Xie 2005 | | , | 00001); I ² : 65 | =82% 79.8 (4.5) | | 5.1 % | 1.38 [0.99, 1.76 |
| Subtotal (95% CI) | 65 | | 65 | | • | 5.1 % | 1.38 [0.99, 1.76 |
| Heterogeneity: not applicab Test for overall effect: Z = 7 3 Citalopram Acler 2009 | | 0.00001) 82 (28) | 10 | 75 (25) | | 3.8 % | 0.25 [-0.63, 1.13 |
| Li 2006 | 50 | 64.36 (8.23) | 49 | 59.17 (9.02) | | 5.0 % | 0.60 [0.19, 1.00 |
| Liu 2006 | 30 | 64.4 (12.1) | 30 | 35.4 (9.1) | | 4.2 % | 2.67 [1.97, 3.38 |
| Subtotal (95% CI) | 90 | | 89 | | | 13.0 % | 1.18 [-0.22, 2.58 |
| Heterogeneity: $Tau^2 = 1.41$ | ; Chi ² = 3 | 28.09, df = 2 (P<0.0 | $000); ^2 =$ | 93% | | | |
| | | | | | -2 -1 0 1 2 | | |
| | | | | F | avours control Favours SSRI | | (Continued |

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | | Std. Mean rrence n,95% Cl | Weight | (Continued) Std. Mean Difference IV,Random,95% Cl |
|--|-------------------------|-----------------------|----------------------------|---------------|---|------------------------------------|---------|--|
| Test for overall effect: Z = | I.65 (P = | 0.099) | | | | | | |
| 4 Paroxetine | | | | | | | | |
| Chen 2002 | 24 | 61 (12.2) | 20 | 51.5 (10.3) | | | 4.5 % | 0.82 [0.20, 1.44] |
| Chen T 2005 | 40 | 65.76 (5.92) | 38 | 51.76 (7.32) | | \rightarrow | 4.6 % | 2.09 [1.53, 2.64] |
| He 2005 | 27 | 84.26 (8.41) | 27 | 78.33 (15.01) | - | _ `` | 4.7 % | 0.48 [-0.06, 1.02] |
| Xu 2006 | 28 | -27.63 (4.81) | 29 | -32.81 (4.13) | | | 4.6 % | 1.14 [0.58, 1.70] |
| Ye 2004 | 30 | 78.75 (14.19) | 30 | 50.26 (13.4) | | \rightarrow | 4.5 % | 2.04 [1.41, 2.67] |
| Subtotal (95% CI) | 149 | | 144 | | | - | 22.9 % | 1.31 [0.67, 1.95] |
| Heterogeneity: $Tau^2 = 0.45$ | 5; Chi ² = 3 | 24.34, df = 4 (P = 0 | 0.00007); l ² = | =84% | | | | |
| Test for overall effect: $Z = $ | 4.01 (P = | 0.000062) | | | | | | |
| 5 Escitalopram | | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | ble | | | | | | | |
| Test for overall effect: not a | applicable | | | | | | | |
| 6 Sertraline or fluoxetine | | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | ble | | | | | | | |
| Test for overall effect: not a | applicable | | | | | | | |
| Total (95% CI) | 673 | | 637 | | | • | 100.0 % | 0.92 [0.62, 1.23] |
| Heterogeneity: Tau ² = 0.45 | 5; Chi² = | 136.49, df = 21 (P< | 0.00001); 12 | =85% | | | | |
| Test for overall effect: $Z = $ | 5.91 (P < | 0.00001) | | | | | | |
| Test for subgroup difference | es: Chi ² = | = 7.11, df = 3 (P = 0 | 0.07), I ² =58 | % | | | | |
| | | | | | | | | |

- | 0 L Favours control Favours SSRI

2

-2

Analysis 1.3. Comparison I SSRI versus control at end of treatment, by SSRI, Outcome 3 Neurological deficit score.

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

Comparison: I SSRI versus control at end of treatment, by SSRI

Outcome: 3 Neurological deficit score

| Study or subgroup | SSRI N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|--|--------------------------------------|--------------------|---------------------------------------|---------------|--|--------|--|
| I Fluoxetine | | | | | | | |
| Chen 2001 | 19 | -49.72 (4.07) | 18 | -43.13 (3.64) | ••••• | 3.0 % | -1.67 [-2.43, -0.91] |
| Cheng 2003 | 25 | 6.5 (3.19) | 32 | 10.96 (8.13) | | 3.5 % | -0.68 [-1.22, -0.14] |
| Chollet 2011 | 57 | 5.8 (3.7) | 55 | 6.9 (4.4) | | 3.8 % | -0.27 [-0.64, 0.10] |
| Dam 1996 | 16 | 44.1 (9.4) | 16 | 46.8 (9.9) | | 3.2 % | -0.27 [-0.97, 0.42] |
| Feng 2004 | 16 | 9.1 (3.2) | 16 | 14.4 (2.2) | | 2.8 % | -1.88 [-2.73, -1.03] |
| Fruehwald 2003 | 26 | -55.5 (4.8) | 24 | -52.8 (5.4) | | 3.4 % | -0.52 [-1.09, 0.04] |
| He 2004 | 36 | 10.41 (6.36) | 35 | 14.43 (7.94) | | 3.6 % | -0.55 [-1.03, -0.08] |
| Huang 2002 | 40 | 4.02 (1.86) | 40 | 8.57 (3.64) | •••• | 3.6 % | -1.56 [-2.06, -1.06] |
| Kong 2007 | 37 | 8.6 (6.4) | 36 | 11.2 (6.4) | | 3.6 % | -0.40 [-0.87, 0.06] |
| Li 2004a | 33 | 6.23 (3.11) | 34 | 12.86 (6.36) | | 3.5 % | -1.30 [-1.83, -0.77] |
| Liang 2003 | 42 | 11.74 (3.23) | 21 | 17.32 (5.19) | | 3.4 % | -1.38 [-1.96, -0.80] |
| Liu 2004 | 30 | 9.2 (2.06) | 30 | 10.47 (9.2) | | 3.6 % | -0.19 [-0.70, 0.32] |
| Wang 2003 | 51 | 9.5 (3.5) | 47 | 15.6 (4.6) | <u> </u> | 3.7 % | -1.49 [-1.94, -1.04] |
| Wen 2006 | 42 | 10.1 (1.9) | 42 | 16.4 (2.5) | • | 3.3 % | -2.81 [-3.42, -2.20] |
| Xu 2001 | 26 | 8.2 (5.2) | 27 | 12.4 (4.3) | | 3.4 % | -0.87 [-1.43, -0.30] |
| Xu 2007 | 36 | 21.89 (1.57) | 36 | 20.78 (4.06) | <u> </u> | 3.6 % | 0.36 [-0.11, 0.82] |
| Zhou 2003 | 28 | 9 (3.8) | 26 | 12.2 (6.1) | | 3.5 % | -0.63 [-1.17, -0.08] |
| Subtotal (95% CI) Heterogeneity: Tau ² = 0.49; Fest for overall effect: Z = 5 | | | 535 | =87% | • | 58.7 % | -0.93 [-1.29, -0.57] |
| 2 Sertraline Burns 1999 | 4 | -29.7 (14.7) | 14 | -32.2 (13.4) | | 3.1 % | 0.17 [-0.57, 0.91] |
| Guo 2009 | 40 | 29.07 (8.02) | 40 | 33.78 (8.63) | | 3.7 % | -0.56 [-1.01, -0.11] |
| Subtotal (95% CI) Heterogeneity: Tau ² = 0.17; | 54 ; Chi ² = 2. | 74, df = 1 (P = 0. | 54 10); l ² =64% |) | - | 6.7 % | -0.26 [-0.96, 0.45] |
| | | | | | -2 -1 0 I 2 Favours SSRI Favours contro | bl | (Continued |

| Study or subgroup | SSRI | | Control | | St Mea Difference | | (Continued Std. Mean Difference |
|--|-----------------------|--------------------|--------------------------|--------------|----------------------------|-----------------------|--|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95 | 5% CI | IV,Random,95% CI |
| Test for overall effect: $Z = 0$ | 0.71 (P = 0) | .48) | | | | | |
| 3 Citalopram Acler 2009 | 10 | 2.3 (2) | 10 | 3.5 (1.3) | | 2.7 % | -0.68 [-1.59, 0.23] |
| | | | | | | | |
| Li 2006 | 50 | 21.89 (1.57) | 49 | 23.77 (1.46) | | 3.7 % | -1.23 [-1.66, -0.80] |
| Liu 2006 | 30 | 13.3 (3.8) | 30 | 22.4 (4.1) | ← | 3.2 % | -2.27 [-2.93, -1.61] |
| Subtotal (95% CI) | 90 | | 89 | | | 9.7 % | -1.43 [-2.25, -0.60] |
| Heterogeneity: Tau ² = 0.41; Test for overall effect: Z = 3 4 Paroxetine | | |)); ² =79% | | | | |
| Chen 2002 | 24 | 10 (4.8) | 20 | 14.8 (4.8) | | 3.3 % | -0.98 [-1.61, -0.35] |
| He 2005 | 27 | 6.48 (1.58) | 27 | 8.33 (3.86) | | 3.5 % | -0.62 [-1.17, -0.07] |
| Li 2002 | 46 | 11.5 (2.8) | 46 | 19 (4) | ← | 3.5 % | -2.15 [-2.67, -1.64] |
| Li 2005 | 74 | 12.9 (5.1) | 74 | 18.7 (5.4) | | 3.8 % | -1.10 [-1.44, -0.75] |
| Xu 2006 | 28 | . (4.32) | 29 | 13.63 (3.15) | | 3.5 % | -0.66 [-1.19, -0.13] |
| Ye 2004 | 30 | 8.3 (3.8) | 30 | 16 (4.8) | | 3.4 % | -1.76 [-2.36, -1.15] |
| Subtotal (95% CI) | 229 | 0.5 (5.6) | 226 | 10 (1.0) | | 21.0 % | -1.21 [-1.68, -0.74] |
| 5 Fluoxetine or sertraline Jia 2005 Subtotal (95% CI) Heterogeneity: not applicabl | 86 86 le | 10.4 (8.5) | 88 88 | 22.6 (8.9) | → | 3.9 % 3.9 % | -1.40 [-1.73, -1.06] -1.40 [-1.73, -1.06] |
| Test for overall effect: $Z = 8$ | | .00001) | | | | | |
| Total (95% CI) | 1019 | , | 992 | | • | 100.0 % | -1.00 [-1.26, -0.75] |
| Heterogeneity: Tau ² = 0.41; | | | 0.00001); l ² | =86% | | | |
| Test for overall effect: $Z = 7$ Test for subgroup difference | ` | , | $0.04)$ $1^2 - 4$ | 10/ | | | |
| lest for subgroup difference | IS. CHI – I | 10.13, di – + (i – | 0.04), 1 -0 | 1 /0 | | | |
| | | | | | -2 -1 0 Favours SSRI Fa | l 2 avours control | |
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Analysis I.4. Comparison I SSRI versus control at end of treatment, by SSRI, Outcome 4 Depression (continuous data).

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

Comparison: I SSRI versus control at end of treatment, by SSRI

Outcome: 4 Depression (continuous data)

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | S Me Differen IV,Random,95% |
|--|-----------|--------------|---|---------------|--|--------|--------------------------------------|
| Fluoxetine | | | | | | | |
| Chen 2001 | 19 | 10.82 (6.25) | 18 | 18.48 (6.28) | | 2.6 % | -1.20 [-1.90, -0.4 |
| Cheng 2003 | 25 | 3.64 (.02) | 32 | 17.98 (12.53) | | 2.7 % | -0.36 [-0.89, 0.1 |
| Chollet 2011 | 56 | 5.4 (4.9) | 54 | 8.4 (7.9) | | 2.7 % | -0.46 [-0.83, -0.0 |
| Dam 1996 | 16 | 8.8 (5.6) | 16 | 9.4 (5.6) | | 2.6 % | -0.10 [-0.80, 0.5 |
| Feng 2004 | 16 | 34.9 (4.6) | 16 | 41.1 (4.7) | • | 2.5 % | -1.30 [-2.07, -0.5 |
| Fruehwald 2003 | 26 | 9.5 (7.9) | 24 | 11.2 (12.4) | | 2.7 % | -0.16 [-0.72, 0.3 |
| He 2004 | 36 | 14.28 (2.31) | 35 | 20.32 (2.82) | ← | 2.6 % | -2.32 [-2.93, -1.7 |
| Huang 2002 | 40 | 4.76 (0.6) | 40 | 16.34 (1.3) | • | 1.8 % | -11.33 [-13.18, -9.4 |
| Ji 2000 | 20 | 5.2 (1.5) | 20 | 14.5 (2.7) | • | 2.3 % | -4.17 [-5.32, -3.0 |
| Kong 2007 | 37 | 12.6 (5.3) | 36 | 16.3 (3.7) | <u> </u> | 2.7 % | -0.80 [-1.28, -0.3 |
| Li 2008 | 58 | 14.5 (2.4) | 28 | 18.7 (3.9) | | 2.7 % | -1.40 [-1.90, -0.9 |
| Liang 2003 | 42 | 9.67 (4.48) | 21 | 19.19 (3.12) | ← | 2.6 % | -2.30 [-2.97, -1.6 |
| Robinson 2000a | 14 | 18.5 (7.6) | 13 | 12.2 (4.7) | | 2.5 % | 0.96 [0.15, 1. |
| Robinson 2000b | 13 | 5.9 (3.8) | 15 | 6.2 (4.6) | | 2.6 % | -0.07 [-0.81, 0.6 |
| Song 2006 | 41 | 40.3 (7.25) | 41 | 48.31 (8.02) | | 2.7 % | -1.04 [-1.50, -0.5 |
| Wang 2003 | 51 | 10.5 (2.9) | 47 | 20 (6.1) | H | 2.7 % | -2.00 [-2.49, -1.5 |
| Wen 2006 | 42 | 7 (1.1) | 42 | 17.7 (1.8) | | 2.3 % | -7.11 [-8.29, -5.9 |
| Wiart 2000 | 16 | 11.8 (6.7) | 15 | 18.7 (10) | | 2.6 % | -0.79 [-1.53, -0.0 |
| Xu 2001 | 26 | 23.6 (3.9) | 27 | 44.7 (2.6) | • | 2.2 % | -6.30 [-7.65, -4.9 |
| Xu 2007 | 36 | 5.61 (5.32) | 36 | 17.73 (3.21) | • | 2.6 % | -2.73 [-3.38, -2.0 |
| Zhou 2003 | 28 | 3.5 (1.3) | 26 | 3.8 (1.6) | | 2.7 % | -0.20 [-0.74, 0.3 |
| ubtotal (95% CI) eterogeneity: Tau ² = 2.16 est for overall effect: Z = | | | 602 <0.00001); l ² | =96% | | 53.3 % | -1.97 [-2.63, -1.3 |

Favours SSRI

Favours control

(Continued ...)

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review) Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. 136

| | | | | | Std. | | (Continued Std |
|---|------------|--------------------|----------------------------|--------------|-------------------------|---------|------------------------|
| Study or subgroup | SSRI | | Control | | Mean Difference | Weight | Mear Difference |
| , , , | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% CI | | IV,Random,95% C |
| 2 Sertraline | | | | | | | |
| Finkenzeller 2009 | 23 | 2. (.05) | 27 | 10.6 (0.97) | | → 2.6 % | 1.47 [0.83, 2.10 |
| Guo 2009 | 40 | 14.82 (8.05) | 40 | 17.61 (8) | | 2.7 % | -0.34 [-0.79, 0.10 |
| Murray 2005 | 62 | 10.5 (9.6) | 61 | 12 (8.5) | -+ | 2.7 % | -0.16 [-0.52, 0.19 |
| Xie 2005 | 65 | 30.9 (7.1) | 65 | 39.7 (5.3) | <u> </u> | 2.7 % | -1.40 [-1.78, -1.01 |
| Subtotal (95% CI) | 190 | | 193 | | | 10.8 % | -0.13 [-1.11, 0.85] |
| Heterogeneity: Tau ² = 0.94; | | | $0000); ^2 = 9$ | 95% | | | |
| Test for overall effect: Z = 0.3 3 Citalopram | 27 (P = 0. | 79) | | | | | |
| Acler 2009 | 10 | 6.6 (3.6) | 10 | 8 (3) | | 2.5 % | -0.40 [-1.29, 0.48 |
| Andersen 1994 | 33 | .4 (5.) | 33 | 4. (4.7) | . | 2.7 % | -0.54 [-1.04, -0.05] |
| Li 2006 | 50 | 5.61 (5.32) | 49 | 20.26 (6.08) | • | 2.7 % | -2.55 [-3.08, -2.01] |
| Liu 2006 | 30 | 17.2 (2.1) | 30 | 25.1 (3.3) | • | 2.6 % | -2.82 [-3.55, -2.09] |
| Miao 2004 | 34 | 6.45 (5.3) | 34 | 23.74 (5.16) | • | 2.6 % | -3.27 [-4.01, -2.53 |
| Subtotal (95% CI) | 157 | . , | 156 | . , | | 13.0 % | -1.92 [-3.08, -0.75] |
| Heterogeneity: $Tau^2 = 1.64;$ | | .70, df = 4 (P<0.0 | - | 94% | | 2010 /0 | |
| Test for overall effect: $Z = 3.2$ | 23 (P = 0. | .0012) | | | | | |
| 4 Paroxetine | | | | | | | |
| Chen 2002 | 24 | 10.3 (3) | 20 | 16.5 (2.5) | ← | 2.6 % | -2.19 [-2.95, -1.42] |
| Chen T 2005 | 40 | 10.98 (3.74) | 38 | 22.45 (3.56) | • | 2.6 % | -3.11 [-3.78, -2.44] |
| He 2005 | 27 | 10.11 (1.08) | 27 | 17.48 (1.05) | • | 2.1 % | -6.82 [-8.26, -5.38] |
| Lai 2006 | 40 | 12.5 (8.4) | 40 | 21.5 (4.3) | | 2.7 % | -1.34 [-1.82, -0.85] |
| Li 2002 | 46 | 10 (3) | 46 | 22 (8) | ← | 2.7 % | -1.97 [-2.47, -1.47] |
| Li 2005 | 74 | 12.6 (2.1) | 74 | 16.8 (2.3) | ← | 2.7 % | -1.90 [-2.29, -1.51] |
| Yang 2011 | 20 | 7 (4) | 22 | 13 (6) | | 2.6 % | -1.14 [-1.80, -0.49] |
| Ye 2004 | 30 | 4.02 (3.07) | 30 | 17.32 (1.66) | • | 2.3 % | -5.32 [-6.43, -4.21] |
| Subtotal (95% CI) | 301 | | 297 | | | 20.3 % | -2.81 [-3.66, -1.96] |
| Heterogeneity: $Tau^2 = 1.35;$ | | , | 0.00001); I ² = | -93% | | | |
| Test for overall effect: Z = 6. 5 Fluoxetine or sertraline | 46 (P < 0. | .00001) | | | | | |
| Jia 2005 | 86 | 6.4 (6.2) | 88 | 16.2 (6.8) | <u> </u> | 2.7 % | -1.50 [-1.84, -1.16 |
| Subtotal (95% CI) | 86 | | 88 | . / | • | 2.7 % | -1.50 [-1.84, -1.16] |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: $Z = 8$. | 71 (P < 0. | .00001) | | | | | |
| 6 Escitalopram Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| | | | | | -2 -1 0 1 | 2 | |
| | | | | | Favours SSRI Favours co | | |
| | | | | | | | (Continued |

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Analysis 1.5. Comparison I SSRI versus control at end of treatment, by SSRI, Outcome 5 Depression (dichotomous data).

| n/N n/N Cl I Fluoxetine I 2/33 8/34 8.7 % 0.26 [0.06, 1.1] Li 2004a 2/33 8/34 13.0 % 0.40 [0.16, 0.9] Zhou 2008 4/36 18/40 12.3 % 0.25 [0.09, 0.6] Subtotal (95% CI) 100 106 34.0 % 0.31 [0.17, 0.57] Total events: I I (SSRI), 39 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0.56, df = 2 (P = 0.76); l ² = 0.0% 34.0 % 0.31 [0.17, 0.57] Test for overall effect: Z = 3.80 (P = 0.00014) 2 Sertraline 2 Sertraline 4 | Zhou 2008 Subtotal (95% CI) Total events: 11 (SSRI), 39 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0. Test for overall effect: Z = 3.80 (P = 2 Sertraline | 4/36 100 5.56, df = 2 (P = 0.00014) | 18/40 106 = 0.76); l ² =0.0% | | 12.3 % 34.0 % | 0.40 [0.16, 0.98] 0.25 [0.09, 0.66] 0.31 [0.17, 0.57] 0.77 [0.34, 1.76] |
|---|--|--|--|---------------|-------------------------|---|
| n/N n/N Cl I Fluoxetine II 2004a 2/33 8/34 8.7 % 0.26 [0.06, 1.1] Li 2004b 5/31 13/32 13.0 % 0.40 [0.16, 0.9] Zhou 2008 4/36 18/40 12.3 % 0.25 [0.09, 0.6] Subtotal (95% CI) 100 106 34.0 % 0.31 [0.17, 0.5] Total events: II (SSRI), 39 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0.56, df = 2 (P = 0.76); l ² = 0.0% 56. df = 2 (P = 0.76); l ² = 0.0% 56. df = 2 (P = 0.76); l ² = 0.0% | Zhou 2008 Subtotal (95% CI) Total events: 11 (SSRI), 39 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0. Test for overall effect: Z = 3.80 (P = | 4/36 100 .56, df = 2 (P = | 18/40 106 | →- →- ◆ | 12.3 % | 0.25 [0.09, 0.66] |
| n/N n/N Cl I Fluoxetine I 2/33 8/34 8.7 % 0.26 [0.06, 1.1] Li 2004a 2/31 13/32 13.0 % 0.40 [0.16, 0.9] Zhou 2008 4/36 18/40 12.3 % 0.25 [0.09, 0.6] Subtotal (95% CI) 100 106 34.0 % 0.31 [0.17, 0.57] | Zhou 2008 Subtotal (95% CI) | 4/36 100 | 18/40 | + + • | 12.3 % | 0.25 [0.09, 0.66] |
| n/N n/N Cl I Fluoxetine I 2/33 8/34 8.7 % 0.26 [0.06, 1.1 Li 2004b 5/31 13/32 13.0 % 0.40 [0.16, 0.9 | | | | | | 2 |
| n/N n/N Cl I Fluoxetine | Li 2004b | 5/31 | 13/32 | | 13.0 % | 0.40 [0.16, 0.98] |
| n/N n/N Cl | | | | | | |
| | | 2/33 | 8/34 | | 8.7 % | 0.26 [0.06, 1.12] |
| | | n/N | n/N | H,Random,95% | | M- H,Random,95 Cl |
| | Study or subgroup | SSRI | Control | | Weight | Risk Ratio |

| Study or subgroup | SSRI | Control | Risk Ratio M- H,Random_95% | Weight | (Continued) Risk Ratio M- H,Random,95% |
|---|--------------------------|--|----------------------------------|---------|--|
| | n/N | n/N | Cl | | Cl |
| Total events: 11 (SSRI), 19 (Co | , | 2 - 0.202 12 - 1.404 | | | |
| Heterogeneity: $Tau^2 = 0.05$; CH Test for overall effect: $Z = 1.37$ | | ² = 0.28); 1 ² = 14% | | | |
| 3 Citalopram | (P = 0.17) | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Contr | | 0 | | 0.0 /0 | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicable | 01) | | | | |
| Test for overall effect: not appli | cable | | | | |
| 4 Paroxetine | | | | | |
| GlaxoSmithKline 1998 | 82/111 | 97/114 | - | 18.5 % | 0.87 [0.76, 0.99] |
| Xu 2006 | 3/28 | 12/29 | | 10.9 % | 0.26 [0.08, 0.82] |
| Subtotal (95% CI) | 139 | 143 | - | 29.5 % | 0.53 [0.15, 1.92] |
| Total events: 85 (SSRI), 109 (C | ontrol) | | | | |
| Heterogeneity: $Tau^2 = 0.71$; Ch | $hi^2 = 5.04, df = 1$ (F | $P = 0.02$; $I^2 = 80\%$ | | | |
| Test for overall effect: $Z = 0.96$ | • (P = 0.33) | | | | |
| 5 Escitalopram | | | | | |
| Robinson 2008 | 5/59 | I 3/58 | | 12.5 % | 0.38 [0.14, 0.99] |
| Subtotal (95% CI) | 59 | 58 | • | 12.5 % | 0.38 [0.14, 0.99] |
| Total events: 5 (SSRI), 13 (Con | trol) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 1.97$ | ' (P = 0.048) | | | | |
| Total (95% CI) | 381 | 390 | • | 100.0 % | 0.43 [0.24, 0.77] |
| Total events: 112 (SSRI), 180 (| , | | | | |
| Heterogeneity: $Tau^2 = 0.49$; Ch | | $(P = 0.00008); I^2 = 7$ | 7% | | |
| Test for overall effect: $Z = 2.82$ | · / | | | | |
| Test for subgroup differences: (| $Chi^2 = 1.93, df = 3$ | $(P = 0.59), I^2 = 0.0\%$ | | | |
| | | | | | |
| | | | 0.01 0.1 1 10 100 | D | |
| | | | Favours SSRI Favours contr | ol | |
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Analysis I.6. Comparison I SSRI versus control at end of treatment, by SSRI, Outcome 6 Anxiety (continuous data).

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

Comparison: I SSRI versus control at end of treatment, by SSRI

Outcome: 6 Anxiety (continuous data)

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Std. Mean Difference |
|--|------------------------|-----------------------------|---------------------------|--------------|----------------------------|----------|----------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| I Fluoxetine | | | | | | | |
| Liu 2004 | 30 | 7.43 (3.63) | 30 | (5.63) | - | 12.9 % | -0.74 [-1.27, -0.22] |
| Robinson 2000a | 14 | 9.8 (4.8) | 13 | 9.9 (5.1) | + | 12.1 % | -0.02 [-0.77, 0.74] |
| Robinson 2000b | 13 | 4.7 (3.8) | 15 | 5.5 (2.9) | + | 12.1 % | -0.23 [-0.98, 0.51] |
| Zhou 2003 | 28 | 3.5 (1.3) | 26 | 3.3 (1.3) | + | 12.9 % | 0.15 [-0.38, 0.69] |
| Subtotal (95% CI) | 85 | | 84 | | • | 50.1 % | -0.23 [-0.67, 0.21] |
| Heterogeneity: Tau ² = 0.10 | ; Chi ² = 5 | .93, df = 3 (P = 0. | I); I ² =49% | 6 | | | |
| Test for overall effect: $Z =$ | I.02 (P = 0 | D.3T) | | | | | |
| 2 Sertraline | | | | | | | |
| Finkenzeller 2009 | 23 | 6.9 (0.57) | 27 | 6.7 (0.53) | Ē | 12.8 % | 0.36 [-0.20, 0.92] |
| Subtotal (95% CI) | 23 | | 27 | | • | 12.8 % | 0.36 [-0.20, 0.92] |
| Heterogeneity: not applicab | ole | | | | | | |
| Test for overall effect: $Z =$ | I.25 (P = 0 | 0.21) | | | | | |
| 3 Citalopram | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicab | | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | |
| 4 Paroxetine He 2005 | 27 | 5.37 (1.66) | 27 | 12.78 (1.93) | + | 11.3 % | -4.06 [-5.01, -3.10 |
| | | . , | | . , | | | |
| Lai 2006 | 40 | 50.2 (9.4) | 40 | 54.2 (15.2) | - | 13.2 % | -0.31 [-0.75, 0.13] |
| Ye 2004 | 30 | 9.82 (2.64) | 30 | 14.02 (2.32) | + | 12.7 % | -1.67 [-2.26, -1.08] |
| Subtotal (95% CI) | 97 | | 9 7 | | • | 37.1 % | -1.97 [-3.81, -0.12] |
| Heterogeneity: $Tau^2 = 2.54$ | ; Chi ² = 5 | 2.14, df = 2 (P<0.0 | $0000); ^2 =$ | 96% | | | |
| Test for overall effect: $Z = 2$ | 2.09 (P = 0 | 0.037) | | | | | |
| 5 Escitalopram | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicab | | | | | | | |
| Test for overall effect: not a Total (95% CI) | 205 | | 208 | | • | 100.0 % | -0.77 [-1.52, -0.02] |
| Heterogeneity: $Tau^2 = 1.05$ | - | $6 \mid 4 df = 7 (P < 0)$ | | 97% | | 100.0 /0 | 10.77 [11.92, 10.02] |
| Test for overall effect: $Z = 2$ | | | | /0 | | | |
| Test for subgroup difference | ` | , | 0.03), I ² =7I | 1% | | | |
| | | | , | | | | |
| | | | | | -10 -5 0 5 | 10 | |
| | | | | | Favours SSRI Favours co | ntrol | |
| | | | | | | | |

Analysis 1.8. Comparison I SSRI versus control at end of treatment, by SSRI, Outcome 8 Cognition (continuous scores end of treatment).

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

Comparison: I SSRI versus control at end of treatment, by SSRI

Outcome: 8 Cognition (continuous scores end of treatment)

| Study or subgroup | SSRI | | Control | | | Std. Mean Difference | Weight | Std. Mean Difference |
|----------------------------------|---------------|----------------------|--------------------------|--------------|----------------------------|----------------------------|---------|----------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Ra | ndom,95% Cl | | IV,Random,95% CI |
| l Fluoxetine | | | | | | | | |
| Robinson 2000a | 14 | 25.9 (7.5) | 13 | 24.5 (6.8) | | | 12.8 % | 0.19 [-0.57, 0.95] |
| Robinson 2000b | 13 | 26.1 (7.5) | 15 | 26.8 (2.4) | | • | 12.9 % | -0.13 [-0.87, 0.62] |
| Wiart 2000 | 16 | 24.8 (3.9) | 15 | 26.2 (3) | • | | 13.2 % | -0.39 [-1.10, 0.32] |
| Xu 2007 | 36 | 28.36 (2.57) | 36 | 27.31 (5.88) | | | 15.2 % | 0.23 [-0.23, 0.69] |
| Subtotal (95% CI) | 79 | | 79 | | - | - | 54.1 % | 0.04 [-0.27, 0.35] |
| Heterogeneity: $Tau^2 = 0.0$; | $Chi^2 = 2.3$ | 38, df = 3 (P = 0.50 |); I ² =0.0% | | | | | |
| Test for overall effect: $Z = 0$ | 0.24 (P = | 0.81) | | | | | | |
| 2 Sertraline | | | | | | | | |
| Guo 2009 | 40 | 19.26 (6.87) | 40 | 15.74 (6.28) | | | 15.3 % | 0.53 [0.08, 0.98] |
| Subtotal (95% CI) | 40 | | 40 | | | - | 15.3 % | 0.53 [0.08, 0.98] |
| Heterogeneity: not applicat | ble | | | | | | | |
| Test for overall effect: $Z = 2$ | 2.33 (P = | 0.020) | | | | | | |
| 3 Citalopram | | | | | | | | |
| Li 2006 | 50 | 28.36 (2.57) | 49 | 24.32 (2.14) | | • | 15.2 % | 1.69 [1.23, 2.16] |
| Subtotal (95% CI) | 50 | | 49 | | | | 15.2 % | 1.69 [1.23, 2.16] |
| Heterogeneity: not applicat | ble | | | | | | | |
| Test for overall effect: $Z = T$ | 7.19 (P < | 0.00001) | | | | | | |
| 4 Escitalopram | 10 | 00 0 <i>(</i> 15 1) | | <u></u> | | _ | 155.04 | |
| Robinson 2008 | 43 | 89.8 (15.1) | 45 | 91 (17.8) | | | 15.5 % | -0.07 [-0.49, 0.35] |
| Subtotal (95% CI) | 43 | | 45 | | | | 15.5 % | -0.07 [-0.49, 0.35] |
| Heterogeneity: not applicat | | | | | | | | |
| Test for overall effect: $Z = 0$ | ` | 0.74) | | | | | | |
| Total (95% CI) | 212 | | 213 | | | | 100.0 % | 0.32 [-0.23, 0.86] |
| Heterogeneity: $Tau^2 = 0.45$ | | | $000); ^2 =$ | 86% | | | | |
| Test for overall effect: Z = | ` | , | | | | | | |
| Test for subgroup difference | es: Chi² = | 40.45, df = 3 (P = | 0.00), I ² =9 | 13% | | | | |
| | | | | | -1 -0.5 | 0 0.5 1 | | |
| | | | | | -1 -0.5 Favours control | 0 0.5 I Favours SSRI | | |
| | | | | | ravours control | Favours SSRI | | |

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

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Analysis I.9. Comparison I SSRI versus control at end of treatment, by SSRI, Outcome 9 Death.

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

Comparison: I SSRI versus control at end of treatment, by SSRI

Outcome: 9 Death

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|-------------------|------|---------|------------------------------|----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95 Cl |
| Fluoxetine | | | | |
| Brown 1998 | 0/10 | 0/10 | | 0.0 [0.0, 0.0] |
| Chen 2001 | 0/21 | 0/20 | | 0.0 [0.0, 0.0] |
| Cheng 2003 | 0/25 | 0/32 | | 0.0 [0.0, 0.0] |
| Chollet 2011 | 1/59 | 1/59 | | 1.00 [0.06, 15.61] |
| Dam 1996 | 0/18 | 0/17 | | 0.0 [0.0, 0.0] |
| Feng 2004 | 0/18 | 0/18 | | 0.0 [0.0, 0.0] |
| Fruehwald 2003 | 1/28 | 0/16 | | 1.76 [0.08, 40.80] |
| He 2004 | 0/36 | 0/35 | | 0.0 [0.0, 0.0] |
| Hu 2002 | 0/42 | 0/30 | | 0.0 [0.0, 0.0] |
| Huang 2002 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Ji 2000 | 0/20 | 0/20 | | 0.0 [0.0, 0.0] |
| Li 2004a | 0/33 | 0/34 | | 0.0 [0.0, 0.0] |
| Li 2004b | 0/37 | 0/36 | | 0.0 [0.0, 0.0] |
| Li 2008 | 0/60 | 0/30 | | 0.0 [0.0, 0.0] |
| Liang 2003 | 0/42 | 0/21 | | 0.0 [0.0, 0.0] |
| Liu 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Robinson 2000a | 0/23 | 1/17 | | 0.25 [0.01, 5.79] |
| Robinson 2000b | 0/17 | 0/16 | | 0.0 [0.0, 0.0] |
| Song 2006 | 0/41 | 0/41 | | 0.0 [0.0, 0.0] |
| Wen 2006 | 0/42 | 0/42 | | 0.0 [0.0, 0.0] |
| Wiart 2000 | 0/16 | 0/15 | | 0.0 [0.0, 0.0] |
| | | | 0.01 0.1 1 10 100 | |
| | | | Favours SSRI Favours control | |

(Continued . . .)

| Study or subgroup | SSRI | Control | Risk Ratio M- | (Continued) Risk Ratio M- |
|---|------|--------------------------------------|---|----------------------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,959 Cl |
| Xu 2001 | 0/32 | 0/31 | | 0.0 [0.0, 0.0] |
| Xu 2007 | 0/36 | 0/36 | | 0.0 [0.0, 0.0] |
| Zhou 2003 | 0/28 | 0/26 | | 0.0 [0.0, 0.0] |
| Zhou 2008 | 0/36 | 0/40 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 790 | 712 | - | 0.78 [0.14, 4.39] |
| Total events: 2 (SSRI), 2 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = Test for overall effect: Z = 0.28 (P 2 Sertraline | | ; I ² =0.0% | | |
| Almeida 2006 | 2/48 | 1/52 | | 2.17 [0.20, 23.14] |
| Burns 1999 | / 4 | 1/14 | | 1.00 [0.07, 14.45] |
| Guo 2009 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Murray 2005 | 0/62 | 2/61 | | 0.20 [0.01, 4.02] |
| Xie 2005 | 0/65 | 0/65 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 3 (SSRI), 4 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = Test for overall effect: $Z = 0.12$ (P 3 Citalopram | , , | 232 ; I ² =0.0% | | 0.91 [0.20, 4.19] |
| Acler 2009 | 0/10 | 0/10 | | 0.0 [0.0, 0.0] |
| Andersen 1994 | 2/33 | 2/33 | -+ | 1.00 [0.15, 6.68] |
| Li 2006 | 1/52 | 2/53 | | 0.5 [0.05, 5.45] |
| Liu 2006 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Miao 2004 | 0/45 | 0/45 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 3 (SSRI), 4 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = Test for overall effect: $Z = 0.35$ (P 4 Paroxetine | , , | 171 ; I ² =0.0% | | 0.77 [0.17, 3.38] |
| Chen T 2005 | 0/40 | 0/38 | | 0.0 [0.0, 0.0] |
| He 2005 | 0/27 | 0/27 | | 0.0 [0.0, 0.0] |
| Lai 2006 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Li 2002 | 0/46 | 0/46 | | 0.0 [0.0, 0.0] |
| Li 2005 | 0/74 | 0/74 | | 0.0 [0.0, 0.0] |
| Xu 2006 | 0/32 | 2/32 | | 0.20 [0.01, 4.01] |
| | | | 0.01 0.1 1 10 100 Favours SSRI Favours control | (Continued) |

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| (Continued Risk Ratio M- H,Random,9. | Risk Ratio M- H,Random,95% | Control | SSRI | Study or subgroup |
|--|----------------------------------|---------------------------|---------------------------------|---|
| Cl | Cl | n/N | n/N | |
| 0.0 [0.0, 0.0] | | 0/57 | 0/64 | Yang 2002 |
| 0.0 [0.0, 0.0] | | 0/22 | 0/20 | Yang 2011 |
| 0.0 [0.0, 0.0] | | 0/30 | 0/30 | Ye 2004 |
| 0.20 [0.01, 4.01] | | 366 | 373 | Subtotal (95% CI) |
| | | | | Total events: 0 (SSRI), 2 (Control) |
| | | l ² =0.0% | 0.0, df = 0 (P = 1.00); I^{2} | Heterogeneity: $Tau^2 = 0.0$; $Chi^2 =$ |
| | | | = 0.29) | Test for overall effect: Z = 1.05 (P |
| | | | | 5 Escitalopram |
| 4.92 [0.24, 100.25] | | 0/58 | 2/59 | Robinson 2008 |
| 4.92 [0.24, 100.25] | | 58 | 59 | Subtotal (95% CI) |
| | | | | Total events: 2 (SSRI), 0 (Control) |
| | | | | Heterogeneity: not applicable |
| | | | = 0.30) | Test for overall effect: Z = 1.04 (P |
| | | | | 6 Sertraline or fluoxetine |
| 0.20 [0.01, 4.11] | | 2/92 | 0/92 | Jia 2005 |
| 0.20 [0.01, 4.11] | | 92 | 92 | Subtotal (95% CI) |
| | | | | Total events: 0 (SSRI), 2 (Control) |
| | | | | Heterogeneity: not applicable |
| | | | = 0.30) | Test for overall effect: $Z = 1.04$ (P |
| 0.76 [0.34, 1.70] | - | 1631 | 1713 | Total (95% CI) |
| | | | ol) | Total events: 10 (SSRI), 14 (Contro |
| | | 5); l ² =0.0% | 5.54, df = 10 (P = 0.85) | Heterogeneity: Tau ² = 0.0; Chi ² = |
| | | | = 0.50) | Test for overall effect: $Z = 0.67$ (P |
| | | 69), I ² =0.0% | = 3.04, df = 5 (P = 0.6 | Test for subgroup differences: Chi ² |
| | | | | |
| | 0.01 0.1 1 10 100 | | | |
| | Favours SSRI Favours control | | | |

Analysis 1.10. Comparison I SSRI versus control at end of treatment, by SSRI, Outcome 10 Seizures.

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

Comparison: I SSRI versus control at end of treatment, by SSRI

Outcome: 10 Seizures

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|-----------|-------------------------|---|-----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,959 Cl |
| Fluoxetine | n/IN | n/in | G | CI |
| Chollet 2011 | 1/59 | 0/59 | _ | 3.00 [0.12, 72.18] |
| Dam 1996 | 2/18 | 0/17 | | 4.74 [0.24, 92.07] |
| He 2004 | 0/36 | 0/35 | | 0.0 [0.0, 0.0] |
| Liang 2003 | 0/42 | 0/21 | | 0.0 [0.0, 0.0] |
| Wiart 2000 | 1/16 | 1/15 | _ | 0.94 [0.06, 13.68] |
| Subtotal (95% CI) | 171 | 147 | | 2.19 [0.41, 11.85] |
| Total events: 4 (SSRI), 1 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0.6 Test for overall effect: Z = 0.91 (P = 0 2 Sertraline | |); I ² =0.0% | | |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable | 0 | 0 | | 0.0 [0.0, 0.0] |
| 3 Citalopram Andersen 1994 | 2/33 | 0/33 | • | 5.00 [0.25, 100.32] |
| Subtotal (95% CI) | 33 | 33 | | 5.00 [0.25, 100.32] |
| Total events: 2 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: Z = 1.05 (P = 0 4 Paroxetine Ye 2004 | | 0/30 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: Z = 0.0 (P < 0.1 5 Escitalopram | 30 | 30 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable | 0 | 0 | | 0.0 [0.0, 0.0] |
| | | | 0.01 0.1 10 100 Favours SSRI Favours control | (Continued) |

| Study or subgroup | SSRI n/N | Control n/N | Risk Ratio M- H,Random,95% Cl | (Continued) Risk Ratio M- H,Random,95% Cl |
|---|------------------------------|---------------------------|--|--|
| 6 Sertraline or fluoxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicab | ble | | | |
| Total (95% CI) | 234 | 210 | | 2.67 [0.61, 11.63] |
| Total events: 6 (SSRI), 1 (Control) | | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = | 0.91, df = 3 (P = 0.82 |); I ² =0.0% | | |
| Test for overall effect: $Z = 1.31$ (P | = 0.19) | | | |
| Test for subgroup differences: Chi | $^2 = 0.22$, df = 1 (P = 0. | 64), I ² =0.0% | | |
| | | | | |

0.01 0.1 1 10 100 Favours SSRI Favours control

Analysis I.II. Comparison I SSRI versus control at end of treatment, by SSRI, Outcome II Gastrointestinal side effects.

| Review: Selective serotonin re | euptake inhibitors (SSRIs) | for stroke recovery | | |
|--------------------------------|----------------------------|---------------------|------------------------------|-----------------------|
| Comparison: I SSRI versus co | ontrol at end of treatmen | t, by SSRI | | |
| Outcome: II Gastrointestinal | l side effects | | | |
| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| I Fluoxetine | | | | |
| Chollet 2011 | 14/59 | 6/59 | | 2.33 [0.96, 5.66] |
| Dam 1996 | 2/18 | 0/17 | | 4.74 [0.24, 92.07] |
| He 2004 | 0/36 | 0/35 | | 0.0 [0.0, 0.0] |
| Hu 2002 | 5/42 | 0/30 | | 7.93 [0.46, 138.20] |
| Huang 2002 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Li 2004a | 3/33 | 0/34 | | 7.21 [0.39, 134.32] |
| Li 2008 | 6/60 | 3/30 | _ | 1.00 [0.27, 3.72] |
| | | | 0.01 0.1 10 100 | |
| | | | Favours SSRI Favours control | |
| | | | | (Continued) |

(... Continued)

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|-----------------------------------|-------------------------|--------------------|------------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95 Cl |
| Liang 2003 | 4/42 | 4/21 | | 0.50 [0.14, 1.80] |
| Liu 2004 | 3/30 | 0/30 | | 7.00 [0.38, 129.93] |
| Wiart 2000 | 1/16 | 3/16 | | 0.33 [0.04, 2.87] |
| Xu 2007 | 4/36 | 1/36 | | 4.00 [0.47, 34.07] |
| Subtotal (95% CI) | 412 | 348 | • | 1.68 [0.82, 3.42] |
| Total events: 42 (SSRI), 17 (Control) Heterogeneity: Tau ² = 0.30; Chi ² = Test for overall effect: Z = 1.43 (P = |) .05, df = 8 (P = 0.1 | | | 1.00 [0.02, 0.12] |
| 2 Sertraline Burns 1999 | 0/14 | 1/14 | | 0.33 [0.01, 7.55] |
| Subtotal (95% CI) | 14 | 14 | | 0.33 [0.01, 7.55] |
| Total events: 0 (SSRI), 1 (Control) Heterogeneity: not applicable Test for overall effect: Z = 0.69 (P = 3 Citalopram | = 0.49) | | | |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable 4 Paroxetine | 0 | 0 | | 0.0 [0.0, 0.0] |
| He 2005 | 9/27 | 0/27 | | 19.00 [1.16, 310.94] |
| Ye 2004 | 2/30 | 0/30 | | 5.00 [0.25, 99.95] |
| Subtotal (95% CI) | 57 | 57 | | 10.21 [1.32, 78.77] |
| Total events: 11 (SSRI), 0 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0 Test for overall effect: Z = 2.23 (P = 5 Escitalopram | , , |); l ² =0.0% | | |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable | 0 | 0 | | 0.0 [0.0, 0.0] |
| 6 Sertraline and paroxetine Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total (95% CI) | 483 | 419 | • | 1.90 [0.94, 3.85] |
| Total events: 53 (SSRI), 18 (Control) Heterogeneity: Tau ² = 0.43; Chi ² = Test for overall effect: Z = 1.79 (P = Test for subgroup differences: Chi ² = | 15.97, df = 11 (P = 0 = 0.073) | , | | |

Analysis 1.12. Comparison I SSRI versus control at end of treatment, by SSRI, Outcome 12 Bleeding.

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

Comparison: I SSRI versus control at end of treatment, by SSRI

Outcome: 12 Bleeding

| Study or subgroup | SSRI | Control | Risk Ratio M- | Weight | Risk Ratio M- |
|--------------------------------------|------------|---------|------------------------------|--------|----------------------|
| | n/N | n/N | H,Random,95% Cl | | H,Random,95 Cl |
| I Fluoxetine | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Contro | ol) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applie | cable | | | | |
| 2 Sertraline | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Contro | ol) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applie | cable | | | | |
| 3 Citalopram | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Contro | ol) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applie | cable | | | | |
| 4 Paroxetine | | | | | |
| GlaxoSmithKline 1998 | 1/112 | 0/117 | | 42.6 % | 3.13 [0.13, 76.10] |
| Subtotal (95% CI) | 112 | 117 | | 42.6 % | 3.13 [0.13, 76.10] |
| Total events: I (SSRI), 0 (Contro | ol) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 0.70$ | (P = 0.48) | | | | |
| 5 Escitalopram | | | | | |
| Robinson 2008 | 1/59 | 1/59 | | 57.4 % | 1.00 [0.06, 15.61] |
| Subtotal (95% CI) | 59 | 59 | | 57.4 % | 1.00 [0.06, 15.61] |
| Total events: (SSRI), (Contro | ol) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 0.0$ (| P = 1.0) | | | | |
| 6 Sertraline or fluoxetine | | | | | |
| | | | | | |
| | | | 0.01 0.1 1 10 100 | | |
| | | | Favours SSRI Favours control | | (Continued) |
| | | | | | (Conunued) |



Analysis 1.14. Comparison I SSRI versus control at end of treatment, by SSRI, Outcome 14 Change in cognition between baseline and end of treatment.

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

Comparison: I SSRI versus control at end of treatment, by SSRI

Outcome: 14 Change in cognition between baseline and end of treatment

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Std. Mean Difference |
|----------------------------|--------------|------------|---------|-----------|-----------------------------|---------|----------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| I Sertraline | | | | | | | |
| Almeida 2006 | 48 | 2.6 (3.04) | 51 | 2.6 (3.9) | - | 100.0 % | 0.0 [-0.39, 0.39] |
| Total (95% CI) | 48 | | 51 | | • | 100.0 % | 0.0 [-0.39, 0.39] |
| Heterogeneity: not app | olicable | | | | | | |
| Test for overall effect: 2 | Z = 0.0 (P = | = 1.0) | | | | | |
| Test for subgroup differ | rences: Not | applicable | | | | | |
| | | | | | | | |
| | | | | | -2 -1 0 1 2 | | |
| | | | | | Favours SSRI Favours contro | l | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

Analysis 1.15. Comparison I SSRI versus control at end of treatment, by SSRI, Outcome 15 Leaving the trial before the end of scheduled follow-up.

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

Comparison: I SSRI versus control at end of treatment, by SSRI

Outcome: 15 Leaving the trial before the end of scheduled follow-up

| Risk Ratio M- | Risk Ratio M- | Control | SSRI | Study or subgroup |
|----------------------|--------------------|---------|-------|-------------------|
| H,Random,95 Cl | H,Random,95% Cl | n/N | n/N | |
| | | | | Fluoxetine |
| 3.00 [0.14, 65.90] | | 0/10 | 1/10 | Brown 1998 |
| 0.95 [0.15, 6.13] | | 2/20 | 2/21 | Chen 2001 |
| 0.0 [0.0, 0.0] | | 0/32 | 0/25 | Cheng 2003 |
| 0.67 [0.12, 3.85] | | 3/59 | 2/59 | Chollet 2011 |
| 0.0 [0.0, 0.0] | | 0/17 | 0/16 | Dam 1996 |
| 1.00 [0.16, 6.35] | | 2/18 | 2/18 | Feng 2004 |
| 0.70 [0.28, 1.74] | | 8/26 | 6/28 | Fruehwald 2003 |
| 1.45 [0.52, 4.08] | | 5/40 | 8/44 | He 2004 |
| 0.0 [0.0, 0.0] | | 0/30 | 0/42 | Hu 2002 |
| 0.0 [0.0, 0.0] | | 0/40 | 0/40 | Huang 2002 |
| 0.0 [0.0, 0.0] | | 0/20 | 0/20 | Ji 2000 |
| 1.60 [0.65, 3.96] | <u> </u> | 6/42 | 11/48 | Kong 2007 |
| 0.0 [0.0, 0.0] | | 0/34 | 0/33 | Li 2004a |
| 1.46 [0.45, 4.74] | | 4/36 | 6/37 | Li 2004b |
| 0.50 [0.07, 3.38] | | 2/30 | 2/60 | Li 2008 |
| 0.0 [0.0, 0.0] | | 0/21 | 0/42 | Liang 2003 |
| 0.0 [0.0, 0.0] | | 0/30 | 0/30 | Liu 2004 |
| 1.66 [0.61, 4.51] | | 4/17 | 9/23 | Robinson 2000a |
| 3.76 [0.47, 30.20] | | 1/16 | 4/17 | Robinson 2000b |
| 1.26 [0.58, 2.73] | | 9/56 | 13/64 | Wang 2003 |
| 0.0 [0.0, 0.0] | | 0/42 | 0/42 | Wen 2006 |
| 0.0 [0.0, 0.0] | | 0/15 | 0/16 | Wiart 2000 |
| | | 4/31 | 6/32 | Xu 2001 |

(Continued . . .)

| Study or subgroup | SSRI | Control | Risk Ratio | (Continued) Risk Ratio |
|---|----------------------------------|------------------------|------------------------------|---|
| | n/N | n/N | M- H,Random,95% Cl | M- H,Random,955 Cl |
| Zhou 2003 | 2/30 | 4/30 | | 0.50 [0.10, 2.53] |
| Zhou 2008 | 0/36 | 0/40 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 74 (SSRI), 54 (Contro | 833 | 752 | • | 1.21 [0.87, 1.67] |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 =$ Test for overall effect: $Z = 1.13$ (P 2 Sertraline | , , | ; I ² =0.0% | | |
| Almeida 2006 | 11/55 | 6/56 | _ | 1.87 [0.74, 4.70] |
| Burns 1999 | 0/14 | 0/14 | | 0.0 [0.0, 0.0] |
| Guo 2009 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Murray 2005 | 24/62 | 30/61 | - | 0.79 [0.53, 1.18] |
| Rasmussen 2003 | 35/70 | 35/67 | + | 0.96 [0.69, 1.33] |
| Xie 2005 | 0/65 | 0/65 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 306 | 303 | • | 0.95 [0.69, 1.32] |
| Heterogeneity: Tau ² = 0.03; Chi ² = Test for overall effect: Z = 0.29 (P 3 Citalopram Acler 2009 | | 0/10 | | 0.0 [0.0, 0.0] |
| Andersen 1994 | 6/33 | 1/33 | | 6.00 [0.76, 47.14] |
| Li 2006 | 2/50 | 4/53 | | 0.53 [0.10, 2.77] |
| Liu 2006 | 0/30 | 0/30 | | 0.05 [0.10, 2.77] |
| Miao 2004 | 11/45 | 11/45 | _ | 1.00 [0.48, 2.07] |
| Subtotal (95% CI) | 168 | 1743 | | 1.20 [0.41 , 3.47] |
| Total events: 19 (SSRI), 16 (Contro Heterogeneity: Tau ² = 0.40; Chi ² : Test for overall effect: Z = 0.33 (P 4 Paroxetine | bl) = 3.52, df = 2 (P = 0.17) | | | 1.20 [0.11, 3.17] |
| Chen 2002 | 0/24 | 4/24 | | 0.11 [0.01, 1.96] |
| Chen T 2005 | 0/40 | 0/38 | | 0.0 [0.0, 0.0] |
| GlaxoSmithKline 1998 | 3/ 2 | 3/ 7 | - | 1.04 [0.51, 2.15] |
| He 2005 | 0/27 | 0/27 | | 0.0 [0.0, 0.0] |
| Lai 2006 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Li 2002 | 0/46 | 0/46 | | 0.0 [0.0, 0.0] |
| Li 2005 | 0/74 | 0/74 | | 0.0 [0.0, 0.0] |
| | | | 0.01 0.1 10 100 | |
| | | | Favours SSRI Favours control | (Continued) |

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(... Continued)

| Study or subgroup | SSRI n/N | Control n/N | Risk Ratio M- H,Random,95% Cl | (Continued) Risk Ratio H,Random,95% CI |
|---|---|------------------------------------|---|--|
| Xu 2006 | 4/32 | 3/32 | | 1.33 [0.32, 5.49] |
| Yang 2002 | 4/64 | 7/57 | | 0.51 [0.16, 1.65] |
| Yang 2011 | 0/20 | 0/22 | | 0.0 [0.0, 0.0] |
| Ye 2004 | 1/31 | 0/30 | | 2.91 [0.12, 68.66] |
| Subtotal (95% CI) Total events: 22 (SSRI), 27 (Contro Heterogeneity: Tau ² = 0.0; Chi ² = Test for overall effect: $Z = 0.45$ (P | 4.00, df = 4 (P = 0.41); | 507 I ² =0.0% | • | 0.88 [0.51, 1.52] |
| 5 Sertraline or fluoxetine Jia 2005 | 4/92 | 4/92 | | 1.00 [0.26, 3.88] |
| Subtotal (95% CI) Total events: 4 (SSRI), 4 (Control) Heterogeneity: not applicable Test for overall effect: Z = 0.0 (P = 6 Escitalopram | 92 = 1.0) | 92 | | 1.00 [0.26, 3.88] |
| Robinson 2008 | 7/59 | 5/58 | | 1.38 [0.46, 4.09] |
| Subtotal (95% CI) Total events: 7 (SSRI), 5 (Control) Heterogeneity: not applicable Test for overall effect: Z = 0.57 (P | 59 = 0.57) | 58 | - | 1.38 [0.46, 4.09] |
| Total (95% CI) Total events: 196 (SSRI), 177 (Con Heterogeneity: Tau ² = 0.0; Chi ² = Test for overall effect: $Z = 0.23$ (P Test for subgroup differences: Chi ² | 1968 trol) 18.94, df = 26 (P = 0.84 = 0.82) | , | • | 1.02 [0.86, 1.21] |
| | | | 0.01 0.1 10 100 Favours SSRI Favours control | |

Analysis 1.16. Comparison I SSRI versus control at end of treatment, by SSRI, Outcome 16 Motor deficits.

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

Comparison: I SSRI versus control at end of treatment, by SSRI

Outcome: 16 Motor deficits

| Study or subgroup | SSRI | | Control | | | | Std. Mean erence | | Weight | Std. Mean Difference |
|-----------------------------------|------------------------|---------------------|---------------------------|------------|----|-----------|------------------------|---|---------|----------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | | IV,Randor | m,95% Cl | | | IV,Random,95% CI |
| I Fluoxetine | | | | | | | | | | |
| Chollet 2011 | 57 | -53.7 (27.8) | 56 | -35.1 (22) | | - | | | 55.3 % | -0.74 [-1.12, -0.35] |
| Dam 1996 | 16 | 32.4 (3.8) | 16 | 31.6 (5) | | - | ⊢ | | 44.7 % | 0.18 [-0.52, 0.87] |
| Total (95% CI) | 73 | | 72 | | | - | - | | 100.0 % | -0.33 [-1.22, 0.56] |
| Heterogeneity: Tau ² = | 0.33; Chi ² | = 5.09, df = 1 (P = | 0.02); I ² =80 | % | | | | | | |
| Test for overall effect: 2 | Z = 0.72 (P | = 0.47) | | | | | | | | |
| Test for subgroup diffe | rences: Not | applicable | | | | | | | | |
| | | | | | | | | | | |
| | | | | | -4 | -2 0 | 2 | 4 | | |

-4 -2 0 2 4 Favours SSRI Favours control

Analysis 2.1. Comparison 2 SSRI versus control, at end of follow-up, by SSRI, Outcome I Dependent on modified Rankin score.

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

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

Outcome: I Dependent on modified Rankin score

| Study or subgroup | SSRI | Control | Risk Ratio M- | Weight | Risk Ratio M- |
|---|---------------|---------|----------------------|---------|---------------------|
| | n/N | n/N | H,Random,95% Cl | | H,Random,959 Cl |
| I Sertraline | | | | | |
| Almeida 2006 | 0/44 | 1/50 | | 100.0 % | 0.38 [0.02, 9.04] |
| Subtotal (95% CI) | 44 | 50 | | 100.0 % | 0.38 [0.02, 9.04] |
| Total events: 0 (SSRI), 1 (Control |) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 0.60$ (I | P = 0.55) | | | | |
| 2 Fluoxetine | 0 | 0 | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control Heterogeneity: not applicable |) | | | | |
| Heterogeneity: not applicable Test for overall effect: not applica | ble | | | | |
| Total (95% CI) | 44 | 50 | | 100.0 % | 0.38 [0.02, 9.04] |
| Total events: 0 (SSRI), 1 (Control | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 0.60$ (I | P = 0.55) | | | | |
| Test for subgroup differences: No | ot applicable | | | | |
| | | | | | |
| | | | 0.01 0.1 10 | 100 | |
| | | | Favours SSRI Favours | control | |
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Analysis 2.2. Comparison 2 SSRI versus control, at end of follow-up, by SSRI, Outcome 2 Disability.

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

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

Outcome: 2 Disability

| Study or subgroup | SSRI | | Control | ntrol | | | Std. Mean Difference | | Std. Mean Difference |
|-----------------------------------|------------------------|-----------------------------------|--------------------------|----------------|--------|-----------|----------------------------|---------|----------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | | IV,Ranc | lom,95% Cl | | IV,Random,95% CI |
| Cheng 2003 | 25 | -23.25 (10.12) | 32 | -28.67 (17.59) | | | - | 50.1 % | 0.36 [-0.17, 0.89] |
| Wang 2003 | 51 | 79 (4.7) | 47 | 62 (5.8) | | | | 49.9 % | 3.21 [2.60, 3.82] |
| Total (95% CI) | 76 | | 79 | | | | | 100.0 % | 1.78 [-1.01, 4.57] |
| Heterogeneity: Tau ² = | 3.97; Chi ² | ² = 48.25, df = 1 (P<0 | 0.00001); l ² | =98% | | | | | |
| Test for overall effect: | Z = 1.25 (| P = 0.21) | | | | | | | |
| Test for subgroup diffe | rences: No | ot applicable | | | | | | | |
| | | | | | | | | | |
| | | | | | -4 | -2 | 0 2 4 | | |
| | | | | | Favour | s control | Favours SSRI | | |
| | | | | | | | | | |

Analysis 2.3. Comparison 2 SSRI versus control, at end of follow-up, by SSRI, Outcome 3 Neurological deficit score (higher score: worse outcome).

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

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

Outcome: 3 Neurological deficit score (higher score: worse outcome)

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Std. Mean Difference |
|----------------------------------|------------------------|----------------------|-------------------------------|--------------|----------------------------|----------------|----------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| I Fluoxetine | | | | | | | |
| Cheng 2003 | 25 | 4.63 (2.37) | 32 | 10.85 (7.97) | | 24.4 % | -0.99 [-1.55, -0.44] |
| Fruehwald 2003 | 22 | -52.9 (6.9) | 18 | -53.8 (6.5) | | 23.4 % | 0.13 [-0.49, 0.75] |
| Wang 2003 | 51 | 7.2 (4.6) | 47 | 13.9 (5.1) | | 26.1 % | -1.37 [-1.81, -0.93] |
| Subtotal (95% CI) | 98 | | 9 7 | | | 7 3.9 % | -0.77 [-1.61, 0.08] |
| Heterogeneity: $Tau^2 = 0.49$ | ; $Chi^2 = I$ | 4.98, df = 2 (P = 0 | 0.00056); l ² : | =87% | | | |
| Test for overall effect: $Z = I$ | I.77 (P = | 0.077) | | | | | |
| 2 Sertraline | | | | | | | |
| Guo 2009 | 40 | 24.46 (8.27) | 40 | 27.04 (12.2) | | 26.1 % | -0.25 [-0.69, 0.19] |
| Subtotal (95% CI) | 40 | | 40 | | - | 26.1 % | -0.25 [-0.69, 0.19] |
| Heterogeneity: not applicab | le | | | | | | |
| Test for overall effect: $Z = I$ | I.09 (P = | 0.27) | | | | | |
| Total (95% CI) | 138 | | 137 | | - | 100.0 % | -0.63 [-1.30, 0.04] |
| Heterogeneity: $Tau^2 = 0.40$; | ; Chi ² = 2 | .0.85, df = 3 (P = 0 | 0.000); ² : | =86% | | | |
| Test for overall effect: $Z = I$ | I.86 (P = | 0.064) | | | | | |
| Test for subgroup difference | es: Chi ² = | 1.14, df = 1 (P = 0 | $(0.29), ^2 = _2$ | % | | | |
| | | | | | | | |

-2 -1 0 1 2 Favours SSRI Favours control

Analysis 2.4. Comparison 2 SSRI versus control, at end of follow-up, by SSRI, Outcome 4 Depression (continuous data).

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

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

Outcome: 4 Depression (continuous data)

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Std. Mean Difference |
|--|------------------------|-----------------------|--------------------------|---------------|----------------------------|---------|----------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| I Fluoxetine | | | | | | | |
| Cheng 2003 | 25 | 12.95 (11.54) | 32 | 18.26 (13.72) | | 25.1 % | -0.41 [-0.94, 0.12] |
| Fruehwald 2003 | 22 | 10.8 (11.6) | 18 | 22.2 (15) | | 24.3 % | -0.84 [-1.50, -0.19] |
| Wang 2003 | 51 | 10 (2.1) | 47 | 21.1 (5.5) | | 25.0 % | -2.69 [-3.24, -2.14] |
| Subtotal (95% CI) | 98 | | 9 7 | | | 74.4 % | -1.32 [-2.74, 0.11] |
| Heterogeneity: $Tau^2 = 1.51$ | ; Chi ² = 3 | 37.03, df = 2 (P<0.0 | 00001); l ² = | -95% | | | |
| Test for overall effect: Z = | I.80 (P = | 0.071) | | | | | |
| 2 Sertraline | | | | | | | |
| Guo 2009 | 40 | 2.7 (4.24) | 40 | 15 (5.34) | - | 25.6 % | -0.47 [-0.91, -0.03] |
| Subtotal (95% CI) | 40 | | 40 | | • | 25.6 % | -0.47 [-0.91, -0.03] |
| Heterogeneity: not applicat | ole | | | | | | |
| Test for overall effect: $Z = 2$ | 2.07 (P = | 0.038) | | | | | |
| Total (95% CI) | 138 | | 137 | | - | 100.0 % | -1.10 [-2.16, -0.04] |
| Heterogeneity: Tau ² = 1.08 | ; Chi ² = 4 | 46.35, df = 3 (P<0.0 | 00001); I ² = | -94% | | | |
| Test for overall effect: $Z = Z$ | 2.04 (P = | 0.041) | | | | | |
| Test for subgroup difference | es: Chi² = | : 1.22, df = 1 (P = 0 | $(0.27), ^2 = _2$ | 3% | | | |
| | | | | | | í. | |

-2 0 2 4 Favours SSRI

-4

Favours control

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Analysis 2.5. Comparison 2 SSRI versus control, at end of follow-up, by SSRI, Outcome 5 Depression (dichotomous data).

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

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

Outcome: 5 Depression (dichotomous data)

| Study or subgroup | SSRI | Control | | F | isk Ratio M- | | Weight | Risk Ratio M- |
|--------------------------------|--------------------|---------|-------|----------|-----------------|---------|---------|---------------------|
| | n/N | n/N | | H,Ran | dom,95% Cl | | | H,Random,95% Cl |
| I Sertraline | | | | | | | | |
| Almeida 2006 | 8/48 | 11/51 | | | F | | 100.0 % | 0.77 [0.34, 1.76] |
| Total (95% CI) | 48 | 51 | | - | - | | 100.0 % | 0.77 [0.34, 1.76] |
| Total events: 8 (SSRI), 11 (0 | Control) | | | | | | | |
| Heterogeneity: not applicat | ole | | | | | | | |
| Test for overall effect: $Z =$ | 0.62 (P = 0.54) | | | | | | | |
| Test for subgroup difference | es: Not applicable | | | | | | | |
| | | | | | | | | |
| | | | 0.01 | 0.1 | 1 10 | 100 | | |
| | | | Favou | irs SSRI | Favours | control | | |

Analysis 2.6. Comparison 2 SSRI versus control, at end of follow-up, by SSRI, Outcome 6 Cognition (higher score is better).

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

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

Outcome: 6 Cognition (higher score is better)

| Study or subgroup | SSRI | Control | | | Diff | Std. Mean ference | Weight | Std. Mean Difference |
|----------------------------|-------------|-------------|----|--------------|-----------------|-------------------------|---------|----------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Rando | IV,Random,95% Cl | | IV,Random,95% CI |
| I Sertraline | | | | | | | | |
| Guo 2009 | 40 | 20.82 (7.4) | 40 | 18.95 (6.59) | - | | 100.0 % | 0.26 [-0.18, 0.70] |
| Total (95% CI) | 40 | | 40 | | - | • | 100.0 % | 0.26 [-0.18, 0.70] |
| Heterogeneity: not app | olicable | | | | | | | |
| Test for overall effect: 2 | Z = 1.18 (P | = 0.24) | | | | | | |
| Test for subgroup diffe | rences: Not | applicable | | | | | | |
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| | | | | | Favours control | Favours SSRI | | |

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

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Analysis 2.7. Comparison 2 SSRI versus control, at end of follow-up, by SSRI, Outcome 7 Change in cognition between baseline and follow-up.

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

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

Outcome: 7 Change in cognition between baseline and follow-up

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% Cl |
|---|--------------------------------------|-----------|--------------|----------|---|---------|--|
| l Sertraline Almeida 2006 | 48 | 3.3 (2.8) | 51 | 2.7 (35) | | 100.0 % | 0.02 [-0.37, 0.42] |
| Total (95% CI) Heterogeneity: not app Test for overall effect: 2 Test for subgroup diffe | 48 blicable Z = 0.12 (P | = 0.91) | 51 | | | 100.0 % | 0.02 [-0.37, 0.42] |
| | | | | | -0.5 -0.25 0 0.25 0.5 Favours control Favours SSRI | | |
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Analysis 2.8. Comparison 2 SSRI versus control, at end of follow-up, by SSRI, Outcome 8 Death.

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

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

Outcome: 8 Death

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio |
|-------------------------------------|--------------------------------|-------------------------|--------------------|---------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% CI |
| Cheng 2003 | 0/25 | 0/32 | | 0.0 [0.0, 0.0] |
| Guo 2009 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Wang 2003 | 0/64 | 5/56 | · • | 0.08 [0.00, 1.41] |
| Total (95% CI) | 129 | 128 | | 0.08 [0.00, 1.41] |
| Total events: 0 (SSRI), 5 (Cont | rol) | | | |
| Heterogeneity: $Tau^2 = 0.0$; Ch | $i^2 = 0.0, df = 0 (P = 1.00)$ |); I ² =0.0% | | |
| Test for overall effect: $Z = 1.73$ | 8 (P = 0.084) | | | |
| Test for subgroup differences: | Not applicable | | | |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |

Favours experimental Favours control

Analysis 3.1. Comparison 3 SSRI versus control (according to time since stroke when recruited), Outcome I Dependent on modified Rankin score.

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

Comparison: 3 SSRI versus control (according to time since stroke when recruited)

Outcome: I Dependent on modified Rankin score

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|--|---------|------------------------------|---------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| Mean time since stroke < 2 weeks | 5 | | | |
| Almeida 2006 | 0/55 | 0/56 | | 0.0 [0.0, 0.0] |
| Chollet 2011 | 42/57 | 50/55 | • | 0.81 [0.68, 0.97] |
| Subtotal (95% CI) | 112 | 111 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Control) |) | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0$ | 0.0, df = 0 (P = 1.00); l ² | =0.0% | | |
| Test for overall effect: $Z = 2.34$ (P = | 0.019) | | | |
| 2 Mean time since stroke 2 weeks to | o 3 months at randomi | sation | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 3 Mean time since stroke 3 to 6 mo | nths at randomisation | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 4 Mean time since stroke > 6 month | hs and < 9 months | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 5 Mean time since stroke at random | isation 9 to 12 months | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 6 Mean time since stroke not knowr | ı | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| Total (95% CI) | 112 | 111 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Control) |) | | | |
| | | | 0.01 0.1 10 100 | |
| | | | Favours SSRI Favours control | |
| | | | | (Continued) |

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| Study or subgroup | SSRI | Control | | Risk Ratio M- ndom,95% | (Continued) Risk Ratio M- H,Random,95% |
|---|---------------------------|---------------|--------------|------------------------------|--|
| | n/N | n/N | | Cl | CI |
| Heterogeneity: Tau ² = 0.0; Chi ² | = 0.0, df = 0 (P = 1.00); | $ ^2 = 0.0\%$ | | | |
| Test for overall effect: $Z = 2.34$ (| P = 0.019) | | | | |
| Test for subgroup differences: No | ot applicable | | | | |
| | | | | | |
| | | | 0.01 0.1 | 1 10 100 | |
| | | | Favours SSRI | Favours control | |
| | | | 1200013 3314 | | |
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Analysis 3.2. Comparison 3 SSRI versus control (according to time since stroke when recruited), Outcome 2 Disability.

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

Comparison: 3 SSRI versus control (according to time since stroke when recruited)

Outcome: 2 Disability

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% Cl |
|--------------------------|-----------|---------------|--------------|----------------|--|--------|--|
| I Mean time since stroke | < 3 month | s | | | | | |
| Acler 2009 | 10 | 82 (28) | 10 | 75 (25) | | 3.8 % | 0.25 [-0.63, 1.13] |
| Chen 2001 | 19 | 79.31 (8.94) | 18 | 71.56 (9.41) | | 4.3 % | 0.83 [0.15, 1.50] |
| Chen T 2005 | 40 | 65.76 (5.92) | 38 | 51.76 (7.32) | | 4.6 % | 2.09 [1.53, 2.64] |
| Cheng 2003 | 25 | -26.38 (14.2) | 32 | -29.15 (17.38) | | 4.7 % | 0.17 [-0.35, 0.69] |
| He 2005 | 27 | 84.26 (8.41) | 27 | 78.33 (15.01) | | 4.7 % | 0.48 [-0.06, 1.02] |
| Kong 2007 | 37 | 60.4 (12.5) | 36 | 52.3 (13.5) | | 4.9 % | 0.62 [0.15, 1.09] |
| Li 2006 | 50 | 64.36 (8.23) | 49 | 59.17 (9.02) | - | 5.0 % | 0.60 [0.19, 1.00] |
| Li 2008 | 58 | 40.8 (3.7) | 28 | 38.4 (5.8) | | 4.9 % | 0.53 [0.07, 0.99] |
| Liu 2004 | 30 | 70.33 (10.74) | 30 | 64.33 (7.74) | | 4.7 % | 0.63 [0.11, 1.15] |
| Robinson 2000a | 14 | 59.2 (11.6) | 13 | 56.2 (7.8) | | 4.1 % | 0.29 [-0.47, 1.05] |
| Robinson 2000b | 13 | 60.5 (10.8) | 15 | 63.1 (8.2) | <u> </u> | 4.1 % | -0.27 [-1.01, 0.48] |
| | | | | | -4 -2 0 2 4 Favours control Favours SSRI | | |

(Continued . . .)

(... Continued)

| Study or subgroup SSR N Wiart 2000 16 Xie 2005 65 | Mean(SD) | Control N | | Std. Mean Difference | Weight | Std Mear Difference |
|---|------------------------|---------------------------|---------------|----------------------------|---------|---------------------------|
| Wiart 2000 I é Xie 2005 65 | · · / | Ν | | | | |
| Xie 2005 65 | 87.4 (22.8) | | Mean(SD) | IV,Random,95% Cl | | IV,Random,95% C |
| | | 15 | 88.7 (25.3) | | 4.3 % | -0.05 [-0.76, 0.65] |
| | 88.7 (7.9) | 65 | 79.8 (4.5) | - | 5.1 % | 1.38 [0.99, 1.76] |
| Xu 2001 26 | 73 (4.4) | 27 | 67 (4.1) | | 4.5 % | 1.39 [0.79, 2.00] |
| Xu 2006 28 | -27.63 (4.81) | 29 | -32.81 (4.13) | | 4.6 % | 1.14 [0.58, 1.70] |
| Ye 2004 30 | 78.75 (14.19) | 30 | 50.26 (13.4) | | 4.5 % | 2.04 [1.41, 2.67] |
| Zhou 2003 28 | -27.8 (7.1) | 26 | -32.5 (7.8) | | 4.7 % | 0.62 [0.07, 1.17] |
| Subtotal (95% CI) 516 | | 488 | | • | 77.5 % | 0.77 [0.47, 1.06] |
| Heterogeneity: Tau ² = 0.30; Chi ² : Test for overall effect: $Z = 5.11$ (P 2 Mean time since stroke 3 to 6 m | < 0.00001) | , | -79% | | | |
| Dam 1996 16 | 61.9 (13) | 16 | 54.1 (21.1) | + | 4.3 % | 0.43 [-0.27, 1.14 |
| Subtotal (95% CI) 16 | | 16 | | - | 4.3 % | 0.43 [-0.27, 1.14] |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: $Z = 1.21$ (P | = 0.23) | | | | | |
| 3 Mean time since stroke > 6 mor | | | | | | |
| Liu 2006 30 | 64.4 (12.1) | 30 | 35.4 (9.1) | | 4.2 % | 2.67 [1.97, 3.38 |
| Subtotal (95% CI) 30 | | 30 | | • | 4.2 % | 2.67 [1.97, 3.38] |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: $Z = 7.40$ (P | , | | | | | |
| 4 Mean time since stroke 9 to 12 | | 0 | | | 0.0.0/ | |
| Subtotal (95% CI) 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0 |
| Heterogeneity: not applicable Test for overall effect: not applicab | | | | | | |
| 5 Mean time since stroke not know | | | | | | |
| Chen 2002 24 | | 20 | 51.5 (10.3) | | 4.5 % | 0.82 [0.20, 1.44 |
| Wang 2003 51 | 75 (4.2) | 47 | 61 (6.9) | | 4.7 % | 2.46 [1.93, 2.98] |
| Xu 2007 36 | 64.4 (8.23) | 36 | 56.9 (6.68) | | 4.8 % | 0.99 [0.50, 1.48] |
| Subtotal (95% CI) 111 | | 103 | | - | 14.0 % | 1.43 [0.40, 2.45] |
| Heterogeneity: $Tau^2 = 0.74$; Chi ² : | = 21.20, df = 2 (P = 0 | .00002); I ² = | =91% | | | |
| Test for overall effect: $Z = 2.73$ (P | = 0.0063) | | | | | |
| Total (95% CI) 673 | | 637 | | • | 100.0 % | 0.92 [0.62, 1.23 |
| Heterogeneity: Tau ² = 0.45; Chi ² : | = 136.50, df = 21 (P< | 0.00001); l ² | =85% | | | |
| Test for overall effect: $Z = 5.91$ (P | , | | | | | |
| Test for subgroup differences: Chi ² | = 26.98, df = 3 (P = | 0.00), 2 =89 | 9% | | | |
| | | | | <u> </u> | | |

Analysis 3.3. Comparison 3 SSRI versus control (according to time since stroke when recruited), Outcome 3 Neurological deficit score.

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

Comparison: 3 SSRI versus control (according to time since stroke when recruited)

Outcome: 3 Neurological deficit score

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|--|------------|-----------------|----------------------------|---------------|--|---------------|--|
| Mean time since stroke < | 3 months | | | | | | |
| Acler 2009 | 10 | 2.3 (2) | 10 | 3.5 (1.3) | | 2.7 % | -0.68 [-1.59, 0.23] |
| Chen 2001 | 19 | -49.72 (4.07) | 18 | -43.13 (3.64) | | 3.0 % | -1.67 [-2.43, -0.91] |
| Cheng 2003 | 25 | 6.5 (3.19) | 32 | 10.96 (8.13) | _ | 3.5 % | -0.68 [-1.22, -0.14] |
| Chollet 2011 | 57 | 5.8 (3.7) | 55 | 6.9 (4.4) | | 3.8 % | -0.27 [-0.64, 0.10] |
| Feng 2004 | 16 | 9.1 (3.2) | 16 | 14.4 (2.2) | 4 | 2.8 % | -1.88 [-2.73, -1.03] |
| Fruehwald 2003 | 26 | -55.5 (4.8) | 24 | -52.8 (5.4) | _ _ | 3.4 % | -0.52 [-1.09, 0.04] |
| He 2004 | 36 | 10.41 (6.36) | 35 | 14.43 (7.94) | | 3.6 % | -0.55 [-1.03, -0.08] |
| He 2005 | 27 | 6.48 (1.58) | 27 | 8.33 (3.86) | | 3.5 % | -0.62 [-1.17, -0.07] |
| Huang 2002 | 40 | 4.02 (1.86) | 40 | 8.57 (3.64) | • | 3.6 % | -1.56 [-2.06, -1.06] |
| Kong 2007 | 37 | 8.6 (6.4) | 36 | 11.2 (6.4) | | 3.6 % | -0.40 [-0.87, 0.06] |
| Li 2004a | 33 | 6.23 (3.11) | 34 | 12.86 (6.36) | <u> </u> | 3.5 % | -1.30 [-1.83, -0.77] |
| Li 2006 | 50 | 21.89 (1.57) | 49 | 23.77 (1.46) | | 3.7 % | -1.23 [-1.66, -0.80] |
| Liang 2003 | 42 | 11.74 (3.23) | 21 | 17.32 (5.19) | | 3.4 % | -1.38 [-1.96, -0.80] |
| Liu 2004 | 30 | 9.2 (2.06) | 30 | 10.47 (9.2) | | 3.6 % | -0.19 [-0.70, 0.32] |
| Wen 2006 | 42 | 10.1 (1.9) | 42 | 16.4 (2.5) | | 3.3 % | -2.81 [-3.42, -2.20] |
| Xu 2001 | 26 | 8.2 (5.2) | 27 | 12.4 (4.3) | | 3.4 % | -0.87 [-1.43, -0.30] |
| Xu 2006 | 28 | . (4.32) | 29 | 3.63 (3.15) | | 3.5 % | -0.66 [-1.19, -0.13] |
| Ye 2004 | 30 | 8.3 (3.8) | 30 | 16 (4.8) | •• | 3.4 % | -1.76 [-2.36, -1.15] |
| Zhou 2003 | 28 | 9 (3.8) | 26 | 12.2 (6.1) | | 3.5 % | -0.63 [-1.17, -0.08] |
| Subtotal (95% CI) Heterogeneity: $Tau^2 = 0.34$; | 602 | 954 df - 19 /P/ | 581 | -07% | • | 65.0 % | -1.01 [-1.31, -0.72] |
| Test for overall effect: $Z = 6$ | | | J.00001); I [_] - | -02/0 | | | |
| 2 Mean time since stroke 3 | to 6 mont | hs | | | | | |
| Dam 1996 | 16 | 44.1 (9.4) | 16 | 46.8 (9.9) | | 3.2 % | -0.27 [-0.97, 0.42] |
| | | | | | -2 -1 0 1 2 | 1 | |
| | | | | | Favours SSRI Favours cont | rol | (Continued) |

| | | | | | Std. Mean | | Std Mear |
|---|---------------------------|-----------------------|--------------------------|--------------|-------------------------------------|--------------|-------------------------|
| Study or subgroup | SSRI | | Control | | Difference | Weight | Difference |
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% CI | | IV,Random,95% C |
| Subtotal (95% CI) | 16 | | 16 | | | 3.2 % | -0.27 [-0.97, 0.42 |
| Heterogeneity: not applicable Test for overall effect: Z = 0.7 | | 44) | | | | | |
| 3 Mean time since stroke 6 to | | , | | | | | |
| Guo 2009 | 40 | 29.07 (8.02) | 40 | 33.78 (8.63) | | 3.7 % | -0.56 [-1.01, -0.11 |
| Liu 2006 | 30 | 13.3 (3.8) | 30 | 22.4 (4.1) | ← | 3.2 % | -2.27 [-2.93, -1.61 |
| Subtotal (95% CI) | 70 | | 70 | | | 6.9 % | -1.40 [-3.08, 0.28] |
| Heterogeneity: $Tau^2 = 1.38;$ | Chi ² = 17 | ′.79, df = 1 (P = 0.0 |)0002); l ² = | =94% | | | |
| Test for overall effect: $Z = 1.6$ | 63 (P = 0. | .10) | | | | | |
| Mean time since stroke 9 to | | ths | 0 | | | 0.0.0/ | |
| Subtotal (95% CI) Heterogeneity: not applicable | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Test for overall effect: not applicable | | | | | | | |
| 5 Mean time since stroke not | | | | | | | |
| Burns 1999 | 14 | -29.7 (14.7) | 14 | -32.2 (13.4) | | 3.1 % | 0.17 [-0.57, 0.91 |
| Chen 2002 | 24 | 10 (4.8) | 20 | 14.8 (4.8) | | 3.3 % | -0.98 [-1.61, -0.35 |
| Jia 2005 | 86 | 10.4 (8.5) | 88 | 22.6 (8.9) | | 3.9 % | -1.40 [-1.73, -1.06 |
| Li 2002 | 46 | 11.5 (2.8) | 46 | 19 (4) | ← | 3.5 % | -2.15 [-2.67, -1.64] |
| Li 2005 | 74 | 12.9 (5.1) | 74 | 18.7 (5.4) | _ — | 3.8 % | -1.10 [-1.44, -0.75] |
| Wang 2003 | 51 | 9.5 (3.5) | 47 | 15.6 (4.6) | | 3.7 % | -1.49 [-1.94, -1.04] |
| Xu 2007 | 36 | 21.89 (1.57) | 36 | 20.78 (4.06) | <u></u> | 3.6 % | 0.36 [-0.11, 0.82] |
| Subtotal (95% CI) | 331 | | 325 | | - | 24.9 % | -0.96 [-1.56, -0.36] |
| Heterogeneity: $Tau^2 = 0.59;$ | | , | $ 00 ; ^2 = 9$ | 92% | | | |
| Test for overall effect: Z = 3. Total (95% CI) | 14 (P = 0. 1019 | .0017) | 992 | | • | 100.0 % | -1.00 [-1.26, -0.75] |
| Heterogeneity: Tau ² = 0.41; | | 93.63. df = 28 (P<0 | | =86% | | 100.0 % | -1.00 [-1.20, -0./ 5] |
| Test for overall effect: $Z = 7.7$ | | | | | | | |
| T . C | $: Chi^2 = 4$ | 4.03, df = 3 (P = 0.2 | 26), I ² =25 | % | | | |
| lest for subgroup differences | | | | | | | |
| lest for subgroup differences | | | | | | | |
| lest for subgroup differences | | | | | -2 -1 0 1 Favours SSRI Favours c | 2 | |

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Analysis 3.4. Comparison 3 SSRI versus control (according to time since stroke when recruited), Outcome 4 Depression (continuous).

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

Comparison: 3 SSRI versus control (according to time since stroke when recruited)

Outcome: 4 Depression (continuous)

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Std. Mean Difference |
|-------------------------|-------|---------------|---------|---------------|----------------------------|--------|----------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% Cl | | IV,Random,95% CI |
| Time since stroke < 3 m | onths | | | | | | |
| Acler 2009 | 10 | 6.6 (3.6) | 10 | 8 (3) | | 2.5 % | -0.40 [-1.29, 0.48] |
| Andersen 1994 | 33 | 11.4 (5.1) | 33 | 4. (4.7) | | 2.7 % | -0.54 [-1.04, -0.05] |
| Chen 2001 | 19 | 10.82 (6.25) | 18 | 18.48 (6.28) | | 2.6 % | -1.20 [-1.90, -0.49] |
| Chen T 2005 | 40 | 10.98 (3.74) | 38 | 22.45 (3.56) | | 2.6 % | -3.11 [-3.78, -2.44] |
| Cheng 2003 | 25 | 13.64 (11.02) | 32 | 17.98 (12.53) | | 2.7 % | -0.36 [-0.89, 0.17] |
| Chollet 2011 | 56 | 5.4 (4.9) | 54 | 8.4 (7.9) | | 2.7 % | -0.46 [-0.83, -0.08] |
| Feng 2004 | 16 | 34.9 (4.6) | 16 | 41.1 (4.7) | - _ | 2.5 % | -1.30 [-2.07, -0.53] |
| Finkenzeller 2009 | 23 | 12.1 (1.05) | 27 | 10.6 (0.97) | | 2.6 % | 1.47 [0.83, 2.10] |
| Fruehwald 2003 | 26 | 9.5 (7.9) | 24 | .2 (2.4) | | 2.7 % | -0.16 [-0.72, 0.39] |
| He 2004 | 36 | 14.28 (2.31) | 35 | 20.32 (2.82) | <u> </u> | 2.6 % | -2.32 [-2.93, -1.71] |
| He 2005 | 27 | 10.11 (1.08) | 27 | 17.48 (1.05) | • | 2.1 % | -6.82 [-8.26, -5.38] |
| Huang 2002 | 40 | 4.76 (0.6) | 40 | 16.34 (1.3) | • | 1.8 % | -11.33 [-13.18, -9.47] |
| Kong 2007 | 37 | 12.6 (5.3) | 36 | 16.3 (3.7) | | 2.7 % | -0.80 [-1.28, -0.32] |
| Lai 2006 | 40 | 12.5 (8.4) | 40 | 21.5 (4.3) | | 2.7 % | -1.34 [-1.82, -0.85] |
| Li 2006 | 50 | 5.61 (5.32) | 49 | 20.26 (6.08) | | 2.7 % | -2.55 [-3.08, -2.01] |
| Li 2008 | 58 | 14.5 (2.4) | 28 | 18.7 (3.9) | <u> </u> | 2.7 % | -1.40 [-1.90, -0.90] |
| Liang 2003 | 42 | 9.67 (4.48) | 21 | 19.19 (3.12) | | 2.6 % | -2.30 [-2.97, -1.63] |
| Robinson 2000a | 14 | 18.5 (7.6) | 13 | 12.2 (4.7) | | 2.5 % | 0.96 [0.15, 1.76] |
| Robinson 2000b | 13 | 5.9 (3.8) | 15 | 6.2 (4.6) | <u> </u> | 2.6 % | -0.07 [-0.81, 0.67] |
| Song 2006 | 41 | 40.3 (7.25) | 41 | 48.31 (8.02) | | 2.7 % | -1.04 [-1.50, -0.58] |
| Wen 2006 | 42 | 7 (1.1) | 42 | 17.7 (1.8) | • | 2.3 % | -7.11 [-8.29, -5.93] |
| Wiart 2000 | 16 | .8 (6.7) | 15 | 18.7 (10) | | 2.6 % | -0.79 [-1.53, -0.06] |
| Xie 2005 | 65 | 30.9 (7.1) | 65 | 39.7 (5.3) | + | 2.7 % | -1.40 [-1.78, -1.01] |

-4 -2 0 2 4 Favours SSRI

Favours control

(Continued ...)

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | (Continue Sto Mear Difference |
|--|-------------------------|--------------------|---------------------------|--------------|----------------------------|---------|---|
| , , , | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% CI | Ū. | IV,Random,95% C |
| Xu 2001 | 26 | 23.6 (3.9) | 27 | 44.7 (2.6) | 4 | 2.2 % | -6.30 [-7.65, -4.94 |
| Yang 2011 | 20 | 7 (4) | 22 | 13 (6) | | 2.6 % | -1.14 [-1.80, -0.49 |
| Ye 2004 | 30 | 4.02 (3.07) | 30 | 17.32 (1.66) | 4 | 2.3 % | -5.32 [-6.43, -4.2] |
| Zhou 2003 | 28 | 3.5 (1.3) | 26 | 3.8 (1.6) | | 2.7 % | -0.20 [-0.74, 0.33 |
| | | J.J (1.J) | | 5.0 (1.0) | • | | - |
| Subtotal (95% CI) Heterogeneity: Tau ² = 2.24 | 873 | 0.40 - 45 - 27 (Dz | 824 | -0/9/ | - | 68.6 % | -1.96 [-2.54, -1.37 |
| Test for overall effect: $Z = 6$ | | | -0.00001); I ⁻ | -96% | | | |
| 2 Time since stroke 3 to 6 i | ` | .00001) | | | | | |
| Dam 1996 | 16 | 8.8 (5.6) | 16 | 9.4 (5.6) | | 2.6 % | -0.10 [-0.80, 0.59 |
| Miao 2004 | 34 | 6.45 (5.3) | 34 | 23.74 (5.16) | • | 2.6 % | -3.27 [-4.01, -2.53 |
| Murray 2005 | 62 | 10.5 (9.6) | 61 | 12 (8.5) | | 2.7 % | -0.16 [-0.52, 0.19 |
| Subtotal (95% CI) | 112 | | 111 | | | 7.9 % | -1.16 [-2.97, 0.65 |
| Heterogeneity: Tau ² = 2.47 Fest for overall effect: $Z = 1$ | ; Chi ² = 57 | | | 97% | | /.//0 | -1.10 [-2.97, 0.09 |
| 3 Time since stroke 6 to 9 i | months | , | | | | | |
| Guo 2009 | 40 | 14.82 (8.05) | 40 | 17.61 (8) | | 2.7 % | -0.34 [-0.79, 0.10 |
| Liu 2006 | 30 | 17.2 (2.1) | 30 | 25.1 (3.3) | <u> </u> | 2.6 % | -2.82 [-3.55, -2.09 |
| Subtotal (95% CI) | 70 | | 70 | | | 5.3 % | -1.56 [-3.99, 0.86 |
| Heterogeneity: Tau ² = 2.97 | ; Chi ² = 32 | | 00001); l ² =9 | 97% | | | |
| Test for overall effect: $Z = 1$ | .26 (P = 0 | 21) | | | | | |
| 4 Time since stroke 9 to 12 | months | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0 |
| Heterogeneity: not applicab | | | | | | | |
| Test for overall effect: not a | | | | | | | |
| 5 Time since stroke not kno | | | 20 | | | 2 / 0/ | |
| Chen 2002 | 24 | 10.3 (3) | 20 | 16.5 (2.5) | | 2.6 % | -2.19 [-2.95, -1.42 |
| Ji 2000 | 20 | 5.2 (1.5) | 20 | 14.5 (2.7) | ← | 2.3 % | -4.17 [-5.32, -3.03 |
| Jia 2005 | 86 | 6.4 (6.2) | 88 | 16.2 (6.8) | | 2.7 % | -1.50 [-1.84, -1.16 |
| Li 2002 | 46 | 10 (3) | 46 | 22 (8) | | 2.7 % | -1.97 [-2.47, -1.47 |
| Li 2005 | 74 | 12.6 (2.1) | 74 | 16.8 (2.3) | | 2.7 % | -1.90 [-2.29, -1.51 |
| Wang 2003 | 51 | 10.5 (2.9) | 47 | 20 (6.1) | | 2.7 % | -2.00 [-2.49, -1.51 |
| Xu 2007 | 36 | 5.61 (5.32) | 36 | 17.73 (3.21) | _ | 2.6 % | -2.73 [-3.38, -2.08 |
| Subtotal (95% CI) | 337 | | 331 | | • | 18.3 % | -2.19 [-2.62, -1.76 |
| Heterogeneity: $Tau^2 = 0.25$ Test for overall effect: Z = 9 | ; Chi ² = 27 | | | =78% | | | |
| Total (95% CI) | 1392 | | 1336 | | • | 100.0 % | -1.91 [-2.34, -1.48 |
| | | 7.95, df = 38 (P< | | | | | |

Favours SSRI Favours control

(Continued . . .)

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| | | | | | | Std. Mean | | (Continued) Std. Mean |
|------------------------------|--------------------|---------------------|--------------------------|----------|--------------|----------------|--------|------------------------------|
| Study or subgroup | SSRI | | Control | | Di | fference | Weight | Difference |
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Rand | lom,95% Cl | | IV,Random,95% CI |
| Test for overall effect: Z = | 8.70 (P < 0.0 | 00001) | | | | | | |
| Test for subgroup differen | ces: $Chi^2 = I$. | 58, df = 3 (P = 0.6 | 6), I ² =0.0% | | | | | |
| | | | | | | | | |
| | | | | | -4 -2 | 0 2 4 | | |
| | | | | | Favours SSRI | Favours contro | 1 | |
| | | | | | | | | |
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Analysis 3.5. Comparison 3 SSRI versus control (according to time since stroke when recruited), Outcome 5 Depression (dichotomous).

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

Comparison: 3 SSRI versus control (according to time since stroke when recruited)

Outcome: 5 Depression (dichotomous)

| Study or subgroup | SSRI | Control | I | Risk Ratio M- | Weight | Risk Ratio M- |
|--|--------------------------------|-------------------------------|--------------|------------------|--------|---------------------|
| | n/N | n/N | H,Rai | ndom,95% Cl | | H,Random,95% Cl |
| I Time since stroke < 3 months | s | | | | | |
| Almeida 2006 | 8/48 | /5 | | | 13.8 % | 0.77 [0.34, 1.76] |
| Li 2004a | 2/33 | 8/34 | | - | 8.7 % | 0.26 [0.06, 1.12] |
| Li 2004b | 5/31 | 13/32 | | - | 13.0 % | 0.40 [0.16, 0.98] |
| Rasmussen 2003 | 3/35 | 8/32 | | - | 10.3 % | 0.34 [0.10, 1.18] |
| Robinson 2008 | 5/59 | 13/58 | | - | 12.5 % | 0.38 [0.14, 0.99] |
| Xu 2006 | 3/28 | 12/29 | | | 10.9 % | 0.26 [0.08, 0.82] |
| Zhou 2008 | 4/36 | 18/40 | | | 12.3 % | 0.25 [0.09, 0.66] |
| Subtotal (95% CI) | 270 | 276 | + | | 81.5 % | 0.39 [0.26, 0.57] |
| Total events: 30 (SSRI), 83 (Cor | ntrol) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; Chi^2 | ² = 4.36, df = 6 (P | = 0.63); l ² =0.0% | | | | |
| Test for overall effect: $Z = 4.8$ I | · / | | | | | |
| 2 Time since stroke 3 to 6 mon | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Contro | ol) | | | | | |
| | | | | | | |
| | | | 0.05 0.2 | 1 5 20 | | |
| | | | Favours SSRI | Favours control | | (Continued) |

| n/N n/N n/N HRadomyski Test for overall effect: not applicable 3 time since stroke 6 to 9 months Subcoal (95% CI) 0 0 Total events: 0 (SSR), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable Test for overall effect: not applicable 1 time since stroke 9 to 12 months Subcoal (95% CI) 0 0 0 Total events: 0 (SSR), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable Test for overall effect: not applicable Total events: 0 (SSR), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable Total events: 28 (SSR), 97 (Control) 111 114 • Heterogeneity: not applicable Test for overall effect: 2 = 2.06 (P = 0.040) • Total events: 112 (SSR), 180 (Control) Heterogeneity: Tau ² = 0.49; Ch ² = 3.048, df = 7 (P = 0.00008); l ² = 77%. • Test for overall effect: Z = 2.20 (P = 0.0049) Test for overall effect: Z = 2.20 (P = 0.0049) • • Test for overall effect: Z = 2.20 (P = 0.0049) Test or subgroup differences: Ch ² = 1.492, df = 1 (P = 0.000, l ² = 93%) • • • 0.05 0.2 5 20 Faours SRN Fao | 0.0 % 0.0 % 18.5 % 18.5 % | M-H,Random,9 CI 0.0 [0.0, 0.0] 0.0 [0.0, 0.0] 0.87 [0.76, 0.99] 0.87 [0.76, 0.99] 0.43 [0.24, 0.77] |
|---|------------------------------------|---|
| Heterogeneity: not applicableIest for overall effect: not applicable3 Time since stroke 6 to 9 monthsSubtotal (95% CI)0OIeterogeneity: not applicableIeterogeneity: not applicableIst for overall effect: not applicableTime since stroke 9 to 12 monthsSubtotal (95% CI)0OTotal events: 0 (SSRI), 0 (Control)Heterogeneity: not applicableIst for overall effect: not applicableIst for overall effect: not applicableSubtotal (95% CI)111I11114Subtotal (95% CI)InterstructureGlaxoSmithKline 199882/11197/114Subtotal (95% CI)111114Total events: 82 (SSRI), 97 (Control)Heterogeneity: not applicableIest for overall effect: Z = 2.06 (P = 0.040)Total events: 112 (SSRI), 180 (Control)Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); l ² = 77%Iest for overall effect: Z = 2.82 (P = 0.0049)Iest for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), l ² = 93% | 0.0 % 18.5 % 18.5 % | 0.0 [0.0, 0.0] 0.0 [0.0, 0.0] 0.87 [0.76, 0.99] 0.87 [0.76, 0.99] |
| 3 Time since stroke 6 to 9 months Subtoral (95% CI) 0 0 Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable 4 Time since stroke 9 to 12 months Subtoral (95% CI) 0 0 Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Total events: 82 (SSRI), 97 (Control) Heterogeneity: not applicable Subtotal (95% CI) 111 Total events: 82 (SSRI), 97 (Control) Heterogeneity: not applicable Test for overall effect: Z = 2.06 (P = 0.040) Total events: 112 (SSRI), 180 (Control) Heterogeneity: not applicable Test for overall effect: Z = 2.06 (P = 0.0409) Test for overall effect: Z = 2.82 (P = 0.0049) Test for overall effect: Z = 2.82 (P = 0.0049) Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), l ² = 93% | 0.0 % 18.5 % 18.5 % | 0.0 [0.0, 0.0] 0.87 [0.76, 0.99] 0.87 [0.76, 0.99] |
| Subtoral (95% CI) 0 0 0 Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable A Time since stroke 9 to 12 months Subtoral (95% CI) 0 0 0 Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable Total events: 82 (SSRI), 97 (Control) Heterogeneity: not applicable Total (95% CI) 381 390 Total events: 112 (SSRI), 180 (Control) Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); l ² = 77% Test for overall effect: $Z = 2.82$ (P = 0.0049) Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), l ² = 93% | 0.0 % 18.5 % 18.5 % | 0.0 [0.0, 0.0] 0.87 [0.76, 0.99] 0.87 [0.76, 0.99] |
| Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable 4 Time since stroke 9 to 12 months Subtotal (95% CI) 0 0 0 Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable 5 Time since stroke unknown GlaxoSmithKline 1998 82/111 97/114 Subtotal (95% CI) 111 114 Subtotal (95% CI) 111 114 Fotal events: 82 (SSRI), 97 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 2.06 (P = 0.040)$ Total (95% CI) 381 390 Total events: 112 (SSRI), 180 (Control) Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); l ² = 77% Test for overall effect: $Z = 2.82 (P = 0.0049)$ Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), l ² = 93% | 0.0 % 18.5 % 18.5 % | 0.0 [0.0, 0.0] 0.87 [0.76, 0.99] 0.87 [0.76, 0.99] |
| Heterogeneity: not applicable Test for overall effect: not applicable 4 Time since stroke 9 to 12 months Subtotal (95% CI) 0 0 0 Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable Test for overall effect: not applicable 5 Time since stroke unknown GlaxoSmithKline 1998 82/111 97/114 Subtotal (95% CI) 111 114 Fotal events: 82 (SSRI), 97 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 2.06 (P = 0.040)$ Total (95% CI) 381 390 Fotal events: 112 (SSRI), 180 (Control) Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); 1 ² = 77% Test for overall effect: $Z = 2.82 (P = 0.0049)$ Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), 1 ² = 93% | 18.5 % 18.5 % | 0.0 [0.0, 0.0] 0.87 [0.76, 0.99] 0.87 [0.76, 0.99] |
| The structure of the s | 18.5 % 18.5 % | 0.87 [0.76, 0.99] 0.87 [0.76, 0.99] |
| The time since stroke 9 to 12 months Subtotal (95% CI) 0 0 0 Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable 5 Time since stroke unknown GlaxoSmithKline 1998 82/11 97/114 Subtotal (95% CI) 111 114 Fotal events: 82 (SSRI), 97 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 2.06$ (P = 0.040) Total (95% CI) 381 390 Fotal events: 112 (SSRI), 180 (Control) Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); l ² = 77% Test for overall effect: $Z = 2.82$ (P = 0.0049) Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), l ² = 93% | 18.5 % 18.5 % | 0.87 [0.76, 0.99] 0.87 [0.76, 0.99] |
| Subtotal (95% CI) 0 0 0 Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable S Time since stroke unknown GlaxoSmithKline 1998 82/11 97/114 Subtotal (95% CI) 111 114 Subtotal (95% CI) 111 114 Fotal events: 82 (SSRI), 97 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 2.06 (P = 0.040)$ Total (95% CI) 381 390 Fotal (95% CI) 381 390 Fotal events: 112 (SSRI), 180 (Control) Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); l ² = 77% Test for overall effect: $Z = 2.82 (P = 0.0049)$ Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), l ² = 93% | 18.5 % 18.5 % | 0.87 [0.76, 0.99] 0.87 [0.76, 0.99] |
| Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable 5 Time since stroke unknown GlaxoSmithKline 1998 82/111 97/114 Subtotal (95% CI) 111 114 Fotal events: 82 (SSRI), 97 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 2.06 (P = 0.040)$ Total (95% CI) 381 390 Fotal events: 112 (SSRI), 180 (Control) Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); l ² = 77% Test for overall effect: $Z = 2.82 (P = 0.0049)$ Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), l ² = 93% | 18.5 % 18.5 % | 0.87 [0.76, 0.99] 0.87 [0.76, 0.99] |
| Heterogeneity: not applicable Test for overall effect: not applicable 5 Time since stroke unknown GlaxoSmithKline 1998 82/111 97/114 Subtotal (95% CI) 111 114 Fotal events: 82 (SSRI), 97 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 2.06$ (P = 0.040) Total (95% CI) 381 390 Fotal events: 112 (SSRI), 180 (Control) Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); I ² = 77% Test for overall effect: $Z = 2.82$ (P = 0.0049) Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), I ² = 93% | 18.5 % | 0.87 [0.76, 0.99] |
| Test for overall effect: not applicable 5 Time since stroke unknown GlaxoSmithKline 1998 82/111 97/114 Subtotal (95% CI) 111 114 Fotal events: 82 (SSRI), 97 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 2.06$ (P = 0.040) Total (95% CI) 381 390 Total events: 112 (SSRI), 180 (Control) Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); I ² = 77% Test for overall effect: $Z = 2.82$ (P = 0.0049) Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), I ² = 93% | 18.5 % | 0.87 [0.76, 0.99] |
| 5 Time since stroke unknown GlaxoSmithKline 1998 $82/111$ $97/114$ Subtotal (95% CI) 111 114 Total events: 82 (SSRI), 97 (Control) Heterogeneity: not applicable Total (95% CI) Total events: 112 (SSRI), 180 (Control) Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); l ² = 77% Test for overall effect: Z = 2.82 (P = 0.0049) Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), l ² = 93% 0.05 0.2 5 20 | 18.5 % | 0.87 [0.76, 0.99] |
| GlaxoSmithKline 1998 $82/111$ $97/114$ Subtotal (95% CI) 111 114 Total events: 82 (SSRI), 97 (Control) Heterogeneity: not applicable Total (95% CI) 381 390 Total events: 112 (SSRI), 180 (Control) Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); l ² = 77% 77% Test for overall effect: $Z = 2.82$ (P = 0.0049) 9000000000000000000000000000000000000 | 18.5 % | 0.87 [0.76, 0.99] |
| Subtotal (95% CI) 111 114 Total events: 82 (SSRI), 97 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 2.06$ (P = 0.040) Total (95% CI) 381 381 390 Total events: 112 (SSRI), 180 (Control) Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); l ² = 77% Test for overall effect: $Z = 2.82$ (P = 0.0049) Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), l ² = 93% 0.05 0.2 5 20 | 18.5 % | 0.87 [0.76, 0.99] |
| Total events: 82 (SSRI), 97 (Control) -leterogeneity: not applicable Test for overall effect: $Z = 2.06$ (P = 0.040) Total (95% CI) 381 381 390 Total events: 112 (SSRI), 180 (Control) -leterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); l ² = 77% Test for overall effect: $Z = 2.82$ (P = 0.0049) Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), l ² = 93% 0.05 0.2 5 20 | | |
| Total events: 82 (SSRI), 97 (Control) -leterogeneity: not applicable Test for overall effect: $Z = 2.06$ (P = 0.040) Total (95% CI) 381 381 390 Total events: 112 (SSRI), 180 (Control) -leterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); l ² = 77% Test for overall effect: $Z = 2.82$ (P = 0.0049) Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), l ² = 93% 0.05 0.2 5 20 | | |
| Heterogeneity: not applicable Test for overall effect: $Z = 2.06 (P = 0.040)$ Total (95% CI) 381 390 Total events: 112 (SSRI), 180 (Control) Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); l ² = 77% Test for overall effect: $Z = 2.82 (P = 0.0049)$ Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), l ² = 93% 0.05 0.2 5 20 | 100.0.04 | 0.43 [0.24, 0.77] |
| Test for overall effect: Z = 2.06 (P = 0.040) Total (95% CI) 381 390 Total events: 112 (SSR), 180 (Control) Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); l ² =77% Test for overall effect: Z = 2.82 (P = 0.0049) Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), l ² =93% 0.05 0.2 5 20 | 100.0.0 | 0.43 [0.24, 0.77] |
| Total (95% CI) 381 390 Total events: I12 (SSRI), 180 (Control) Heterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); I ² =77% Test for overall effect: Z = 2.82 (P = 0.0049) Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), I ² =93% 0.05 0.2 5 20 | 100.0.04 | 0.43 [0.24, 0.77] |
| Total events: I 12 (SSR), 180 (Control) -leterogeneity: Tau ² = 0.49; Chi ² = 30.48, df = 7 (P = 0.00008); l ² =77% Test for overall effect: Z = 2.82 (P = 0.0049) Test for subgroup differences: Chi ² = 14.92, df = 1 (P = 0.00), l ² =93% 0.05 0.2 5 20 | | 0.45 [0.24, 0.//] |
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Analysis 3.7. Comparison 3 SSRI versus control (according to time since stroke when recruited), Outcome 7 Anxiety (continuous).

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

Comparison: 3 SSRI versus control (according to time since stroke when recruited)

Outcome: 7 Anxiety (continuous)

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|--|--|-------------|--|--------------|--|----------------|--|
| I Time since stroke < 3 m | onths | | | | | | |
| Finkenzeller 2009 | 23 | 6.9 (0.57) | 27 | 6.7 (0.53) | | 12.8 % | 0.36 [-0.20, 0.92] |
| He 2005 | 27 | 5.37 (1.66) | 27 | 12.78 (1.93) | • | 11.3 % | -4.06 [-5.01, -3.10] |
| Lai 2006 | 40 | 50.2 (9.4) | 40 | 54.2 (15.2) | | 13.2 % | -0.3 [-0.75, 0.13] |
| Liu 2004 | 30 | 7.43 (3.63) | 30 | II (5.63) | _ _ | 12.9 % | -0.74 [-1.27, -0.22] |
| Robinson 2000a | 14 | 9.8 (4.8) | 13 | 9.9 (5.1) | + | 12.1 % | -0.02 [-0.77, 0.74] |
| Robinson 2000b | 13 | 4.7 (3.8) | 15 | 5.5 (2.9) | | 12.1 % | -0.23 [-0.98, 0.51] |
| Ye 2004 | 30 | 9.82 (2.64) | 30 | 14.02 (2.32) | ← ■ | 12.7 % | -1.67 [-2.26, -1.08] |
| Zhou 2003 | 28 | 3.5 (1.3) | 26 | 3.3 (1.3) | | 12.9 % | 0.15 [-0.38, 0.69] |
| Subtotal (95% CI) | 205 | | 208 | | | 100.0 % | -0.77 [-1.52, -0.02] |
| 2 Time since stroke 3 to 6 Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: not a 3 Time since stroke 6 to 9 Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: not a 4 Time since stroke 9 to 1 | 0 ble applicable months 0 ble applicable | | 0 | | | 0.0 % 0.0 % | 0.0 [0.0, 0.0] 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: not a | applicable | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| 5 Time since stroke unkno Subtotal (95% CI) Heterogeneity: not applica | 0 ble | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Test for overall effect: not a Total (95% CI) Heterogeneity: $Tau^2 = 1.0!$ Test for overall effect: $Z =$ Test for subgroup difference | 205 5; Chi ² = 8 2.02 (P = 0 |).043) | 208 00001); I ² = | 92% | | 100.0 % | -0.77 [-1.52, -0.02] |
| | | | | | -2 -1 0 I 2 Favours SSRI Favours contr | | |

Analysis 3.8. Comparison 3 SSRI versus control (according to time since stroke when recruited), Outcome 8 Cognition.

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

Comparison: 3 SSRI versus control (according to time since stroke when recruited)

Outcome: 8 Cognition

| Study or subgroup | SSRI | | Control | | | Std. Mean erence | Weight | Std. Mean Difference |
|--|----------------------|---------------------|-----------------------------|--------------|--------------|------------------------|---------------|----------------------------|
| | Ν | Mean(SD) | N | Mean(SD) | IV,Rando | m,95% Cl | | IV,Random,95% CI |
| I Time since stroke < 3 mor Li 2006 | ths 50 | 28.36 (2.57) | 49 | 24.32 (2.14) | | | 15.2 % | 1.69 [1.23, 2.16] |
| | | · · · · | | · · · · | | | | |
| Robinson 2000a | 14 | 25.9 (7.5) | 13 | 24.5 (6.8) | | | 12.8 % | 0.19 [-0.57, 0.95] |
| Robinson 2000b | 13 | 26.1 (7.5) | 15 | 26.8 (2.4) | | | 12.9 % | -0.13 [-0.87, 0.62] |
| Robinson 2008 | 43 | 89.8 (15.1) | 45 | 91 (17.8) | | | 15.5 % | -0.07 [-0.49, 0.35] |
| Wiart 2000 | 16 | 24.8 (3.9) | 15 | 26.2 (3) | ← ■ | | 13.2 % | -0.39 [-1.10, 0.32] |
| Subtotal (95% CI) | 136 | | 137 | | | | 69.6 % | 0.28 [-0.57, 1.13] |
| Heterogeneity: $Tau^2 = 0.83$; | Chi ² = 4 | 1.94, df = 4 (P<0.0 | 0000 I); I ² =9 | 90% | | | | |
| Test for overall effect: $Z = 0.0$ | 64 (P =) | 0.52) | | | | | | |
| 2 Time since stroke 3 to 6 m | | | | | | | | |
| Subtotal (95% CI) Heterogeneity: not applicable | 0 | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Test for overall effect: not ap | | | | | | | | |
| 3 Time since stroke 6 to 9 m | | | | | | | | |
| Guo 2009 | 40 | 19.26 (6.87) | 40 | 15.74 (6.28) | | | 15.3 % | 0.53 [0.08, 0.98] |
| Subtotal (95% CI) | 40 | | 40 | | | | 15.3 % | 0.53 [0.08, 0.98] |
| Heterogeneity: not applicable | 9 | | | | | | | |
| Test for overall effect: $Z = 2.3$ | 33 (P = | 0.020) | | | | | | |
| 4 Time since stroke 9 to 12 r | | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | I | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicable | | | | | | | | |
| Test for overall effect: not ap | | | | | | | | |
| 5 Time since stroke unknowr Xu 2007 | י 36 | 28.36 (2.57) | 36 | 27.31 (5.88) | | | 15.2 % | 0.23 [-0.23, 0.69 - |
| Subtotal (95% CI) | 36 | · · · | 36 | . , | | | 15.2 % | 0.23 [-0.23, 0.69] |
| Heterogeneity: not applicable | | | 50 | | | | 19.2 /0 | 0.25 [-0.25, 0.07] |
| Test for overall effect: $Z = 0.9$ | 97 (P = | 0.33) | | | | | | |
| Total (95% CI) | 212 | | 213 | | _ | | 100.0 % | 0.32 [-0.23, 0.86] |
| Heterogeneity: $Tau^2 = 0.45;$ | Chi ² = 4 | 2.83, df = 6 (P<0.0 | 0000 l); l ² =8 | 36% | | | | |
| Test for overall effect: $Z = I$. | I5 (P = | 0.25) | | | | | | |
| Test for subgroup differences | : Chi² = | 0.89, df = 2 (P = 0 | 0.64), l ² =0.0 | % | | | | |
| | | | | | | | | |
| | | | | | -1 -0.5 0 | 0.5 I | | |
| | | | | | Favours SSRI | Favours conti | rol | |

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

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Analysis 3.9. Comparison 3 SSRI versus control (according to time since stroke when recruited), Outcome 9 Death.

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

Comparison: 3 SSRI versus control (according to time since stroke when recruited)

Outcome: 9 Death

| n/N 0/10 2/48 | n/N 0/10 1/52 | H,Random,95% Cl | H,Random,95% Cl 0.0 [0.0, 0.0] |
|---------------------|--|--|---|
| 2/48 | | | |
| 2/48 | | | 100 00100 |
| | 1/50 | | 0.0 [0.0, 0.0] |
| | 1/52 | | 2.17 [0.20, 23.14] |
| 2/33 | 2/33 | _ | 1.00 [0.15, 6.68] |
| 0/21 | 0/20 | | 0.0 [0.0, 0.0] |
| 0/40 | 0/38 | | 0.0 [0.0, 0.0] |
| 0/25 | 0/32 | | 0.0 [0.0, 0.0] |
| 1/59 | 1/59 | | 1.00 [0.06, 15.61] |
| 0/18 | 0/18 | | 0.0 [0.0, 0.0] |
| 1/28 | 0/16 | | 1.76 [0.08, 40.80] |
| 0/36 | 0/35 | | 0.0 [0.0, 0.0] |
| 0/27 | 0/27 | | 0.0 [0.0, 0.0] |
| 0/42 | 0/30 | | 0.0 [0.0, 0.0] |
| 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| 0/33 | 0/34 | | 0.0 [0.0, 0.0] |
| 0/37 | 0/36 | | 0.0 [0.0, 0.0] |
| 1/52 | 2/53 | | 0.51 [0.05, 5.45] |
| 0/60 | 0/30 | | 0.0 [0.0, 0.0] |
| 0/42 | 0/21 | | 0.0 [0.0, 0.0] |
| | | | |
| | | 0.01 0.1 1 10 100 | |
| | 0/36 0/27 0/42 0/40 0/40 0/33 0/37 1/52 0/60 | 0/360/350/270/270/420/300/400/400/400/400/330/340/370/361/522/530/600/30 | 0/36 0/35 0/27 0/27 0/42 0/30 0/40 0/40 0/33 0/34 0/37 0/36 1/52 2/53 |

(Continued . . .)

| Study or subgroup | SSRI | Control | Risk Ratio | (Continued) Risk Ratio |
|---|-------------|-------------------------------------|------------------------------|----------------------------|
| | | | M- H,Random <u>,</u> 95% | M- H,Random,955 |
| Liu 2004 | n/N 0/30 | n/N 0/30 | Cl | CI 0.0 [0.0, 0.0] |
| Liu 2006 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Robinson 2000a | 0/23 | 1/17 | | 0.25 [0.01, 5.79] |
| Robinson 2000b | 0/17 | 0/16 | | 0.0 [0.0, 0.0] |
| Robinson 2008 | 2/59 | 0/58 | | 4.92 [0.24, 100.25] |
| | 0/41 | 0/41 | | 4.72 [0.24, 100.23] |
| Song 2006 | | | | |
| Wen 2006 | 0/42 | 0/42 | | 0.0 [0.0, 0.0] |
| Wiart 2000 | 0/16 | 0/15 | | 0.0 [0.0, 0.0] |
| Xie 2005 | 0/65 | 0/65 | | 0.0 [0.0, 0.0] |
| Xu 2001 | 0/32 | 0/31 | | 0.0 [0.0, 0.0] |
| Xu 2006 | 0/32 | 2/32 | | 0.20 [0.01, 4.01] |
| Yang 2011 | 0/20 | 0/22 | | 0.0 [0.0, 0.0] |
| Ye 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Zhou 2003 | 0/28 | 0/26 | | 0.0 [0.0, 0.0] |
| Zhou 2008 | 0/36 | 0/40 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 9 (SSRI), 9 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 3.7 Test for overall effect: Z = 0.12 (P = 0.12) P = 100000000000000000000000000000000000 | | 1119 I ² =0.0% | | 0.94 [0.38, 2.36] |
| Dam 1996 | 0/18 | 0/17 | | 0.0 [0.0, 0.0] |
| Miao 2004 | 0/45 | 0/45 | | 0.0 [0.0, 0.0] |
| Murray 2005 | 0/62 | 2/61 | - _ | 0.20 [0.01, 4.02] |
| Yang 2002 | 0/64 | 0/57 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Fotal events: 0 (SSRI), 2 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0.0 Test for overall effect: Z = 1.06 (P = 0 3 Time since stroke 6 to 9 months | | 180 2 =0.0% | | 0.20 [0.01, 4.02] |
| Guo 2009 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Liu 2006 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0.0 Test for overall effect: Z = 0.0 (P < 0.0) | | 70 ; I ² =0.0% | | 0.0 [0.0, 0.0] |
| | | | 0.01 0.1 1 10 100 | |
| | | | Favours SSRI Favours control | |
| | | | | (Continued) |
| Study or subgroup | SSRI Control | | Risk Ratio M | (Continued) Risk Ratio M- | |
|---|--------------------------|--------------------------|--------------------|----------------------------------|--|
| | n/N | n/N | H,Random,95% Cl | H,Random,959 Cl | |
| 4 Time since stroke 9 to 12 month | IS | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] | |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | e | | | | |
| 5 Time since stroke unknown | | | | | |
| Brown 1998 | 0/10 | 0/10 | | 0.0 [0.0, 0.0] | |
| Burns 1999 | / 4 | 1/14 | | 1.00 [0.07, 14.45] | |
| Ji 2000 | 0/20 | 0/20 | | 0.0 [0.0, 0.0] | |
| Jia 2005 | 0/92 | 2/92 | | 0.20 [0.01, 4.11] | |
| Li 2002 | 0/46 | 0/46 | | 0.0 [0.0, 0.0] | |
| Li 2005 | 0/74 | 0/74 | | 0.0 [0.0, 0.0] | |
| Xu 2007 | 0/36 | 0/36 | | 0.0 [0.0, 0.0] | |
| Subtotal (95% CI) | 292 | 292 | - | 0.49 [0.07, 3.65] | |
| Total events: I (SSRI), 3 (Control) | | | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = | 0.63, df = 1 (P = 0.43); | $ ^2 = 0.0\%$ | | | |
| Test for overall effect: $Z = 0.69$ (P | = 0.49) | | | | |
| Total (95% CI) | 1743 | 1661 | - | 0.76 [0.34, 1.70] | |
| Total events: 10 (SSRI), 14 (Contro | ol) | | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = | 5.54, df = 10 (P = 0.85) | ; 2 =0.0% | | | |
| Test for overall effect: $Z = 0.67$ (P | = 0.50) | | | | |
| Test for subgroup differences: Chi ² | = 1.16, df = 2 (P = 0.5 | 6), l ² =0.0% | | | |
| | | | | | |

D.01 0.1 1 10 100 Favours SSRI Favours control

Analysis 3.10. Comparison 3 SSRI versus control (according to time since stroke when recruited), Outcome 10 Seizure.

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

Comparison: 3 SSRI versus control (according to time since stroke when recruited)

Outcome: 10 Seizure

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|---|------------------|-------------------------|------------------------------|-----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,959 Cl |
| I Time since stroke < 3 months | | | | |
| Andersen 1994 | 2/33 | 0/33 | | 5.00 [0.25, 100.32] |
| Chollet 2011 | 1/59 | 0/59 | | 3.00 [0.12, 72.18] |
| He 2004 | 0/36 | 0/35 | | 0.0 [0.0, 0.0] |
| Liang 2003 | 0/42 | 0/21 | | 0.0 [0.0, 0.0] |
| Wiart 2000 | 1/16 | 1/15 | | 0.94 [0.06, 3.68] |
| Ye 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 216 | 193 | | 2.22 [0.41, 12.06] |
| Total events: 4 (SSRI), 1 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0.73, Test for overall effect: Z = 0.92 (P = 0.3 2 Time since stroke 3 to 6 months | 36) |); I ² =0.0% | | |
| Dam 1996 | 2/18 | 0/17 | | 4.74 [0.24, 92.07] |
| Subtotal (95% CI) Total events: 2 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: Z = 1.03 (P = 0.3 3 Time since stroke 6 to 9 months | 18 30) | 17 | | 4.74 [0.24, 92.07] |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable | 0 | 0 | | 0.0 [0.0, 0.0] |
| 4 Time since stroke 9 to 12 months Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable | 0 | 0 | | 0.0 [0.0, 0.0] |
| 5 Time since stroke unknown Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable | 0 | 0 | | 0.0 [0.0, 0.0] |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |
| | | | Favours SSRI Favours control | (Continued) |

| Study or subgroup | SSRI n/N | Control n/N | H,R2 | Risk Ratio M- andom,95% Cl | (Continued) Risk Ratio M- H,Random,95% Cl |
|---|--------------------------------|---------------------------|--------------|-------------------------------------|--|
| Total (95% CI) | 234 | 210 | | - | 2.67 [0.61, 11.63] |
| Total events: 6 (SSRI), 1 (Control |) | | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² : | = 0.91, df = 3 (P = 0.82) | ; I ² =0.0% | | | |
| Test for overall effect: Z = 1.31 (I | P = 0.19) | | | | |
| Test for subgroup differences: Ch | $i^2 = 0.19, df = 1 (P = 0.6)$ | 66), l ² =0.0% | | | |
| | | | | | |
| | | | 0.01 0.1 | 1 10 100 | |
| | | | Favours SSRI | Favours control | |

Analysis 3.11. Comparison 3 SSRI versus control (according to time since stroke when recruited), Outcome II Gastrointestinal side effects.

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

Comparison: 3 SSRI versus control (according to time since stroke when recruited)

Outcome: II Gastrointestinal side effects

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--------------------------------|-------|---------|---|------------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| I Time since stroke < 3 months | | | | |
| Chollet 2011 | 14/59 | 6/59 | | 2.33 [0.96, 5.66] |
| He 2004 | 0/36 | 0/35 | | 0.0 [0.0, 0.0] |
| He 2005 | 9/27 | 0/27 | ₽_→ | 19.00 [1.16, 310.94] |
| Hu 2002 | 5/42 | 0/30 | | 7.93 [0.46, 138.20] |
| Huang 2002 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Li 2004a | 3/33 | 0/34 | | 7.21 [0.39, 134.32] |
| Li 2008 | 6/60 | 3/30 | | 1.00 [0.27, 3.72] |
| Liang 2003 | 4/42 | 4/21 | | 0.50 [0.14, 1.80] |
| Liu 2004 | 3/30 | 0/30 | | 7.00 [0.38, 129.93] |
| Wiart 2000 | 1/16 | 3/16 | | 0.33 [0.04, 2.87] |
| | | | | |
| | | | 0.01 0.1 1 10 100 Favours SSRI Favours control | |
| | | | | · · · · · |

(Continued . . .)

| Study or subgroup | SSRI | Control | Risk Ratio M- | (Continued) Risk Ratio M- |
|--|----------------------|---------------------------|------------------------------|----------------------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,959 Cl |
| Ye 2004 | 2/30 | 0/30 | | 5.00 [0.25, 99.95] |
| Subtotal (95% CI) | 415 | 352 | • | 1.92 [0.83, 4.45] |
| Total events: 47 (SSRI), 16 (Control) | | | | |
| Heterogeneity: Tau ² = 0.61; Chi ² = 13. | .95, df = 8 (P = 0.0 | 8); I ² =43% | | |
| Test for overall effect: $Z = 1.53$ (P = 0. | 13) | | | |
| 2 Time since stroke 3 to 6 months | | | | |
| Dam 1996 | 2/18 | 0/17 | | 4.74 [0.24, 92.07] |
| Subtotal (95% CI) | 18 | 17 | | 4.74 [0.24, 92.07] |
| Total events: 2 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 1.03$ (P = 0.2 | 30) | | | |
| 3 Time since stroke 6 to 9 months | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 4 Time since stroke 9 to 12 months | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 5 Time since stroke unknown | | | | |
| Burns 1999 | 0/14 | / 4 | | 0.33 [0.01, 7.55] |
| Xu 2007 | 4/36 | 1/36 | | 4.00 [0.47, 34.07] |
| Subtotal (95% CI) | 50 | 50 | | 1.51 [0.14, 16.29] |
| Total events: 4 (SSRI), 2 (Control) | | | | |
| Heterogeneity: $Tau^2 = 1.22$; $Chi^2 = 1.6$ | 6, df = 1 (P = 0.20 |); I ² =40% | | |
| Test for overall effect: $Z = 0.34$ (P = 0.7) | 73) | | | |
| Total (95% CI) | 483 | 419 | ◆ | 1.90 [0.94, 3.85] |
| Total events: 53 (SSRI), 18 (Control) | | | | |
| Heterogeneity: $Tau^2 = 0.43$; $Chi^2 = 15$. | .97, df = 11 (P = 0. | 4); ² =3 % | | |
| Test for overall effect: $Z = 1.79$ (P = 0.0 | 073) | | | |
| Test for subgroup differences: $Chi^2 = 0$ | .39, df = 2 (P = 0.8 | 32), I ² =0.0% | | |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |
| | | | Favours SSRI Favours control | |

Analysis 3.12. Comparison 3 SSRI versus control (according to time since stroke when recruited), Outcome 12 Leaving the trial early.

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

Comparison: 3 SSRI versus control (according to time since stroke when recruited)

Outcome: 12 Leaving the trial early

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|------------------------------|-------|---------|---|----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| Time since stroke < 3 months | | | | |
| Acler 2009 | 0/10 | 0/10 | | 0.0 [0.0, 0.0] |
| Almeida 2006 | 11/55 | 6/56 | | 1.87 [0.74, 4.70] |
| Andersen 1994 | 6/33 | 1/33 | | 6.00 [0.76, 47.14] |
| Chen 2001 | 2/21 | 2/20 | · · · · · | 0.95 [0.15, 6.13] |
| Chen T 2005 | 0/40 | 0/38 | | 0.0 [0.0, 0.0] |
| Cheng 2003 | 0/25 | 0/32 | | 0.0 [0.0, 0.0] |
| Chollet 2011 | 2/59 | 3/59 | · | 0.67 [0.12, 3.85] |
| Feng 2004 | 2/18 | 2/18 | · | 1.00 [0.16, 6.35] |
| Fruehwald 2003 | 6/28 | 8/26 | · · · · · · · · · · · · · · · · · · · | 0.70 [0.28, 1.74] |
| He 2004 | 8/44 | 5/40 | | 1.45 [0.52, 4.08] |
| He 2005 | 0/27 | 0/27 | | 0.0 [0.0, 0.0] |
| Hu 2002 | 0/42 | 0/30 | | 0.0 [0.0, 0.0] |
| Huang 2002 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Kong 2007 | 11/48 | 6/42 | | 1.60 [0.65, 3.96] |
| Lai 2006 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Li 2004a | 0/33 | 0/34 | | 0.0 [0.0, 0.0] |
| Li 2004b | 6/37 | 4/36 | · | 1.46 [0.45, 4.74] |
| Li 2006 | 2/50 | 4/53 | + | 0.53 [0.10, 2.77] |
| Li 2008 | 2/60 | 2/30 | * | 0.50 [0.07, 3.38] |
| Liang 2003 | 0/42 | 0/21 | | 0.0 [0.0, 0.0] |
| Liu 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Rasmussen 2003 | 35/70 | 35/67 | | 0.96 [0.69, 1.33] |
| Robinson 2000a | 9/23 | 4/17 | | 1.66 [0.61, 4.51] |
| | | | | |
| | | | 0.5 0.7 I.5 2 Favours SSRI Favours control | |
| | | | | |

(Continued . . .)

| Study or subgroup | SSRI | Control | Risk Ratio M- | (Continued) Risk Ratio M- |
|---|-----------------------|------------------------------|---|----------------------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| Robinson 2000b | 4/17 | 1/16 | | 3.76 [0.47, 30.20] |
| Robinson 2008 | 7/59 | 5/58 | · | 1.38 [0.46, 4.09] |
| Wen 2006 | 0/42 | 0/42 | | 0.0 [0.0, 0.0] |
| Wiart 2000 | 0/16 | 0/15 | | 0.0 [0.0, 0.0] |
| Xie 2005 | 0/65 | 0/65 | | 0.0 [0.0, 0.0] |
| Xu 2001 | 6/32 | 4/3 | · · · · · · · · · · · · · · · · · · · | 1.45 [0.45, 4.66] |
| Xu 2006 | 4/32 | 3/32 | · | 1.33 [0.32, 5.49] |
| Yang 2011 | 0/20 | 0/22 | | 0.0 [0.0, 0.0] |
| Ye 2004 | 1/31 | 0/30 | · | 2.91 [0.12, 68.66] |
| Zhou 2003 | 2/30 | 4/30 | * | 0.50 [0.10, 2.53] |
| Zhou 2008 | 0/36 | 0/40 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 1255 | 1180 | - | 1.12 [0.90, 1.40] |
| Test for overall effect: Z = 1.00 (P = 0 2 Time since stroke 3 to 6 months Dam 1996 | 0/16 | 0/17 | | 0.0 [0.0, 0.0] |
| Miao 2004 | 11/45 | 11/45 | ← → | 1.00 [0.48, 2.07] |
| Murray 2005 | 24/62 | 30/61 | _ | 0.79 [0.53, 1.18] |
| Subtotal (95% CI) | 123 | 123 | | 0.83 [0.59, 1.19] |
| Total events: 35 (SSRI), 41 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0.32 Test for overall effect: $Z = 1.02$ (P = 0. 3 Time since stroke 6 to 9 months Guo 2009 | 2, df = 1 (P = 0.57); | | | 0.0 [0.0, 0.0] |
| | | | | |
| Liu 2006 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0.0, Test for overall effect: $Z = 0.0$ (P < 0.0 4 Time since stroke 9 to 12 months | | 70 ; 1 ² =0.0% | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable 5 Time since stroke not known | 0 | 0 | | 0.0 [0.0, 0.0] |
| Brown 1998 | 1/10 | 0/10 | <→ | 3.00 [0.14, 65.90] |
| | | | 0.5 0.7 I.5 2 Favours SSRI Favours control | (Continued) |

| Study or subgroup | SSRI | Control | Risk Ratio M- | (Continued) Risk Ratio M- |
|--|--------------------------------------|------------------------|---|----------------------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| Burns 1999 | 0/14 | 0/14 | | 0.0 [0.0, 0.0] |
| Chen 2002 | 0/24 | 4/24 | <u>ــــــــــــــــــــــــــــــــــــ</u> | 0.11 [0.01, 1.96] |
| GlaxoSmithKline 1998 | 3/ 2 | 3/ 7 | | 1.04 [0.51, 2.15] |
| Ji 2000 | 0/20 | 0/20 | | 0.0 [0.0, 0.0] |
| Jia 2005 | 4/92 | 4/92 | · | 1.00 [0.26, 3.88] |
| Li 2002 | 0/46 | 0/46 | | 0.0 [0.0, 0.0] |
| Li 2005 | 0/74 | 0/74 | | 0.0 [0.0, 0.0] |
| Wang 2003 | 13/64 | 9/56 | | 1.26 [0.58, 2.73] |
| Yang 2002 | 4/64 | 7/57 | · | 0.51 [0.16, 1.65] |
| Subtotal (95% CI) | 520 | 510 | | 0.97 [0.62, 1.51] |
| Total events: 35 (SSRI), 37 (Contro Heterogeneity: Tau ² = 0.0; Chi ² = | 4.44, df = 5 (P = 0.49); | l ² =0.0% | | |
| Test for overall effect: Z = 0.14 (P Total (95% CI) | = 0.89) 1968 | 1883 | • | 1.02 [0.86, 1.21] |
| Total events: 196 (SSRI), 177 (Cor | -, | 1005 | | 1.02 [0.00, 1.21] |
| Heterogeneity: Tau ² = 0.0; Chi ² = | , | ł); l² =0.0% | | |
| Test for overall effect: $Z = 0.23$ (P | = 0.82) | | | |
| Test for subgroup differences: Chi ⁻ | ² = 2.00, df = 2 (P = 0.3 | 7), l ² =0% | | |
| | | | | |
| | | | 0.5 0.7 1.5 2 | |

Favours SSRI

Favours control

Analysis 3.13. Comparison 3 SSRI versus control (according to time since stroke when recruited), Outcome 13 Bleeding.

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

Comparison: 3 SSRI versus control (according to time since stroke when recruited)

Outcome: 13 Bleeding

| Study or subgroup | SSRI | Control | Risk Ratio M | Weight | Risk Ratio M- |
|-------------------------------------|---------------------------|----------------------------------|--------------------|---------|----------------------|
| | n/N | n/N | H,Random,95% Cl | | H,Random,95% Cl |
| I Time since stroke < 3 month | IS | | | | |
| Robinson 2008 | 1/59 | 1/59 | | 57.4 % | 1.00 [0.06, 15.61] |
| Subtotal (95% CI) | 59 | 59 | | 57.4 % | 1.00 [0.06, 15.61] |
| Total events: (SSRI), (Contr | rol) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 0.0$ | (P = 1.0) | | | | |
| 2 Time since stroke not known | 1 | | | | |
| GlaxoSmithKline 1998 | 1/112 | 0/117 | | 42.6 % | 3.13 [0.13, 76.10] |
| Subtotal (95% CI) | 112 | 117 | | 42.6 % | 3.13 [0.13, 76.10] |
| Total events: I (SSRI), 0 (Contr | rol) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 0.70$ |) (P = 0.48) | | | | |
| Total (95% CI) | 171 | 176 | | 100.0 % | 1.63 [0.20, 13.05] |
| Total events: 2 (SSRI), 1 (Contr | (lor | | | | |
| Heterogeneity: $Tau^2 = 0.0$; Chi | $^{2} = 0.28$, df = 1 (P | $r = 0.59$); $ ^2 = 0.0\%$ | | | |
| Test for overall effect: $Z = 0.46$ | e (P = 0.65) | | | | |
| Test for subgroup differences: (| $Chi^2 = 0.28, df = 1$ | (P = 0.60), I ² =0.0% | | | |

0.01 0.1 1 10 100 Favours SSRI Favours control

Analysis 3.14. Comparison 3 SSRI versus control (according to time since stroke when recruited), Outcome 14 Motor deficits.

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

Comparison: 3 SSRI versus control (according to time since stroke when recruited)

Outcome: 14 Motor deficits

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% Cl |
|---|------------------------|----------------------|---------------------------|------------|--|---------|--|
| I < 3 months | | | | | | | |
| Chollet 2011 | 57 | -53.7 (27.8) | 56 | -35.1 (22) | | 55.3 % | -0.74 [-1.12, -0.35] |
| Subtotal (95% CI) | 57 | | 56 | | • | 55.3 % | -0.74 [-1.12, -0.35] |
| Heterogeneity: not applicab | le | | | | | | |
| Test for overall effect: $Z = 3$ | 8.78 (P = | 0.00016) | | | | | |
| 2 3 to 6 months | | | | | | | |
| Dam 1996 | 16 | 32.4 (3.8) | 16 | 31.6 (5) | | 44.7 % | 0.18 [-0.52, 0.87] |
| Subtotal (95% CI) | 16 | | 16 | | + | 44.7 % | 0.18 [-0.52, 0.87] |
| Heterogeneity: not applicab | le | | | | | | |
| Test for overall effect: $Z = C$ |).50 (P = | 0.62) | | | | | |
| Total (95% CI) | 73 | | 72 | | - | 100.0 % | -0.33 [-1.22, 0.56] |
| Heterogeneity: Tau ² = 0.33; | ; Chi ² = 5 | 5.09, df = 1 (P = 0. | .02); I ² =80% | | | | |
| Test for overall effect: $Z = C$ |).72 (P = | 0.47) | | | | | |
| Test for subgroup difference | es: Chi² = | 5.09, df = 1 (P = | 0.02), I ² =80 | % | | | |

-2

-4 Favours SSRI 0

2 4

Favours control

Analysis 4.1. Comparison 4 SSRI versus control according to depression at time of recruitment, Outcome I Modified Rankin score.

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

Comparison: 4 SSRI versus control according to depression at time of recruitment

Outcome: I Modified Rankin score

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|-----------------------------------|---------|--------------------|---------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% CI |
| I Had to have depression at recruitme | ent | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 2 Did not have to have depression at | recruitment | | | |
| Almeida 2006 | 0/55 | 0/56 | | 0.0 [0.0, 0.0] |
| Chollet 2011 | 42/57 | 50/55 | — | 0.81 [0.68, 0.97] |
| Subtotal (95% CI) | 112 | 111 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Control) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, | $df = 0 (P = 1.00); I^{2}$ | 2 =0.0% | | |
| Test for overall effect: $Z = 2.34$ (P = 0 | .019) | | | |
| Total (95% CI) | 112 | 111 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Control) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, | df = 0 (P = 1.00); l ² | 2 =0.0% | | |
| Test for overall effect: $Z = 2.34$ (P = 0 | .019) | | | |
| Test for subgroup differences: Not app | licable | | | |
| | | | | |
| | | | 0.05 0.2 5 20 | |

Favours SSRI Favours control

Analysis 4.2. Comparison 4 SSRI versus control according to depression at time of recruitment, Outcome 2 Disability.

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

Comparison: 4 SSRI versus control according to depression at time of recruitment

Outcome: 2 Disability

| Study or subgroup | SSRI N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% CI | Weight | Std. Mean Difference IV,Random,95% CI |
|--|-------------|---------------|--------------|----------------|---|---------------|--|
| I Had to have depression | at recruitm | nent | | | | | |
| Chen 2001 | 19 | 79.31 (8.94) | 18 | 71.56 (9.41) | | 4.3 % | 0.83 [0.15, 1.50] |
| Chen 2002 | 24 | 61 (12.2) | 20 | 51.5 (10.3) | | 4.5 % | 0.82 [0.20, 1.44] |
| Chen T 2005 | 40 | 65.76 (5.92) | 38 | 51.76 (7.32) | | 4.6 % | 2.09 [1.53, 2.64] |
| Cheng 2003 | 25 | -26.38 (14.2) | 32 | -29.15 (17.38) | | 4.7 % | 0.17 [-0.35, 0.69] |
| He 2005 | 27 | 84.26 (8.41) | 27 | 78.33 (15.01) | + | 4.7 % | 0.48 [-0.06, 1.02] |
| Li 2006 | 50 | 64.36 (8.23) | 49 | 59.17 (9.02) | | 5.0 % | 0.60 [0.19, 1.00] |
| Li 2008 | 58 | 40.8 (3.7) | 28 | 38.4 (5.8) | | 4.9 % | 0.53 [0.07, 0.99] |
| Liu 2006 | 30 | 64.4 (12.1) | 30 | 35.4 (9.1) | | 4.2 % | 2.67 [1.97, 3.38] |
| Robinson 2000a | 14 | 59.2 (11.6) | 13 | 56.2 (7.74) | | 4.1 % | 0.29 [-0.47, 1.05] |
| Wang 2003 | 51 | 75 (4.2) | 47 | 61 (6.9) | | 4.7 % | 2.46 [1.93, 2.98] |
| Wiart 2000 | 16 | 87.4 (22.8) | 15 | 88.7 (25.3) | | 4.3 % | -0.05 [-0.76, 0.65] |
| Xie 2005 | 65 | 88.7 (7.9) | 65 | 79.8 (4.5) | - | 5.1 % | 1.38 [0.99, 1.76] |
| Xu 2001 | 26 | 73 (4.4) | 27 | 67 (4.1) | - | 4.5 % | 1.39 [0.79, 2.00] |
| Xu 2007 | 36 | 64.4 (8.23) | 36 | 56.9 (6.68) | . | 4.8 % | 0.99 [0.50, 1.48] |
| Ye 2004 | 30 | 78.75 (14.19) | 30 | 50.26 (13.4) | | 4.5 % | 2.04 [1.41, 2.67] |
| Subtotal (95% CI) Heterogeneity: $Tau^2 = 0.5$ Test for overall effect: $Z =$ | | | 475 | =88% | - | 68.9 % | 1.11 [0.71, 1.51] |
| 2 Did not have to have de | ` | , | | | | | |
| Acler 2009 | 10 | 82 (28) | 10 | 75 (25) | | 3.8 % | 0.25 [-0.63, 1.13] |
| Dam 1996 | 16 | 61.9 (13) | 16 | 54.1 (21.1) | | 4.3 % | 0.43 [-0.27, 1.14] |
| Kong 2007 | 37 | 60.4 (12.5) | 36 | 52.3 (13.5) | | 4.9 % | 0.62 [0.15, 1.09] |
| Liu 2004 | 30 | 70.33 (10.74) | 30 | 64.33 (7.7) | | 4.7 % | 0.63 [0.11, 1.15] |
| Robinson 2000b | 13 | 60.5 (10.8) | 15 | 63.1 (8.2) | | 4.1 % | -0.27 [-1.01, 0.48] |
| | | | | | -1 -0.5 0 0.5 I Favours control Favours SSRI | | |

(Continued ...)

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | | Std. Mean ference om,95% Cl | Weight | (Continuec Std. Mean Difference IV,Random,95% CI |
|---|---|--------------------------------|--|---------------|-------------------------------|--------------------------------------|---------|---|
| Xu 2006 | 28 | -27.63 (4.81) | 29 | -32.81 (4.13) | | \longrightarrow | 4.6 % | 1.14 [0.58, 1.70] |
| Zhou 2003 | 28 | -27.8 (7.1) | 26 | -32.5 (7.8) | | | 4.7 % | 0.62 [0.07, 1.17] |
| Subtotal (95% CI) Heterogeneity: Tau ² = 0.06 Test for overall effect: Z = 3 | | | 162 5); ² =37% | | | | 31.1 % | 0.55 [0.27, 0.84] |
| Total (95% CI) Heterogeneity: Tau ² = 0.45 Test for overall effect: Z = 1 Test for subgroup difference | 673 5; Chi ² = 13 5.91 (P < 0 | 36.49, df = 21 (P< 0.00001) | | | | | 100.0 % | 0.92 [0.62, 1.23] |
| | | | | | - I -0.5 (Favours control | 0 0.5 I Favours SSRI | | |
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Analysis 4.3. Comparison 4 SSRI versus control according to depression at time of recruitment, Outcome 3 Neurological deficit score.

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

Comparison: 4 SSRI versus control according to depression at time of recruitment

Outcome: 3 Neurological deficit score

| Study or subgroup | SSRI N | Mean(SD) | Control N | Mean(SD) | | Std. Mean ference om,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|---|-------------|---------------|---------------|---------------|-------------------------|--------------------------------------|--------|--|
| I Had to have depression a | t recruitme | ent | | | | | | |
| Chen 2001 | 19 | -49.72 (4.07) | 18 | -43.13 (3.64) | ←→── | | 3.0 % | -1.67 [-2.43, -0.91] |
| Chen 2002 | 24 | 10 (4.8) | 20 | 14.8 (4.8) | | | 3.3 % | -0.98 [-1.61, -0.35] |
| Cheng 2003 | 25 | 6.5 (3.19) | 32 | 10.96 (8.13) | | | 3.5 % | -0.68 [-1.22, -0.14] |
| Feng 2004 | 16 | 9.1 (3.2) | 16 | 14.4 (2.2) | 41 | | 2.8 % | -1.88 [-2.73, -1.03] |
| Fruehwald 2003 | 26 | -55.5 (4.8) | 24 | -52.8 (5.4) | | - | 3.4 % | -0.52 [-1.09, 0.04] |
| Guo 2009 | 40 | 29.07 (8.02) | 40 | 33.78 (8.63) | <u> </u> | | 3.7 % | -0.56 [-1.01, -0.11] |
| He 2005 | 27 | 6.48 (1.58) | 27 | 8.33 (3.86) | | | 3.5 % | -0.62 [-1.17, -0.07] |
| Huang 2002 | 40 | 4.02 (1.86) | 40 | 8.57 (3.64) | | | 3.6 % | -1.56 [-2.06, -1.06] |
| Jia 2005 | 86 | 10.4 (8.5) | 88 | 22.6 (8.9) | _ — | | 3.9 % | -1.40 [-1.73, -1.06] |
| Li 2002 | 46 | 11.5 (2.8) | 46 | 19 (4) | ← | | 3.5 % | -2.15 [-2.67, -1.64] |
| Li 2004a | 33 | 6.23 (3.11) | 34 | 12.86 (6.36) | <u> </u> | | 3.5 % | -1.30 [-1.83, -0.77] |
| Li 2005 | 74 | 12.9 (5.1) | 74 | 18.7 (5.4) | | | 3.8 % | -1.10 [-1.44, -0.75] |
| Li 2006 | 50 | 21.89 (1.57) | 49 | 23.77 (1.46) | <u> </u> | | 3.7 % | -1.23 [-1.66, -0.80] |
| Liang 2003 | 42 | .74 (3.23) | 21 | 17.32 (5.19) | - | | 3.4 % | -1.38 [-1.96, -0.80] |
| Liu 2006 | 30 | 3.3 (3.8) | 30 | 22.4 (4.1) | ← | | 3.2 % | -2.27 [-2.93, -1.61] |
| Wang 2003 | 51 | 9.5 (3.5) | 47 | 15.6 (4.6) | <u> </u> | | 3.7 % | -1.49 [-1.94, -1.04] |
| Xu 2001 | 26 | 8.2 (5.2) | 27 | 12.4 (4.3) | | | 3.4 % | -0.87 [-1.43, -0.30] |
| Xu 2007 | 36 | 21.89 (1.57) | 36 | 20.78 (4.06) | - | | 3.6 % | 0.36 [-0.11, 0.82] |
| Ye 2004 | 30 | 8.3 (3.8) | 30 | 16 (4.8) | ~ | | 3.4 % | -1.76 [-2.36, -1.15] |
| Subtotal (95% CI) | 721 | | 699 | | • | | 66.1 % | -1.19 [-1.47, -0.91] |
| Heterogeneity: $Tau^2 = 0.31$; Test for overall effect: $Z = 8$ 2 Did not have to have dep | 3.37 (P < C | 0.00001) | <0.00001); 12 | =82% | | | | |
| Acler 2009 | 10 | 2.3 (2) | 10 | 3.5 (1.3) | | - | 2.7 % | -0.68 [-1.59, 0.23] |
| | | | | | -2 -1 (Favours SSRI | 0 I 2 Favours control | | (Continued) |

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV.Random,95% Cl | Weight | (Continued) Std. Mean Difference IV,Random,95% Cl |
|--|-------------|--------------|--------------|--------------|--|--------|--|
| Burns 1999 | 14 | -29.7 (14.7) | 14 | -32.2 (13.4) | ```` | 3.1 % | 0.17 [-0.57, 0.91] |
| Chollet 2011 | 57 | 5.8 (3.7) | 55 | 6.9 (4.4) | | 3.8 % | -0.27 [-0.64, 0.10] |
| Dam 1996 | 16 | 44.1 (9.4) | 16 | 46.8 (9.9) | · | 3.2 % | -0.27 [-0.97, 0.42] |
| He 2004 | 36 | 10.41 (6.36) | 35 | 14.43 (7.94) | | 3.6 % | -0.55 [-1.03, -0.08] |
| Kong 2007 | 37 | 8.6 (6.4) | 36 | 11.2 (6.4) | - _ | 3.6 % | -0.40 [-0.87, 0.06] |
| Liu 2004 | 30 | 9.2 (2.06) | 30 | 10.47 (9.2) | | 3.6 % | -0.19 [-0.70, 0.32] |
| Wen 2006 | 42 | 10.1 (1.9) | 42 | 16.4 (2.5) | • | 3.3 % | -2.81 [-3.42, -2.20] |
| Xu 2006 | 28 | . (4.32) | 29 | 13.63 (3.15) | | 3.5 % | -0.66 [-1.19, -0.13] |
| Zhou 2003 | 28 | 9 (3.8) | 26 | 12.2 (6.1) | | 3.5 % | -0.63 [-1.17, -0.08] |
| Subtotal (95% CI) | 298 | | 293 | | - | 33.9 % | -0.63 [-1.08, -0.17] |
| Test for overall effect: $Z = \frac{1}{2}$ | 7.71 (P < 0 | , | , | | | | |
| ÷ , | 7.71 (P < 0 | .00001) | , | | | | |
| Test for overall effect: $Z = \frac{1}{2}$ | 7.71 (P < 0 | .00001) | , | | -2 -1 0 1 2 Favours SSRI Favours contr | | |

Analysis 4.4. Comparison 4 SSRI versus control according to depression at time of recruitment, Outcome 4 Depression (continuous).

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

Comparison: 4 SSRI versus control according to depression at time of recruitment

Outcome: 4 Depression (continuous)

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Std. Mean Difference |
|--------------------------|--------------|---------------|---------|---------------|----------------------------|--------|----------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% Cl | | IV,Random,95% CI |
| I Had to have depression | at recruitme | ent | | | | | |
| Andersen 1994 | 33 | 11.4 (5.1) | 33 | 4. (4.7) | -+- | 2.7 % | -0.54 [-1.04, -0.05] |
| Chen 2001 | 19 | 10.82 (6.25) | 18 | 18.48 (6.28) | | 2.6 % | -1.20 [-1.90, -0.49] |
| Chen 2002 | 24 | 10.3 (3) | 20 | 16.5 (2.5) | | 2.6 % | -2.19 [-2.95, -1.42] |
| Chen T 2005 | 40 | 10.98 (3.74) | 38 | 22.45 (3.56) | | 2.6 % | -3.11 [-3.78, -2.44] |
| Cheng 2003 | 25 | 13.64 (11.02) | 32 | 17.98 (12.53) | | 2.7 % | -0.36 [-0.89, 0.17] |
| Feng 2004 | 16 | 34.9 (4.6) | 16 | 41.1 (4.7) | | 2.5 % | -1.30 [-2.07, -0.53] |
| Finkenzeller 2009 | 23 | 12.1 (1.05) | 27 | 10.6 (0.97) | | 2.6 % | 1.47 [0.83, 2.10] |
| Fruehwald 2003 | 26 | 9.5 (7.9) | 24 | 11.2 (12.4) | | 2.7 % | -0.16 [-0.72, 0.39] |
| Guo 2009 | 40 | 14.82 (8.05) | 40 | 17.61 (8) | | 2.7 % | -0.34 [-0.79, 0.10] |
| He 2005 | 27 | 10.11 (1.08) | 27 | 17.48 (1.05) | • | 2.1 % | -6.82 [-8.26, -5.38] |
| Huang 2002 | 40 | 4.76 (0.6) | 40 | 16.34 (1.3) | | 1.8 % | -11.33 [-13.18, -9.47] |
| Ji 2000 | 20 | 5.2 (1.5) | 20 | 14.5 (2.7) | ← | 2.3 % | -4.17 [-5.32, -3.03] |
| Jia 2005 | 86 | 6.4 (6.2) | 88 | 16.2 (6.8) | + | 2.7 % | -1.50 [-1.84, -1.16] |
| Lai 2006 | 40 | 12.5 (8.4) | 40 | 21.5 (4.3) | | 2.7 % | -1.34 [-1.82, -0.85] |
| Li 2002 | 46 | 10 (3) | 46 | 22 (8) | | 2.7 % | -1.97 [-2.47, -1.47] |
| Li 2005 | 74 | 12.6 (2.1) | 74 | 16.8 (2.3) | - | 2.7 % | -1.90 [-2.29, -1.51] |
| Li 2006 | 50 | 5.61 (5.32) | 49 | 20.26 (6.08) | | 2.7 % | -2.55 [-3.08, -2.01] |
| Li 2008 | 58 | 14.5 (2.4) | 28 | 18.7 (3.9) | | 2.7 % | -1.40 [-1.90, -0.90] |
| Liang 2003 | 42 | 9.67 (4.48) | 21 | 19.19 (3.12) | <u> </u> | 2.6 % | -2.30 [-2.97, -1.63] |
| Liu 2006 | 30 | 17.2 (2.1) | 30 | 25.1 (3.3) | <u> </u> | 2.6 % | -2.82 [-3.55, -2.09] |
| Miao 2004 | 34 | 6.45 (5.3) | 34 | 23.74 (5.16) | ←── | 2.6 % | -3.27 [-4.01, -2.53] |
| Murray 2005 | 62 | 10.5 (9.6) | 61 | 12 (8.5) | -+ | 2.7 % | -0.16 [-0.52, 0.19] |
| Robinson 2000a | 14 | 18.5 (7.6) | 13 | 12.2 (4.7) | | 2.5 % | 0.96 [0.15, 1.76] |

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Favours SSRI Favours control

(Continued ...)

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| Study or subgroup SSR Control Difference Weight Difference Weight Difference N Mean(SD) N N Mean(SD) N | | | | | | Sto | 4 | (Continued |
|---|-------------------------------|---------------|--------------------|--------------------------|---------------|---------|---------|------------------------|
| N Mean(SD) N Mean(SD) IVRandom;95% CI IVRandom;95% CI Song 2006 41 403 (725) 41 4631 (802) 27 % -1.04 [-1.50, 0.5 Wang 2003 51 10.5 (2.9) 47 20 (61) 27 % -2.00 [-2.49, 1.5 Wart 2000 16 11.8 (67) 15 187 (10) - 26 % -0.79 [-1.53, 0.0 Xu 2001 26 23.6 (3.9) 27 44.7 (2.6) - 22 % -6.30 [-7.65, 4.9 Xu 2007 36 5.61 (5.32) 36 17.73 (3.21) 2.6 % -2.14 [-1.80, 0.4 Yu 2001 20 7 (4) 22 13 (6) - 2.6 % -2.73 [-3.38, -2.0 Yang 2011 20 7 (4) 22 13 (6) - 2.3 % 5.32 [-6.4.3, -4.2 Subtotal (95% CI) 1154 1102 - 79.4 % -2.06 [-2.5.4, -1.56 Text rowerall effect: Z = 8.40 (P < 0.00001): 21 - 25 % -0.40 [-1.29, 0.4 | Cturely and an endergroup | CCDI | | Cantural | | Mea | n | Mean |
| $ \begin{array}{c ccccccccccccccccccccccccccccccccccc$ | Study or subgroup | | Mean(SD) | | Mean(SD) | | - | |
| Wart 2000 16 118 (67) 15 187 (10) 26% 0.79 [-153, 00] Xie 2005 65 309 (71) 65 397 (53) $$ 2.7% 1.40 [-1.78, -10] Xu 2001 26 23.6 (39) 27 44.7 (2.6) $ 2.2\%$ 6.30 [-7.65, -49] Xu 2007 36 5.61 (532) 36 17.73 (3.21) $ 2.6\%$ -2.73 [-3.38, -20] Yang 2011 20 7 (4) 22 13 (6) $ 2.6\%$ -1.14 [-1.80, -04] Ye 2004 30 402 (307) 30 17.32 (1.66) $ 2.3\%$ -5.32 [-6.43, -42] Subtotal (95% CI) 1154 1102 $ 2.6\%$ -1.14 [-1.80, -04] Z for overall effect: Z = 8.40 (P < 0.00001) 10 8 (3) $ 2.5\%$ -0.40 [-1.29, 04] Cholet 2011 56 5.4 (4.9) 54 8.4 (79) $ 2.6\%$ -2.23 [-2.93, -1.75] Kong 2007 37 12.6 (5.3) 36 16.3 (3.7) $ 2.7\%$ -0.30 [-1.28, 0.3] Wen | Song 2006 | | . , | | , , | | | -1.04 [-1.50, -0.58] |
| Xie 2005 65 309 (7.1) 65 397 (5.3) - 2.7 % -1.40 [-1.78, -1.0] Xie 2001 2.6 2.3.6 (3.9) 2.7 44.7 (2.6) - 2.2 % -6.30 [-7.65, 4.9] Xie 2007 3.6 5.61 (5.32) 3.6 17.73 (3.21) - 2.6 % -2.73 [-3.38, -2.0] Yang 2011 2.0 7 (4) 2.2 13 (6) - 2.6 % -1.14 [-1.80, 0.4] Ye 2004 3.0 4.02 (307) 3.0 17.32 (1.6) - 2.6 % -2.06 [-2.54, -1.56] Stabtcal (95% CI) 1154 1102 - - 79.4 % -2.06 [-2.54, -1.56] Pieterogeneity: Tau ² = 1.71; Chi ² = 644.21, df = 30 (P<0.00001); Pi = 95% | Wang 2003 | 51 | 10.5 (2.9) | 47 | 20 (6.1) | | 2.7 % | -2.00 [-2.49, -1.51 |
| Xu 2001 26 236 (39) 27 447 (2.6) Xu 2007 36 5.61 (5.32) 36 17.73 (3.21) Yang 2011 20 7 (4) 22 13 (6) Yang 2011 20 7 (4) 22 13 (6) Yang 2011 20 7 (4) 22 13 (6) Yang 2011 20 7 (4) 22 13 (6) Subtoal (95% CI) 1154 1102 Peterogeneity: Tau ² = 1.71; Chi ² = 644.21, df = 30 (P<0.00001); l ² = 95% fest for overall effect: $Z = 8.40$ (P < 0.00001) 2 Did not have to have depression at recruitment Acter 2009 10 6.6 (3.6) 10 8 (3) Dam 1996 16 8.8 (5.6) 16 9.4 (5.6) He 2004 36 1428 (2.31) 35 20.32 (2.82) He 2004 36 1428 (2.31) 35 20.32 (2.82) Action 2005 13 5.9 (3.8) 15 6.2 (4.6) Ven 2006 42 7 (1.1) 42 17.7 (1.8) Subtoal (95% CI) 238 234 Heterogeneity: Tau ² = 1.93; Chi ² = 149.72, df = 7 (P<0.00001); l ² = 95% fest for overall effect: $Z = 2.67$ (P = 0.0076) For all (95% CI) 1392 1336 Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 3 (P<0.00001); l ² = 95% fest for overall effect: $Z = 2.67$ (P = 0.0076) For all (95% CI) 238 234 Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 3 (P<0.00001); l ² = 95% fest for overall effect: $Z = 2.67$ (P = 0.0076) For all (95% CI) 238 234 Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² = 95% fest for overall effect: $Z = 2.67$ (P = 0.0076) For all (95% CI) 1392 1336 Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² = 95% fest for overall effect: $Z = 2.67$ (P = 0.0076) For all (95% CI) 238 234 Heterogeneity: Tau ² = 1.75, df = 1 (P = 0.21), l ² = 36% | Wiart 2000 | 16 | 11.8 (6.7) | 15 | 18.7 (10) | | 2.6 % | -0.79 [-1.53, -0.06 |
| Xu 2007 36 5.61 (5.32) 36 17.73 (3.21) 2.6% -2.73 [-3.36, -2.0] Yang 2011 20 7 (4) 22 13 (6) 2.6% -1.14 [-1.80, -0.4] Ye 2004 30 4.02 (3.07) 30 17.32 (1.66) 2.3% -5.32 [-6.43, -4.2] Subtocal (95% CI) 1154 1102 $ -$ | Xie 2005 | 65 | 30.9 (7.1) | 65 | 39.7 (5.3) | | 2.7 % | -1.40 [-1.78, -1.01] |
| Yang 2011 20 7 (4) 22 13 (6) 26 % -1.14 [-1.800.4 Ye 2004 30 402 (307) 30 17.32 (1.66) 23 % -5.32 [-643. 42 Subtocal (95% CI) 1154 1102 $ -2.06$ [-2.54, -1.58] Hetrogeneity: Tax ² = 1.71; Chi ² = 644.21, df = 30 (P<0.00001); I ² = 95% $ -2.06$ [-2.54, -1.58] Petrogeneity: Tax ² = 1.71; Chi ² = 644.21, df = 30 (P<0.00001); I ² = 95% $ -$ </td <td>Xu 2001</td> <td>26</td> <td>23.6 (3.9)</td> <td>27</td> <td>44.7 (2.6)</td> <td>•</td> <td>2.2 %</td> <td>-6.30 [-7.65, -4.94</td> | Xu 2001 | 26 | 23.6 (3.9) | 27 | 44.7 (2.6) | • | 2.2 % | -6.30 [-7.65, -4.94 |
| Ye 2004 30 4.02 (3.07) 30 17.32 (1.66) 2.3 % $5.32 [-6.43, -42]$ Subbotal (95% CI) 1154 1102 79.4 % $-2.06 [-2.54, -1.58]$ Heterogeneity: Tau ² = 1.71; Chi ² = 644.21, df = 30 (P < 0.00001); l ² = 95% 79.4 % $-2.06 [-2.54, -1.58]$ Test for overall effect: Z = 8.40 (P < 0.00001); U 200001); U 27.8 $-0.40 [-1.29, 0.4]$ Cholet 2011 56 5.4 (4.9) 54 8.4 (7.9) 27.8 $-0.46 [-0.83, -0.0]$ Dam 1996 16 8.8 (5.6) 16 9.4 (5.6) 2.6 % $-0.10 [-0.80, 0.5]$ He 2004 36 14.28 (2.31) 35 20.32 (2.82) -2.6% -2.37% $-0.46 [-0.83, -0.0]$ Dam 1996 16 8.8 (5.6) 16 9.4 (5.6) -2.6% -2.27% $-0.46 [-0.83, -0.0]$ Robinson 2000b 13 5.9 (3.8) 15 $6.2 (4.6)$ -2.6% -2.7% $-0.80 [-1.28, -0.3]$ Wen 2006 42 7 (1.1) 42 $17.7 (1.8)$ 2.7% $-0.20 [-0.74, 0.3]$ Subtocal (95% CI) 238 234 $-0.20 [-0.74, 0.3]$ $2.$ | Xu 2007 | 36 | 5.61 (5.32) | 36 | 17.73 (3.21) | | 2.6 % | -2.73 [-3.38, -2.08 |
| Subtotal (95% CI) 1154 1102 79.4 % -2.06 [-2.54, -1.58] Heterogeneity: Tau ² = 1.71; Chi ² = 644.21, df = 30 (P<0.00001); l ² = 95% 79.4 % -2.06 [-2.54, -1.58] Test for overall effect: Z = 8.40 (P < 0.00001) | Yang 2011 | 20 | 7 (4) | 22 | 13 (6) | | 2.6 % | -1.14 [-1.80, -0.49] |
| Heterogeneity: Tau ² = 1.71; Chi ² = 644.21, df = 30 (P<0.00001); l ² = 95% Test for overall effect: $Z = 8.40$ (P < 0.00001) 2 Did not have to have depression at recruitment Ader 2009 10 6.6 (3.6) 10 8 (3) 2.5 % -0.40 [-1.29, 0.4 Chollet 2011 56 5.4 (4.9) 54 8.4 (7.9) 2.7 % -0.46 [-0.83, -0.0 Dam 1996 16 8.8 (5.6) 16 9.4 (5.6) 2.6 % -0.10 [-0.80, 0.5 He 2004 36 14.28 (2.31) 35 20.32 (2.82) 2.6 % -2.32 [-2.93, -1.7 Kong 2007 37 12.6 (5.3) 36 16.3 (3.7) 2.7 % -0.80 [-1.28, -0.3 Robinson 2000b 13 5.9 (3.8) 15 6.2 (4.6) 2.6 % -0.007 [-0.81, 0.6 Wen 2006 42 7 (1.1) 42 17.7 (1.8) 2.3 % -7.11 [-8.29, -5.9 Zhou 2003 28 3.5 (1.3) 26 3.8 (1.6) 2.7 % -0.20 [-0.74, 0.3 Subtocal (95% CI) 2.38 2.34 2.7 % -0.20 [-0.74, 0.3 Est for overall effect: $Z = 2.67$ (P = 0.0076) Total (95% CI) 1392 1336 4. Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² = 95% Test for overall effect: $Z = 8.70$ (P < 0.00001) Test for overall effect: $Z = 8.70$ (P < 0.00001) Test for subgroup differences: Chi ² = 1.55, df = 1 (P = 0.21), l ² = 36% | Ye 2004 | 30 | 4.02 (3.07) | 30 | 17.32 (1.66) | | 2.3 % | -5.32 [-6.43, -4.21 |
| Heterogeneity: Tau ² = 1.71; Chi ² = 644.21, df = 30 (P<0.00001); l ² = 95% Test for overall effect: $Z = 8.40$ (P < 0.00001) 2 Did not have to have depression at recruitment Ader 2009 10 6.6 (3.6) 10 8 (3) 2.5 % -0.40 [-1.29, 0.4 Chollet 2011 56 5.4 (4.9) 54 8.4 (7.9) 2.7 % -0.46 [-0.83, -0.0 Dam 1996 16 8.8 (5.6) 16 9.4 (5.6) 2.6 % -0.10 [-0.80, 0.5 He 2004 36 14.28 (2.31) 35 20.32 (2.82) 2.6 % -2.32 [-2.93, -1.7 Kong 2007 37 12.6 (5.3) 36 16.3 (3.7) 2.7 % -0.80 [-1.28, -0.3 Robinson 2000b 13 5.9 (3.8) 15 6.2 (4.6) 2.6 % -0.007 [-0.81, 0.6 Wen 2006 42 7 (1.1) 42 17.7 (1.8) 2.3 % -7.11 [-8.29, -5.9 Zhou 2003 28 3.5 (1.3) 26 3.8 (1.6) 2.7 % -0.20 [-0.74, 0.3 Subtocal (95% CI) 2.38 2.34 2.7 % -0.20 [-0.74, 0.3 Est for overall effect: $Z = 2.67$ (P = 0.0076) Total (95% CI) 1392 1336 4. Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² = 95% Test for overall effect: $Z = 8.70$ (P < 0.00001) Test for overall effect: $Z = 8.70$ (P < 0.00001) Test for subgroup differences: Chi ² = 1.55, df = 1 (P = 0.21), l ² = 36% | Subtotal (95% CI) | 1154 | | 1102 | | • | 79.4 % | -2.06 [-2.54, -1.58] |
| Acter 2009 10 $6.6 (3.6)$ 10 $8 (3)$ 25 % $-0.40 [-1.29, 0.4]$ Chollet 2011 56 $5.4 (4.9)$ 54 $8.4 (7.9)$ 27 % $-0.46 [-0.83, -0.0]$ Dam 1996 16 $8.8 (5.6)$ 16 $9.4 (5.6)$ 2.6 % $-0.10 [-0.80, 0.5]$ He 2004 36 14.28 (2.31) 35 20.32 (2.82) 26 % $-2.32 [-2.93, -1.7]$ Kong 2007 37 12.6 (5.3) 36 16.3 (3.7) 27 % $-0.80 [-1.28, -0.3]$ Robinson 2000b 13 5.9 (3.8) 15 6.2 (4.6) 2.6 % $-0.07 [-0.81, 0.6]$ Ven 2006 42 7 (1.1) 42 17.7 (1.8) 2.3 % $-7.11 [-8.29, -5.9]$ Zhou 2003 28 3.5 (1.3) 26 3.8 (1.6) 2.7 % $-0.20 [-0.74, 0.3]$ Subtotal (95% CI) 238 234 20.6 % $-1.35 [-2.35, -0.36]$ 100.0 % $-1.91 [-2.34, -1.48]$ Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² = 95% 100.0 % $-1.91 [-2.34, -1.48]$ 100.0 % $-1.91 [-2.34, -1.48]$ Test for overall effect: Z = 8.70 (P < 0.0001) <td>Heterogeneity: $Tau^2 = 1.71$</td> <td></td> <td></td> <td>0.00001); I²</td> <td>=95%</td> <td></td> <td></td> <td></td> | Heterogeneity: $Tau^2 = 1.71$ | | | 0.00001); I ² | =95% | | | |
| Chollet 2011 56 5.4 (4.9) 54 8.4 (7.9) 2.7% -0.46 [-0.83 , -0.0 Dam 1996 16 8.8 (5.6) 16 9.4 (5.6) 2.6% -0.10 [-0.80 , 0.5 He 2004 36 14.28 (2.31) 35 20.32 (2.82) 2.6% -2.32 [-2.93 , -1.7 Kong 2007 37 12.6 (5.3) 36 16.3 (3.7) 2.7% -0.80 [-1.28 , -0.3 Robinson 2000b 13 5.9 (3.8) 15 6.2 (4.6) 2.6% -0.07 [-0.81 , 0.6 Wen 2006 42 7 (1.1) 42 17.7 (1.8) 2.3% -7.11 [-8.29 , -5.9 Zhou 2003 28 3.5 (1.3) 26 3.8 (1.6) 2.7% -0.20 [-0.74 , 0.3 Subtotal (95% CI) 238 234 $ 20.6\%$ -1.35 [-2.35 , -0.36 Heterogeneity: Tau ² = 1.93; Chi ² = 149.72, df = 7 (P<0.00001); I ² = 95% 100.0% -1.91 [-2.34 , -1.44 Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); I ² = 95% 100.0% -1.91 [-2.34 , -1.44 Test for overall effect: Z = 8.70 (P < 0.00001) | 2 Did not have to have dep | pression at r | ecruitment | | | | | |
| Dam 1996168.8 (5.6)169.4 (5.6)2.6 % $-0.10 [-0.80, 05]$ He 20043614.28 (2.31)3520.32 (2.82)2.6 % $-2.32 [-2.93, -1.7]$ Kong 20073712.6 (5.3)3616.3 (3.7)2.7 % $-0.80 [-1.28, -0.3]$ Robinson 2000b135.9 (3.8)156.2 (4.6)2.6 % $-0.07 [-0.81, 0.6]$ Wen 2006427 (1.1)4217.7 (1.8)2.3 % $-7.11 [-8.29, -5.9]$ Zhou 2003283.5 (1.3)2.63.8 (1.6)2.7 % $-0.20 [-0.74, 0.3]$ Subtotal (95% CI)23823420.6 % $-1.35 [-2.35, -0.36]$ Heterogeneity: Tau ² = 1.93; Chi ² = 149.72, df = 7 (P<0.00001); l ² = 95%100.0 % $-1.91 [-2.34, -1.48]$ Test for overall effect: Z = 2.67 (P = 0.0076)13921336100.0 % $-1.91 [-2.34, -1.48]$ Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² = 95%100.0 % $-1.91 [-2.34, -1.48]$ Test for overall effect: Z = 8.70 (P < 0.00001) | Acler 2009 | 10 | 6.6 (3.6) | 10 | 8 (3) | | 2.5 % | -0.40 [-1.29, 0.48 |
| He 2004 36 14.28 (2.31) 35 20.32 (2.82) 2.6% -2.32 [$-2.93, -1.7$ Kong 2007 37 12.6 (5.3) 36 16.3 (3.7) 2.7% -0.80 [$-1.28, -0.3$ Robinson 2000b 13 5.9 (3.8) 15 6.2 (4.6) 2.6% -0.07 [$-0.81, 0.6$ Wen 2006 42 7 (1.1) 42 17.7 (1.8) 2.3% -7.11 [$-8.29, -5.9$ Zhou 2003 28 3.5 (1.3) 2.6 3.8 (1.6) 2.7% -0.20 [$-0.74, 0.3$ Subtotal (95% CI) 238 234 2.6% -1.35 [$-2.35, -0.36$ Heterogeneity: Tau ² = 1.93; Chi ² = 149.72, df = 7 (P<0.00001); l ² = 95% 2.6% -1.35 [$-2.34, -1.48$ Test for overall effect: Z = 2.67 (P = 0.0076) 1392 1336 4 -1.91 [$-2.34, -1.48$ Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² = 95% 100.0% -1.91 [$-2.34, -1.48$ Test for overall effect: Z = 8.70 (P < 0.00001) | Chollet 2011 | 56 | 5.4 (4.9) | 54 | 8.4 (7.9) | | 2.7 % | -0.46 [-0.83, -0.08 |
| Kong 2007 37 12.6 (5.3) 36 16.3 (3.7) - 2.7 % -0.80 [-1.28 , -0.37 Robinson 2000b 13 5.9 (3.8) 15 6.2 (4.6) 2.6 % -0.07 [-0.81 , 0.6 Wen 2006 42 7 (1.1) 42 17.7 (1.8) 2.3 % -7.11 [$-8.29, -5.9$ Zhou 2003 28 3.5 (1.3) 26 3.8 (1.6) 2.7 % -0.20 [-0.74 , 0.3 Subtotal (95% CI) 238 234 $ 20.6$ % -1.35 [-2.35 , -0.36 Heterogeneity: Tau ² = 1.93 ; Chi ² = 149.72 , df = 7 (P<0.00001); l ² = 95% $ 20.6$ % -1.91 [-2.34 , -1.448 Heterogeneity: Tau ² = 1.74 ; Chi ² = 817.95 , df = 38 (P<0.00001); l ² = 95% $ 100.0$ % -1.91 [-2.34 , -1.448 Heterogeneity: Tau ² = 1.74 ; Chi ² = 817.95 , df = 38 (P<0.00001); l ² = 95% $ -$ Test for overall effect: Z = 8.70 (P < 0.00001) $ -$ <td>Dam 1996</td> <td>16</td> <td>8.8 (5.6)</td> <td>16</td> <td>9.4 (5.6)</td> <td></td> <td>2.6 %</td> <td>-0.10 [-0.80, 0.59</td> | Dam 1996 | 16 | 8.8 (5.6) | 16 | 9.4 (5.6) | | 2.6 % | -0.10 [-0.80, 0.59 |
| Robinson 2000b 13 5.9 (3.8) 15 6.2 (4.6) 2.6% -0.07 [$-0.81, 0.6$ Wen 2006 42 7 (1.1) 42 17.7 (1.8) 2.3% -7.11 [$-8.29, -5.9$ Zhou 2003 28 3.5 (1.3) 26 3.8 (1.6) 2.7% -0.20 [$-0.74, 0.3$ Subtotal (95% CI) 238 234 20.6% -1.35 [$-2.35, -0.36$ Heterogeneity: Tau ² = 1.93; Chi ² = 149.72, df = 7 (P<0.00001); l ² =95% 20.6% -1.91 [$-2.34, -1.48$ Total (95% CI) 1392 1336 100.0% -1.91 [$-2.34, -1.48$ Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² =95% 100.0% -1.91 [$-2.34, -1.48$ Test for overall effect: Z = 8.70 (P < 0.00001) | He 2004 | 36 | 14.28 (2.31) | 35 | 20.32 (2.82) | | 2.6 % | -2.32 [-2.93, -1.71 |
| Wen 2006 42 7 (1.1) 42 17.7 (1.8) 2.3 % -7.1 [-8.29, -5.9] Zhou 2003 28 3.5 (1.3) 26 3.8 (1.6) 2.7 % -0.20 [-0.74, 0.3] Subtotal (95% CI) 238 234 20.6 % -1.35 [-2.35, -0.36] Heterogeneity: Tau ² = 1.93; Chi ² = 149.72, df = 7 (P<0.00001); l ² = 95% 20.6 % -1.35 [-2.35, -0.36] Total (95% CI) 1392 1336 100.0 % -1.91 [-2.34, -1.48] Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² = 95% 100.0 % -1.91 [-2.34, -1.48] Test for overall effect: Z = 8.70 (P < 0.00001) | Kong 2007 | 37 | 12.6 (5.3) | 36 | 16.3 (3.7) | | 2.7 % | -0.80 [-1.28, -0.32 |
| Zhou 2003 28 $3.5 (1.3)$ 26 $3.8 (1.6)$ 2.7% $-0.20 [-0.74, 0.3]$ Subtotal (95% CI) 238 234 20.6% $-1.35 [-2.35, -0.36]$ Heterogeneity: Tau ² = 1.93; Chi ² = 149.72, df = 7 (P<0.00001); l ² =95% 2.7% $-0.20 [-0.74, 0.3]$ Total (95% CI) 1392 1336 $-1.35 [-2.35, -0.36]$ Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² =95% $-1.91 [-2.34, -1.48]$ Test for overall effect: Z = 8.70 (P < 0.00001) | Robinson 2000b | 13 | 5.9 (3.8) | 15 | 6.2 (4.6) | | 2.6 % | -0.07 [-0.81, 0.67 |
| Subtotal (95% CI) 238 234 Heterogeneity: Tau ² = 1.93; Chi ² = 149.72, df = 7 (P<0.00001); l ² =95% Test for overall effect: Z = 2.67 (P = 0.0076) Total (95% CI) 1392 1336 Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² =95% Test for overall effect: Z = 8.70 (P < 0.00001) | Wen 2006 | 42 | 7 (1.1) | 42 | 17.7 (1.8) | 4 | 2.3 % | -7.11 [-8.29, -5.93 |
| Heterogeneity: Tau ² = 1.93; Chi ² = 149.72, df = 7 (P<0.00001); l ² = 95% Test for overall effect: $Z = 2.67$ (P = 0.0076) Total (95% CI) 1392 1336 • 100.0 % -1.91 [-2.34, -1.48 Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² = 95% Test for overall effect: $Z = 8.70$ (P < 0.00001) Test for subgroup differences: Chi ² = 1.55, df = 1 (P = 0.21), l ² = 36% | Zhou 2003 | 28 | 3.5 (1.3) | 26 | 3.8 (1.6) | | 2.7 % | -0.20 [-0.74, 0.33 |
| Test for overall effect: $Z = 2.67$ (P = 0.0076) Total (95% CI) 1392 Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² = 95% Test for overall effect: $Z = 8.70$ (P < 0.00001) | Subtotal (95% CI) | 238 | | 234 | | - | 20.6 % | -1.35 [-2.35, -0.36] |
| Total (95% CI) 1392 1336 100.0 % -1.91 [-2.34, -1.48 Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² = 95% 100.0 % -1.91 [-2.34, -1.48 Test for overall effect: Z = 8.70 (P < 0.00001) | ÷ , | | | 00001); 2 = | -95% | | | |
| Heterogeneity: Tau ² = 1.74; Chi ² = 817.95, df = 38 (P<0.00001); l ² =95% Test for overall effect: Z = 8.70 (P < 0.00001) Test for subgroup differences: Chi ² = 1.55, df = 1 (P = 0.21), l ² =36% | | | 0076) | 1336 | | • | 100.0 % | -1.91 [-2.34, -1.48] |
| Test for subgroup differences: $Chi^2 = 1.55$, df = 1 (P = 0.21), l ² = 36% | 0 , | | | 0.00001); I ² | =95% | | | |
| · · · · · | | | | | | | | |
| -4 -2 0 2 4 | Test for subgroup difference | es: Chi² = I | .55, df = 1 (P = 0 | .21), 1² =369 | % | | | |
| | | | | | | -4 -2 0 | 2 4 | |
| Favours SSRI Favours control | | | | | | | | |
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| | elective serotonin reup | take inhih | itors (SSRIs) fo | r stroke re | covery (Revie | *) | | |

Analysis 4.5. Comparison 4 SSRI versus control according to depression at time of recruitment, Outcome 5 Depression (dichotomous).

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

Comparison: 4 SSRI versus control according to depression at time of recruitment

Outcome: 5 Depression (dichotomous)

| Study or subgroup | SSRI | Control | Risk Ratio M- | Weight | Risk Ratio M- |
|---|--|---------------------------------|--------------------|---------|---------------------|
| | n/N | n/N | H,Random,95% Cl | | H,Random,959 Cl |
| I Had to have depression at re | cruitment | | | | |
| GlaxoSmithKline 1998 | 82/111 | 97/114 | • | 18.5 % | 0.87 [0.76, 0.99] |
| Li 2004b | 5/31 | 13/32 | | 13.0 % | 0.40 [0.16, 0.98] |
| Subtotal (95% CI) | 142 | 146 | • | 31.5 % | 0.66 [0.30, 1.46] |
| Total events: 87 (SSRI), 110 (Co Heterogeneity: Tau ² = 0.25; Ch Test for overall effect: $Z = 1.03$ 2 Did not have to have depress | $hi^2 = 3.33, df = 1$ (F (P = 0.30) | P = 0.07); I ² =70% | | | |
| Almeida 2006 | 8/48 | 11/51 | | 13.8 % | 0.77 [0.34, 1.76] |
| Li 2004a | 2/33 | 8/34 | | 8.7 % | 0.26 [0.06, 1.12] |
| Rasmussen 2003 | 3/35 | 8/32 | | 10.3 % | 0.34 [0.10, 1.18] |
| Robinson 2008 | 5/59 | 13/58 | | 12.5 % | 0.38 [0.14, 0.99] |
| Xu 2006 | 3/28 | 12/29 | | 10.9 % | 0.26 [0.08, 0.82] |
| Zhou 2008 | 4/36 | 18/40 | | 12.3 % | 0.25 [0.09, 0.66] |
| Subtotal (95% CI) | 239 | 244 | • | 68.5 % | 0.38 [0.25, 0.59] |
| Total events: 25 (SSRI), 70 (Cor | ntrol) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; Chi ² | ² = 4.36, df = 5 (P | = 0.50); l ² =0.0% | | | |
| Test for overall effect: $Z = 4.37$ | (P = 0.000012) | | | | |
| Total (95% CI) | 381 | 390 | • | 100.0 % | 0.43 [0.24, 0.77] |
| Total events: 112 (SSRI), 180 (C | Control) | | | | |
| Heterogeneity: $Tau^2 = 0.49$; Ch | $m^2 = 30.48, df = 7$ (| $P = 0.00008$; $I^2 = 77\%$ | | | |
| Test for overall effect: $Z = 2.82$ | (P = 0.0049) | | | | |
| Test for subgroup differences: C | $Chi^2 = 1.33, df = 1$ | (P = 0.25), I ² =25% | | | |

0.01 0.1 Favours SSRI Favours control

10 100

Analysis 4.6. Comparison 4 SSRI versus control according to depression at time of recruitment, Outcome 6 Anxiety (continuous).

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

Comparison: 4 SSRI versus control according to depression at time of recruitment

Outcome: 6 Anxiety (continuous)

| He 2005 27 5.37 (1.66) 27 12.78 (1.93) He 2006 40 502 (9.4) 40 542 (15.2) 11.3 $\%$ -4.06 [-5.01, -3.1] Lai 2006 40 502 (9.4) 40 542 (15.2) 13.2 $\%$ -0.31 [-0.75, 0.1] Robinson 2000a 14 9.8 (4.8) 13 9.9 (5.1) 12.1 $\%$ -0.02 [-0.77, 0.7] Ye 2004 30 9.82 (2.64) 30 14.02 (2.32) 12.7 $\%$ -1.67 [-2.26, -1.0] Subtotal (95% CI) 13.4 137 62.0 $\%$ -1.10 [-2.32, 0.12] Est for overall effect: Z = 1.77 ($P = 0.077$) 2 Did not have to have depression at recruitment Liu 2004 30 7.43 (3.63) 30 11 (5.63) 12.9 $\%$ -0.74 [-1.27, -0.2] Robinson 2000b 13 4.7 (3.8) 15 5.5 (2.9) 12.1 $\%$ -0.23 [-0.98, 0.5] Zhou 2003 2.8 3.5 (1.3) 2.6 3.3 (1.3) 12.9 $\%$ 0.15 [-0.38, 0.6] Subtotal (95% CI) 7.1 71 71 Heterogeneity: Tau ² = 0.16; Chi ² = 55.2, df = 2 ($P = 0.06$); $l2 = 64\%$ Test for overall effect: Z = 0.97 ($P = 0.33$) Total (95% CI) 205 208 Heterogeneity: Tau ² = 1.05; Chi ² = 86.14, df = 7 ($P < 0.0000$ 1); $l2 = 92\%$ Test for subgroup differences: Chi ² = 1.42, df = 1 ($P = 0.23$), $l2 = 30\%$ -4 -2 0 2 4 | Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | | 0 | Std Mear Difference IV,Random,95% C |
|---|----------------------------------|------------------------|-------------------|------------------------------|--------------|--------------|-----------------|--|
| Finkenzeller 2009 23 $6.9 (0.57)$ 27 $6.7 (0.53)$ 12.8 % 0.36 [-0.20, 0.9] He 2005 27 $5.37 (1.66)$ 27 $12.78 (1.93)$ 11.3 % $-4.06 [-5.01, -3.1]$ Lai 2006 40 $502 (9.4)$ 40 $542 (15.2)$ 13.2 % $-0.31 [-0.75, 0.1]$ Robinson 2000a 14 9.8 (4.8) 13 $9.9 (5.1)$ 12.1 % $-0.02 [-0.77, 0.7]$ Ye 2004 30 9.82 (2.64) 30 14.02 (2.32) - 12.7 % $-1.10 [-2.32, 0.12]$ Subtocal (95% CI) 134 137 62.0 % $-1.10 [-2.32, 0.12]$ 62.0 % $-1.10 [-2.32, 0.12]$ Not thave to have depression at recruitment 11.2 % $-0.27 [-1.27, -0.2]$ $-0.74 [-1.27, -0.2]$ Zhou 2003 28 3.5 (1.3) 26 3.3 (1.3) 12.9 % $-0.28 [-0.85, 0.29]$ Subtocal (95% CI) 71 71 71 38.0 % $-0.28 [-0.85, 0.29]$ 100.0 % $-0.77 [-1.52, -0.02]$ Heterogeneity: Tau ² = 0.16; Chi ² = 55.2, df = 2 (P = 0.06); l ² = 64% 100.0 % $-0.77 [-1.52, -0.02]$ 100.0 % $-0.77 [-1.52, -0.02]$ | Had to have depression a | t recruitm | ent | | | | | |
| Lai 2006 40 502 (9.4) 40 542 (15.2) Robinson 2000a 14 9.8 (4.8) 13 9.9 (5.1) Ye 2004 30 9.82 (2.64) 30 14.02 (2.32) The terogeneity: Tau ² = 1.81; Chi ² = 77.25, df = 4 (P <0.00001); I ² =95% Test for overall effect: Z = 1.77 (P = 0.077) 2 Did not have to have depression at recruitment Liu 2004 30 7.43 (3.63) 30 11 (5.63) Robinson 2000b 13 4.7 (3.8) 15 5.5 (2.9) Zhou 2003 28 3.5 (1.3) 26 3.3 (1.3) Subtocal (95% CI) 71 71 Heterogeneity: Tau ² = 0.16; Chi ² = 552, df = 2 (P = 0.06); I ² = 64% Test for overall effect: Z = 0.97 (P = 0.03) Total (95% CI) 205 208 Heterogeneity: Tau ² = 1.05; Chi ² = 8.614, df = 7 (P <0.00001); I ² =92% Test for subgroup differences: Chi ² = 1.42, df = 1 (P = 0.23), I ² = 30% -4 -2 0 2 4 | 1 | | | 27 | 6.7 (0.53) | | 12.8 % | 0.36 [-0.20, 0.92] |
| Robinson 2000a 14 9.8 (4.8) 13 9.9 (5.1) Ye 2004 30 9.82 (2.64) 30 14.02 (2.32) 12.1% -0.02 [-0.77, 0.7 Subtotal (95% CI) 134 137 62.0% -1.10 [-2.32, 0.12 Heterogeneity: Tau ² = 1.81; Chi ² = 77.25, df = 4 (P<0.00001); l ² = 95% 62.0% -1.10 [-2.32, 0.12 2 Did not have to have depression at recruitment 12.0% -0.74 [-1.27, -0.2 Robinson 2000b 13 4.7 (3.8) 15 5.5 (2.9) 12.1% -0.23 [-0.98, 0.5] Zhou 2003 28 3.5 (1.3) 2.6 3.3 (1.3) 12.9% 0.15 [-0.38, 0.6] Subtotal (95% CI) 71 71 71 38.0% -0.28 [-0.85, 0.29] Heterogeneity: Tau ² = 0.16; Chi ² = 5.52, df = 2 (P = 0.06); l ² = 64\% 38.0% -0.28 [-0.85, 0.29] Total (95% CI) 205 208 100.0% -0.77 [-1.52, -0.02 Heterogeneity: Tau ² = 1.05; Chi ² = 86.14, df = 7 (P<0.00001); l ² = 92\% -4 -2 2 4 | He 2005 | 27 | 5.37 (1.66) | 27 | 12.78 (1.93) | ⊷ | 11.3 % | -4.06 [-5.01, -3.10] |
| Ye 2004 30 9.82 (2.64) 30 14.02 (2.32) Image: constraint of the state of the sta | Lai 2006 | 40 | 50.2 (9.4) | 40 | 54.2 (15.2) | | 13.2 % | -0.31 [-0.75, 0.13] |
| Subtotal (95% CI) 134 Heterogeneity: Tau ² = 1.81; Chi ² = 77.25, df = 4 (P<000001); l ² = 95% Test for overall effect: $Z = 1.77$ (P = 0.077) 2 Did not have to have depression at recruitment Liu 2004 30 7.43 (3.63) 30 11 (5.63) Robinson 2000b 13 4.7 (3.8) 15 5.5 (2.9) Zhou 2003 28 3.5 (1.3) 26 3.3 (1.3) Subtotal (95% CI) 71 71 Heterogeneity: Tau ² = 0.16; Chi ² = 5.52, df = 2 (P = 0.06); l ² = 64% Test for overall effect: $Z = 0.97$ (P = 0.33) Total (95% CI) 205 208 Heterogeneity: Tau ² = 1.05; Chi ² = 86.14, df = 7 (P<0.00001); l ² = 92% Test for subgroup differences: Chi ² = 1.42, df = 1 (P = 0.23), l ² = 30% -4 -2 0 Z 4 | Robinson 2000a | 14 | 9.8 (4.8) | 13 | 9.9 (5.1) | | 12.1 % | -0.02 [-0.77, 0.74] |
| Heterogeneity: Tau ² = 1.81; Chi ² = 77.25, df = 4 (P<0.00001); l ² = 95% Test for overall effect: $Z = 1.77$ (P = 0.077) 2 Did not have to have depression at recruitment Liu 2004 30 7.43 (3.63) 30 11 (5.63) - 12.9 % -0.74 [-1.27, -0.2 Robinson 2000b 13 4.7 (3.8) 15 5.5 (2.9) - 12.1 % -0.23 [-0.98, 0.5 Zhou 2003 28 3.5 (1.3) 26 3.3 (1.3) 12.9 % 0.15 [-0.38, 0.6 Subtotal (95% CI) 71 71 71 Heterogeneity: Tau ² = 0.16; Chi ² = 5.52, df = 2 (P = 0.06); l ² = 64% Test for overall effect: $Z = 0.97$ (P = 0.33) Total (95% CI) 205 208 Heterogeneity: Tau ² = 1.05; Chi ² = 86.14, df = 7 (P<0.00001); l ² = 92% Test for overall effect: $Z = 2.02$ (P = 0.043) Test for subgroup differences: Chi ² = 1.42, df = 1 (P = 0.23), l ² = 30% | Ye 2004 | 30 | 9.82 (2.64) | 30 | 14.02 (2.32) | | 12.7 % | -1.67 [-2.26, -1.08] |
| Test for overall effect: $Z = 1.77$ (P = 0.077) 2 Did not have to have depression at recruitment Liu 2004 30 7.43 (3.63) 30 II (5.63) $-$ I2.9 % -0.74 [-1.27, -0.2 Robinson 2000b I3 4.7 (3.8) I5 5.5 (2.9) I2.1 % -0.23 [-0.98, 0.5 Zhou 2003 28 3.5 (1.3) 26 3.3 (1.3) I2.9 % 0.15 [-0.38, 0.6 Subtotal (95% CI) 71 71 71 Heterogeneity: Tau ² = 0.16; Chi ² = 5.52, df = 2 (P = 0.06); I ² = 64% Test for overall effect: $Z = 0.97$ (P = 0.33) Total (95% CI) 205 208 Heterogeneity: Tau ² = 1.05; Chi ² = 86.14, df = 7 (P<0.00001); I ² = 92% Test for overall effect: $Z = 2.02$ (P = 0.043) Test for subgroup differences: Chi ² = 1.42, df = I (P = 0.23), I ² = 30% $-4 -2 \ 2 \ 2 \ 4$ | Subtotal (95% CI) | 134 | | 137 | | - | 62.0 % | -1.10 [-2.32, 0.12] |
| 2 Did not have to have depression at recruitment Liu 2004 30 7.43 (3.63) 30 11 (5.63) Robinson 2000b 13 4.7 (3.8) 15 5.5 (2.9) Zhou 2003 28 3.5 (1.3) 26 3.3 (1.3) Subtotal (95% CI) 71 71 Heterogeneity: Tau ² = 0.16; Chi ² = 5.52, df = 2 (P = 0.06); l ² = 64% Test for overall effect: $Z = 0.97$ (P = 0.33) Total (95% CI) 205 208 Heterogeneity: Tau ² = 1.05; Chi ² = 86.14, df = 7 (P<0.00001); l ² = 92% Test for overall effect: $Z = 2.02$ (P = 0.043) Test for subgroup differences: Chi ² = 1.42, df = 1 (P = 0.23), l ² = 30% -4 -2 0 2 4 | | ; Chi ² = 7 | 7.25, df = 4 (P<0 | 0.0000 l); l ² = | 95% | | | |
| Liu 2004 30 7.43 (3.63) 30 11 (5.63) Robinson 2000b 13 4.7 (3.8) 15 5.5 (2.9) Zhou 2003 28 3.5 (1.3) 26 3.3 (1.3) Subtotal (95% CI) 71 71 71 Heterogeneity: Tau ² = 0.16; Chi ² = 5.52, df = 2 (P = 0.06); l ² = 64% Test for overall effect: $Z = 0.97$ (P = 0.33) Total (95% CI) 205 208 Heterogeneity: Tau ² = 1.05; Chi ² = 86.14, df = 7 (P<0.00001); l ² = 92% Test for overall effect: $Z = 2.02$ (P = 0.043) Test for subgroup differences: Chi ² = 1.42, df = 1 (P = 0.23), l ² = 30% -4 -2 0 2 4 | Test for overall effect: $Z =$ | I.77 (P = (| 0.077) | | | | | |
| Robinson 2000b 13 4.7 (3.8) 15 5.5 (2.9) 12.1 % -0.23 [-0.98 , 0.5 Zhou 2003 28 3.5 (1.3) 26 3.3 (1.3) 12.9 % 0.15 [-0.38 , 0.6 Subtotal (95% CI) 71 71 71 71 71 71 Heterogeneity: Tau ² = 0.16; Chi ² = 5.52, df = 2 (P = 0.06); l ² = 64% 38.0 % -0.28 [-0.85 , 0.29 Total (95% CI) 205 208 100.0 % -0.77 [-1.52 , -0.02 Heterogeneity: Tau ² = 1.05; Chi ² = 86.14, df = 7 (P<0.00001); l ² = 92% 100.0 % -0.77 [-1.52 , -0.02 Test for overall effect: Z = 2.02 (P = 0.043) Test for subgroup differences: Chi ² = 1.42, df = 1 (P = 0.23), l ² = 30% -4 -2 0 2 | 2 Did not have to have dep | ression at | recruitment | | | | | |
| Zhou 2003 28 $3.5 (1.3)$ 26 $3.3 (1.3)$ 12.9% $0.15 [-0.38, 0.6]$ Subtotal (95% CI) 71 71 38.0% $-0.28 [-0.85, 0.29]$ Heterogeneity: Tau ² = 0.16; Chi ² = 5.52, df = 2 (P = 0.06); l ² = 64% 38.0% $-0.28 [-0.85, 0.29]$ Total (95% CI) 205 208 100.0% $-0.77 [-1.52, -0.02]$ Heterogeneity: Tau ² = 1.05; Chi ² = 86.14, df = 7 (P<0.00001); l ² = 92% 100.0% $-0.77 [-1.52, -0.02]$ Test for overall effect: Z = 2.02 (P = 0.043) $-4 -2 $ $2 4$ 4 | Liu 2004 | 30 | 7.43 (3.63) | 30 | 11 (5.63) | | 12.9 % | -0.74 [-1.27, -0.22 |
| Subtotal (95% CI) 71 71 Heterogeneity: Tau ² = 0.16; Chi ² = 5.52, df = 2 (P = 0.06); l ² = 64% 38.0 % -0.28 [-0.85, 0.29 Test for overall effect: Z = 0.97 (P = 0.33) 100.0 % -0.77 [-1.52, -0.02 Total (95% CI) 205 208 Heterogeneity: Tau ² = 1.05; Chi ² = 86.14, df = 7 (P<0.00001); l ² = 92% 100.0 % -0.77 [-1.52, -0.02 Test for overall effect: Z = 2.02 (P = 0.043) Test for subgroup differences: Chi ² = 1.42, df = 1 (P = 0.23), l ² = 30% -4 -2 2 | Robinson 2000b | 13 | 4.7 (3.8) | 15 | 5.5 (2.9) | | 2. % | -0.23 [-0.98, 0.51] |
| Heterogeneity: Tau ² = 0.16; Chi ² = 5.52, df = 2 (P = 0.06); l ² = 64% Test for overall effect: $Z = 0.97$ (P = 0.33) Total (95% CI) 205 208 Heterogeneity: Tau ² = 1.05; Chi ² = 86.14, df = 7 (P<0.00001); l ² = 92% Test for overall effect: $Z = 2.02$ (P = 0.043) Test for subgroup differences: Chi ² = 1.42, df = 1 (P = 0.23), l ² = 30% -4 -2 0 2 4 | Zhou 2003 | 28 | 3.5 (1.3) | 26 | 3.3 (1.3) | + | 12.9 % | 0.15 [-0.38, 0.69] |
| Test for overall effect: $Z = 0.97$ (P = 0.33) Total (95% CI) 205 208 Heterogeneity: Tau ² = 1.05; Chi ² = 86.14, df = 7 (P<0.00001); l ² =92% Test for overall effect: $Z = 2.02$ (P = 0.043) Test for subgroup differences: Chi ² = 1.42, df = 1 (P = 0.23), l ² = 30% | Subtotal (95% CI) | 71 | | 71 | | • | 38.0 % | -0.28 [-0.85, 0.29] |
| | Test for overall effect: $Z = 2$ | 2.02 (P = 0 |).043) | , | | | | |
| | | | | | | | <u> </u> | |
| Eavours: SSRI Eavours: control | | | | | | | 2 4 | |
| | | | | | | Favours SSRI | Favours control | |
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Analysis 4.8. Comparison 4 SSRI versus control according to depression at time of recruitment, Outcome 8 Cognition.

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

Comparison: 4 SSRI versus control according to depression at time of recruitment

Outcome: 8 Cognition

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% CI | Weight | Std. Mean Difference IV,Random,95% Cl |
|--|------------------------|----------------------|---------------------------|--------------|--|---------|--|
| I Had to have depression a | at recruitm | ient | | | | | |
| Guo 2009 | 40 | 19.26 (6.87) | 40 | 15.74 (6.28) | | 15.3 % | 0.53 [0.08, 0.98] |
| Li 2006 | 50 | 28.36 (2.57) | 49 | 24.32 (2.14) | | 15.2 % | 1.69 [1.23, 2.16] |
| Robinson 2000a | 4 | 25.9 (7.5) | 13 | 24.5 (6.8) | | 12.8 % | 0.19 [-0.57, 0.95] |
| Wiart 2000 | 16 | 24.8 (3.9) | 15 | 26.2 (3) | | 13.2 % | -0.39 [-1.10, 0.32] |
| Xu 2007 | 36 | 28.36 (2.57) | 36 | 27.31 (5.88) | | 15.2 % | 0.23 [-0.23, 0.69] |
| Subtotal (95% CI) | 156 | | 153 | | | 71.6 % | 0.48 [-0.21, 1.17] |
| Heterogeneity: $Tau^2 = 0.54$ | ; Chi ² = 3 | 2.64, df = 4 (P<0.0 | $(00001); 1^2 =$ | 88% | | | |
| Test for overall effect: Z = | I.35 (P = 0 | 0.18) | , | | | | |
| 2 Did not have to have dep | pression at | recruitment | | | | | |
| Robinson 2000b | 13 | 26.1 (7.5) | 15 | 26.8 (2.4) | | 12.9 % | -0.13 [-0.87, 0.62] |
| Robinson 2008 | 43 | 89.8 (15.1) | 45 | 91 (17.8) | | 15.5 % | -0.07 [-0.49, 0.35] |
| Subtotal (95% CI) | 56 | | 60 | | • | 28.4 % | -0.08 [-0.45, 0.28] |
| Heterogeneity: $Tau^2 = 0.0;$ | $Chi^2 = 0.0$ | 02, df = 1 (P = 0.90 | D); I ² =0.0% | | | | |
| Test for overall effect: $Z = 0$ | 0.46 (P = 0 | 0.65) | | | | | |
| Total (95% CI) | 212 | | 213 | | - | 100.0 % | 0.32 [-0.23, 0.86] |
| Heterogeneity: Tau ² = 0.45 | ; Chi ² = 4 | 2.83, df = 6 (P<0.0 | $(00001); 1^2 =$ | 86% | | | |
| Test for overall effect: Z = | I.I5 (P = 0 | 0.25) | | | | | |
| Test for subgroup difference | es: Chi² = | 1.99, df = 1 (P = 0 | 0.16), I ² =50 | % | | | |
| | | | | | | | |

Favours control

Favours SSRI

Analysis 4.9. Comparison 4 SSRI versus control according to depression at time of recruitment, Outcome 9 Death.

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

Comparison: 4 SSRI versus control according to depression at time of recruitment

Outcome: 9 Death

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|---------------------------------|------|---------|------------------------------|----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| Had to have depression at recru | | | | |
| Andersen 1994 | 2/33 | 2/33 | | 1.00 [0.15, 6.68] |
| Chen 2001 | 0/21 | 0/20 | | 0.0 [0.0, 0.0] |
| Chen T 2005 | 0/40 | 0/38 | | 0.0 [0.0, 0.0] |
| Cheng 2003 | 0/25 | 0/32 | | 0.0 [0.0, 0.0] |
| Feng 2004 | 0/18 | 0/18 | | 0.0 [0.0, 0.0] |
| Fruehwald 2003 | 1/28 | 0/16 | | 1.76 [0.08, 40.80] |
| Guo 2009 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| He 2004 | 0/36 | 0/35 | | 0.0 [0.0, 0.0] |
| He 2005 | 0/27 | 0/27 | | 0.0 [0.0, 0.0] |
| Hu 2002 | 0/42 | 0/30 | | 0.0 [0.0, 0.0] |
| Huang 2002 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Ji 2000 | 0/20 | 0/20 | | 0.0 [0.0, 0.0] |
| Jia 2005 | 0/92 | 2/92 | | 0.20 [0.01, 4.11] |
| Lai 2006 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Li 2002 | 0/46 | 0/46 | | 0.0 [0.0, 0.0] |
| Li 2004b | 0/37 | 0/36 | | 0.0 [0.0, 0.0] |
| Li 2005 | 0/74 | 0/74 | | 0.0 [0.0, 0.0] |
| Li 2006 | 1/52 | 2/53 | | 0.51 [0.05, 5.45] |
| Li 2008 | 0/60 | 0/30 | | 0.0 [0.0, 0.0] |
| Liang 2003 | 0/42 | 0/21 | | 0.0 [0.0, 0.0] |
| Liu 2006 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Miao 2004 | 0/45 | 0/45 | | 0.0 [0.0, 0.0] |
| Murray 2005 | 0/62 | 2/61 | | 0.20 [0.01, 4.02] |
| Robinson 2000a | 0/23 | 1/17 | | 0.25 [0.01, 5.79] |
| 1001120004 | 0/25 | 1717 | | 0.25 [0.01, 0.77] |
| | | | 0.01 0.1 1 10 100 | |
| | | | Favours SSRI Favours control | (Continued) |

| Study or subgroup | SSRI | Control | Risk Ratio | (Continued Risk Ratio |
|---|--------------------------|-------------------------|--------------------|---------------------------|
| | | N 1 | M- H,Random,95% | M- H,Random,9 |
| Song 2006 | n/N 0/41 | n/N 0/41 | Cl | CI 0.0 [0.0, 0.0] |
| Wiart 2000 | 0/16 | 0/15 | | 0.0 [0.0, 0.0] |
| Xie 2005 | 0/65 | 0/65 | | 0.0 [0.0, 0.0] |
| Xu 2001 | 0/32 | 0/31 | | 0.0 [0.0, 0.0] |
| Xu 2007 | 0/36 | 0/36 | | 0.0 [0.0, 0.0] |
| Yang 2002 | 0/64 | 0/57 | | 0.0 [0.0, 0.0] |
| Yang 2011 | 0/20 | 0/22 | | 0.0 [0.0, 0.0] |
| Ye 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 1277 | 1191 | - | 0.53 [0.18, 1.54] |
| Iest for overall effect: Z = 1.17 (P 2 Did not have to have depression Acler 2009 | , | 0/10 | | 0.0 [0.0, 0.0] |
| Heterogeneity: $Tau^2 = 0.0$; Chi ² = Test for overall effect: Z = 1.17 (P | = 0.24) | | | |
| | | | | |
| Almeida 2006 | 2/48 | 1/52 | | 2.17 [0.20, 23.14] |
| Brown 1998 | 0/10 | 0/10 | | 0.0 [0.0, 0.0] |
| Burns 1999 | 1/14 | 1/14 | | 1.00 [0.07, 14.45] |
| Chollet 2011 | 1/59 | 1/59 | | 1.00 [0.06, 15.61] |
| Dam 1996 | 0/18 | 0/17 | | 0.0 [0.0, 0.0] |
| Li 2004a | 0/33 | 0/34 | | 0.0 [0.0, 0.0] |
| Liu 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Robinson 2000b | 0/17 | 0/16 | | 0.0 [0.0, 0.0] |
| Robinson 2008 | 2/59 | 0/58 | | 4.92 [0.24, 100.25] |
| Wen 2006 | 0/42 | 0/42 | | 0.0 [0.0, 0.0] |
| Xu 2006 | 0/32 | 2/32 | | 0.20 [0.01, 4.01] |
| Zhou 2003 | 0/28 | 0/26 | | 0.0 [0.0, 0.0] |
| Zhou 2008 | 0/36 | 0/40 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 436 | 440 | - | 1.22 [0.36, 4.13] |
| Total events: 6 (SSRI), 5 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = Test for overall effect: $Z = 0.32$ (P | 2.49, df = 4 (P = 0.65); | l ² =0.0% | | |
| Total (95% CI) | 1713 | 1631 | + | 0.76 [0.34, 1.70] |
| Total events: 10 (SSRI), 14 (Contri- Heterogeneity: Tau ² = 0.0; Chi ² = Test for overall effect: $Z = 0.67$ (P | 5.54, df = 10 (P = 0.85) |); l ² =0.0% | | |

Favours SSRI Favours control

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

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(Continued . . .)

| Study or subgroup | SSRI n/N | Control n/N | | Risk Ratio M- ndom,95% Cl | (Continued) Risk Ratio M- H,Random,95% Cl |
|-----------------------------------|-------------|----------------|--------------|------------------------------------|--|
| Test for subgroup differences: Ch | | | | | |
| | | | | | |
| | | | 0.01 0.1 | I IO IOO | |
| | | | Favours SSRI | Favours control | |
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Analysis 4.10. Comparison 4 SSRI versus control according to depression at time of recruitment, Outcome 10 Seizures.

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

Comparison: 4 SSRI versus control according to depression at time of recruitment

Outcome: 10 Seizures

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|---|----------------------------|----------------------|------------------------------|-----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| I Had to have depression at recru | uitment | | | |
| Andersen 1994 | 2/33 | 0/33 | | 5.00 [0.25, 100.32] |
| Liang 2003 | 0/42 | 0/21 | | 0.0 [0.0, 0.0] |
| Wiart 2000 | 1/16 | 1/15 | | 0.94 [0.06, 3.68] |
| Ye 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 121 | 99 | - | 1.97 [0.27, 14.55] |
| Total events: 3 (SSRI), 1 (Control) |) | | | |
| Heterogeneity: $Tau^2 = 0.0$; Chi ² = | = 0.68, df = 1 (P = 0.41); | $ ^2 = 0.0\%$ | | |
| Test for overall effect: $Z = 0.67$ (F | P = 0.51 | | | |
| 2 Did not have to have depressio | n at recruitment | | | |
| Chollet 2011 | 1/59 | 0/59 | | 3.00 [0.12, 72.18] |
| Dam 1996 | 2/18 | 0/17 | | 4.74 [0.24, 92.07] |
| He 2004 | 0/36 | 0/35 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 113 | 111 | | 3.83 [0.44, 33.53] |
| Total events: 3 (SSRI), 0 (Control) |) | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = | = 0.04, df = 1 (P = 0.84); | l ² =0.0% | | |
| Test for overall effect: $Z = 1.21$ (F | P = 0.23) | | | |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |
| | | | Favours SSRI Favours control | |
| | | | | (Continued) |

| Study or subgroup | SSRI n/N | Control n/N | H, | Risk Ratio M- Random,95% Cl | (Continued) Risk Ratio M- H,Random,95% Cl |
|---|--------------------------------|---------------------------|--------------|--------------------------------------|--|
| Total (95% CI) | 234 | 210 | | - | 2.67 [0.61, 11.63] |
| Total events: 6 (SSRI), 1 (Control |) | | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = | = 0.91, df = 3 (P = 0.82) | ; l ² =0.0% | | | |
| Test for overall effect: $Z = 1.31$ (F | P = 0.19) | | | | |
| Test for subgroup differences: Ch | $i^2 = 0.19, df = 1 (P = 0.6)$ | 66), l ² =0.0% | | | |
| | | | | | |
| | | | 0.01 0.1 | 1 10 100 | |
| | | | Favours SSRI | Favours control | |

Analysis 4.11. Comparison 4 SSRI versus control according to depression at time of recruitment, Outcome II Gastrointestinal side effects.

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

Comparison: 4 SSRI versus control according to depression at time of recruitment

Outcome: II Gastrointestinal side effects

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|---------|---------------------------------------|---|------------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| I Had to have depression at recru | uitment | | | |
| He 2005 | 9/27 | 0/27 | ∎ → | 19.00 [1.16, 310.94] |
| Hu 2002 | 5/42 | 0/30 | | 7.93 [0.46, 38.20] |
| Huang 2002 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Li 2008 | 6/60 | 3/30 | _ | 1.00 [0.27, 3.72] |
| Liang 2003 | 4/42 | 4/21 | | 0.50 [0.14, 1.80] |
| Wiart 2000 | 1/16 | 3/16 | | 0.33 [0.04, 2.87] |
| Xu 2007 | 4/36 | 1/36 | | 4.00 [0.47, 34.07] |
| Ye 2004 | 2/30 | 0/30 | | 5.00 [0.25, 99.95] |
| Subtotal (95% CI) Total events: 31 (SSRI), 11 (Contr Heterogeneity: Tau ² = 1.00; Chi ² | · | 230 6); l ² =50% | - | 1.72 [0.58, 5.12] |
| <u> </u> | × × | , | | |
| | | | 0.01 0.1 10 100 Favours SSRI Favours control | (Continued) |

| Study or subgroup | SSRI Control | | Risk Ratio M- | (Continued) Risk Ratio M- | |
|--|--------------------------|--------------------------|--------------------|----------------------------------|--|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl | |
| Test for overall effect: $Z = 0.98$ (P = | = 0.33) | | | | |
| 2 Did not have to have depression | at recruitment | | | | |
| Burns 1999 | 0/14 | 1/14 | | 0.33 [0.01, 7.55] | |
| Chollet 2011 | 14/59 | 6/59 | - | 2.33 [0.96, 5.66] | |
| Dam 1996 | 2/18 | 0/17 | | 4.74 [0.24, 92.07] | |
| He 2004 | 0/36 | 0/35 | | 0.0 [0.0, 0.0] | |
| Li 2004a | 3/33 | 0/34 | | 7.21 [0.39, 134.32] | |
| Liu 2004 | 3/30 | 0/30 | | 7.00 [0.38, 129.93] | |
| Subtotal (95% CI) | 190 | 189 | * | 2.53 [1.18, 5.42] | |
| Total events: 22 (SSRI), 7 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2$ | 2.80, df = 4 (P = 0.59); | $ ^2 = 0.0\%$ | | | |
| Test for overall effect: $Z = 2.39$ (P = | = 0.017) | | | | |
| Total (95% CI) | 483 | 419 | ◆ | 1.90 [0.94, 3.85] | |
| Total events: 53 (SSRI), 18 (Control |) | | | | |
| Heterogeneity: $Tau^2 = 0.43$; Chi ² = | : 15.97, df = 11 (P = 0. | 4); ² =3 % | | | |
| Test for overall effect: $Z = 1.79$ (P = | = 0.073) | | | | |
| Test for subgroup differences: Chi ² | = 0.32, df = 1 (P = 0.5 | 7), I ² =0.0% | | | |
| | | | | | |
| | | | 0.01 0.1 1 10 100 | | |

Favours SSRI F

Favours control

Analysis 4.12. Comparison 4 SSRI versus control according to depression at time of recruitment, Outcome 12 Leaving the trial early.

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

Comparison: 4 SSRI versus control according to depression at time of recruitment

Outcome: 12 Leaving the trial early

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|----------------------------------|--------|---------|--------------------|----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| Had to have depression at recrui | itment | | | |
| Andersen 1994 | 6/33 | 1/33 | | 6.00 [0.76, 47.14] |
| Chen 2001 | 2/21 | 2/20 | | 0.95 [0.15, 6.13] |
| Chen 2002 | 0/24 | 4/24 | | 0.11 [0.01, 1.96] |
| Chen T 2005 | 0/40 | 0/38 | | 0.0 [0.0, 0.0] |
| Cheng 2003 | 0/25 | 0/32 | | 0.0 [0.0, 0.0] |
| Feng 2004 | 2/18 | 2/18 | | 1.00 [0.16, 6.35] |
| Fruehwald 2003 | 6/28 | 8/26 | | 0.70 [0.28, 1.74] |
| GlaxoSmithKline 1998 | 3/ 2 | 3/ 7 | - | 1.04 [0.51, 2.15] |
| Guo 2009 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| He 2004 | 8/44 | 5/40 | | 1.45 [0.52, 4.08] |
| He 2005 | 0/27 | 0/27 | | 0.0 [0.0, 0.0] |
| Hu 2002 | 0/42 | 0/30 | | 0.0 [0.0, 0.0] |
| Huang 2002 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Ji 2000 | 0/20 | 0/20 | | 0.0 [0.0, 0.0] |
| Jia 2005 | 4/92 | 4/92 | | 1.00 [0.26, 3.88] |
| Lai 2006 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Li 2002 | 0/46 | 0/46 | | 0.0 [0.0, 0.0] |
| Li 2004a | 0/33 | 0/34 | | 0.0 [0.0, 0.0] |
| Li 2004b | 6/37 | 4/36 | | 1.46 [0.45, 4.74] |
| Li 2005 | 0/74 | 0/74 | | 0.0 [0.0, 0.0] |
| Li 2006 | 2/50 | 4/53 | | 0.53 [0.10, 2.77] |
| Li 2008 | 2/60 | 2/30 | | 0.50 [0.07, 3.38] |
| Liang 2003 | 0/42 | 0/21 | | 0.0 [0.0, 0.0] |

(Continued . . .)

| Study or subgroup | SSRI | Control | Risk Ratio | (Continued) Risk Ratio | |
|---|---------------------|--------------------------|--------------------------|--|--|
| | n/N | n/N | M- H,Random,95% Cl | M- H,Random,95 Cl | |
| Liu 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] | |
| Liu 2006 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] | |
| Miao 2004 | 11/45 | 11/45 | - | 1.00 [0.48, 2.07] | |
| Murray 2005 | 24/62 | 30/61 | - | 0.79 [0.53, 1.18] | |
| Robinson 2000a | 9/23 | 4/17 | | 1.66 [0.61, 4.51] | |
| Wang 2003 | 13/64 | 9/56 | | 1.26 [0.58, 2.73] | |
| Wiart 2000 | 0/16 | 0/15 | | 0.0 [0.0, 0.0] | |
| Xie 2005 | 0/65 | 0/65 | | 0.0 [0.0, 0.0] | |
| Xu 2001 | 6/32 | 4/31 | | 1.45 [0.45, 4.66] | |
| Yang 2002 | 4/64 | 7/57 | | 0.51 [0.16, 1.65] | |
| Yang 2011 | 0/20 | 0/22 | | 0.0 [0.0, 0.0] | |
| Ye 2004 | | | | | |
| Subtotal (95% CI) | 1/31 1470 | 0/30 1390 | | 2.91 [0.12, 68.66] 0.97 [0.77, 1.21] | |
| leterogeneity: Tau ² = 0.0; Chi ² = est for overall effect: $Z = 0.30$ (P Did not have to have depression | = 0.76) | ′); I ² =0.0% | | | |
| est for overall effect: 2 – 0.30 (P 2 Did not have to have depression | , | | | | |
| Acler 2009 | 0/10 | 0/10 | | 0.0 [0.0, 0.0] | |
| Almeida 2006 | 11/55 | 6/56 | | 1.87 [0.74, 4.70] | |
| Brown 1998 | 1/10 | 0/10 | | 3.00 [0.14, 65.90] | |
| Burns 1999 | 0/14 | 0/14 | | 0.0 [0.0, 0.0] | |
| Chollet 2011 | 2/59 | 3/59 | | 0.67 [0.12, 3.85] | |
| Dam 1996 | 0/16 | 0/17 | | 0.0 [0.0, 0.0] | |
| Kong 2007 | 11/48 | 6/42 | | 1.60 [0.65, 3.96] | |
| Rasmussen 2003 | 35/70 | 35/67 | + | 0.96 [0.69, 1.33] | |
| Robinson 2000b | 4/17 | 1/16 | | 3.76 [0.47, 30.20] | |
| Robinson 2008 | 7/59 | 5/58 | | 1.38 [0.46, 4.09] | |
| Wen 2006 | 0/42 | 0/42 | | 0.0 [0.0, 0.0] | |
| Xu 2006 | 4/32 | 3/32 | | 1.33 [0.32, 5.49] | |
| Zhou 2003 | 2/30 | 4/30 | | 0.50 [0.10, 2.53] | |
| Zhou 2008 | 0/36 | 0/40 | | 0.0 [0.0, 0.0] | |
| | 498 | 493 | ↓ | 1.10 [0.84, 1.44] | |

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(Continued . . .)

| Study or subgroup | SSRI | SSRI Control | | isk Ratio M- | (Continued) Risk Ratio M- |
|--|-------------------------------------|--------------------------|--------------|-----------------|----------------------------------|
| | n/N | n/N | H,Ranc | dom,95% Cl | H,Random,95% Cl_ |
| Heterogeneity: $Tau^2 = 0.0$; Chi^2 | = 6.06, df = 8 (P = 0.64); | $ ^2 = 0.0\%$ | | | |
| Test for overall effect: $Z = 0.70$ | (P = 0.48) | | | | |
| Total (95% CI) | 1968 | 1883 | • | | 1.02 [0.86, 1.21] |
| Total events: 196 (SSRI), 177 (C | Control) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; Chi^2 | = 18.94, df = 26 (P = 0.84 | ł); l ² =0.0% | | | |
| Test for overall effect: $Z = 0.23$ | (P = 0.82) | | | | |
| Test for subgroup differences: C | $hi^2 = 0.53$, $df = 1$ (P = 0.47) | 7), I ² =0.0% | | | |
| | | | | | |
| | | | 0.01 0.1 1 | 10 100 | |
| | | | Favours SSRI | Favours control | |
| | | | | | |
| | | | | | |

Analysis 4.13. Comparison 4 SSRI versus control according to depression at time of recruitment, Outcome 13 Bleeding.

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

Comparison: 4 SSRI versus control according to depression at time of recruitment

Outcome: 13 Bleeding

| Study or subgroup | SSRI | Control | Risk Ratio M- | Weight | Risk Ratio M- |
|--------------------------------------|------------|---------|----------------------------|--------|----------------------|
| | n/N | n/N | H,Random,95% Cl | | H,Random,95% Cl |
| I Depression at onset | | | | | |
| GlaxoSmithKline 1998 | 1/112 | 0/117 | | 42.6 % | 3.13 [0.13, 76.10] |
| Subtotal (95% CI) | 112 | 117 | | 42.6 % | 3.13 [0.13, 76.10] |
| Total events: I (SSRI), 0 (Contro | ol) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 0.70$ | (P = 0.48) | | | | |
| 2 No depression at onset | | | | | |
| Robinson 2008 | 1/59 | 1/59 | | 57.4 % | 1.00 [0.06, 15.61] |
| Subtotal (95% CI) | 59 | 59 | | 57.4 % | 1.00 [0.06, 15.61] |
| Total events: (SSRI), (Contro | ol) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 0.0$ (| P = 1.0) | | | | |
| | | | | | |
| | | | 0.01 0.1 1 10 10 | 00 | |
| | | | Favours SSRI Favours contr | rol | |
| | | | | | (Continued) |



Analysis 4.14. Comparison 4 SSRI versus control according to depression at time of recruitment, Outcome 14 Motor deficits.

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

Comparison: 4 SSRI versus control according to depression at time of recruitment

Outcome: 14 Motor deficits

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Std. Mean Difference |
|--------------------------------|-------------------------|-----------------------|--------------------------|------------|----------------------------|---------|----------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| I No depression at onset | | | | | | | |
| Chollet 2011 | 57 | -53.7 (27.8) | 56 | -35.1 (22) | | 55.3 % | -0.74 [-1.12, -0.35] |
| Dam 1996 | 16 | 32.4 (3.8) | 16 | 31.6 (5) | | 44.7 % | 0.18 [-0.52, 0.87] |
| Subtotal (95% CI) | 73 | | 72 | | - | 100.0 % | -0.33 [-1.22, 0.56] |
| Heterogeneity: $Tau^2 = 0.33$ | 3; Chi ² = 5 | 5.09, df = 1 (P = 0.0 | 02); I ² =80% | | | | |
| Test for overall effect: Z = | 0.72 (P = | 0.47) | | | | | |
| 2 Depression at onset | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applica | ble | | | | | | |
| Test for overall effect: not a | applicable | | | | | | |
| Total (95% CI) | 73 | | 72 | | - | 100.0 % | -0.33 [-1.22, 0.56] |
| Heterogeneity: $Tau^2 = 0.33$ | 3; Chi ² = 5 | 5.09, df = 1 (P = 0.0 | 02); I ² =80% | | | | |
| Test for overall effect: Z = | 0.72 (P = | 0.47) | | | | | |
| Test for subgroup difference | es: Not ap | plicable | | | | | |
| | | | | | | 1 | |
| | | | | - | 4 -2 0 2 | 4 | |
| | | | | | Favours SSRI Favours co | ntrol | |

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

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Analysis 5.1. Comparison 5 SSRI versus control, end of treatment, randomisation: low risk of bias, Outcome I Dependent on modified Rankin score (mRS 3 to 5).

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

Comparison: 5 SSRI versus control, end of treatment, randomisation: low risk of bias

Outcome: I Dependent on modified Rankin score (mRS 3 to 5)

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|---------------------------|--------------------|------------------------------|---------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| Fluoxetine | | | | |
| Chollet 2011 | 42/57 | 50/55 | - | 0.81 [0.68, 0.97] |
| Subtotal (95% CI) | 57 | 55 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Control | l) | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 2.34$ (P = | = 0.019) | | | |
| 2 Sertraline | | | | |
| Almeida 2006 | 0/55 | 0/56 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 55 | 56 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 0.0 (P $<$ | 0.00001) | | | |
| Total (95% CI) | 112 | 111 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Control | l) | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0$ | 0.0, df = 0 (P = 1.00); l | ² =0.0% | | |
| Test for overall effect: $Z = 2.34$ (P = | = 0.019) | | | |
| Test for subgroup differences: Not a | applicable | | | |
| | | | <u> </u> | |
| | | | 0.01 0.1 1 10 100 | |
| | | | Favours SSRI Favours control | |
| | | | | |
| | | | | |

Analysis 5.2. Comparison 5 SSRI versus control, end of treatment, randomisation: low risk of bias, Outcome 2 Disability.

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

Comparison: 5 SSRI versus control, end of treatment, randomisation: low risk of bias

Outcome: 2 Disability

| Study or subgroup | SSRI N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% CI | Weight | Std. Mean Difference IV,Random,95% CI |
|---|-----------|---------------|--|--------------|--|-----------|--|
| I Fluoxetine | | | | | _ | | |
| Kong 2007 | 37 | 60.4 (12.5) | 36 | 52.3 (13.5) | | 21.9 % | 0.62 [0.15, 1.09] |
| Li 2008 | 58 | 40.8 (3.7) | 28 | 38.4 (5.8) | | 22.8 % | 0.53 [0.07, 0.99] |
| Liu 2004 | 30 | 70.33 (10.74) | 30 | 64.33 (7.74) | | → 18.5 % | 0.63 [0.11, 1.15] |
| Robinson 2000a | 14 | 59.2 (11.6) | 13 | 56.2 (7.8) | | 9.3 % | 0.29 [-0.47, 1.05] |
| Robinson 2000b | 13 | 60.5 (10.8) | 15 | 63.1 (8.2) | • | 9.7 % | -0.27 [-1.01, 0.48] |
| Wiart 2000 | 16 | 87.4 (22.8) | 15 | 88.7 (25.3) | | 10.7 % | -0.05 [-0.76, 0.65] |
| Subtotal (95% CI) Heterogeneity: $Tau^2 = 0.03$ Test for overall effect: $Z = 2$ | | | 137 25); I ² =24% | | - | 92.9 % | 0.38 [0.11, 0.66] |
| 2 Sertraline Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: not a 3 Citalopram | | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Acler 2009 | 10 | 82 (28) | 10 | 75 (25) | | → 7.1 % | 0.25 [-0.63, 1.13] |
| Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: Z = 0 | | 0.57) | 10 | | | 7.1 % | 0.25 [-0.63, 1.13] |
| 4 Paroxetine Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: not a | | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| 5 Escitalopram Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: not a | | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| 6 Sertraline or fluoxetine Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: not a | | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| | | | | | -1 -0.5 0 0.5 Favours control Favours | I SSRI | (Continued) |



Analysis 5.3. Comparison 5 SSRI versus control, end of treatment, randomisation: low risk of bias, Outcome 3 Neurological deficit score.

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

Comparison: 5 SSRI versus control, end of treatment, randomisation: low risk of bias

Outcome: 3 Neurological deficit score

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Std. Mean Difference |
|------------------------------|-------------------------|---------------------|---------------------------|--------------|----------------------------|--------|----------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% Cl | | IV,Random,95% CI |
| I Fluoxetine | | | | | | | |
| Chollet 2011 | 57 | 5.8 (3.7) | 55 | 6.9 (4.4) | | 11.3 % | -0.27 [-0.64, 0.10] |
| Fruehwald 2003 | 26 | -55.5 (4.8) | 24 | -52.8 (5.4) | | 10.0 % | -0.52 [-1.09, 0.04] |
| Kong 2007 | 37 | 8.6 (6.4) | 36 | 11.2 (6.4) | | 10.7 % | -0.40 [-0.87, 0.06] |
| Li 2004a | 33 | 6.23 (3.11) | 34 | 12.86 (6.36) | _ _ | 10.3 % | -1.30 [-1.83, -0.77] |
| Liu 2004 | 30 | 9.2 (2.06) | 30 | 10.47 (9.2) | | 10.4 % | -0.19 [-0.70, 0.32] |
| Subtotal (95% CI) | 183 | | 179 | | • | 52.7 % | -0.52 [-0.89, -0.15] |
| Heterogeneity: $Tau^2 = 0.1$ | 2; Chi ² = 1 | 1.89, df = 4 (P = 0 | 0.02); l ² =66 | % | | | |
| Test for overall effect: Z = | 2.75 (P = | 0.0060) | | | | | |
| 2 Sertraline | | | | | | | |
| Burns 1999 | 14 | -29.7 (14.7) | 14 | -32.2 (13.4) | | 8.7 % | 0.17 [-0.57, 0.91] |
| Guo 2009 | 40 | 29.07 (8.02) | 40 | 33.78 (8.63) | | 10.8 % | -0.56 [-1.01, -0.11] |
| | | | | | -2 -1 0 1 2 | | |

Favours SSRI Favours control

(Continued . . .)

(... Continued) Std. Std. Mean Mean Difference Difference SSRI Control Study or subgroup Weight IV,Random,95% CI IV,Random,95% Cl Ν Mean(SD) Ν Mean(SD) Subtotal (95% CI) 54 54 19.5 % -0.26 [-0.96, 0.45] Heterogeneity: Tau² = 0.17; Chi² = 2.74, df = 1 (P = 0.10); I^2 =64% Test for overall effect: Z = 0.71 (P = 0.48) 3 Citalopram Acler 2009 10 7.5 % -0.68 [-1.59, 0.23] 10 2.3 (2) 3.5 (1.3) Li 2006 50 21.89 (1.57) 49 23.77 (1.46) 11.0 % -1.23 [-1.66, -0.80] Liu 2006 30 13.3 (3.8) 30 22.4 (4.1) 9.3 % -2.27 [-2.93, -1.61] Subtotal (95% CI) 90 89 27.8 % -1.43 [-2.25, -0.60] Heterogeneity: Tau² = 0.41; Chi² = 9.73, df = 2 (P = 0.01); I² = 79% Test for overall effect: Z = 3.40 (P = 0.00068) 4 Paroxetine Subtotal (95% CI) 0 0.0 % 0 0.0 [0.0, 0.0] Heterogeneity: not applicable Test for overall effect: not applicable 5 Fluoxetine or sertraline Subtotal (95% CI) 0 0 0.0 % 0.0 [0.0, 0.0] Heterogeneity: not applicable Test for overall effect: not applicable Total (95% CI) 327 322 100.0 % -0.72 [-1.11, -0.33] Heterogeneity: Tau² = 0.31; Chi² = 49.37, df = 9 (P<0.00001); $I^2 = 82\%$ Test for overall effect: Z = 3.63 (P = 0.00029) Test for subgroup differences: $Chi^2 = 4.96$, df = 2 (P = 0.08), I² = 60% -2 - | 2 0 ī. Favours SSRI Favours control

Analysis 5.4. Comparison 5 SSRI versus control, end of treatment, randomisation: low risk of bias, Outcome 4 Depression (continuous data).

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

Comparison: 5 SSRI versus control, end of treatment, randomisation: low risk of bias

Outcome: 4 Depression (continuous data)

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|---|-----------|--------------|---|-------------|--|--------|--|
| I Fluoxetine | 5.4 | 5.4.4.0 | 5.4 | | _ | | |
| Chollet 2011 | 56 | 5.4 (4.9) | 54 | 8.4 (7.9) | - | 11.1 % | -0.46 [-0.83, -0.08] |
| Fruehwald 2003 | 26 | 9.5 (7.9) | 24 | .2 (2.4) | - | 10.2 % | -0.16 [-0.72, 0.39] |
| Kong 2007 | 37 | 12.6 (5.3) | 36 | 16.3 (3.7) | - | 10.6 % | -0.80 [-1.28, -0.32] |
| Li 2008 | 58 | 14.5 (2.4) | 28 | 18.7 (3.9) | | 10.5 % | -1.40 [-1.90, -0.90] |
| Robinson 2000a | 14 | 18.5 (7.6) | 13 | 12.2 (4.7) | | 8.7 % | 0.96 [0.15, 1.76] |
| Robinson 2000b | 13 | 5.9 (3.8) | 15 | 6.2 (4.6) | | 9.0 % | -0.07 [-0.81, 0.67] |
| Subtotal (95% CI) | 204 | | 170 | | • | 60.1 % | -0.38 [-0.91, 0.16] |
| Heterogeneity: $Tau^2 = 0.37$ Test for overall effect: $Z = 1$ 2 Sertraline | | | 0.00002); I ² = | -83% | | | |
| Finkenzeller 2009 | 23 | 12.1 (1.05) | 27 | 10.6 (0.97) | | 9.7 % | 1.47 [0.83, 2.10] |
| Guo 2009 | 40 | 14.82 (8.05) | 40 | 17.61 (8) | - | 10.8 % | -0.34 [-0.79, 0.10] |
| Murray 2005 | 62 | 10.5 (9.6) | 61 | 12 (8.5) | - | 11.2 % | -0.16 [-0.52, 0.19] |
| Subtotal (95% CI) Heterogeneity: Tau ² = 0.60 Test for overall effect: Z = 0 3 Citalopram | | | 128 00001); l ² =9 | 92% | | 31.7 % | 0.28 [-0.63, 1.20] |
| Acler 2009 | 10 | 6.6 (3.6) | 10 | 8 (3) | | 8.2 % | -0.40 [-1.29, 0.48] |
| Subtotal (95% CI) | 10 | | 10 | | - | 8.2 % | -0.40 [-1.29, 0.48] |
| Heterogeneity: not applicab Test for overall effect: $Z = 0$ 4 Paroxetine | |).37) | | | | | |
| Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: not a | | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| 5 Fluoxetine or sertraline Subtotal (95% CI) Heterogeneity: not applicab | | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Test for overall effect: not a | pplicable | | | | -4 -2 0 2 4 Favours SSRI Favours contr | | (Continued |



Analysis 5.5. Comparison 5 SSRI versus control, end of treatment, randomisation: low risk of bias, Outcome 5 Depression (dichotomous data).

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

Comparison: 5 SSRI versus control, end of treatment, randomisation: low risk of bias

Outcome: 5 Depression (dichotomous data)

| Study or subgroup | SSRI | Control | Risk Ratio M- | Weight | Risk Ratio M- |
|---------------------------------------|-------------|---------|----------------------|--------|---------------------|
| | n/N | n/N | H,Random,95% Cl | | H,Random,95% Cl_ |
| l Fluoxetine | | | | | |
| Li 2004a | 2/33 | 8/34 | | 16.4 % | 0.26 [0.06, 1.12] |
| Subtotal (95% CI) | 33 | 34 | - | 16.4 % | 0.26 [0.06, 1.12] |
| Total events: 2 (SSRI), 8 (Contro | ol) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 1.80$ (| (P = 0.071) | | | | |
| 2 Sertraline | | | | | |
| Almeida 2006 | 8/48 | /5 | | 47.7 % | 0.77 [0.34, 1.76] |
| Subtotal (95% CI) | 48 | 51 | • | 47.7 % | 0.77 [0.34, 1.76] |
| Total events: 8 (SSRI), 11 (Contr | rol) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 0.62$ (| (P = 0.54) | | | | |
| 3 Citalopram | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Contro | bl) | | | | |
| | | | 0.01 0.1 10 | | |
| | | | Favours SSRI Favours | | |
| | | | | | (Continued) |

| Study or subgroup | SSRI | Control | Risk Ratio M- | Weight | (Continued) Risk Ratio M- |
|--|--------------------------------|--------------------------------|--------------------|---------|----------------------------------|
| | n/N | n/N | H,Random,95% Cl | | H,Random,95% Cl |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not application | able | | | | |
| 4 Paroxetine | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Contro | ol) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not application | able | | | | |
| 5 Escitalopram | | | | | |
| Robinson 2008 | 5/59 | 13/58 | | 35.9 % | 0.38 [0.14, 0.99] |
| Subtotal (95% CI) | 59 | 58 | - | 35.9 % | 0.38 [0.14, 0.99] |
| Total events: 5 (SSRI), 13 (Contr | rol) | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 1.97$ (| (P = 0.048) | | | | |
| Total (95% CI) | 140 | 143 | • | 100.0 % | 0.50 [0.27, 0.92] |
| Total events: 15 (SSRI), 32 (Con | trol) | | | | |
| Heterogeneity: $Tau^2 = 0.03$; Chi | ² = 2.21, df = 2 (| P = 0.33); I ² =9% | | | |
| Test for overall effect: $Z = 2.22$ (| (P = 0.026) | | | | |
| Test for subgroup differences: Ch | hi ² = 2.18, df = 2 | (P = 0.34), I ² =8% | | | |
| | | | | | |
| | | | 0.01 0.1 10 | 100 | |
| | | | 5 600 5 | | |

Favours SSRI Favours control

Analysis 5.6. Comparison 5 SSRI versus control, end of treatment, randomisation: low risk of bias, Outcome 6 Anxiety (continuous data).

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

Comparison: 5 SSRI versus control, end of treatment, randomisation: low risk of bias

Outcome: 6 Anxiety (continuous data)

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|--|-------------------------|----------------------|--------------------------|-----------|--|---------|--|
| L Electronic e | IN | Tiedil(5D) | IN | Tiean(SD) | 14,1 & 10011,75% Ci | | IV,Nandom,73% Cr |
| l Fluoxetine Liu 2004 | 30 | 7.43 (3.63) | 30 | (5.63) | • • | 45.1 % | -0.74 [-1.27, -0.22] |
| | | . , | | , , | | | |
| Robinson 2000a | 14 | 9.8 (4.8) | 13 | 9.9 (5.1) | | 27.2 % | -0.02 [-0.77, 0.74] |
| Robinson 2000b | 13 | 4.7 (3.8) | 15 | 5.5 (2.9) | | 27.7 % | -0.23 [-0.98, 0.51] |
| Subtotal (95% CI) | 57 | | 58 | | | 100.0 % | -0.40 [-0.85, 0.05] |
| Heterogeneity: $Tau^2 = 0.05$ | 5; Chi ² = 2 | .78, df = 2 (P = 0.2 | 25); I ² =28% | | | | |
| Test for overall effect: Z = | I.76 (P = 0 | 0.078) | | | | | |
| 2 Sertraline | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applica | | | | | | | |
| Test for overall effect: not a | applicable | | | | | | |
| 3 Citalopram | | | | | | 0.0.0/ | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applica | | | | | | | |
| Test for overall effect: not a 4 Paroxetine | applicable | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applica | | | Ū | | | 0.0 /0 | 0.0 [0.0, 0.0] |
| Test for overall effect: not a | | | | | | | |
| 5 Escitalopram | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applica | ble | | | | | | |
| Test for overall effect: not a | applicable | | | | | | |
| Total (95% CI) | 57 | | 58 | | | 100.0 % | -0.40 [-0.85, 0.05] |
| Heterogeneity: $Tau^2 = 0.05$ | 5; Chi ² = 2 | .78, df = 2 (P = 0.2 | 25); I ² =28% | | | | |
| Test for overall effect: $Z =$ | I.76 (P = 0 | 0.078) | | | | | |
| Test for subgroup difference | es: Not ap | plicable | | | | | |
| | | | | | | 1 | |
| | | | | | -1 -0.5 0 0.5 | I | |
| | | | | | Favours SSRI Favours co | ntrol | |
| | | | | | | | |
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| | | | | | | | |
Analysis 5.8. Comparison 5 SSRI versus control, end of treatment, randomisation: low risk of bias, Outcome 8 Cognition (continuous scores end of treatment).

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

Comparison: 5 SSRI versus control, end of treatment, randomisation: low risk of bias

Outcome: 8 Cognition (continuous scores end of treatment)

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | | Std. Mean ference om,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|----------------------------------|------------------------|-----------------------|--------------------------|--------------|-----------------|--------------------------------------|---------|--|
| l Fluoxetine | | | | | | | | |
| Robinson 2000a | 14 | 25.9 (7.5) | 13 | 24.5 (6.8) | | | 15.7 % | 0.19 [-0.57, 0.95] |
| Robinson 2000b | 13 | 26.1 (7.5) | 15 | 26.8 (2.4) | | | 16.1 % | -0.13 [-0.87, 0.62] |
| Subtotal (95% CI) | 27 | | 28 | | | | 31.8 % | 0.03 [-0.50, 0.56] |
| Heterogeneity: $Tau^2 = 0.0$; | | 4. df = $ (P = 0.5)$ | | | | | 0110 /0 | |
| Test for overall effect: $Z = 0$ | | | -,, · · · · · · · · | | | | | |
| 2 Sertraline | | | | | | | | |
| Guo 2009 | 40 | 19.26 (6.87) | 40 | 15.74 (6.28) | | | 32.8 % | 0.53 [0.08, 0.98] |
| Subtotal (95% CI) | 40 | | 40 | | | • | 32.8 % | 0.53 [0.08, 0.98] |
| Heterogeneity: not applicab | ble | | | | | | | |
| Test for overall effect: $Z = 2$ | 2.33 (P = 0 | 0.020) | | | | | | |
| 3 Citalopram | | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicab | ble | | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | | |
| 4 Escitalopram | | | | | | | | |
| Robinson 2008 | 43 | 89.8 (15.1) | 45 | 91 (17.8) | | | 35.4 % | -0.07 [-0.49, 0.35] |
| Subtotal (95% CI) | 43 | | 45 | | - | ► | 35.4 % | -0.07 [-0.49, 0.35] |
| Heterogeneity: not applicab | ble | | | | | | | |
| Test for overall effect: $Z = 0$ | 0.34 (P = 0 | 0.74) | | | | | | |
| Total (95% CI) | 110 | | 113 | | - | • | 100.0 % | 0.16 [-0.18, 0.49] |
| Heterogeneity: $Tau^2 = 0.04$ | ; Chi ² = 4 | .39, df = 3 (P = 0.1 | 22); I ² =32% | | | | | |
| Test for overall effect: $Z = 0$ | 0.92 (P = 0 | 0.36) | | | | | | |
| Test for subgroup difference | es: Chi² = | 4.05, df = 2 (P = 0 | $1.13), 1^2 = 513$ | % | | | | |
| | | | | | | | L | |
| | | | | | -2 -1 (|) I 2 | 2 | |
| | | | | | Favours control | Favours SSRI | | |

Analysis 5.9. Comparison 5 SSRI versus control, end of treatment, randomisation: low risk of bias, Outcome 9 Death.

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

Comparison: 5 SSRI versus control, end of treatment, randomisation: low risk of bias

Outcome: 9 Death

| Study or subgroup | SSRI | Control | Risk Ratio | Risk Ratio |
|--|-----------|-------------|------------------------------|--------------------------|
| | n/N | n/N | M- H,Random,95% Cl | M- H,Random,959 Cl |
| I Fluoxetine | | | | |
| Chollet 2011 | 1/59 | 1/59 | + | 1.00 [0.06, 15.61] |
| Fruehwald 2003 | 1/28 | 0/16 | | 1.76 [0.08, 40.80] |
| Li 2004a | 0/33 | 0/34 | | 0.0 [0.0, 0.0] |
| Li 2008 | 0/60 | 0/30 | | 0.0 [0.0, 0.0] |
| Liu 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Robinson 2000a | 0/23 | 1/17 | | 0.25 [0.01, 5.79] |
| Robinson 2000b | 0/17 | 0/16 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 250 | 202 | | 0.78 [0.14, 4.39] |
| Heterogeneity: Tau ² = 0.0; Chi ² = 0.79 Test for overall effect: Z = 0.28 (P = 0 2 Sertraline | , |), 1 -0.078 | | |
| 2 Sertraline | | | | |
| Almeida 2006 | 2/48 | 1/52 | | 2.17 [0.20, 23.14] |
| Burns 1999 | 1/14 | 1/14 | | 1.00 [0.07, 14.45] |
| Guo 2009 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Murray 2005 | 0/62 | 2/61 | | 0.20 [0.01, 4.02] |
| Subtotal (95% CI) Total events: 3 (SSRI), 4 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 1.54 Test for overall effect: $Z = 0.12$ (P = 0 3 Citalopram | | 167 | | 0.91 [0.20, 4.19] |
| Acler 2009 | 0/10 | 0/10 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: Z = 0.0 (P < 0.0 4 Paroxetine | 10 | 10 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| | | | 0.01 0.1 10 100 | |
| | | | Favours SSRI Favours control | (Continued) |

| Study or subgroup | SSRI | Control | Risk Ratio M- | (Continued) Risk Ratio M- H.Random,95% |
|--|----------------------|---------------------------|--------------------------|--|
| | n/N | n/N | H,Random,95% Cl | H,Random,75% Cl |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 5 Escitalopram | | | | |
| Robinson 2008 | 2/59 | 0/58 | | ★ 4.92 [0.24, 100.25] |
| Subtotal (95% CI) | 59 | 58 | | 4.92 [0.24, 100.25] |
| Total events: 2 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 1.04$ (P = 0 |).30) | | | |
| 6 Sertraline or fluoxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| Total (95% CI) | 483 | 437 | - | 1.06 [0.36, 3.09] |
| Total events: 7 (SSRI), 6 (Control) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.4$ | 6, df = 6 (P = 0.75) | ; I ² =0.0% | | |
| Test for overall effect: $Z = 0.11$ (P = 0 |).91) | | | |
| Test for subgroup differences: $Chi^2 =$ | 1.16, df = 2 (P = 0. | 56), I ² =0.0% | | |
| | | | | · |
| | | | 0.01 0.1 10 1 | 00 |
| | | | Favours SSRI Favours con | trol |

Analysis 5.10. Comparison 5 SSRI versus control, end of treatment, randomisation: low risk of bias, Outcome 10 Seizures.

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

Comparison: 5 SSRI versus control, end of treatment, randomisation: low risk of bias

Outcome: 10 Seizures

| Study or subgroup | SSRI | Control | Risk Ratio M- | Weight | : Risk Ratio M- | |
|---|---------|---------|------------------------------|---------|----------------------|--|
| | n/N | n/N | H,Random,95% Cl | | H,Random, C | |
| l Fluoxetine | | | | | | |
| Chollet 2011 | 1/59 | 0/59 | | 100.0 % | 3.00 [0.12, 72.18] | |
| Subtotal (95% CI) | 59 | 59 | | 100.0 % | 3.00 [0.12, 72.18] | |
| Total events: (SSRI), 0 (Control) | | | | | | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 0.68 (P = | = 0.50) | | | | | |
| 2 Sertraline | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] | |
| Total events: 0 (SSRI), 0 (Control) | | | | | | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: not applicable | : | | | | | |
| 3 Citalopram | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0 | |
| Total events: 0 (SSRI), 0 (Control) | | | | | | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: not applicable | 2 | | | | | |
| 4 Paroxetine | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0 | |
| Total events: 0 (SSRI), 0 (Control) | | | | | • | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: not applicable | 2 | | | | | |
| 5 Escitalopram | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] | |
| Total events: 0 (SSRI), 0 (Control) | | | | / | | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: not applicable | | | | | | |
| 6 Sertraline or fluoxetine | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0 | |
| Total events: 0 (SSRI), 0 (Control) | | | | / | | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: not applicable | | | | | | |
| Total (95% CI) | 59 | 59 | | 100.0 % | 3.00 [0.12, 72.18 | |
| Total events: 1 (SSRI), 0 (Control) | | | | | | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 0.68 (P = | = 0.50) | | | | | |
| Test for subgroup differences: Not a | , | | | | | |
| | | | | | | |
| | | | 0.01 0.1 10 100 | | | |
| | | | Favours SSRI Favours control | | | |

Analysis 5.11. Comparison 5 SSRI versus control, end of treatment, randomisation: low risk of bias, Outcome 11 Gastrointestinal side effects.

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

Comparison: 5 SSRI versus control, end of treatment, randomisation: low risk of bias

Outcome: II Gastrointestinal side effects

| Study or subgroup | SSRI | Control | F | Risk Ratio M- | Weight | Risk Ratio M- |
|---|------------|-------------------------------|--------------|------------------|--------|-----------------------|
| | n/N | n/N | H,Rar | idom,95% Cl | | H,Random,959 Cl |
| I Fluoxetine | | | | | | |
| Chollet 2011 | 14/59 | 6/59 | | | 58.2 % | 2.33 [0.96, 5.66] |
| Li 2004a | 3/33 | 0/34 | | | 5.3 % | 7.21 [0.39, 134.32] |
| Li 2008 | 6/60 | 3/30 | - | | 26.4 % | 1.00 [0.27, 3.72] |
| Liu 2004 | 3/30 | 0/30 | | | 5.4 % | 7.00 [0.38, 129.93] |
| Subtotal (95% CI) Total events: 26 (SSRI), 9 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 2 | 182 | 153 | | • | 95.3 % | 2.09 [1.05, 4.18] |
| Test for overall effect: $Z = 2.09$ (P = 2 Sertraline | | – 0.44); 1 ⁻ –0.0% | | | | |
| Burns 1999 | 0/14 | 1/14 | | | 4.7 % | 0.33 [0.01, 7.55] |
| Subtotal (95% CI) | 14 | 14 | | | 4.7 % | 0.33 [0.01, 7.55] |
| Total events: 0 (SSRI), 1 (Control) Heterogeneity: not applicable | | | | | | |
| Test for overall effect: $Z = 0.69$ (P = | 0.49) | | | | | |
| 3 Citalopram | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: not applicable 4 Paroxetine | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | /- | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: not applicable | | | | | | |
| 5 Escitalopram | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: not applicable | | | | | | |
| | | | 0.01 0.1 | 10 100 | | |
| | | | Favours SSRI | Favours control | | |
| | | | | . 10019 (0100) | | (Continued) |

| Study or subgroup | SSRI | Control | | Risk Ratio M- H,Random,95% | Weight | (Continued) Risk Ratio M- H,Random,95% |
|--|--------------------------------|-------------------------------|------|----------------------------------|---------|--|
| | n/N | n/N | | Cl | | CI |
| 6 Sertraline and paroxetine | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Contr | rol) | | | | | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: not appli | icable | | | | | |
| Total (95% CI) | 196 | 167 | | • | 100.0 % | 1.92 [0.98, 3.77] |
| Total events: 26 (SSRI), 10 (Co | ntrol) | | | | | |
| Heterogeneity: Tau ² = 0.0; Chi | ² = 3.92, df = 4 (P | = 0.42); I ² =0.0% | | | | |
| Test for overall effect: Z = 1.89 | 9 (P = 0.059) | | | | | |
| Test for subgroup differences: (| $Chi^2 = 1.27, df = 1$ | $(P = 0.26), ^2 = 2 \%$ | | | | |
| | | | | | | |
| | | | 0.01 | 0.1 1 10 100 |) | |

Favours SSRI Favours control

Analysis 5.14. Comparison 5 SSRI versus control, end of treatment, randomisation: low risk of bias, Outcome 14 Change in cognition between baseline and end of treatment.

Review: Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery Comparison: 5 SSRI versus control, end of treatment, randomisation: low risk of bias

Outcome: 14 Change in cognition between baseline and end of treatment

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | | | Std. Mean fference om,95% Cl | Weight | Std. Mean Difference IV,Random,95% Cl |
|----------------------------|--------------|------------|--------------|-----------|----|------------|---------------------------------------|----------|--|
| I Sertraline | 40 | 24 (204) | F 1 | 27 (20) | | | | 100.0.9/ | |
| Almeida 2006 | 48 | 2.6 (3.04) | 51 | 2.6 (3.9) | | • | | 100.0 % | 0.0 [-0.39, 0.39] |
| Total (95% CI) | 48 | | 51 | | | • | > | 100.0 % | 0.0 [-0.39, 0.39] |
| Heterogeneity: not app | licable | | | | | | | | |
| Test for overall effect: Z | Z = 0.0 (P = | 1.0) | | | | | | | |
| Test for subgroup differ | ences: Not | applicable | | | | | | | |
| | | | | | | | , <u> </u> | | |
| | | | | | -2 | -1 | 0 1 2 | | |
| | | | | | Fa | vours SSRI | Favours contro | ol | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |

Analysis 5.15. Comparison 5 SSRI versus control, end of treatment, randomisation: low risk of bias, Outcome 15 Leaving the trial before the end of scheduled follow-up.

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

Comparison: 5 SSRI versus control, end of treatment, randomisation: low risk of bias

Outcome: 15 Leaving the trial before the end of scheduled follow-up

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|------------------------|--------------------------------------|------------------------------|----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,959 Cl |
| I Fluoxetine | | | | |
| Chollet 2011 | 2/59 | 3/59 | | 0.67 [0.12, 3.85] |
| Fruehwald 2003 | 6/28 | 8/26 | | 0.70 [0.28, 1.74] |
| Kong 2007 | /48 | 6/42 | | 1.60 [0.65, 3.96] |
| Li 2004a | 0/33 | 0/34 | | 0.0 [0.0, 0.0] |
| Li 2008 | 2/60 | 2/30 | | 0.50 [0.07, 3.38] |
| Liu 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Robinson 2000a | 9/23 | 4/17 | | 1.66 [0.61, 4.51] |
| Robinson 2000b | 4/17 | 1/16 | | 3.76 [0.47, 30.20] |
| Subtotal (95% CI) | 298 | 254 | + | 1.16 [0.72, 1.89] |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4$ Test for overall effect: $Z = 0.61$ (P = 2 Sertraline | | $ ^2 = 0.0\%$ | | |
| 2 Sertraline | 0.5 1) | | | |
| Almeida 2006 | 11/55 | 6/56 | | 1.87 [0.74, 4.70] |
| Burns 1999 | 0/14 | 0/14 | | 0.0 [0.0, 0.0] |
| Guo 2009 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Murray 2005 | 24/62 | 30/61 | - | 0.79 [0.53, 1.18] |
| Rasmussen 2003 | 35/70 | 35/67 | + | 0.96 [0.69, 1.33] |
| Subtotal (95% CI) Total events: 70 (SSRI), 71 (Control) Heterogeneity: Tau ² = 0.03; Chi ² = Test for overall effect: $Z = 0.29$ (P = | 2.93, df = 2 (P = 0.23 | 238); I ² =32% | • | 0.95 [0.69, 1.32] |
| 3 Citalopram Acler 2009 | 0/10 | 0/10 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable | 10 | 10 | | 0.0 [0.0, 0.0] |
| | | | 0.05 0.2 5 20 | |
| | | | Favours SSRI Favours control | (Continued) |

| Study or subgroup | SSRI | Control | Risk Ratio M- H,Random,95% | (Continued) Risk Ratio M- H,Random,95% |
|---|-----------------------|--------------------------|----------------------------------|--|
| Test for overall effect: $Z = 0.0$ (P < 0.0 | n/N | n/N | Cl | Cl |
| 1 est for overall effect: $\angle = 0.0$ (P < 0.0 4 Paroxetine | JUUUT) | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | U | U | | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 5 Sertraline or fluoxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | Ũ | ũ | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 6 Escitalopram | | | | |
| Robinson 2008 | 7/59 | 5/58 | <u> </u> | 1.38 [0.46, 4.09] |
| Subtotal (95% CI) | 59 | 58 | | 1.38 [0.46, 4.09] |
| Total events: 7 (SSRI), 5 (Control) | | - | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.57$ (P = 0 |).57) | | | |
| Total (95% CI) | 608 | 560 | + | 0.99 [0.80, 1.23] |
| Total events: III (SSRI), 100 (Control |) | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 8.6$ | I, df = 9 (P = 0.47); | $ ^2 = 0.0\%$ | | |
| Test for overall effect: $Z = 0.10$ (P = 0 |).92) | | | |
| Test for subgroup differences: $Chi^2 = 0$ | 0.73, df = 2 (P = 0.6 | 9), l ² =0.0% | | |
| | | | | |
| | | | 0.05 0.2 5 20 | |

0.05 0.2 Favours SSRI

Favours control

Analysis 5.16. Comparison 5 SSRI versus control, end of treatment, randomisation: low risk of bias, Outcome 16 Bleeding.

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

Comparison: 5 SSRI versus control, end of treatment, randomisation: low risk of bias

Outcome: 16 Bleeding

| Study or subgroup | SSRI | Control | Risk R M | - | Weight | Risk Ratio M- H,Random,95% Cl | |
|----------------------------------|--------------------|---------|----------------|---------------|---------|--|--|
| | n/N | n/N | H,Random, C | | | | |
| Robinson 2008 | 1/59 | 1/59 | | | 100.0 % | 1.00 [0.06, 15.61] | |
| Total (95% CI) | 59 | 59 | | | 100.0 % | 1.00 [0.06, 15.61] | |
| Total events: (SSRI), (Co | | | | | | | |
| Heterogeneity: not applicab | | | | | | | |
| Test for overall effect: $Z = 0$ | | | | | | | |
| Test for subgroup difference | es: Not applicable | | | | | | |
| | | | 0.01 0.1 | 10 100 | | | |
| | | | | vours control | | | |
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Analysis 6.1. Comparison 6 SSRI versus control at end of treatment, concealment of allocation: low risk, Outcome I Dependent on modified Rankin score (mRS 3 to 5).

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

Comparison: 6 SSRI versus control at end of treatment, concealment of allocation: low risk

Outcome: I Dependent on modified Rankin score (mRS 3 to 5)

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|---|---------------------------|---------|--------------------|---------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| Fluoxetine | | | | |
| Chollet 2011 | 42/57 | 50/55 | + | 0.81 [0.68, 0.97] |
| Subtotal (95% CI) | 57 | 55 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Contro | l) | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 2.34$ (P | = 0.019) | | | |
| 2 Sertraline | | | | |
| Almeida 2006 | 0/55 | 0/56 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 55 | 56 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.0$ (P < | 0.00001) | | | |
| Total (95% CI) | 112 | 111 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Contro | l) | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = | 0.0, df = 0 (P = 1.00); I | 2 =0.0% | | |
| Test for overall effect: $Z = 2.34$ (P | = 0.019) | | | |
| Test for subgroup differences: Not | applicable | | | |
| | | | | |
| | | | 0.01 0.1 1 10 10 | 0 |

Favours SSRI Favours control

Analysis 6.2. Comparison 6 SSRI versus control at end of treatment, concealment of allocation: low risk, Outcome 2 Disability.

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

Comparison: 6 SSRI versus control at end of treatment, concealment of allocation: low risk

Outcome: 2 Disability

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% CI | Weight | Std. Mean Difference IV.Random,95% CI |
|---|------------|-----------------------|---------------------------|--------------|--|---------|--|
| Fluoxetine | | | | | | | · · · · · · · · · · · · · · · · · · · |
| Robinson 2000a | 14 | 59.2 (11.6) | 13 | 56.2 (7.8) | | 33.0 % | 0.29 [-0.47, 1.05] |
| | | | | () | _ | | |
| Robinson 2000b | 13 | 60.5 (10.8) | 15 | 63.1 (8.2) | | 33.1 % | -0.27 [-1.01, 0.48] |
| Subtotal (95% CI) | 27 | | 28 | | + | 66.0 % | 0.01 [-0.54, 0.56] |
| Heterogeneity: $Tau^2 = 0.01$ | | | D); I ² =5% | | | | |
| Test for overall effect: $Z = 0$ | 0.03 (P = | 0.98) | | | | | |
| 2 Sertraline | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicab | | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | |
| 3 Citalopram | 0 | | 0 | | | 0.0.0/ | |
| Subtotal (95% CI) | | | U | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicab Test for overall effect: not a | | | | | | | |
| 4 Paroxetine | ррпсаріе | | | | | | |
| Ye 2004 | 30 | 78.75 (14.19) | 30 | 50.26 (13.4) | | 34.0 % | 2.04 [1.41, 2.67 |
| | | 70.75 (11.17) | | 50.20 (15.1) | | | |
| Subtotal (95% CI) | 30 | | 30 | | • | 34.0 % | 2.04 [1.41, 2.67] |
| Heterogeneity: not applicab | | | | | | | |
| Test for overall effect: $Z = 6$ | 6.33 (P < | 0.00001) | | | | | |
| 5 Escitalopram | 0 | | 0 | | | 0.0.0/ | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicab Test for overall effect: not a | | | | | | | |
| 6 Sertraline or fluoxetine | ррпсаріе | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicab | | | Ū | | | 0.0 /0 | 0.0 [0.0, 0.0] |
| Test for overall effect: not a | | | | | | | |
| Total (95% CI) | 5 7 | | 58 | | | 100.0 % | 0.70 [-0.73, 2.13] |
| Heterogeneity: $Tau^2 = 1.46$ | | 24.26, df = 2 (P<0.00 | 0001 ; $ ^2 = 9$ | 2% | | | |
| Test for overall effect: $Z = 0$ | | | , | | | | |
| Test for subgroup difference | ` | , | 0.00), l ² =96 | 6% | | | |
| | | | , | | | 1 | |
| | | | | | -4 -2 0 2 | 4 | |
| | | | | | Favours control Favours | SSRI | |

Analysis 6.3. Comparison 6 SSRI versus control at end of treatment, concealment of allocation: low risk, Outcome 3 Neurological deficit score.

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

Comparison: 6 SSRI versus control at end of treatment, concealment of allocation: low risk

Outcome: 3 Neurological deficit score

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% C | Weight | Std. Mean Difference IV,Random,95% CI |
|---|------------|-------------------|---------------------------|--------------|---|----------|--|
| l Fluoxetine | | 5.0 (27) | | | _ | | |
| Chollet 2011 | 57 | 5.8 (3.7) | 55 | 6.9 (4.4) | - | 26.9 % | -0.27 [-0.64, 0.10] |
| Fruehwald 2003 | 26 | -55.5 (4.8) | 24 | -52.8 (5.4) | | 24.4 % | -0.52 [-1.09, 0.04] |
| Li 2004a | 33 | 6.23 (3.11) | 34 | 12.86 (6.36) | | 24.9 % | -1.30 [-1.83, -0.77] |
| Subtotal (95% CI) | 116 | | 113 | | | 76.1 % | -0.68 [-1.30, -0.06] |
| Heterogeneity: $Tau^2 = 0.24$; Test for overall effect: $Z = 2$. 2 Sertraline | | | .01); 2 =80% | 6 | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicable Test for overall effect: not ap | | | | | | | |
| 3 Citalopram Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicable | e | | | | | | |
| Test for overall effect: not ap | plicable | | | | | | |
| 4 Paroxetine | | | | | | | |
| Ye 2004 | 30 | 8.3 (3.8) | 30 | 16 (4.8) | 4∎ | 23.9 % | -1.76 [-2.36, -1.15] |
| Subtotal (95% CI) | 30 | | 30 | | - | 23.9 % | -1.76 [-2.36, -1.15] |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: $Z = 5$. | .72 (P < (| 0.00001) | | | | | |
| 5 Fluoxetine or sertraline | 0 | | 0 | | | 0.0.0/ | |
| Subtotal (95% CI) Heterogeneity: not applicable | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Test for overall effect: not applicable | | | | | | | |
| Total (95% CI) | 146 | | 143 | | | 100.0 % | -0.94 [-1.63, -0.26] |
| Heterogeneity: $Tau^2 = 0.42;$ | | 1.89, df = 3 (P = | | =86% | | 10000 /0 | 0,1[100, 020] |
| Test for overall effect: $Z = 2$. | | | | | | | |
| Test for subgroup differences | s: Chi² = | 5.93, df = 1 (P = | 0.01), I ² =83 | 8% | | | |
| | | | | | | • | |
| | | | | | -2 -1 0 1 | 2 | |
| | | | | | Favours SSRI Favours | control | |
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Analysis 6.4. Comparison 6 SSRI versus control at end of treatment, concealment of allocation: low risk, Outcome 4 Depression (continuous data).

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

Comparison: 6 SSRI versus control at end of treatment, concealment of allocation: low risk

Outcome: 4 Depression (continuous data)

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV.Random,95% CI |
|--|------------------------------------|-----------------------|--------------------------|--------------|--|-----------------|--|
| Fluoxetine | | . / | | . , | | | |
| Chollet 2011 | 56 | 5.4 (4.9) | 54 | 8.4 (7.9) | - | 15.3 % | -0.46 [-0.83, -0.08 - |
| Fruehwald 2003 | 26 | | 24 | .2 (2.4) | _ | 14.7 % | -0.16 [-0.72, 0.39 |
| | | 9.5 (7.9) | | . , | | | |
| Robinson 2000a | 14 | 18.5 (7.6) | 13 | 12.2 (4.7) | | 13.6 % | 0.96 [0.15, 1.76] |
| Robinson 2000b | 13 | 5.9 (3.8) | 15 | 6.2 (4.6) | | 13.9 % | -0.07 [-0.81, 0.67] |
| Subtotal (95% CI) | 109 | | 106 | | + | 57.6 % | -0.01 [-0.54, 0.53] |
| Heterogeneity: Tau ² = 0.20; Test for overall effect: Z = 0 Sertraline | | | 02); I ² =699 | 6 | | | |
| Murray 2005 | 62 | 10.5 (9.6) | 61 | 12 (8.5) | - | 15.4 % | -0.16 [-0.52, 0.19] |
| Subtotal (95% CI) | 62 | | 61 | | • | 15.4 % | -0.16 [-0.52, 0.19] |
| Heterogeneity: not applicabl Test for overall effect: Z = 0 Citalopram Andersen 1994 | | 0.36) | 33 | 14.1 (4.7) | - | 14.9 % | -0.54 [-1.04, -0.05 |
| | | 11.4 (5.1) | | 14.1 (4.7) | _ | | L · · |
| Subtotal (95% CI) Heterogeneity: not applicabl est for overall effect: Z = 2 Paroxetine Ye 2004 | | 0.030) 4.02 (3.07) | 33 30 | 17.32 (1.66) | | 14.9 % | - 0.54 [- 1.04, -0.05] -5.32 [-6.43, -4.21] |
| Subtotal (95% CI) Heterogeneity: not applicabl est for overall effect: Z = 9 Fluoxetine or sertraline | | 0.00001) | 30 | | | 12.1 % | -5.32 [-6.43, -4.21] |
| Subtotal (95% CI) Heterogeneity: not applicabl | 0 e | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Total (95% CI) Heterogeneity: Tau ² = 1.05; | 234 Chi ² = 9 | | 230 | 93% | - | 1 00.0 % | -0.72 [-1.52, 0.07] |
| est for overall effect: Z = 1 est for subgroup difference | | , | 0.00), l ² =9 | 96% | | | |
| | | | | | -4 -2 0 2 4 | | |
| | | | | | Favours SSRI Favours contr | rol | |

Analysis 6.5. Comparison 6 SSRI versus control at end of treatment, concealment of allocation: low risk, Outcome 5 Depression (dichotomous data).

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

Comparison: 6 SSRI versus control at end of treatment, concealment of allocation: low risk

Outcome: 5 Depression (dichotomous data)

| Study or subgroup | SSRI | Control | Risk Ratio M- | Weight | Risk Ratio M- |
|--|----------------|---------------------------|------------------------------|----------------|---------------------|
| | n/N | n/N | H,Random,95% Cl | | H,Random,9. Cl |
| I Fluoxetine | | | | | |
| Li 2004a | 2/33 | 8/34 | | 34.2 % | 0.26 [0.06, 1.12] |
| Subtotal (95% CI) | 33 | 34 | | 34.2 % | 0.26 [0.06, 1.12] |
| Total events: 2 (SSRI), 8 (Control) | 00 | 0 - | | u = / · | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 1.80$ (P = | 0.071) | | | | |
| 2 Sertraline | | | | | |
| Almeida 2006 | 8/48 | /5 | - | 65.8 % | 0.77 [0.34, 1.76] |
| Subtotal (95% CI) | 48 | 51 | • | 65.8 % | 0.77 [0.34, 1.76] |
| Total events: 8 (SSRI), 11 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 0.62$ (P = | 0.54) | | | | |
| 3 Citalopram | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 4 Paroxetine | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 5 Escitalopram | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| Total (95% CI) | 81 | 85 | | 100.0 % | 0.53 [0.19, 1.49] |
| Total events: 10 (SSRI), 19 (Control) | | | | | |
| Heterogeneity: Tau ² = 0.25; Chi ² = | | $P = 0.20$; $I^2 = 40\%$ | | | |
| Test for overall effect: $Z = 1.20$ (P = | , | | | | |
| Test for subgroup differences: Chi ² = | = 1.63, df = 1 | $(P = 0.20), I^2 = 39\%$ | | | |
| | | | 0.01 0.1 10 100 | | |
| | | | | | |
| | | | Favours SSRI Favours control | | |
| | | | | | |

Analysis 6.6. Comparison 6 SSRI versus control at end of treatment, concealment of allocation: low risk, Outcome 6 Anxiety (continuous data).

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

Comparison: 6 SSRI versus control at end of treatment, concealment of allocation: low risk

Outcome: 6 Anxiety (continuous data)

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Std. Mean Difference |
|--------------------------------|-------------------------|---------------------|--------------------------|--------------|----------------------------|-----------|----------------------------|
| Study of subgroup | N | Mean(SD) | N | Mean(SD) | IV,Random,95% Cl | V Veigint | IV,Random,95% CI |
| l Fluoxetine | | | | | | | |
| Robinson 2000a | 14 | 9.8 (4.8) | 13 | 9.9 (5.1) | + | 32.6 % | -0.02 [-0.77, 0.74] |
| Robinson 2000b | 13 | 4.7 (3.8) | 15 | 5.5 (2.9) | | 32.7 % | -0.23 [-0.98, 0.51] |
| Subtotal (95% CI) | 27 | | 28 | | + | 65.3 % | -0.13 [-0.66, 0.40] |
| Heterogeneity: $Tau^2 = 0.0$; | ; $Chi^2 = 0.1$ | 5, df = 1 (P = 0.69 | 9); I ² =0.0% | | | | |
| Test for overall effect: $Z =$ | 0.47 (P = | 0.64) | | | | | |
| 2 Sertraline | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applica | ble | | | | | | |
| Test for overall effect: not | applicable | | | | | | |
| 3 Citalopram | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applica | ble | | | | | | |
| Test for overall effect: not a | applicable | | | | | | |
| 4 Paroxetine | | | | | | | |
| Ye 2004 | 30 | 9.82 (2.64) | 30 | 14.02 (2.32) | - | 34.7 % | -1.67 [-2.26, -1.08] |
| Subtotal (95% CI) | 30 | | 30 | | • | 34.7 % | -1.67 [-2.26, -1.08] |
| Heterogeneity: not applica | ble | | | | | | |
| Test for overall effect: Z = | | 0.00001) | | | | | |
| 5 Escitalopram | , | , | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applica | ble | | | | | | |
| Test for overall effect: not | applicable | | | | | | |
| Total (95% CI) | 57 | | 58 | | - | 100.0 % | -0.66 [-1.74, 0.42] |
| Heterogeneity: $Tau^2 = 0.7$ | 9; Chi ² = 1 | 4.57, df = 2 (P = 0 | 0.00069); I ² | =86% | | | |
| Test for overall effect: Z = | I.20 (P = | 0.23) | | | | | |
| Test for subgroup difference | ces: Chi ² = | 14.41, df = 1 (P = | 0.00), $ ^2 = 9$ | 93% | | | |
| | | | , | | | | |
| | | | | | -4 -2 0 2 | 4 | |
| | | | | | Favours SSRI Favours cor | ntrol | |
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Analysis 6.8. Comparison 6 SSRI versus control at end of treatment, concealment of allocation: low risk, Outcome 8 Cognition (continuous scores end of treatment).

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

Comparison: 6 SSRI versus control at end of treatment, concealment of allocation: low risk

Outcome: 8 Cognition (continuous scores end of treatment)

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Sto Mea Differenc |
|---|---|--------------------|---------------------------|------------|---------------------------------------|---------|-------------------------|
| | Ν | Mean(SD) | N | Mean(SD) | IV,Random,95% Cl | | IV,Random,95% (|
| l Fluoxetine | | | | | | | |
| Robinson 2000a | 14 | 25.9 (7.5) | 13 | 24.5 (6.8) | | 49.1 % | 0.19 [-0.57, 0.95 |
| Robinson 2000b | 13 | 26.1 (7.5) | 15 | 26.8 (2.4) | | 50.9 % | -0.13 [-0.87, 0.62 |
| Subtotal (95% CI) | 27 | | 28 | | + | 100.0 % | 0.03 [-0.50, 0.56 |
| Heterogeneity: $Tau^2 = 0.0;$ | $Chi^2 = 0.3$ | 4, df = 1 (P = 0.5 | 56); I ² =0.0% | | | | |
| Test for overall effect: $Z = 0$ |). (P = C |).92) | | | | | |
| 2 Sertraline | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0 |
| Heterogeneity: not applicab | le | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | |
| 3 Citalopram | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0 |
| Heterogeneity: not applicab | le | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | |
| 4 Escitalopram | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0 |
| Heterogeneity: not applicab | le | | | | | | |
| Heterogeneity: not applicad | | | | | | | |
| 0 / 11 | | | | | | | |
| Heterogeneity: not applicad Test for overall effect: not a Total (95% CI) | | | 28 | | • | 100.0 % | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) | pplicable 27 | 4. df = 1 (P = 0.5 | | | + | 100.0 % | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; | pplicable 27 Chi ² = 0.3 | | | | • | 100.0 % | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | • | 100.0 % | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | - | 100.0 % | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | -4 Fax | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | -2 0 2 4 purs control Favours SSRI | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 | pplicable 27 Chi ² = 0.3).11 (P = 0 |).92) | | | | ŧ | 0.03 [-0.50, 0.56 |

Analysis 6.9. Comparison 6 SSRI versus control at end of treatment, concealment of allocation: low risk, Outcome 9 Death.

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

Comparison: 6 SSRI versus control at end of treatment, concealment of allocation: low risk

Outcome: 9 Death

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|-----------|---------------------------------------|---|----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,959 Cl |
| I Fluoxetine | | | | |
| Chollet 2011 | 1/59 | 1/59 | | 1.00 [0.06, 15.61] |
| Fruehwald 2003 | 1/28 | 0/16 | | 1.76 [0.08, 40.80] |
| Li 2004a | 0/33 | 0/34 | | 0.0 [0.0, 0.0] |
| Robinson 2000a | 0/23 | 1/17 | | 0.25 [0.01, 5.79] |
| Robinson 2000b | 0/17 | 0/16 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 160 | 142 | - | 0.78 [0.14, 4.39] |
| Total events: 2 (SSRI), 2 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0.79 Test for overall effect: $Z = 0.28$ (P = 0 2 Sertraline | | ; I ² =0.0% | | |
| Almeida 2006 | 2/48 | 1/52 | | 2.17 [0.20, 23.14] |
| Murray 2005 | 0/62 | 2/61 | | 0.20 [0.01, 4.02] |
| Subtotal (95% CI) Total events: 2 (SSRI), 3 (Control) Heterogeneity: Tau ² = 1.02; Chi ² = 1.1 Test for overall effect: $Z = 0.20$ (P = 0 3 Citalopram | , | 113 2); I ² =35% | | 0.79 [0.08, 8.19] |
| Andersen 1994 | 2/33 | 2/33 | _ | 1.00 [0.15, 6.68] |
| Subtotal (95% CI) Total events: 2 (SSRI), 2 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 0.0$ (P = 1.0 4 Paroxetine | 33 | 33 | | 1.00 [0.15, 6.68] |
| Ye 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 0.0$ (P < 0.0 | 30 | 30 | | 0.0 [0.0, 0.0] |
| 5 Escitalopram Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| | | | 0.01 0.1 10 100 Favours SSRI Favours control | (Continued) |

| Study or subgroup | ssri n/N | Control n/N | Risk Ratio M- H,Random,95% Cl | (Continued) Risk Ratio M- H,Random,95% Cl |
|--|------------------------|--------------------------|--|--|
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 6 Sertraline or fluoxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| Total (95% CI) | 333 | 318 | - | 0.87 [0.30, 2.50] |
| Total events: 6 (SSRI), 7 (Control) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.2$ | 35, df = 5 (P = 0.80); | $ ^2 = 0.0\%$ | | |
| Test for overall effect: $Z = 0.26$ (P = | 0.80) | | | |
| Test for subgroup differences: $Chi^2 =$ | 0.04, df = 2 (P = 0.9 | 8), I ² =0.0% | | |
| | | | | |
| | | | 0.01 0.1 10 100 | |
| | | | Favours SSRI Favours control | |

Analysis 6.10. Comparison 6 SSRI versus control at end of treatment, concealment of allocation: low risk, Outcome 10 Seizures.

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

Comparison: 6 SSRI versus control at end of treatment, concealment of allocation: low risk

Outcome: 10 Seizures

| I Fluoxetine Chollet 2011 Subtotal (95% CI) Total events: I (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: Z = 0.68 (P = 0.50 2 Sertraline Subtotal (95% CI) | n/N 1/59 59 | n/N 0/59 59 | M- H,Random,95% Cl | M- H,Random,95 CI 3.00 [0.12, 72.18] |
|--|--------------------------|--------------------------|------------------------------|---|
| Chollet 2011 Subtotal (95% CI) Total events: 1 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: Z = 0.68 (P = 0.50 2 Sertraline | 59 | | | 3.00 [0.12, 72.18] |
| Subtotal (95% CI) Total events: I (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: Z = 0.68 (P = 0.50 2 Sertraline | 59 | | | 3.00 [0.12, 72.18] |
| Total events: 1 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: Z = 0.68 (P = 0.50 2 Sertraline | | 59 | | |
| Heterogeneity: not applicable Test for overall effect: Z = 0.68 (P = 0.50 2 Sertraline | N | | | 3.00 [0.12, 72.18] |
| Test for overall effect: $Z = 0.68 (P = 0.50)$ 2 Sertraline | | | | |
| 2 Sertraline | n) | | | |
| | ワークション | | | |
| Subtotal (95% CI) | | | | |
| | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 3 Citalopram | | | | |
| Andersen 1994 | 2/33 | 0/33 | | 5.00 [0.25, 100.32] |
| Subtotal (95% CI) | 33 | 33 | | 5.00 [0.25, 100.32] |
| Total events: 2 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 1.05$ (P = 0.29 | ') | | | |
| 4 Paroxetine | | | | |
| Ye 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 30 | 30 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.0 (P < 0.000)$ | 01) | | | |
| 5 Escitalopram | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 6 Sertraline or fluoxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| | | | | |
| | | | 0.01 0.1 10 100 | |
| | | | Favours SSRI Favours control | (Continued |

| Study or subgroup | SSRI n/N | Control n/N | | Risk Ratio M- ndom,95% Cl | (Continued) Risk Ratio H,Random,95% Cl |
|---|----------------------------------|---------------------------|--------------|------------------------------------|--|
| Total (95% CI) | 122 | 122 | _ | - | 3.93 [0.44, 34.85] |
| Total events: 3 (SSRI), 0 (Contro | ol) | | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² | = 0.05, df = 1 (P = 0.82) | ; I ² =0.0% | | | |
| Test for overall effect: $Z = 1.23$ | (P = 0.22) | | | | |
| Test for subgroup differences: C | $hi^2 = 0.05, df = 1 (P = 0.05)$ | 82), I ² =0.0% | | | |
| | | | | | |
| | | | 0.01 0.1 | 1 10 100 | |
| | | | Favours SSRI | Favours control | |
| | | | | | |
| | | | | | |

Analysis 6.11. Comparison 6 SSRI versus control at end of treatment, concealment of allocation: low risk, Outcome II Gastrointestinal side effects.

| Study or subgroup | SSRI | Control | R | isk Ratio M- | Weight | Risk Ratio M- |
|-------------------------------------|-------------|---------|----------|-----------------|--------|---------------------|
| | n/N | n/N | H,Ran | dom,95% Cl | | H,Random,9 Cl |
| Fluoxetine | | | | | | |
| Chollet 2011 | 14/59 | 6/59 | - | | 92.0 % | 2.33 [0.96, 5.66] |
| Subtotal (95% CI) | 59 | 59 | | • | 92.0 % | 2.33 [0.96, 5.66] |
| Total events: 14 (SSRI), 6 (Contr | rol) | | | | | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: $Z = 1.88$ | (P = 0.061) | | | | | |
| 2 Sertraline | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Fotal events: 0 (SSRI), 0 (Contro |) | | | | | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: not applic | able | | | | | |
| 3 Citalopram | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Fotal events: 0 (SSRI), 0 (Contro | ol) | | | | | |
| Heterogeneity: not applicable | | | | | | |
| | | | 0.01 0.1 | | | |
| | | | | 10 100 | | |

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review) Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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

| Study or subgroup | SSRI | Control | Risk Ratio | Weight | (Continued) Risk Ratio M | |
|---|---------------|----------------------------------|--------------------------|---------|---------------------------------|--|
| | n/N | n/N | M- H,Random,95% Cl | | M- H,Random,9 Cl | |
| est for overall effect: not applicable | | | | | | |
| Paroxetine | | | | | | |
| Ye 2004 | 2/30 | 0/30 | | 8.0 % | 5.00 [0.25, 99.95] | |
| Subtotal (95% CI) | 30 | 30 | | 8.0 % | 5.00 [0.25, 99.95] | |
| otal events: 2 (SSRI), 0 (Control) Heterogeneity: not applicable | | | | | | |
| Test for overall effect: $Z = 1.05$ (P = | : 0.29) | | | | | |
| Escitalopram | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] | |
| otal events: 0 (SSRI), 0 (Control) | | | | | | |
| leterogeneity: not applicable | | | | | | |
| est for overall effect: not applicable | | | | | | |
| Sertraline and paroxetine | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] | |
| Total events: 0 (SSRI), 0 (Control) | | | | | | |
| Heterogeneity: not applicable | | | | | | |
| est for overall effect: not applicable | | | | | | |
| Total (95% CI) | 89 | 89 | • | 100.0 % | 2.48 [1.06, 5.80] | |
| otal events: 16 (SSRI), 6 (Control) | | | | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = 0 | 123 df = 1 (F | $P = 0.63 \cdot 1^2 = 0.0\%$ | | | | |
| Test for overall effect: $Z = 2.10$ (P = | | - 0.03), 1 -0.078 | | | | |
| | 00361 | | | | | |
| | | | | | | |
| | | $(P = 0.63), I^2 = 0.09$ | % | | | |
| Test for subgroup differences: $Chi^2 =$ | | (P = 0.63), I ² =0.05 | % • • • • • | | | |
| | | (P = 0.63), I ² =0.05 | % 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.05 | | | | |
| | | (P = 0.63), I ² =0.05 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |
| | | (P = 0.63), I ² =0.09 | 0.01 0.1 10 100 | | | |

Analysis 6.14. Comparison 6 SSRI versus control at end of treatment, concealment of allocation: low risk, Outcome 14 Change in cognition between baseline and end of treatment.

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

Comparison: 6 SSRI versus control at end of treatment, concealment of allocation: low risk

Outcome: 14 Change in cognition between baseline and end of treatment

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% CI | Weight | Std. Mean Difference IV,Random,95% CI |
|--|-------------|------------|--------------|-----------|--|----------------|--|
| I Sertraline Almeida 2006 | 48 | 2.6 (3.04) | 51 | 2.6 (3.9) | | 100.0 % | 0.0 [-0.39, 0.39] |
| | | 2.0 (3.04) | | 2.0 (3.7) | I | | |
| Total (95% CI) Heterogeneity: not app Test for overall effect: 2 | | : 1.0) | 51 | | | 100.0 % | 0.0 [-0.39, 0.39] |
| Test for subgroup differ | rences: Not | applicable | | | | | |
| | | | | | -2 -1 0 I 2 Favours SSRI Favours control | | |
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Analysis 6.15. Comparison 6 SSRI versus control at end of treatment, concealment of allocation: low risk, Outcome 15 Leaving the trial before the end of scheduled follow-up.

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

Comparison: 6 SSRI versus control at end of treatment, concealment of allocation: low risk

Outcome: 15 Leaving the trial before the end of scheduled follow-up

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|---|-----------|------------------------|------------------------------|----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| I Fluoxetine | | | | |
| Chollet 2011 | 2/59 | 3/59 | | 0.67 [0.12, 3.85] |
| Fruehwald 2003 | 6/28 | 8/26 | | 0.70 [0.28, 1.74] |
| Li 2004a | 0/33 | 0/34 | | 0.0 [0.0, 0.0] |
| Robinson 2000a | 9/23 | 4/17 | | 1.66 [0.61, 4.51] |
| Robinson 2000b | 4/17 | 1/16 | | 3.76 [0.47, 30.20] |
| Subtotal (95% CI) | 160 | 152 | + | 1.11 [0.58, 2.11] |
| Total events: 21 (SSRI), 16 (Control) Heterogeneity: Tau ² = 0.04; Chi ² = 3 Test for overall effect: $Z = 0.31$ (P = 0 2 Sertraline | , , |); l ² =9% | | |
| Almeida 2006 | I I/55 | 6/56 | + | 1.87 [0.74, 4.70] |
| Murray 2005 | 24/62 | 30/61 | - | 0.79 [0.53, 1.18] |
| Subtotal (95% CI) | 117 | 117 | + | 1.10 [0.47, 2.54] |
| Heterogeneity: Tau ² = 0.26; Chi ² = 2 Test for overall effect: $Z = 0.22$ (P = 0 3 Citalopram Andersen 1994 | |); l ² =66% | | 6.00 [0.76, 47.14] |
| Subtotal (95% CI) | 33 | 33 | | 6.00 [0.76, 47.14] |
| Total events: 6 (SSRI), 1 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 1.70$ (P = 0 4 Paroxetine | | 55 | | 0.00 [0.70, 17.11] |
| Ye 2004 | 1/30 | 0/31 | | 3.10 [0.13, 73.16] |
| Subtotal (95% CI) Total events: I (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 0.70$ (P = 0 5 Sertraline or fluoxetine | 30 | 31 | | 3.10 [0.13, 73.16] |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |
| | | | Favours SSRI Favours control | (Continued) |

(Continued \dots)

| Study or subgroup | ssri n/N | Control n/N | Risk Ratio M- H,Random,95% Cl | (Continued) Risk Ratio H,Random,95% Cl |
|--|-----------------------|---------------------------|--|--|
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 6 Escitalopram | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| Total (95% CI) | 340 | 333 | + | 1.21 [0.75, 1.95] |
| Total events: 63 (SSRI), 53 (Control) | | | | |
| Heterogeneity: Tau ² = 0.14; Chi ² = | 0.42, df = 7 (P = 0.1 | 7); I ² =33% | | |
| Test for overall effect: $Z = 0.77$ (P = | 0.44) | | | |
| Test for subgroup differences: $Chi^2 =$ | 2.77, df = 3 (P = 0.4 | 43), I ² =0.0% | | |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |

Favours SSRI

Favours control

Analysis 7.1. Comparison 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias, Outcome I Dependent on modified Rankin score (mRS 3 to 5).

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

Comparison: 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias

Outcome: I Dependent on modified Rankin score (mRS 3 to 5)

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|---------------------------|---------|--------------------|---------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| I Fluoxetine | | | | |
| Chollet 2011 | 42/57 | 50/55 | + | 0.81 [0.68, 0.97] |
| Subtotal (95% CI) | 57 | 55 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Contro | ol) | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 2.34$ (P | = 0.019) | | | |
| 2 Sertraline | | | | |
| Almeida 2006 | 0/55 | 0/56 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 55 | 56 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.0$ (P < | < 0.00001) | | | |
| Total (95% CI) | 112 | 111 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Contro | ol) | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 =$ | 0.0, df = 0 (P = 1.00); l | 2 =0.0% | | |
| Test for overall effect: $Z = 2.34$ (P | = 0.019) | | | |
| Test for subgroup differences: Not | applicable | | | |
| | | | | |
| | | | 0.01 0.1 10 100 | C |

Favours SSRI Favours control

Analysis 7.2. Comparison 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias, Outcome 2 Disability.

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

Comparison: 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias

Outcome: 2 Disability

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% CI | Weight | Std. Mean Difference IV,Random,95% CI |
|---|-------------|-------------|---------------------------|-------------|--|--------|--|
| I Fluoxetine | | | | | _ | | |
| Dam 1996 | 16 | 61.9 (13) | 16 | 54.1 (21.1) | | 11.2 % | 0.43 [-0.27, 1.14] |
| Kong 2007 | 37 | 60.4 (12.5) | 36 | 52.3 (13.5) | | 24.9 % | 0.62 [0.15, 1.09] |
| Li 2008 | 58 | 40.8 (3.7) | 28 | 38.4 (5.8) | | 26.2 % | 0.53 [0.07, 0.99] |
| Robinson 2000a | 14 | 59.2 (11.6) | 13 | 56.2 (7.8) | | 9.6 % | 0.29 [-0.47, 1.05] |
| Robinson 2000b | 13 | 60.5 (10.8) | 15 | 63.I (8.2) | | 9.9 % | -0.27 [-1.01, 0.48] |
| Wiart 2000 | 16 | 87.4 (22.8) | 15 | 88.7 (25.3) | _ | 11.1 % | -0.05 [-0.76, 0.65] |
| Subtotal (95% CI) | 154 | | 123 | | • | 92.9 % | 0.35 [0.08, 0.61] |
| Heterogeneity: $Tau^2 = 0.01$ Test for overall effect: $Z = 2$ 2 Sertraline | | | 3); I ² = I 3% | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | ble | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | |
| 3 Citalopram | | | | | | | |
| Acler 2009 | 10 | 82 (28) | 10 | 75 (25) | | 7.1 % | 0.25 [-0.63, 1.13] |
| Subtotal (95% CI) | 10 | | 10 | | | 7.1 % | 0.25 [-0.63, 1.13] |
| Heterogeneity: not applicat | | | | | | | |
| Test for overall effect: $Z = 0$ 4 Paroxetine | 0.56 (P = 0 | .57) | | | | | |
| 4 Paroxetine Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicab | | | U | | | 0.0 /0 | 0.0 [0.0, 0.0] |
| Test for overall effect: not a | | | | | | | |
| 5 Escitalopram | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicab | ble | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | |
| 6 Sertraline or fluoxetine | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | |
| | | | | | -2 -1 0 1 2 | | |
| | | | | - | -2 -1 0 1 2 avours control Favours SSRI | | |
| | | | | F | | | (Continued) |



Analysis 7.3. Comparison 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias, Outcome 3 Neurological deficit score.

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

Comparison: 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias

Outcome: 3 Neurological deficit score

| | | | | | Std. Mean | | Std. Mean |
|--|-----------|-------------------|--|---------------|--|--------|------------------------|
| Study or subgroup | SSRI | | Control | | Difference | Weight | Difference |
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| I Fluoxetine | | | | | | | |
| Chollet 2011 | 57 | 5.8 (3.7) | 55 | 6.9 (4.4) | -=+ | 35.9 % | -0.27 [-0.64, 0.10] |
| Dam 1996 | 16 | 44.1 (9.4) | 16 | 46.8 (9.9) | | 10.3 % | -0.27 [-0.97, 0.42] |
| Fruehwald 2003 | 26 | -55.5 (4.8) | 24 | -52.8 (5.4) | | 15.6 % | -0.52 [-1.09, 0.04] |
| Kong 2007 | 37 | 8.6 (6.4) | 36 | 11.2 (6.4) | | 23.1 % | -0.40 [-0.87, 0.06] |
| Subtotal (95% CI) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 2 2 Sertraline | | | 131 9); I ² =0.0% | | • | 84.9 % | -0.35 [-0.59, -0.11] |
| Burns 1999 | 14 | -29.7 (14.7) | 14 | -32.2 (3.4) | | 9.0 % | 0.17 [-0.57, 0.91] |
| Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: Z = 0 | | 0.65) | 14 | | | 9.0 % | 0.17 [-0.57, 0.91] |
| | | | | | -2 -1 0 I 2 Favours SSRI Favours contro | | (Continued) |
| Selective serotonin reup | take inhi | bitors (SSRIs) fo | or stroke re | ecovery (Revi | ew) | | 236 |

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| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% CI | Weight | (Continued Std. Mean Difference IV,Random,95% CI |
|--|---------------------------|---------------------|----------------------------|-----------|--|---------|---|
| 3 Citalopram Acler 2009 | 10 | 2.2.(2) | 10 | 2 5 (1 2) | | (0.9) | 0.000 1.00 0.000 1 |
| | 10 | 2.3 (2) | 10 | 3.5 (1.3) | | 6.0 % | -0.68 [-1.59, 0.23] |
| Subtotal (95% CI) | 10 | | 10 | | | 6.0 % | -0.68 [-1.59, 0.23] |
| Heterogeneity: not applic | | | | | | | |
| Test for overall effect: Z = 4 Paroxetine | = 1.47 (P = C |).14) | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applic | | | Ū | | | 0.0 /0 | 0.0 [0.0, 0.0] |
| Test for overall effect: not | | | | | | | |
| 5 Fluoxetine or sertraline | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applic | able | | | | | | |
| Test for overall effect: not | applicable | | | | | | |
| Total (95% CI) | 160 | | 155 | | • | 100.0 % | -0.32 [-0.55, -0.10] |
| Heterogeneity: $Tau^2 = 0.0$ |); Chi ² = 3.0 | 0, df = 5 (P = 0.7 | 0); I ² =0.0% | | | | |
| Test for overall effect: Z = | | | | | | | |
| Test for subgroup differen | ices: $Chi^2 = 2$ | 2.37, df = 2 (P = 0 | 0.31), I ² =159 | 6 | | | |
| | | | | | | 1 | |
| | | | | | -2 -1 0 1 | 2 | |
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Analysis 7.4. Comparison 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias, Outcome 4 Depression (continuous data).

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

Comparison: 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias

Outcome: 4 Depression (continuous data)

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|---|-----------|------------|--|-------------|--|--------|--|
| I Fluoxetine | | | | | | | |
| Chollet 2011 | 56 | 5.4 (4.9) | 54 | 8.4 (7.9) | | 11.3 % | -0.46 [-0.83, -0.08] |
| Dam 1996 | 16 | 8.8 (5.6) | 16 | 9.4 (5.6) | | 8.1 % | -0.10 [-0.80, 0.59] |
| Fruehwald 2003 | 26 | 9.5 (7.9) | 24 | 11.2 (12.4) | | 9.5 % | -0.16 [-0.72, 0.39] |
| Kong 2007 | 37 | 12.6 (5.3) | 36 | 16.3 (3.7) | _ | 10.3 % | -0.80 [-1.28, -0.32] |
| Li 2008 | 58 | 14.5 (2.4) | 28 | 18.7 (3.9) | _ _ | 10.1 % | -1.40 [-1.90, -0.90] |
| Robinson 2000a | 14 | 18.5 (7.6) | 13 | 12.2 (4.7) | | 7.1 % | 0.96 [0.15, 1.76] |
| Robinson 2000b | 13 | 5.9 (3.8) | 15 | 6.2 (4.6) | | 7.7 % | -0.07 [-0.81, 0.67] |
| Wiart 2000 | 16 | .8 (6.7) | 15 | 18.7 (10) | | 7.7 % | -0.79 [-1.53, -0.06] |
| Subtotal (95% CI) Heterogeneity: $Tau^2 = 0.29$ Test for overall effect: Z = 2 Sertraline | | | 201 0.00005); I ² = | =78% | - | 71.8 % | -0.40 [-0.83, 0.03] |
| Murray 2005 | 62 | 10.5 (9.6) | 61 | 12 (8.5) | | 11.6 % | -0.16 [-0.52, 0.19] |
| Subtotal (95% CI) Heterogeneity: not applicat Test for overall effect: Z = 3 Citalopram | | .36) | 61 | | - | 11.6 % | -0.16 [-0.52, 0.19] |
| Acler 2009 | 10 | 6.6 (3.6) | 10 | 8 (3) | | 6.4 % | -0.40 [-1.29, 0.48] |
| Andersen 1994 | 33 | 11.4 (5.1) | 33 | 14.1 (4.7) | | 10.2 % | -0.54 [-1.04, -0.05] |
| Subtotal (95% CI) Heterogeneity: $Tau^2 = 0.0$; Test for overall effect: $Z =$ 4 Paroxetine | | | 43 9); I ² =0.0% | | • | 16.6 % | -0.51 [-0.94, -0.08] |
| Subtotal (95% CI) Heterogeneity: not applicat Test for overall effect: not a | | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| 5 Fluoxetine or sertraline Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| | | | | | -2 -1 0 1 2 Favours SSRI Favours contro | 1 | (Continued) |



Analysis 7.5. Comparison 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias, Outcome 5 Depression (dichotomous data).

| Comparison: 7 SSRI versus contr Outcome: 5 Depression (dichoto | | eatment, patient/per | sonnel blind: low risk of bias | | |
|---|----------------|----------------------------------|--------------------------------|--------|--------------------------|
| Outcome: 5 Depression (dichoto | omous data) | | | | |
| | | | | | |
| Study or subgroup | SSRI | Control | Risk Ratio | Weight | Risk Ratio |
| | n/N | n/N | M- H,Random,95% Cl | | M- H,Random,955 Cl |
| I Fluoxetine | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable 2 Sertraline | 2 | | | | |
| Almeida 2006 | 8/48 | /5 | | 46.2 % | 0.77 [0.34, 1.76] |
| Rasmussen 2003 | 3/35 | 8/32 | | 20.4 % | 0.34 [0.10, 1.18] |
| Subtotal (95% CI) | 83 | 83 | • | 66.6 % | 0.59 [0.28, 1.25] |
| Total events: 11 (SSRI), 19 (Control |) | | | | |
| Heterogeneity: Tau ² = 0.05; Chi ² = | 1.16, df = 1 (| P = 0.28); I ² = I 4% | | | |
| Test for overall effect: Z = 1.37 (P = | = 0.17) | | | | |
| 3 Citalopram | | | | | |
| | | | <u> </u> | | |
| | | | 0.01 0.1 1 10 100 | | |
| | | | Favours SSRI Favours control | | (Continued) |
| | | | | | (continued) |
| elective serotonin reuptake inl | | | | | 239 |

| n/Nn/NSubtotal (95% CI)00Total events: 0 (SSRI), 0 (Control)Heterogeneity: not applicable $4 Paroxetine$ Subtotal (95% CI)00Total events: 0 (SSRI), 0 (Control)00Total events: 0 (SSRI), 0 (Control)Heterogeneity: not applicable $4 Paroxetine$ Subtotal (95% CI)000Total events: 0 (SSRI), 0 (Control)Heterogeneity: not applicable $5 Escitalopram$ Robinson 20085/5913/58Subtotal (95% CI)5958Total events: 5 (SSRI), 13 (Control)Heterogeneity: not applicableTest for overall effect: Z = 1.97 (P = 0.048)Total events: 16 (SSRI), 32 (Control)Heterogeneity: not applicable142141Total events: 16 (SSRI), 32 (Control)Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); l ² = 0.0%Test for overall effect: Z = 2.32 (P = 0.020)Test for overall effect: Z = 2.32 (P = 0.020) | H,Random,95% Cl | 0.0 % 0.0 % 33.4 % 33.4 % 100.0 % | M- H,Random,95 CI 0.0 [0.0, 0.0] 0.0 [0.0, 0.0] 0.38 [0.14, 0.99] 0.38 [0.14, 0.99] 0.52 [0.30, 0.90] |
|---|------------------------------|---|--|
| Subtotal (95% CI)00Total events: 0 (SSRI), 0 (Control)Heterogeneity: not applicableTest for overall effect: not applicable4 ParoxetineSubtotal (95% CI)0Total events: 0 (SSRI), 0 (Control)Heterogeneity: not applicableTest for overall effect: not applicableSubtotal (95% CI)59Subtotal (95% CI)59Total events: 5 (SSRI), 13 (Control)Heterogeneity: not applicableTest for overall effect: Z = 1.97 (P = 0.048)Total (95% CI)142Total events: 16 (SSRI), 32 (Control)Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); I ² = 0.0%Test for overall effect: Z = 2.32 (P = 0.020) | | 0.0 % 33.4 % 33.4 % | 0.0 [0.0, 0.0] 0.0 [0.0, 0.0] 0.38 [0.14, 0.99] 0.38 [0.14, 0.99] |
| Heterogeneity: not applicable 4 Paroxetine Subtotal (95% CI) 0 0 0 Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable Test for overall effect: not applicable 5 Escitalopram Robinson 2008 5/59 13/58 Subtotal (95% CI) 59 5 Escitalopram Robinson 2008 5/59 13/58 Subtotal (95% CI) 59 164 59 Total events: 5 (SSRI), 13 (Control) Heterogeneity: not applicable Test for overall effect: Z = 1.97 (P = 0.048) Total (95% CI) 142 141 Total events: 16 (SSRI), 32 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); l ² = 0.0% Test for overall effect: Z = 2.32 (P = 0.020) | | 33.4 % 33.4 % | 0.38 [0.14, 0.99] 0.38 [0.14, 0.99] |
| Test for overall effect: not applicable4 ParoxetineSubtotal (95% CI)0OTotal events: 0 (SSRI), 0 (Control)Heterogeneity: not applicableTest for overall effect: not applicable5 EscitalopramRobinson 20085/59Subtotal (95% CI)595 Sex Subtotal (95% CI)595 Sex Subtotal (95% CI)596 Subtotal (95% CI)1421 Attain the events: 5 (SSRI), 13 (Control)Heterogeneity: not applicableTest for overall effect: Z = 1.97 (P = 0.048)Total (95% CI)1421 Attain the events: 16 (SSRI), 32 (Control)Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); l ² = 0.0%Test for overall effect: Z = 2.32 (P = 0.020) | • | 33.4 % 33.4 % | 0.38 [0.14, 0.99] 0.38 [0.14, 0.99] |
| 4 ParoxetineSubtotal (95% CI)0O0Total events: 0 (SSRI), 0 (Control)Heterogeneity: not applicableTest for overall effect: not applicable5 EscitalopramRobinson 2008 $5/59$ 13/58Subtotal (95% CI)5958Total events: 5 (SSRI), 13 (Control)Heterogeneity: not applicableTest for overall effect: Z = 1.97 (P = 0.048)Total (95% CI)142141Total events: 16 (SSRI), 32 (Control)Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); l ² = 0.0%Test for overall effect: Z = 2.32 (P = 0.020) | - | 33.4 % 33.4 % | 0.38 [0.14, 0.99] 0.38 [0.14, 0.99] |
| Subtotal (95% CI) 0 0 Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Image: State of the stat | • | 33.4 % 33.4 % | 0.38 [0.14, 0.99] 0.38 [0.14, 0.99] |
| Total events: 0 (SSRI), 0 (Control)Heterogeneity: not applicableTest for overall effect: not applicable5 EscitalopramRobinson 2008 $5/59$ $13/58$ Subtotal (95% CI)5958Total events: 5 (SSRI), 13 (Control)Heterogeneity: not applicableTest for overall effect: Z = 1.97 (P = 0.048)Total (95% CI)142141Total effect: Z = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); I ² = 0.0%Test for overall effect: Z = 2.32 (P = 0.020) | • | 33.4 % 33.4 % | 0.38 [0.14, 0.99] 0.38 [0.14, 0.99] |
| Heterogeneity: not applicableTest for overall effect: not applicable5 EscitalopramSubtotal (95% CI)5/5913/58Subtotal (95% CI)5958Total events: 5 (SSRI), 13 (Control)Heterogeneity: not applicableTotal (95% CI)142141Total (95% CI)121.41Total (95% CI)142141Total (95% CI)121.41Total events: 16 (SSRI), 32 (Control)Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); I ² = 0.0%Test for overall effect: Z = 2.32 (P = 0.020) | | 33.4 % | 0.38 [0.14, 0.99] |
| Test for overall effect: not applicable5 Escitalopram5/5913/58Subtotal (95% CI)5958Total events: 5 (SSRI), 13 (Control)Heterogeneity: not applicableTotal (95% CI)142141Total (95% CI)142141Total (95% CI)142141Total (95% CI)142141Total (95% CI)142141Total events: 16 (SSRI), 32 (Control)Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); I ² = 0.0%Test for overall effect: Z = 2.32 (P = 0.020) | • | 33.4 % | 0.38 [0.14, 0.99] |
| 5 Escitalopram Robinson 2008 5/59 13/58 Subtotal (95% CI) 59 58 Total events: 5 (SSRI), 13 (Control) 59 58 Heterogeneity: not applicable 5000000000000000000000000000000000000 | • | 33.4 % | 0.38 [0.14, 0.99] |
| Robinson 2008 5/59 13/58 Subtotal (95% CI) 59 58 Total events: 5 (SSRI), 13 (Control) 59 58 Heterogeneity: not applicable 5 5 Total (95% CI) 142 141 Total events: 16 (SSRI), 32 (Control) 142 141 Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); l ² = 0.0% 152 for overall effect: Z = 2.32 (P = 0.20) | • | 33.4 % | 0.38 [0.14, 0.99] |
| Subtotal (95% CI) 59 58 Total events: 5 (SSRI), 13 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 1.97$ (P = 0.048) Total (95% CI) 142 141 Total events: 16 (SSRI), 32 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); l ² = 0.0% Test for overall effect: $Z = 2.32$ (P = 0.020) | • | 33.4 % | 0.38 [0.14, 0.99] |
| Total events: 5 (SSRI), I 3 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 1.97$ (P = 0.048) Total (95% CI) 142 141 Total events: I 6 (SSRI), 32 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); I ² = 0.0% Test for overall effect: $Z = 2.32$ (P = 0.020) | • | | |
| Heterogeneity: not applicable Test for overall effect: $Z = 1.97$ (P = 0.048) Total (95% CI) 142 141 Total events: 16 (SSRI), 32 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); I ² = 0.0% Test for overall effect: $Z = 2.32$ (P = 0.020) | • | 100.0 % | 0.52 [0.30. 0.90] |
| Test for overall effect: $Z = 1.97$ (P = 0.048) Total (95% CI) 142 141 Total events: 16 (SSRI), 32 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); l ² = 0.0% Test for overall effect: $Z = 2.32$ (P = 0.020) | • | 100.0 % | 0.52 [0.30, 0.90] |
| Total (95% CI)142141Total events: 16 (SSRI), 32 (Control)Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); l ² = 0.0%Test for overall effect: $Z = 2.32$ (P = 0.020) | • | 100.0 % | 0.52 [0.30. 0.90] |
| Total events: 16 (SSRI), 32 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); l ² = 0.0% Test for overall effect: $Z = 2.32$ (P = 0.020) | • | 100.0 % | 0.52 [0.30, 0.90] |
| Heterogeneity: Tau ² = 0.0; Chi ² = 1.76, df = 2 (P = 0.41); l ² = 0.0% Test for overall effect: $Z = 2.32$ (P = 0.020) | | | |
| Test for overall effect: $Z = 2.32$ (P = 0.020) | | | |
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Analysis 7.6. Comparison 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias, Outcome 6 Anxiety (continuous data).

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

Comparison: 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias

Outcome: 6 Anxiety (continuous data)

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|-----------------------------------|-----------------|--------------------|--------------------------|-----------|--|---------|--|
| | IN | (SD) | IN | riedn(SD) | IV,Rahuom,73% Ci | | IV,Random,73% CI |
| l Fluoxetine Robinson 2000a | 14 | 9.8 (4.8) | 13 | 9.9 (5.1) | _ _ | 49.4 % | -0.02 [-0.77, 0.74] |
| Robinson 2000b | 13 | 4.7 (3.8) | 15 | 5.5 (2.9) | | 50.6 % | -0.23 [-0.98, 0.51] |
| Subtotal (95% CI) | 27 | | 28 | | - | 100.0 % | -0.13 [-0.66, 0.40] |
| Heterogeneity: $Tau^2 = 0.0$; | ; $Chi^2 = 0.1$ | 5, df = 1 (P = 0.6 | 9); l ² =0.0% | | | | |
| Test for overall effect: Z = | 0.47 (P = 0 | 0.64) | | | | | |
| 2 Sertraline | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applical | ble | | | | | | |
| Test for overall effect: not a | applicable | | | | | | |
| 3 Citalopram | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applical | | | | | | | |
| Test for overall effect: not a | applicable | | | | | | |
| 4 Paroxetine Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applical | | | U | | | 0.0 % | 0.0 [0.0, 0.0] |
| Test for overall effect: not a | | | | | | | |
| 5 Escitalopram | аррпсавіс | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applical | | | Ū | | | 010 /0 | 010 [010, 010] |
| Test for overall effect: not a | | | | | | | |
| Total (95% CI) | 27 | | 28 | | - | 100.0 % | -0.13 [-0.66, 0.40] |
| Heterogeneity: $Tau^2 = 0.0$; | ; $Chi^2 = 0.1$ | 5, df = 1 (P = 0.6 | 9); l ² =0.0% | | | | |
| Test for overall effect: Z = | 0.47 (P = 0 | 0.64) | | | | | |
| Test for subgroup difference | es: Not ap | plicable | | | | | |
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Analysis 7.8. Comparison 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias, Outcome 8 Cognition (continuous scores end of treatment).

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

Comparison: 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias

Outcome: 8 Cognition (continuous scores end of treatment)

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | | Std. Mean ference om,95% Cl | Weight | Std. Mean Difference IV,Random,95% Cl |
|---|---------------------------------------|--------------------|-----------------------------|------------|-----------------|--------------------------------------|---------------|--|
| l Fluoxetine | | | | | | | | |
| Robinson 2000a | 4 | 25.9 (7.5) | 13 | 24.5 (6.8) | | | 15.5 % | 0.19 [-0.57, 0.95] |
| Robinson 2000b | 13 | 26.1 (7.5) | 15 | 26.8 (2.4) | | | 16.1 % | -0.13 [-0.87, 0.62] |
| Wiart 2000 | 16 | 24.8 (3.9) | 15 | 26.2 (3) | ←∎ | | 17.5 % | -0.39 [-1.10, 0.32] |
| Subtotal (95% CI) | 43 | | 43 | | | | 49.1 % | -0.12 [-0.55, 0.30] |
| Heterogeneity: $Tau^2 = 0.0$; | | | 5); I ² =0.0% | | | | | |
| Test for overall effect: $Z = 0$ | 0.56 (P = 0 |).58) | | | | | | |
| 2 Sertraline Subtotal (95% CI) | 0 | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | | | Ū | | | | 010 /0 | |
| Test for overall effect: not a | pplicable | | | | | | | |
| 3 Citalopram | | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat Test for overall effect: not a | | | | | | | | |
| 4 Escitalopram | pheaolo | | | | | | | |
| Robinson 2008 | 43 | 89.8 (15.1) | 45 | 91 (17.8) | | | 50.9 % | -0.07 [-0.49, 0.35] |
| Subtotal (95% CI) | 43 | | 45 | | | | 50.9 % | -0.07 [-0.49, 0.35] |
| Heterogeneity: not applicat | | | | | | | | |
| Test for overall effect: $Z = 0$ | · · · · · · · · · · · · · · · · · · · |).74) | 00 | | _ | | 100.0.0/ | |
| Total (95% CI) Heterogeneity: $Tau^2 = 0.0$; | 86 | 2 df = 3 (P = 0.7) | 88 | | | | 100.0 % | -0.10 [-0.39, 0.20] |
| Test for overall effect: $Z = 0$ | | |), 1 -0.070 | | | | | |
| Test for subgroup difference | ` | , | 0.87), I ² =0.09 | % | | | | |
| | | | | | <u> </u> | | | |
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| | | | | | Favours control | Favours SSRI | | |
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Analysis 7.9. Comparison 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias, Outcome 9 Death.

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

Comparison: 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias

Outcome: 9 Death

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|--------------------------------------|-----------------------------------|---|--------------------------|
| | n/N | n/N | M- H,Random,95% Cl | M- H,Random,959 Cl |
| l Fluoxetine | | | | |
| Brown 1998 | 0/10 | 0/10 | | 0.0 [0.0, 0.0] |
| Chollet 2011 | 1/59 | 1/59 | _ | 1.00 [0.06, 15.61] |
| Dam 1996 | 0/18 | 0/17 | | 0.0 [0.0, 0.0] |
| Fruehwald 2003 | 1/28 | 0/16 | | 1.76 [0.08, 40.80] |
| Li 2008 | 0/60 | 0/30 | | 0.0 [0.0, 0.0] |
| Robinson 2000a | 0/23 | 1/17 | | 0.25 [0.01, 5.79] |
| Robinson 2000b | 0/17 | 0/16 | | 0.0 [0.0, 0.0] |
| Wiart 2000 | 0/16 | 0/15 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 231 | 180 | - | 0.78 [0.14, 4.39] |
| 2 Sertraline Almeida 2006 | 2/48 | 1/52 | | 2.17 [0.20, 23.14] |
| 2 Sertraline | | | | |
| Burns 1999 | / 4 | / 4 | | 1.00 [0.07, 14.45] |
| Murray 2005 | 0/62 | 2/61 | | 0.20 [0.01, 4.02] |
| Subtotal (95% CI) Total events: 3 (SSRI), 4 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = Test for overall effect: Z = 0.12 (P | 124 1.54, df = 2 (P = 0.46 | 127 | - | 0.91 [0.20, 4.19] |
| 3 Citalopram Acler 2009 | 0/10 | 0/10 | | 0.0 [0.0, 0.0] |
| Andersen 1994 | 2/33 | 2/33 | | |
| | | | | 1.00 [0.15, 6.68] |
| Subtotal (95% CI) Total events: 2 (SSRI), 2 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = Test for overall effect: Z = 0.0 (P = 4 Paroxetine | 0.0, df = 0 (P = 1.00); | 43 I ² =0.0% | | 1.00 [0.15, 6.68] |
| | | | I I | |
| | | | 0.01 0.1 10 100 Favours SSRI Favours control | (Continued) |

| Study or subgroup | SSRI | Control | Risk Ratio | (Continued) Risk Ratio M- |
|--|----------------------|---------------------------|--------------------|----------------------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 5 Escitalopram | | | | |
| Robinson 2008 | 2/59 | 0/58 | | 4.92 [0.24, 100.25] |
| Subtotal (95% CI) | 59 | 58 | | 4.92 [0.24, 100.25] |
| Total events: 2 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 1.04$ (P = C | 0.30) | | | |
| 6 Sertraline or fluoxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| Total (95% CI) | 45 7 | 408 | + | 1.05 [0.41, 2.66] |
| Total events: 9 (SSRI), 8 (Control) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.4$ | 6, df = 7 (P = 0.84) | ; l ² =0.0% | | |
| Test for overall effect: $Z = 0.09$ (P = 0 | 0.93) | | | |
| Test for subgroup differences: $Chi^2 =$ | 1.16, df = 3 (P = 0. | 76), l ² =0.0% | | |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |

0.01 0.1 I Favours SSRI

Favours control

Analysis 7.10. Comparison 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias, Outcome 10 Seizures.

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

Comparison: 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias

Outcome: 10 Seizures

| Study or subgroup | SSRI | Control | Risk Ratio M- | Weight | Risk Ratio M- |
|---|-------------------|--|---|--------|-----------------------|
| | n/N | n/N | H,Random,95% Cl | | H,Random,955 Cl |
| I Fluoxetine | | | | | |
| Chollet 2011 | 1/59 | 0/59 | | 21.4 % | 3.00 [0.12, 72.18] |
| Dam 1996 | 2/18 | 0/17 | | 24.5 % | 4.74 [0.24, 92.07] |
| Wiart 2000 | 1/16 | 1/15 | | 30.1 % | 0.94 [0.06, 3.68] |
| Subtotal (95% CI) | 93 | 91 | - | 76.0 % | 2.19 [0.41, 11.85] |
| Total events: 4 (SSRI), 1 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = Test for overall effect: $Z = 0.91$ (F | = 0.69, df = 2 (I | ^D = 0.71); I ² =0.0% | | | |
| 2 Sertraline Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable | | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| 3 Citalopram Andersen 1994 | 2/33 | 0/33 | | 24.0 % | 5.00 [0.25, 100.32] |
| Subtotal (95% CI) Total events: 2 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: Z = 1.05 (F | | 33 | | 24.0 % | 5.00 [0.25, 100.32] |
| 4 Paroxetine Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applical | | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| 5 Escitalopram Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applical | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| 6 Sertraline or fluoxetine Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| | | | 0.01 0.1 10 100 Favours SSRI Favours control | | (Continued) |


Analysis 7.11. Comparison 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias, Outcome 11 Gastrointestinal side effects.

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

Comparison: 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias

Outcome: II Gastrointestinal side effects

| Study or subgroup | SSRI | Control | Risk Ratio M- | Weight | Risk Ratio M- |
|---|-------------------------|---------------------------|------------------------------|--------|----------------------|
| | n/N | n/N | H,Random,95% Cl | | H,Random,95% Cl |
| I Fluoxetine | | | | | |
| Chollet 2011 | 14/59 | 6/59 | | 48.1 % | 2.33 [0.96, 5.66] |
| Dam 1996 | 2/18 | 0/17 | | 6.5 % | 4.74 [0.24, 92.07] |
| Li 2008 | 6/60 | 3/30 | | 27.5 % | 1.00 [0.27, 3.72] |
| Wiart 2000 | 1/16 | 3/16 | | 11.9 % | 0.33 [0.04, 2.87] |
| Subtotal (95% CI) | 153 | 122 | • | 94.1 % | 1.48 [0.65, 3.39] |
| Total events: 23 (SSRI), 12 (Co | ontrol) | | | | |
| Heterogeneity: Tau ² = 0.15; C | $hi^2 = 3.74, df = 3$ (| $P = 0.29$; $I^2 = 20\%$ | | | |
| Test for overall effect: $Z = 0.93$ | 3 (P = 0.35) | | | | |
| 2 Sertraline | | | | | |
| Burns 1999 | 0/14 | / 4 | | 5.9 % | 0.33 [0.01, 7.55] |
| Subtotal (95% CI) | 14 | 14 | | 5.9 % | 0.33 [0.01, 7.55] |
| | | | 0.01 0.1 10 100 | | _ |
| | | | Favours SSRI Favours control | | |
| | | | | | (Continued) |

| Study or subgroup | SSRI | Control | Risk Ratio M- | Weight | (Continued) Risk Ratio M- |
|---|-------------------------------------|----------------------------------|---|---------|----------------------------------|
| | n/N | n/N | H,Random,95% Cl | | H,Random,95 Cl |
| Total events: 0 (SSRI), 1 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 0.69$ (P | = 0.49) | | | | |
| 3 Citalopram | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | e | | | | |
| 4 Paroxetine | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | e | | | | |
| 5 Escitalopram | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | e | | | | |
| 6 Sertraline and paroxetine | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | e | | | | |
| | 167 | 136 | + | 100.0 % | 1.37 [0.63, 2.98] |
| Iotal (95% CI) | 10/ | | | | |
| Total (95% CI) Total events: 23 (SSRI), 13 (Contro | | -0- | | | |
| Total events: 23 (SSRI), 13 (Contro | ol) | | | | |
| | ol) = 4.67, df = 4 (F | | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | 0.01 0.1 10 100 Favours SSRI Favours control | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | 0.01 0.1 10 100 Favours SSRI Favours control | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |
| Total events: 23 (SSRI), 13 (Contro Heterogeneity: Tau ² = 0.12; Chi ² = Test for overall effect: Z = 0.79 (P | ol) = 4.67, df = 4 (F = 0.43) | 9 = 0.32); ² = 4% | | | |

Analysis 7.14. Comparison 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias, Outcome 14 Change in cognition between baseline and end of treatment.

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

Comparison: 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias

Outcome: 14 Change in cognition between baseline and end of treatment

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% CI | Weight | Std Mean Difference IV,Random,95% C |
|--|------------|------------|--------------|-----------|--|---------|--|
| I Sertraline Almeida 2006 | 48 | 2.6 (3.04) | 51 | 2.6 (3.9) | - | 100.0 % | 0.0 [-0.39, 0.39] |
| | | 2.0 (3.01) | | 2.0 (3.7) | Ţ | | |
| Total (95% CI) Heterogeneity: not app | | | 51 | | | 100.0 % | 0.0 [-0.39, 0.39] |
| Test for overall effect: Z Test for subgroup differ | | | | | | | |
| lest for subgroup differ | ences: Not | аррисаріе | | | | | |
| | | | | | -2 -1 0 1 2 Favours SSRI Favours control | I | |
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Analysis 7.15. Comparison 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias, Outcome 15 Leaving the trial before the end of scheduled follow-up.

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

Comparison: 7 SSRI versus control at end of treatment, patient/personnel blind: low risk of bias

Outcome: 15 Leaving the trial before the end of scheduled follow-up

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|---|--------------------------|-------------------------|------------------------------|----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95 Cl |
| I Fluoxetine | | | | |
| Brown 1998 | 1/10 | 0/10 | | 3.00 [0.14, 65.90] |
| Chollet 2011 | 2/59 | 3/59 | | 0.67 [0.12, 3.85] |
| Dam 1996 | 0/16 | 0/17 | | 0.0 [0.0, 0.0] |
| Fruehwald 2003 | 6/28 | 8/26 | | 0.70 [0.28, 1.74] |
| Kong 2007 | /48 | 6/42 | | 1.60 [0.65, 3.96] |
| Li 2008 | 2/60 | 2/30 | · | 0.50 [0.07, 3.38] |
| Robinson 2000a | 9/23 | 4/17 | | 1.66 [0.61, 4.51] |
| Robinson 2000b | 4/17 | 1/16 | | 3.76 [0.47, 30.20] |
| Wiart 2000 | 0/16 | 0/15 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 277 | 232 | • | 1.19 [0.74, 1.92] |
| Almeida 2006 | 11/55 | 6/56 | + | 1.87 [0.74, 4.70] |
| 2 Sertraline | | | | |
| Burns 1999 | 0/14 | 0/14 | | 0.0 [0.0, 0.0] |
| Murray 2005 | 24/62 | 30/61 | - | 0.79 [0.53, 1.18] |
| Rasmussen 2003 | 35/70 | 35/67 | + | 0.96 [0.69, 1.33] |
| Subtotal (95% CI) | 201 | 198 | • | 0.95 [0.69, 1.32] |
| Total events: 70 (SSRI), 71 (Contro Heterogeneity: Tau ² = 0.03; Chi ² = Test for overall effect: Z = 0.29 (P | = 2.93, df = 2 (P = 0.23 | 3); I ² =32% | | |
| 3 Citalopram | _ 0.77) | | | |
| Acler 2009 | 0/10 | 0/10 | | 0.0 [0.0, 0.0] |
| Andersen 1994 | 6/33 | 1/33 | | 6.00 [0.76, 47.14] |
| Subtotal (95% CI) | 43 | 43 | - | 6.00 [0.76, 47.14] |
| Total events: 6 (SSRI), 1 (Control) | | | | |
| | | | 0.01 0.1 1 10 100 | |
| | | | Favours SSRI Favours control | (Continued) |

| Study or subgroup | ssRi n/N | Control n/N | Risk Ratio M- H,Random,95% Cl | (Continued) Risk Ratio M- H,Random,95% |
|--|-----------------------|------------------------------|--|--|
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$ | | | Ci | <u> </u> |
| Test for overall effect: $Z = 1.70$ (P = 1 | , , | | | |
| 4 Paroxetine |) | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 5 Sertraline or fluoxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 6 Escitalopram | | | | |
| Robinson 2008 | 7/59 | 5/58 | | 1.38 [0.46, 4.09] |
| Subtotal (95% CI) | 59 | 58 | - | 1.38 [0.46, 4.09] |
| Total events: 7 (SSRI), 5 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.57$ (P = | 0.57) | | | |
| Total (95% CI) | 580 | 531 | + | 1.05 [0.82, 1.36] |
| Total events: 118 (SSRI), 101 (Contro | ol) | | | |
| Heterogeneity: Tau ² = 0.02; Chi ² = 1 | 2.31, df = 11 (P = 0 | .34); I ² = I I % | | |
| Test for overall effect: $Z = 0.41$ (P = | 0.68) | | | |
| Test for subgroup differences: $Chi^2 =$ | 3.57, df = 3 (P = 0.3 | | | |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |

Favours SSRI Favours control

Analysis 8.1. Comparison 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias, Outcome I Dependent on modified Rankin score (mRS 3 to 5).

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

Comparison: 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias

Outcome: I Dependent on modified Rankin score (mRS 3 to 5)

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|---|---------------------------|---------|--------------------|---------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| I Fluoxetine | | | | |
| Chollet 2011 | 42/57 | 50/55 | + | 0.81 [0.68, 0.97] |
| Subtotal (95% CI) | 57 | 55 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Contr | ol) | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 2.34$ (P | = 0.019) | | | |
| 2 Sertraline | | | | |
| Almeida 2006 | 0/55 | 0/56 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 55 | 56 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.0$ (P \cdot | < 0.00001) | | | |
| Total (95% CI) | 112 | 111 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Contro | ol) | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 =$ | = 0.0, df = 0 (P = 1.00); | 2 =0.0% | | |
| Test for overall effect: $Z = 2.34$ (P | = 0.019) | | | |
| Test for subgroup differences: Not | t applicable | | | |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |

0.01 0.1 I Favours SSRI

Favours control

Analysis 8.2. Comparison 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias, Outcome 2 Disability.

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

Comparison: 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias

Outcome: 2 Disability

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Std. Mean Difference |
|----------------------------------|------------|-------------------------|--------------------|--------------|----------------------------|--------------------------------|----------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% Cl | - | IV,Random,95% C |
| l Fluoxetine | | | | | | | |
| Kong 2007 | 37 | 60.4 (12.5) | 36 | 52.3 (13.5) | | 27.1 % | 0.62 [0.15, 1.09] |
| Li 2008 | 58 | 40.8 (3.7) | 28 | 38.4 (5.8) | - | 27.3 % | 0.53 [0.07, 0.99] |
| Subtotal (95% CI) | 95 | | 64 | | • | 54.4 % | 0.57 [0.24, 0.90] |
| Heterogeneity: $Tau^2 = 0.0;$ | | 07, df = 1 (P = 0.80) | | | | <i>J</i> 1 <i>1 7 0</i> | |
| Test for overall effect: $Z = 3$ | | , | | | | | |
| 2 Sertraline | | , | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicab | le | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | |
| 3 Citalopram | | | | | | | |
| Acler 2009 | 10 | 82 (28) | 10 | 75 (25) | | 20.9 % | 0.25 [-0.63, 1.13] |
| Subtotal (95% CI) | 10 | | 10 | | - | 20.9 % | 0.25 [-0.63, 1.13] |
| Heterogeneity: not applicab | le | | | | | | |
| Test for overall effect: $Z = 0$ |).56 (P = | 0.57) | | | | | |
| 4 Paroxetine | | | | | | | |
| Ye 2004 | 30 | 78.75 (14.19) | 30 | 50.26 (13.4) | | 24.8 % | 2.04 [1.41, 2.67 |
| Subtotal (95% CI) | 30 | | 30 | | • | 24.8 % | 2.04 [1.41, 2.67] |
| Heterogeneity: not applicab | le | | | | | | |
| Test for overall effect: $Z = 6$ | 5.33 (P < | 0.00001) | | | | | |
| 5 Escitalopram | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicab | le | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | |
| 6 Sertraline or fluoxetine | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicab | le | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | |
| Total (95% CI) | 135 | | 104 | | • | 100.0 % | 0.87 [0.16, 1.58] |
| Heterogeneity: $Tau^2 = 0.43$; | | | $00041); 1^2 =$ | 83% | | | |
| Test for overall effect: $Z = 2$ | 2.39 (P = | 0.017) | | | | | |
| Test for subgroup difference | es: Chi² = | 18.08, $df = 2 (P = C)$ | $(0.00), ^2 = 89$ | 9% | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | Fav | ours control Favours SSRI | | |

Analysis 8.3. Comparison 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias, Outcome 3 Neurological deficit score.

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

Comparison: 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias

Outcome: 3 Neurological deficit score

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|---|---|------------------------|--------------------------|--------------|--|--------------|--|
| I Fluoxetine | | | | | | | |
| Chollet 2011 | 57 | 5.8 (3.7) | 55 | 6.9 (4.4) | | 14.1 % | -0.27 [-0.64, 0.10] |
| Fruehwald 2003 | 26 | -55.5 (4.8) | 24 | -52.8 (5.4) | | 12.0 % | -0.52 [-1.09, 0.04] |
| He 2004 | 36 | 10.41 (6.36) | 35 | 14.43 (7.94) | | 13.0 % | -0.55 [-1.03, -0.08] |
| Kong 2007 | 37 | 8.6 (6.4) | 36 | 11.2 (6.4) | | 13.1 % | -0.40 [-0.87, 0.06] |
| Subtotal (95% CI) | 156 | | 150 | | • | 52.2 % | -0.41 [-0.63, -0.18] |
| Heterogeneity: $Tau^2 = 0.0$; Test for overall effect: $Z = 3$ 2 Sertraline | | | 9); I ² =0.0% | | | | |
| Guo 2009 | 40 | 29.07 (8.02) | 40 | 33.78 (8.63) | | 13.3 % | -0.56 [-1.01, -0.11] |
| Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: Z = 2 | | 0.014) | 40 | | • | 13.3 % | -0.56 [-1.01, -0.11] |
| 3 Citalopram | | | | | | | |
| Acler 2009 | 10 | 2.3 (2) | 10 | 3.5 (1.3) | | 8.5 % | -0.68 [-1.59, 0.23] |
| Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: Z = 1 4 Paroxetine Ye 2004 | | 0.14) 8.3 (3.8) | 10 30 | 16 (4.8) | | 8.5 % | -0.68 [-1.59, 0.23] -1.76 [-2.36, -1.15] |
| Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: Z = 5 5 Fluoxetine or sertraline Jia 2005 | | 0.00001) 10.4 (8.5) | 30 88 | 22.6 (8.9) | - | 11.6 % | -1.76 [-2.36, -1.15] -1.40 [-1.73, -1.06] |
| Subtotal (95% CI) | 86 | | 88 | | • | 14.5 % | -1.40 [-1.73, -1.06] |
| Heterogeneity: not applicab Test for overall effect: $Z = 8$ Total (95% CI) Heterogeneity: Tau ² = 0.24; Test for overall effect: $Z = 3$ Test for subgroup difference | ale 3.23 (P < 322 ; Chi ² = 3 3.89 (P = | 95.74, df = 7 (P<0.0 | 318 | | • | 100.0 % | -0.76 [-1.15, -0.38] |
| | | | | | -2 -1 0 1 Favours SSRI Favours con | 2 trol | |

Analysis 8.4. Comparison 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias, Outcome 4 Depression (continuous data).

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

Comparison: 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias

Outcome: 4 Depression (continuous data)

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Std. Mean Difference |
|--|-------------------------|--------------------|--------------------------|--------------|----------------------------|--------|----------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| I Fluoxetine | | | | | | | |
| Chollet 2011 | 56 | 5.4 (4.9) | 54 | 8.4 (7.9) | - | 10.5 % | -0.46 [-0.83, -0.08] |
| Fruehwald 2003 | 26 | 9.5 (7.9) | 24 | .2 (2.4) | • | 10.2 % | -0.16 [-0.72, 0.39] |
| He 2004 | 36 | 4.28 (2.31) | 35 | 20.32 (2.82) | + | 10.1 % | -2.32 [-2.93, -1.71] |
| Kong 2007 | 37 | 12.6 (5.3) | 36 | 16.3 (3.7) | - | 10.4 % | -0.80 [-1.28, -0.32] |
| Li 2008 | 58 | 14.5 (2.4) | 28 | 18.7 (3.9) | - | 10.3 % | -1.40 [-1.90, -0.90] |
| Subtotal (95% CI) | 213 | | 177 | | • | 51.4 % | -1.01 [-1.69, -0.34] |
| Heterogeneity: $Tau^2 = 0.52$ | | | 00001); 12 = | 89% | | | |
| Test for overall effect: Z = | 2.95 (P = | 0.0031) | | | | | |
| 2 Sertraline Guo 2009 | 40 | 14.82 (8.05) | 40 | 17.61 (8) | _ | 10.4 % | -0.34 [-0.79, 0.10] |
| | | · · · · | | | | | 2 3 |
| Murray 2005 | 62 | 10.5 (9.6) | 61 | 12 (8.5) | | 10.6 % | -0.16 [-0.52, 0.19] |
| Subtotal (95% CI) | 102 | 20 IC - I (D - 0 C | 101 | | • | 21.0 % | -0.23 [-0.51, 0.04] |
| Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = | | | 3); 12 =0.0% | | | | |
| 3 Citalopram | | 0.070) | | | | | |
| Acler 2009 | 10 | 6.6 (3.6) | 10 | 8 (3) | + | 9.3 % | -0.40 [-1.29, 0.48] |
| Miao 2004 | 34 | 6.45 (5.3) | 34 | 23.74 (5.16) | + | 9.7 % | -3.27 [-4.01, -2.53] |
| Subtotal (95% CI) | 44 | | 44 | | - | 19.0 % | -1.85 [-4.65, 0.96] |
| Heterogeneity: $Tau^2 = 3.93$ | 3; Chi ² = 2 | 3.61, df = 1 (P<0. | 00001); I ² = | 96% | | | |
| Test for overall effect: $Z =$ | I.29 (P = | 0.20) | | | | | |
| 4 Paroxetine Ye 2004 | 30 | 4.02 (3.07) | 30 | 17.32 (1.66) | | 8.6 % | -5.32 [-6.43, -4.21] |
| | | 4.02 (3.07) | | 17.52 (1.66) | _ | | |
| Subtotal (95% CI) | 30 | | 30 | | • | 8.6 % | -5.32 [-6.43, -4.21] |
| Heterogeneity: not applical Test for overall effect: Z = | | 0.00001.) | | | | | |
| 5 Fluoxetine or sertraline | 7.1 <u>2</u> (i | 0.00001) | | | | | |
| | | | | | | | |
| | | | | | -10 -5 0 5 | 10 | |
| | | | | | Favours SSRI Favours co | ntrol | (Continued) |
| | | | | | | | (Conunued) |

| | | | | | | | | | | | | (Continued) |
|--------------------------------|---------------------------|--------------------|---------------------------|----------|------|----------------------------|------|-------|---------|--------|----------------------------|------------------------|
| Study or subgroup | SSRI | | Control | | | Std. Mean Difference | | | | Weight | Std. Mean Difference | |
| | Ν | Mean(SD) | Ν | Mean(SD) | | IV,Ran | ndoi | m,95% | 6 Cl | | | IV,Random,95% CI |
| Subtotal (95% CI) | 0 | | 0 | | | | | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applica | able | | | | | | | | | | | |
| Test for overall effect: not | applicable | | | | | | | | | | | |
| Total (95% CI) | 389 | | 352 | | | • | • | | | | 100.0 % | -1.39 [-2.10, -0.68] |
| Heterogeneity: $Tau^2 = 1.2$ | 0; Chi ² = 16 | 61.35, df = 9 (P<0 | .00001); 12 = | 94% | | | | | | | | |
| Test for overall effect: $Z =$ | 3.86 (P = 0 | 0.00012) | | | | | | | | | | |
| Test for subgroup difference | ces: Chi ² = 1 | 78.73, df = 3 (P = | 0.00), l ² =96 | 6% | | | | | | | | |
| | | | | | | | | | ı | | | |
| | | | | | -10 | -5 | 0 | | 5 | 10 | | |
| | | | | | Favo | urs SSRI | | Favo | ours co | ontrol | | |
| | | | | | | | | | | | | |
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Analysis 8.5. Comparison 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias, Outcome 5 Depression (dichotomous data).

| Comparison: 8 SSRI versus contr | ol at end of tr | eatment, outcome | assessor blind: low risk o | f bias | | |
|---|-----------------|------------------|----------------------------|----------------------|--------|----------------------------------|
| Outcome: 5 Depression (dichoto | omous data) | | | | | |
| Study or subgroup | SSRI | Control | | Ratio M- m,95% | Weight | Risk Ratio M- H,Random,95% |
| | n/N | n/N | | ĊI | | Cl |
| I Fluoxetine | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: not applicable | 2 | | | | | |
| 2 Sertraline | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | | |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: not applicable | 9 | | | | | |
| 3 Citalopram | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | | |
| | | | | <u> </u> | | |
| | | | 0.01 0.1 1 | 10 100 | | |
| | | | Favours SSRI | Favours control | | (Continued) |
| | | | | | | (Continued) |

| Study or subgroup | SSRI | Control Risk Ratic | | | Weight | (Continued) Risk Ratio M- | | |
|-------------------------------------|----------------|--------------------|--------------------|--------|---------|----------------------------------|--|--|
| | n/N | n/N | H,Random,95% Cl | | | H,Random,95% Cl | | |
| Heterogeneity: not applicable | | | | | | | | |
| Test for overall effect: not applie | able | | | | | | | |
| 4 Paroxetine | | | | | | | | |
| Subtotal (95% CI) | 0 | 0 | | | 0.0 % | 0.0 [0.0, 0.0] | | |
| Total events: 0 (SSRI), 0 (Contro | ol) | | | | | | | |
| Heterogeneity: not applicable | | | | | | | | |
| Test for overall effect: not applie | able | | | | | | | |
| 5 Escitalopram | | | | | | | | |
| Robinson 2008 | 5/59 | 13/58 | | | 100.0 % | 0.38 [0.14, 0.99] | | |
| Subtotal (95% CI) | 59 | 58 | • | | 100.0 % | 0.38 [0.14, 0.99] | | |
| Total events: 5 (SSRI), 13 (Cont | rol) | | | | | | | |
| Heterogeneity: not applicable | | | | | | | | |
| Test for overall effect: Z = 1.97 | (P = 0.048) | | | | | | | |
| Total (95% CI) | 59 | 58 | - | | 100.0 % | 0.38 [0.14, 0.99] | | |
| Total events: 5 (SSRI), 13 (Cont | rol) | | | | | | | |
| Heterogeneity: not applicable | | | | | | | | |
| Test for overall effect: $Z = 1.97$ | (P = 0.048) | | | | | | | |
| Test for subgroup differences: N | lot applicable | | | | | | | |
| | | | | | | | | |
| | | | 0.01 0.1 1 | 10 100 | | | | |
| | | | E | E | | | | |

Favours SSRI Favours control

Analysis 8.6. Comparison 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias, Outcome 6 Anxiety (continuous data).

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

Comparison: 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias

Outcome: 6 Anxiety (continuous data)

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|--------------------------------|-------------|-------------|--------------|--------------|--|---------|--|
| I Fluoxetine | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | 1 | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applical | ble | | | | | | |
| Test for overall effect: not a | applicable | | | | | | |
| 2 Sertraline | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applical | ble | | | | | | |
| Test for overall effect: not a | applicable | | | | | | |
| 3 Citalopram | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applical | ble | | | | | | |
| Test for overall effect: not a | applicable | | | | | | |
| 4 Paroxetine | | | | | | | |
| Ye 2004 | 30 | 9.82 (2.64) | 30 | 14.02 (2.32) | + | 100.0 % | -1.67 [-2.26, -1.08] |
| Subtotal (95% CI) | 30 | | 30 | | • | 100.0 % | -1.67 [-2.26, -1.08] |
| Heterogeneity: not applical | ble | | | | | | |
| Test for overall effect: Z = | 5.52 (P < 0 |).00001) | | | | | |
| 5 escitalopram | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applical | ble | | | | | | |
| Test for overall effect: not a | applicable | | | | | | |
| Total (95% CI) | 30 | | 30 | | • | 100.0 % | -1.67 [-2.26, -1.08] |
| Heterogeneity: not applical | ble | | | | | | |
| Test for overall effect: $Z =$ | 5.52 (P < 0 |).00001) | | | | | |
| Test for subgroup difference | es: Not app | olicable | | | | | |
| | | | | | | | |
| | | | | | -10 -5 0 5 | 10 | |
| | | | | | Favours SSRI Favours cor | ntrol | |
| | | | | | | | |
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Analysis 8.8. Comparison 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias, Outcome 8 Cognition (continuous scores end of treatment).

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

Comparison: 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias

Outcome: 8 Cognition (continuous scores end of treatment)

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% Cl |
|--|--------------------|---------------------|------------------------------|---------------|--|---------------|--|
| I Fluoxetine Subtotal (95% CI) Heterogeneity: not applicabl | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Test for overall effect: not ap 2 Sertraline | | | | | | | |
| Guo 2009 | 40 | 19.26 (6.87) | 40 | 15.74 (6.82) | | 49.1 % | 0.51 [0.06, 0.95 |
| Subtotal (95% CI) | 40 | | 40 | | • | 49.1 % | 0.51 [0.06, 0.95 |
| Heterogeneity: not applicabl Test for overall effect: $Z = 2$ | | 0.025) | | | | | |
| 3 Citalopram Subtotal (95% CI) Heterogeneity: not applicabl | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0 |
| Test for overall effect: not applicable 4 Escitalopram | | | | | | | |
| Robinson 2008 | 43 | 89.8 (15.1) | 45 | 91 (17.8) | | 50.9 % | -0.07 [-0.49, 0.35 |
| Subtotal (95% CI) Heterogeneity: not applicabl | 43 | | 45 | | - | 50.9 % | -0.07 [-0.49, 0.35] |
| Test for overall effect: Z = 0 Total (95% CI) | .34 (P = 83 | 0.74) | 85 | | - | 100.0 % | 0.21 [-0.36, 0.78] |
| Heterogeneity: $Tau^2 = 0.12;$ | $Chi^2 = 3$ | 8.47, df = 1 (P = 0 | 0.06); I ² =7 I % | | | | |
| Test for overall effect: $Z = 0$ | | | | | | | |
| Test for subgroup difference | s: Chi² = | 3.47, df = 1 (P = | $0.06), ^2 = 7 $ | % | | | |
| | | | | | -2 -1 0 1 | 2 | |
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| | | | | | | | |
| elective serotonin reupt | ake inhi | ibitors (SSRIs) | for stroke r | acovery (Revi | ew) | | 2 |

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Analysis 8.9. Comparison 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias, Outcome 9 Death.

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

Comparison: 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias

Outcome: 9 Death

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|---|------------------------------------|--------------------------------------|---|----------------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,959 Cl |
| I Fluoxetine | | | | |
| Brown 1998 | 0/10 | 0/10 | | 0.0 [0.0, 0.0] |
| Chollet 2011 | 1/59 | 1/59 | | 1.00 [0.06, 15.61] |
| Fruehwald 2003 | 1/28 | 0/16 | | 1.76 [0.08, 40.80] |
| He 2004 | 0/36 | 0/35 | | 0.0 [0.0, 0.0] |
| Li 2008 | 0/60 | 0/30 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 193 | 150 | | 1.28 [0.16, 10.11] |
| Total events: 2 (SSRI), I (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 1 Test for overall effect: $Z = 0.23$ (P = 2 Sertraline | | l); l ² =0.0% | | |
| Guo 2009 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Murray 2005 | 0/62 | 2/61 | | 0.20 [0.01, 4.02] |
| Subtotal (95% CI) Total events: 0 (SSRI), 2 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 1 Test for overall effect: Z = 1.06 (P = 3 Citalopram Acler 2009 | | 101 ; I ² =0.0% | | 0.20 [0.01, 4.02] |
| Miao 2004 | 0/45 | 0/45 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 1 Test for overall effect: $Z = 0.0$ (P < 4 Paroxetine | 55 0.0, df = 0 (P<0.0000 | 55 | | 0.0 [0.0, 0.0] |
| Ye 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: Z = 0.0 (P < | 30 | 30 | | 0.0 [0.0, 0.0] |
| | | | | |
| | | | 0.01 0.1 1 10 100 Favours SSRI Favours control | (Continued) |

| Study or subgroup | SSRI n/N | Control n/N | Risk Ratio M- H,Random,95% Cl | (Continued) Risk Ratio H,Random,95% Cl |
|---|-------------------------|----------------------------|--|--|
| 5 Escitalopram | 11/14 | 11/1 N | G | <u> </u> |
| Robinson 2008 | 2/59 | 0/58 | | 4.92 [0.24, 100.25] |
| Subtotal (95% CI) | 59 | 58 | | 4.92 [0.24, 100.25] |
| Total events: 2 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 1.04 (P = | = 0.30) | | | |
| 6 Sertraline or fluoxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | 2 | | | |
| Total (95% CI) | 439 | 394 | | 1.13 [0.25, 4.97] |
| Total events: 4 (SSRI), 3 (Control) | | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = $\frac{1}{2}$ | 2.29, df = 3 (P = 0.51) |); I ² =0.0% | | |
| Test for overall effect: $Z = 0.16$ (P = | = 0.88) | | | |
| Test for subgroup differences: Chi^2 | = 2.22, df = 2 (P = 0. | 33), I ² = I 0% | | |
| | | | | |
| | | | 0.01 0.1 1 10 100 |) |
| | | | Favours SSRI Favours contro | bl |

Analysis 8.10. Comparison 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias, Outcome 10 Seizures.

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

Comparison: 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias

Outcome: 10 Seizures

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratic M- |
|--|--------------------|--------------------|------------------------------|----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random, C |
| Fluoxetine | | | | |
| Chollet 2011 | 1/59 | 0/59 | | 3.00 [0.12, 72.18] |
| He 2004 | 0/36 | 0/35 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 95 | 94 | | 3.00 [0.12, 72.18] |
| Total events: 1 (SSRI), 0 (Control) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, | df = 0 (P = 1.00); | ² =0.0% | | |
| Test for overall effect: $Z = 0.68$ (P = 0.5 | 50) | | | |
| 2 Sertraline | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 3 Citalopram | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| lest for overall effect: not applicable | | | | |
| 1 Paroxetine | | | | |
| Ye 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0 |
| Subtotal (95% CI) | 30 | 30 | | 0.0 [0.0, 0.0 |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.0$ (P < 0.00 | 0001) | | | |
| 5 Escitalopram | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0 |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 6 Sertraline or fluoxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0 |
| otal events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| | | | 0.01 0.1 1 10 100 | |
| | | | Favours SSRI Favours control | |
| | | | | (Continued |

| Study or subgroup | SSRI | Control | | ik Ratio M- om,95% | (Continued) Risk Ratio M- H,Random,95% |
|---|---------------------------|----------|--------------|--------------------------|--|
| | n/N | n/N | , | ĊI | Ċ |
| Total (95% CI) | 125 | 124 | | | 3.00 [0.12, 72.18] |
| Total events: I (SSRI), 0 (Contro | I) | | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² | = 0.0, df = 0 (P = 1.00); | 12 =0.0% | | | |
| Test for overall effect: $Z = 0.68$ (| P = 0.50) | | | | |
| Test for subgroup differences: No | ot applicable | | | | |
| | | | | | |
| | | | 0.01 0.1 1 | 10 100 | |
| | | | Favours SSRI | Favours control | |

Analysis 8.11. Comparison 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias, Outcome 11 Gastrointestinal side effects.

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

Comparison: 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias

Outcome: II Gastrointestinal side effects

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|--------------------------|-----------------------|------------------------------|---------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| I Fluoxetine | | | | |
| Chollet 2011 | 14/59 | 6/59 | - | 2.33 [0.96, 5.66] |
| He 2004 | 0/36 | 0/35 | | 0.0 [0.0, 0.0] |
| Li 2008 | 6/60 | 3/30 | - | 1.00 [0.27, 3.72] |
| Subtotal (95% CI) | 155 | 124 | ~ | 1.77 [0.81, 3.85] |
| Total events: 20 (SSRI), 9 (Contro |) | | | |
| Heterogeneity: Tau ² = 0.03; Chi ² | = 1.10, df = 1 (P = 0.29 |); l ² =9% | | |
| Test for overall effect: $Z = 1.43$ (F | P = 0.15) | | | |
| 2 Sertraline | | | | |
| Burns 1999 | 0/14 | / 4 | | 0.33 [0.01, 7.55] |
| Subtotal (95% CI) | 14 | 14 | | 0.33 [0.01, 7.55] |
| Total events: 0 (SSRI), 1 (Control) |) | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.69$ (F | P = 0.49) | | | |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |
| | | | Favours SSRI Favours control | |
| | | | | (Continued) |

| Study or subgroup | SSRI | Control | Risk Ratio M- H.Random,95% | (Continued) Risk Ratio M- H,Random,95% |
|---|----------------------|---------------------------|----------------------------------|--|
| | n/N | n/N | CI | CI |
| 3 Citalopram | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 4 Paroxetine | | | | |
| Ye 2004 | 2/30 | 0/30 | | 5.00 [0.25, 99.95] |
| Subtotal (95% CI) | 30 | 30 | | 5.00 [0.25, 99.95] |
| Total events: 2 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 1.05$ (P = 0.1) | 29) | | | |
| 5 Escitalopram | , | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 6 Sertraline and paroxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| Total (95% CI) | 199 | 168 | - | 1.74 [0.87, 3.49] |
| Total events: 22 (SSRI), 10 (Control) | | | | |
| Heterogeneity: Tau ² = 0.0; Chi^2 = 2.66 | , df = 3 (P = 0.45) | ; l ² =0.0% | | |
| Test for overall effect: $Z = 1.56$ (P = 0. | 12) | | | |
| Test for subgroup differences: $Chi^2 = I$ | .55, df = 2 (P = 0.4 | 46), I ² =0.0% | | |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |

Favours SSRI Favours control

Analysis 8.15. Comparison 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias, Outcome 15 Leaving the trial before the end of scheduled follow-up.

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

Comparison: 8 SSRI versus control at end of treatment, outcome assessor blind: low risk of bias

Outcome: 15 Leaving the trial before the end of scheduled follow-up

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|---------------------------|------------------------------------|------------------------------|----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,9 Cl |
| l Fluoxetine | | | | |
| Brown 1998 | 1/10 | 0/10 | | 3.00 [0.14, 65.90] |
| Chollet 2011 | 2/59 | 3/59 | | 0.67 [0.12, 3.85] |
| Fruehwald 2003 | 6/28 | 8/26 | | 0.70 [0.28, 1.74] |
| He 2004 | 8/44 | 5/40 | | 1.45 [0.52, 4.08] |
| Kong 2007 | /48 | 6/42 | | 1.60 [0.65, 3.96] |
| Li 2008 | 2/60 | 2/30 | | 0.50 [0.07, 3.38] |
| Subtotal (95% CI) | 249 | 207 | + | 1.07 [0.65, 1.76] |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 =$ Test for overall effect: $Z = 0.28$ (P 2 Sertraline | P = 0.78) | | | |
| Guo 2009 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Murray 2005 | 24/62 | 30/61 | - | 0.79 [0.53, 1.18] |
| Subtotal (95% CI) Total events: 24 (SSRI), 30 (Contr Heterogeneity: Tau ² = 0.0; Chi ² = Test for overall effect: Z = 1.16 (P 3 Citalopram | = 0.0, df = 0 (P = 1.00); | 101 1 ² =0.0% | | 0.79 [0.53, 1.18] |
| Acler 2009 | 0/10 | 0/10 | | 0.0 [0.0, 0.0] |
| Miao 2004 | I I/45 | 11/45 | - | 1.00 [0.48, 2.07] |
| Subtotal (95% CI) Total events: 11 (SSRI), 11 (Contri- Heterogeneity: Tau ² = 0.0; Chi ² = Test for overall effect: Z = 0.0 (P = | = 0.0, df = 0 (P = 1.00); | 55 I ² =0.0% | + | 1.00 [0.48, 2.07] |
| 4 Paroxetine Ye 2004 | 1/30 | 0/31 | | 3.10 [0.13, 73.16] |
| Subtotal (95% CI) | 30 | 31 | | 3.10 [0.13, 73.16] |
| Total events: 1 (SSRI), 0 (Control) Heterogeneity: not applicable | - | - | | |
| | | | 0.01 0.1 1 10 100 | |
| | | | Favours SSRI Favours control | |
| | | | | (Continued |

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review) Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

| Study or subgroup | SSRI | Control | Risk Ratio M | (Continued) Risk Ratio M- |
|---|------------------------|---------------------------|--------------------|----------------------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| Test for overall effect: $Z = 0.70$ (P = | 0.48) | | | |
| 5 Sertraline or fluoxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 6 Escitalopram | | | | |
| Robinson 2008 | 7/59 | 5/58 | | 1.38 [0.46, 4.09] |
| Subtotal (95% CI) | 59 | 58 | - | 1.38 [0.46, 4.09] |
| Total events: 7 (SSRI), 5 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.57$ (P = | 0.57) | | | |
| Total (95% CI) | 495 | 452 | + | 0.94 [0.71, 1.24] |
| Total events: 73 (SSRI), 70 (Control) | | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = 5 | .44, df = 9 (P = 0.79) | ; 2 =0.0% | | |
| Test for overall effect: $Z = 0.43$ (P = | 0.67) | | | |
| Test for subgroup differences: Chi ² = | = 2.06, df = 4 (P = 0. | 72), I ² =0.0% | | |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |

Favours SSRI Favours control

Analysis 9.1. Comparison 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias, Outcome I Dependent on modified Rankin score (mRS 3 to 5).

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

Comparison: 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias

Outcome: I Dependent on modified Rankin score (mRS 3 to 5)

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|---------------------------|---------|--------------------|---------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,959 Cl |
| I Fluoxetine | | | | |
| Chollet 2011 | 42/57 | 50/55 | + | 0.81 [0.68, 0.97] |
| Subtotal (95% CI) | 57 | 55 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Contro | ol) | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 2.34$ (P | = 0.019) | | | |
| 2 Sertraline | | | | |
| Almeida 2006 | 0/55 | 0/56 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 55 | 56 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.0$ (P < | < 0.00001) | | | |
| Total (95% CI) | 112 | 111 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Contro | ol) | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 =$ | 0.0, df = 0 (P = 1.00); l | 2 =0.0% | | |
| Test for overall effect: $Z = 2.34$ (P | = 0.019) | | | |
| Test for subgroup differences: Not | applicable | | | |
| | | | | |
| | | | 0.01 0.1 10 10 | 0 |

Favours SSRI Favours control

Analysis 9.2. Comparison 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias, Outcome 2 Disability.

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

Comparison: 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias

Outcome: 2 Disability

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% Cl |
|--|-------------------------------------|-------------------------|--|------------------------|--|--------|--|
| I Fluoxetine | | | | | | | |
| Cheng 2003 | 25 | 26.38 (14.2) | 32 | 29.15 (17.38) | - | 10.3 % | -0.17 [-0.69, 0.35] |
| Kong 2007 | 37 | 60.4 (12.5) | 36 | 52.3 (13.5) | - | 10.5 % | 0.62 [0.15, 1.09] |
| Liu 2004 | 30 | 70.33 (10.74) | 30 | 64.33 (7.74) | - | 10.3 % | 0.63 [0.11, 1.15] |
| Robinson 2000a | 14 | 59.2 (11.6) | 13 | 56.2 (7.8) | * | 9.3 % | 0.29 [-0.47, 1.05] |
| Robinson 2000b | 13 | 60.5 (10.8) | 15 | 63.1 (8.2) | + | 9.4 % | -0.27 [-1.01, 0.48] |
| Wiart 2000 | 16 | 87.4 (22.8) | 15 | 88.7 (25.3) | + | 9.6 % | -0.05 [-0.76, 0.65] |
| Subtotal (95% CI) | 135 | | 141 | | • | 59.3 % | 0.22 [-0.12, 0.55] |
| Heterogeneity: Tau ² = 0.08; Test for overall effect: $Z = 1$ 2 Sertraline | | | 19); I ² =47% | | | | |
| Xie 2005 | 65 | 88.7 (7.9) | 65 | 79.8 (4.5) | - | 10.7 % | 1.38 [0.99, 1.76] |
| Subtotal (95% CI) | 65 | | 65 | | • | 10.7 % | 1.38 [0.99, 1.76] |
| Heterogeneity: not applicab Test for overall effect: Z = 7 3 Citalopram Liu 2006 | | 0.00001) 64.4 (12.1) | 30 | 35.4 (9.1) | | 9.6 % | 2.67 [1.97, 3.38] |
| | | 01.1 (12.1) | | зэ. т (7.т) | | | |
| Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: Z = 7 4 Paroxetine | | 0.00001) | 30 | | | 9.6 % | 2.67 [1.97, 3.38] |
| Chen T 2005 | 40 | 65.76 (5.92) | 38 | 51.76 (7.32) | + | 10.2 % | 2.09 [1.53, 2.64] |
| He 2005 | 27 | 84.26 (8.41) | 27 | 78.33 (15.01) | - | 10.2 % | 0.48 [-0.06, 1.02] |
| Subtotal (95% CI) Heterogeneity: Tau ² = 1.21; | 67 ; Chi ² = 1 | 6.45, df = (P = 0 | 65 .00005); I ² = | =94% | • | 20.4 % | 1.28 [-0.29, 2.86] |
| Test for overall effect: $Z = I$ 5 Escitalopram | | 0.11) | | | | | |
| Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: not applicable ap | | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| | | | | | -10 -5 0 5 10 Favours control Favours SSRI | | (Continued) |

| Study or subgroup | SSRI | | Control | | D | Std. Mean ifference | Weight | (Continued) Std. Mean Difference |
|--|--------------------------|----------------------|----------------------------|----------|---------------|---------------------------|---------|--|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Ranc | lom,95% Cl | | IV,Random,95% CI |
| 6 Sertraline or fluoxetine Subtotal (95% CI) | 0 | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | ole | | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | | |
| Total (95% CI) | 297 | | 301 | | | • | 100.0 % | 0.77 [0.22, 1.33] |
| Heterogeneity: $Tau^2 = 0.70$ |); Chi ² = 86 | .62, df = 9 (P<0.0 | 0001); 2 =909 | 6 | | | | |
| Test for overall effect: $Z = 2$ | 2.75 (P = 0 | .0060) | | | | | | |
| Test for subgroup difference | es: Chi ² = 4 | 15.82, df = 3 (P = 0 | 0.00), I ² =93% | | | | | |
| | | | | | | | | |
| | | | | - | 10 -5 | 0 5 IC |) | |
| | | | | Fa | vours control | Favours SSRI | | |

Analysis 9.3. Comparison 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias, Outcome 3 Neurological deficit score.

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

Comparison: 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias

Outcome: 3 Neurological deficit score

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV.Random.95% Cl | Weight | Std. Mean Difference IV.Random,95% Cl |
|-------------------|-----------|--------------|--------------|--------------|--|--------|--|
| L Eluciontin e | | Ticari(SD) | 11 | 1 (Call(3D) | | | rv,rvandorn,7576 Cr |
| l Fluoxetine | | | | | | | |
| Chollet 2011 | 57 | 5.8 (3.7) | 55 | 6.9 (4.4) | | 8.2 % | -0.27 [-0.64, 0.10] |
| He 2004 | 36 | 10.41 (6.36) | 35 | 14.43 (7.94) | _ _ | 7.9 % | -0.55 [-1.03, -0.08] |
| Huang 2002 | 40 | 4.02 (1.86) | 40 | 8.57 (3.64) | | 7.8 % | -1.56 [-2.06, -1.06] |
| Li 2004a | 33 | 6.23 (3.11) | 34 | 12.86 (6.36) | — — | 7.7 % | -1.30 [-1.83, -0.77] |
| Liang 2003 | 42 | 11.74 (3.23) | 21 | 17.32 (5.19) | _ | 7.5 % | -1.38 [-1.96, -0.80] |
| Liu 2004 | 30 | 9.2 (2.06) | 30 | 10.47 (9.2) | | 7.8 % | -0.19 [-0.70, 0.32] |
| Wen 2006 | 42 | 10.1 (1.9) | 42 | 16.4 (2.5) | • | 7.4 % | -2.81 [-3.42, -2.20] |
| | | | | | | | |
| | | | | | -2 -1 0 1 2 | | |

Favours SSRI Favours control

(Continued . . .)

(... Continued) Std. Std. Mean Mean Difference Difference SSRI Study or subgroup Control Weight Ν Mean(SD) Ν Mean(SD) IV,Random,95% CI IV,Random,95% CI Subtotal (95% CI) 280 257 54.2 % -1.14 [-1.78, -0.49] Heterogeneity: Tau² = 0.68; Chi² = 69.39, df = 6 (P<0.00001); $|^2 = 91\%$ Test for overall effect: Z = 3.46 (P = 0.00053) 2 Sertraline Burns 1999 -29.7 (14.7) 0.17 [-0.57, 0.91] 14 14 -32.2 (13.4) 6.9 % Guo 2009 40 29.07 (8.02) 40 33.78 (8.63) 8.0 % -0.56 [-1.01, -0.11] Subtotal (95% CI) 54 54 14.9 % -0.26 [-0.96, 0.45] Heterogeneity: Tau² = 0.17; Chi² = 2.74, df = 1 (P = 0.10); l² = 64% Test for overall effect: Z = 0.71 (P = 0.48) 3 Citalopram Liu 2006 13.3 (3.8) 7.3 % -2.27 [-2.93, -1.61] 30 30 22.4 (4.1) Subtotal (95% CI) 30 30 -2.27 [-2.93, -1.61] 7.3 % Heterogeneity: not applicable Test for overall effect: Z = 6.77 (P < 0.00001) 4 Paroxetine He 2005 -0.62 [-1.17, -0.07] 27 6.48 (1.58) 27 8.33 (3.86) 7.6 % Li 2002 46 46 -2.15 [-2.67, -1.64] 11.5 (2.8) 19 (4) 77% Li 2005 74 12.9 (5.1) 74 18.7 (5.4) 8.2 % -1.10 [-1.44, -0.75] -1.29 [-2.09, -0.49] Subtotal (95% CI) 147 147 23.6 % Heterogeneity: Tau² = 0.44; Chi² = 17.57, df = 2 (P = 0.00015); l² = 89% Test for overall effect: Z = 3.17 (P = 0.0015) 5 Fluoxetine or sertraline Subtotal (95% CI) 0 0 0.0 % 0.0 [0.0, 0.0] Heterogeneity: not applicable Test for overall effect: not applicable 488 100.0 % -1.12 [-1.55, -0.68] Total (95% CI) 511 Heterogeneity: Tau² = 0.57; Chi² = 118.36, df = 12 (P<0.00001); l² =90% Test for overall effect: Z = 5.01 (P < 0.00001) Test for subgroup differences: $Chi^2 = 16.97$, df = 3 (P = 0.00), $l^2 = 82\%$ -2 - | 2 Т Favours SSRI Favours control

Analysis 9.4. Comparison 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias, Outcome 4 Depression (continuous data).

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

Comparison: 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias

Outcome: 4 Depression (continuous data)

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Std. Mean Difference |
|--|-------------------|---------------------------|--|--------------|-----------------------------|----------|----------------------------|
| study of subgroup | N | Mean(SD) | N | Mean(SD) | IV,Random,95% Cl | , veigne | IV,Random,95% CI |
| I Fluoxetine | | | | | | | |
| Chollet 2011 | 56 | 5.4 (4.9) | 54 | 8.4 (7.9) | | 5.1 % | -0.46 [-0.83, -0.08] |
| Huang 2002 | 40 | 4.76 (0.6) | 40 | 16.34 (1.3) | • | 3.5 % | - .33[- 3. 8, -9.47] |
| Ji 2000 | 20 | 5.2 (1.5) | 20 | 14.5 (2.7) | ← | 4.4 % | -4.17 [-5.32, -3.03] |
| Li 2002 | 46 | 10 (3) | 46 | 22 (8) | | 5.0 % | -1.97 [-2.47, -1.47] |
| Liang 2003 | 42 | 9.67 (4.48) | 21 | 19.19 (3.12) | | 4.9 % | -2.30 [-2.97, -1.63] |
| Robinson 2000a | 14 | 18.5 (7.6) | 13 | 12.2 (4.7) | | 4.7 % | 0.96 [0.15, 1.76] |
| Robinson 2000b | 13 | 5.9 (3.8) | 15 | 6.2 (4.6) | | 4.8 % | -0.07 [-0.81, 0.67] |
| Song 2006 | 41 | 40.3 (7.25) | 41 | 48.31 (8.02) | | 5.0 % | -1.04 [-1.50, -0.58] |
| Wen 2006 | 42 | 7 (1.1) | 42 | 17.7 (1.8) | • | 4.3 % | -7.11 [-8.29, -5.93] |
| Wiart 2000 | 16 | 11.8 (6.7) | 15 | 18.7 (10) | | 4.8 % | -0.79 [-1.53, -0.06] |
| Subtotal (95% CI) | 330 | | 307 | | - | 46.4 % | -2.65 [-3.88, -1.41] |
| Test for overall effect: Z = - 2 Sertraline Guo 2009 | 4.20 (P =) 40 | 0.000027) 4.82 (8.05) | 40 | 17.61 (8) | - | 5.0 % | -0.34 [-0.79, 0.10] |
| | | · · · · | | | | | |
| Murray 2005 | 62 | 10.5 (9.6) | 61 | 12 (8.5) | _] | 5.1 % | -0.16 [-0.52, 0.19] |
| Xie 2005 | 65 | 30.9 (7.1) | 65 | 39.7 (5.3) | | 5.0 % | -1.40 [-1.78, -1.01] |
| Subtotal (95% CI) Heterogeneity: $Tau^2 = 0.43$ Test for overall effect: Z = | | | 166 0.00001); I ² = | 91% | • | 15.1 % | -0.64 [-1.41, 0.14] |
| 3 Citalopram Andersen 1994 | 33 | .4 (5.) | 33 | 14.1 (4.7) | -+- | 5.0 % | -0.54 [-1.04, -0.05] |
| Liu 2006 | 30 | 17.2 (2.1) | 30 | 25.1 (3.3) | | 4.8 % | -2.82 [-3.55, -2.09] |
| Subtotal (95% CI) Heterogeneity: Tau ² = 2.49 | | | 63 0.00001); I ² = | =96% | | 9.8 % | -1.67 [-3.89, 0.56] |
| Test for overall effect: $Z =$ | I.46 (P = | 0.14) | | | | | |
| | | | | | -4 -2 0 2 4 | | |
| | | | | | Favours SSRI Favours contro | ıl | (Continued |
| | | | | | | | |

Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery (Review) Copyright 0 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% | Weight | (Continued) Std. Mean Difference IV,Random,95% Cl |
|---|--|--------------|--|--------------|---|---------|--|
| 4 Paroxetine Chen T 2005 | 40 | 10.98 (3.74) | 38 | 22.45 (3.56) | <u> </u> | 4.9 % | -3. [-3.78, -2.44] |
| He 2005 | 27 | 10.11 (1.08) | 27 | 17.48 (1.05) | • | 4.0 % | -6.82 [-8.26, -5.38] |
| Lai 2006 | 40 | 12.5 (8.4) | 40 | 21.5 (4.3) | | 5.0 % | -1.34 [-1.82, -0.85] |
| Li 2002 | 46 | 10 (3) | 46 | 22 (8) | | 5.0 % | -1.97 [-2.47, -1.47] |
| Li 2005 | 74 | 12.6 (2.1) | 74 | 16.8 (2.3) | - | 5.0 % | -1.90 [-2.29, -1.51] |
| Yang 2011 | 20 | 7 (4) | 22 | 13 (6) | | 4.9 % | -1.14 [-1.80, -0.49] |
| Subtotal (95% CI) Heterogeneity: Tau ² = 1.00 Test for overall effect: Z = 5 Fluoxetine or sertraline | | | 247 00001); I ² = | 93% | • | 28.7 % | -2.50 [-3.37, -1.63] |
| Subtotal (95% CI) Heterogeneity: not applica | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Test for overall effect: not a Total (95% CI) Heterogeneity: Tau ² = 1.8: Test for overall effect: Z = Test for subgroup difference | 807 7; Chi ² = 4 6.96 (P < 0 | 0.00001) | | | -4 -2 0 2 Favours SSRI Favo | 100.0 % | -2.16 [-2.77, -1.55] |
| | | | | | | | |
| | | | | | | | |
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Analysis 9.5. Comparison 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias, Outcome 5 Depression (dichotomous data).

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

Comparison: 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias

Outcome: 5 Depression (dichotomous data)

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|---|-----------------------|----------------------|------------------------------|---------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95 Cl |
| l Fluoxetine | | | | |
| Li 2004a | 2/33 | 8/34 | | 0.26 [0.06, 1.12] |
| Liu 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Zhou 2008 | 4/36 | 18/40 | | 0.25 [0.09, 0.66] |
| Subtotal (95% CI) | 99 | 104 | • | 0.25 [0.11, 0.57] |
| Total events: 6 (SSRI), 26 (Control) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$ |), df = 1 (P = 0.96); | l ² =0.0% | | |
| Test for overall effect: $Z = 3.32$ (P = 0.1) | 00091) | | | |
| 2 Sertraline | | | | |
| Almeida 2006 | 8/48 | 11/51 | - | 0.77 [0.34, 1.76] |
| Rasmussen 2003 | 3/35 | 8/32 | | 0.34 [0.10, 1.18] |
| Subtotal (95% CI) | 83 | 83 | • | 0.59 [0.28, 1.25] |
| Total events: 11 (SSRI), 19 (Control) | | | | |
| Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 1.1$ | 6, df = 1 (P = 0.28 |); $ ^2 = 4\%$ | | |
| Test for overall effect: $Z = 1.37$ (P = 0. | 17) | | | |
| 3 Citalopram | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 4 Paroxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 5 Escitalopram | | | _ | |
| Robinson 2008 | 5/59 | 13/58 | | 0.38 [0.14, 0.99] |
| Subtotal (95% CI) | 59 | 58 | - | 0.38 [0.14, 0.99] |
| Total events: 5 (SSRI), 13 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 1.97$ (P = 0. | | | | |
| Total (95% CI) | 241 | 245 | ▲ | 0.41 [0.26, 0.65] |
| | | | 0.01 0.1 10 100 | |
| | | | Favours SSRI Favours control | (Continued |
| | | | | (Continued |

| Study or subgroup | SSRI Control | | F | Risk Ratio M- 1.Random,95% | (Continued) Risk Ratio M- H.Random,95% |
|---|---------------------------------|---------------------------|-------------|----------------------------------|--|
| | n/N | n/N | | ĊI | Ċl |
| Total events: 22 (SSRI), 58 (Cont | trol) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; Chi ² | = 3.84, df = 4 (P = 0.43); | $ ^2 = 0.0\%$ | | | |
| Test for overall effect: $Z = 3.79$ (| P = 0.00015) | | | | |
| Test for subgroup differences: Ch | $m^2 = 2.29$, df = 2 (P = 0.3) | 2), I ² = I 3% | | | |
| | | | | | |
| | | | 0.01 0.1 | 10 100 | |
| | | | Favours SSF | RI Favours control | |
| | | | | | |
| | | | | | |

Analysis 9.6. Comparison 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias, Outcome 6 Anxiety (continuous data).

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

Comparison: 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias

Outcome: 6 Anxiety (continuous data)

| Study or subgroup | SSRI | | | Std. Mean Difference | | Weight | Std. Mean Difference | |
|--|-------------------------|---------------------|--------------------------|----------------------------|--------------|----------------|----------------------------|------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Rano | dom,95% Cl | | IV,Random,95% CI |
| I Fluoxetine | | | | | | | | |
| Liu 2004 | 30 | 7.43 (3.63) | 30 | (5.63) | | • | 20.8 % | -0.74 [-1.27, -0.22] |
| Robinson 2000a | 14 | 9.8 (4.8) | 13 | 9.9 (5.1) | | + | 19.7 % | -0.02 [-0.77, 0.74] |
| Robinson 2000b | 13 | 4.7 (3.8) | 15 | 5.5 (2.9) | | • | 19.8 % | -0.23 [-0.98, 0.51] |
| Subtotal (95% CI) | 57 | | 58 | | | • | 60.3 % | -0.40 [-0.85, 0.05] |
| Heterogeneity: $Tau^2 = 0.05$; | ; Chi ² = 2. | 78, df = 2 (P = 0.2 | 25); I ² =28% | | | | | |
| Test for overall effect: $Z = I$ | .76 (P = 0 | 0.078) | | | | | | |
| 2 Sertraline | | | | | | | | |
| Subtotal (95% CI) Heterogeneity: not applicab | 0 le | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Test for overall effect: not a | pplicable | | | | | | | |
| 3 Citalopram | | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicab | le | | | | | | | |
| | | | | | | | | |
| | | | | - | 10 -5 | 0 5 10 | | |
| | | | | | Favours SSRI | Favours contro | bl | |

(Continued ...)

| | | | | | | Std. | | (Continued) Std. |
|--|--------------------------|---------------------|---------------------------|--------------|-------|--------------------|----------------|------------------------|
| Study or subgroup | SSRI | Control | | | | Mean Difference | Weight | Mean Difference |
| , , , | Ν | Mean(SD) | Ν | Mean(SD) | IV,R | andom,95% Cl | 0 | IV,Random,95% CI |
| Test for overall effect: not a | pplicable | | | | | | | |
| 4 Paroxetine | | | | | | | | |
| He 2005 | 27 | 5.37 (1.66) | 27 | 12.78 (1.93) | + | | 18.6 % | -4.06 [-5.01, -3.10] |
| Lai 2006 | 40 | 50.2 (9.4) | 40 | 54.2 (15.2) | | - | 21.1 % | -0.31 [-0.75, 0.13] |
| Subtotal (95% CI) | 67 | | 67 | | | | 39. 7 % | -2.16 [-5.83, 1.51] |
| Heterogeneity: Tau ² = 6.86 | ; Chi ² = 48 | 8.47, df = 1 (P<0.0 | 0001); 12 =9 | 98% | | | | |
| Test for overall effect: Z = | I.I5 (P = 0 | .25) | | | | | | |
| 5 Escitalopram | | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | ole | | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | | |
| Total (95% CI) | 124 | | 125 | | | • | 100.0 % | -1.03 [-2.09, 0.04] |
| Heterogeneity: Tau ² = 1.34 | ł; Chi ² = 54 | 4.85, df = 4 (P<0.0 | 0001 ; $l^2 = 9$ | 93% | | | | |
| Test for overall effect: Z = | I.89 (P = 0 | .058) | | | | | | |
| Test for subgroup difference | es: Chi ² = (| 0.87, df = 1 (P = 0 | .35), I ² =0.0 | 9% | | | | |
| | | | | | | | 1 | |
| | | | | - | 10 -5 | 0 5 | 10 | |

Favours SSRI Favours control

Analysis 9.8. Comparison 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias, Outcome 8 Cognition (continuous scores end of treatment).

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

Comparison: 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias

Outcome: 8 Cognition (continuous scores end of treatment)

| Study or subgroup | SSRI | | Control | | Dit | Std. Mean fference | Weight | Std. Mean Difference |
|--|-------------------------|---------------------|---------------------------|--------------|---------------|--------------------------|---------|----------------------------|
| , , , | Ν | Mean(SD) | Ν | Mean(SD) | IV,Rand | om,95% Cl | - | IV,Random,95% CI |
| I Fluoxetine | | | | | | | | |
| Robinson 2000a | 14 | 25.9 (7.5) | 13 | 24.5 (6.8) | | | 4. % | 0.19 [-0.57, 0.95] |
| Robinson 2000b | 13 | 26.1 (7.5) | 15 | 26.8 (2.4) | | | 14.4 % | -0.13 [-0.87, 0.62] |
| Wiart 2000 | 16 | 24.8 (3.9) | 15 | 26.2 (3) | ← ∎ | | 15.4 % | -0.39 [-1.10, 0.32] |
| Subtotal (95% CI) | 43 | | 43 | | | | 43.9 % | -0.12 [-0.55, 0.30] |
| Heterogeneity: Tau ² = 0.0; | Chi ² = 1.1 | 9, df = 2 (P = 0.55 |); I ² =0.0% | | | | | |
| Test for overall effect: $Z = 0$ | 0.56 (P = 0 | 0.58) | | | | | | |
| 2 Sertraline | | | | | | | | |
| Guo 2009 | 40 | 19.26 (6.87) | 40 | 15.74 (6.28) | | | 27.2 % | 0.53 [0.08, 0.98] |
| Subtotal (95% CI) | 40 | | 40 | | | | 27.2 % | 0.53 [0.08, 0.98] |
| Heterogeneity: not applicab | ole | | | | | | | |
| Test for overall effect: $Z = 2$ | 2.33 (P = 0 | 0.020) | | | | | | |
| 3 Citalopram | | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicab | ole | | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | | |
| 4 Escitalopram | | | | | | | | |
| Robinson 2008 | 43 | 89.8 (15.1) | 45 | 91 (17.8) | | | 28.9 % | -0.07 [-0.49, 0.35] |
| Subtotal (95% CI) | 43 | | 45 | | | | 28.9 % | -0.07 [-0.49, 0.35] |
| Heterogeneity: not applicab | ole | | | | | | | |
| Test for overall effect: $Z = 0$ | 0.34 (P = 0 |).74) | | | | | | |
| Total (95% CI) | 126 | | 128 | | - | - | 100.0 % | 0.07 [-0.26, 0.40] |
| Heterogeneity: Tau ² = 0.05 | ; Chi ² = 6. | 44, df = 4 (P = 0.1 | 7); I ² =38% | | | | | |
| Test for overall effect: $Z = 0$ | 0.42 (P = 0 |).67) | | | | | | |
| Test for subgroup difference | es: Chi ² = | 5.24, df = 2 (P = 0 | .07), l ² =62% | 6 | | | | |
| | | | | | | | | |
| | | | | | - 1 -0.5 | 0 0.5 I | | |
| | | | | Fa | vours control | Favours SSRI | | |
| | | | | | | | | |
| | | | | | | | | |

Analysis 9.9. Comparison 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias, Outcome 9 Death.

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

Comparison: 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias

Outcome: 9 Death

| Study or subgroup | SSRI | Control | Risk Ratio M- H,Random,95% | Risk Ratio M- H,Random,95% |
|--|---------------------------|--------------------------------|---|----------------------------------|
| | n/N | n/N | Cl | Cl |
| I Fluoxetine | | | | |
| Brown 1998 | 0/10 | 0/10 | | 0.0 [0.0, 0.0] |
| Chollet 2011 | 1/59 | 1/59 | | 1.00 [0.06, 15.61] |
| Hu 2002 | 0/42 | 0/30 | | 0.0 [0.0, 0.0] |
| Huang 2002 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Ji 2000 | 0/20 | 0/20 | | 0.0 [0.0, 0.0] |
| Li 2002 | 0/46 | 0/46 | | 0.0 [0.0, 0.0] |
| Li 2004a | 0/33 | 0/34 | | 0.0 [0.0, 0.0] |
| Liang 2003 | 0/42 | 0/21 | | 0.0 [0.0, 0.0] |
| Liu 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Robinson 2000a | 0/23 | 1/17 | | 0.25 [0.01, 5.79] |
| Robinson 2000b | 0/17 | 0/16 | | 0.0 [0.0, 0.0] |
| Song 2006 | 0/41 | 0/41 | | 0.0 [0.0, 0.0] |
| Wen 2006 | 0/42 | 0/42 | | 0.0 [0.0, 0.0] |
| Wiart 2000 | 0/16 | 0/15 | | 0.0 [0.0, 0.0] |
| Zhou 2008 | 0/36 | 0/40 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 497 | 461 | - | 0.55 [0.07, 4.34] |
| Total events: 1 (SSRI), 2 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = Test for overall effect: Z = 0.57 (F 2 Sertraline Almeida 2006 | = 0.43, df = 1 (P = 0.51) | ; I ² =0.0% I/52 | | 2.17 [0.20, 23.14] |
| Burns 1999 | 1/14 | / 4 | _ | 1.00 [0.07, 14.45] |
| Guo 2009 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Murray 2005 | 0/62 | 2/61 | | 0.20 [0.01, 4.02] |
| Xie 2005 | 0/65 | 0/65 | | 0.0 [0.0, 0.0] |
| | | | 0.01 0.1 10 100 Favours SSRI Favours control | (|

(Continued . . .)

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|-----------------------|-------------------------|--------------------|-----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,9 Cl |
| Subtotal (95% CI) | 229 | 232 | - | 0.91 [0.20, 4.19] |
| Total events: 3 (SSRI), 4 (Control) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.5$ | 54, df = 2 (P = 0.46) | ; l ² =0.0% | | |
| Test for overall effect: $Z = 0.12$ (P = | 0.90) | | | |
| 3 Citalopram | | | | |
| Andersen 1994 | 2/33 | 2/33 | | 1.00 [0.15, 6.68] |
| Liu 2006 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 63 | 63 | | 1.00 [0.15, 6.68] |
| Total events: 2 (SSRI), 2 (Control) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$ |), df = 0 (P = 1.00); | l ² =0.0% | | |
| Test for overall effect: $Z = 0.0$ (P = 1. | 0) | | | |
| 4 Paroxetine | | | | |
| Chen T 2005 | 0/40 | 0/38 | | 0.0 [0.0, 0.0] |
| He 2005 | 0/27 | 0/27 | | 0.0 [0.0, 0.0] |
| Lai 2006 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Li 2002 | 0/46 | 0/46 | | 0.0 [0.0, 0.0] |
| Li 2005 | 0/74 | 0/74 | | 0.0 [0.0, 0.0] |
| Yang 2011 | 0/20 | 0/22 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 247 | 247 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$ |), df = 0 (P<0.0000 I |); l ² =0.0% | | |
| Test for overall effect: $Z = 0.0 (P < 0.0)$ | 00001) | | | |
| 5 Escitalopram | | | | |
| Robinson 2008 | 2/59 | 0/58 | | 4.92 [0.24, 100.25] |
| Subtotal (95% CI) | 59 | 58 | | 4.92 [0.24, 100.25] |
| Total events: 2 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 1.04$ (P = | 0.30) | | | |
| 6 Sertraline or fluoxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | 1005 | 10(1 | | |
| Total (95% CI) | 1095 | 1061 | | 0.99 [0.37, 2.64] |
| Total events: 8 (SSRI), 8 (Control) | | 12 -0.09/ | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = 3.3 First for overall effect: $Z = 0.01$ (P = 0.01) | , , | r; 1 ² —0.0% | | |
| Test for subgroup differences: Chi ² = | , | $70) ^2 = 0.0\%$ | | |
| reaction subgroup differences. Chir – | | /0],1 =0.076 | | |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |

Analysis 9.10. Comparison 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias, Outcome 10 Seizures.

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

Comparison: 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias

Outcome: 10 Seizures

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|---|--------------------|-------------------------|---|-----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,959 Cl |
| I Fluoxetine | | | | |
| Chollet 2011 | 1/59 | 0/59 | | 3.00 [0.12, 72.18] |
| Liang 2003 | 0/42 | 0/21 | | 0.0 [0.0, 0.0] |
| Wiart 2000 | 1/16 | 1/15 | _ | 0.94 [0.06, 3.68] |
| Subtotal (95% CI) | 117 | 95 | - | 1.52 [0.20, 11.80] |
| Total events: 2 (SSRI), 1 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0.30 Test for overall effect: Z = 0.40 (P = 0 | |); I ² =0.0% | | |
| 2 Sertraline Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable | 0 | 0 | | 0.0 [0.0, 0.0] |
| Test for overall effect: not applicable | | | | |
| 3 Citalopram | | | | |
| Andersen 1994 | 2/33 | 0/33 | | 5.00 [0.25, 100.32] |
| Subtotal (95% CI) Total events: 2 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: Z = 1.05 (P = 0 4 Paroxetine | 33 1.29) | 33 | | 5.00 [0.25, 100.32] |
| He 2005 | 0/27 | 0/27 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 0.0$ (P < 0.0 5 Escitalopram | 27 | 27 | | 0.0 [0.0, 0.0] |
| S Escitaiopram Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable | 0 | 0 | | 0.0 [0.0, 0.0] |
| | | | 0.01 0.1 10 100 Favours SSRI Favours control | (Continued) |

| Study or subgroup | SSRI | Control | Risk Ratio M- H,Random,95% | (Continued) Risk Ratio M- H,Random,95% |
|---|---------------------------------|---------------------------|----------------------------------|--|
| | n/N | n/N | Cl | CI |
| 6 Sertraline or fluoxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) |) | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applica | ble | | | |
| Total (95% CI) | 177 | 155 | | 2.22 [0.41, 12.06] |
| Total events: 4 (SSRI), 1 (Control) |) | | | |
| Heterogeneity: $Tau^2 = 0.0$; Chi ² = | = 0.73, df = 2 (P = 0.70 |); I ² =0.0% | | |
| Test for overall effect: $Z = 0.92$ (F | P = 0.36) | | | |
| Test for subgroup differences: Ch | $i^2 = 0.4$ I, df = I (P = 0.4) | 52), I ² =0.0% | | |
| | | | | |
| | | | 0.01 0.1 10 100 | |

Favours SSRI Favours control

Analysis 9.11. Comparison 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias, Outcome 11 Gastrointestinal side effects.

| Study or subgroup SSRI Control Risk Ratio M- H,Random,95% CI Risk Ratio M- H,Random,95% CI Risk Ratio M- H,Random,95% CI 1 Fluoxetine | M- M- M- H,Random,95% H,Random,95% I Fluoxetine I fluoxetine Chollet 2011 14/59 Hu 2002 5/42 0/40 0/40 Huang 2002 0/40 Uiang 2003 4/42 4/42 4/21 Wiart 2000 1/16 3/16 0.33 [0.04, 2.87] | | | | |
|---|---|-------|--|--|--|
| Study or subgroup SSRI Control Risk Ratio M- H,Random,95% 1 Fluoxetine 0.014/59 6/59 2.33 [0.96, 5.66] | Study or subgroup SSRI Control Risk Ratio M- H,Random,95% 1 Fluoxetine 0.096,5.66] 0.33 [0.96, 5.66] 0.33 [0.96, 5.66] 0.00 [0.0, 0.0] Hu 2002 5/42 0/30 0/40 0.00 [0.0, 0.0] 0.00 [0.0, 0.0] Huang 2002 0/40 0/40 0.00 [0.0, 0.0] 0.00 [0.0, 0.0] 0.00 [0.0, 0.0] Liang 2003 4/42 4/21 0.50 [0.14, 1.80] 0.50 [0.38, 129.93] 7.00 [0.38, 129.93] | 229 | 196 | - | 1.43 [0.47, 4.36] |
| Study or subgroup SSRI Control Risk Ratio M- H,Random,95% Risk Ratio M- H,Random,95% Risk Ratio M- H,Random,95% I Fluoxetine I 14/59 6/59 2.33 [0.96, 5.66] Hu 2002 5/42 0/30 7.93 [0.46, 138.20] Huang 2002 0/40 0/40 0.0 [0.0, 0.0] Liang 2003 4/42 4/21 - 0.50 [0.14, 1.80] | Study or subgroup SSRI Control Risk Ratio M- H,Random,95% Risk Ratio M- H,Random,95% Risk Ratio M- H,Random,95% I Fluoxetine I 14/59 6/59 - 2.33 [0.96, 5.66] Hu 2002 5/42 0/30 - 7.93 [0.46, 138.20] Huang 2002 0/40 0/40 0.0 [0.0, 0.0] Liang 2003 4/42 4/21 - 0.50 [0.14, 1.80] | 1/16 | 3/16 | | 0.33 [0.04, 2.87] |
| Study or subgroup SSRI Control Risk Ratio M- H,Random,95% Risk Ratio M- H,Random,95% Risk Ratio M- H,Random,95% 1 Fluoxetine 14/59 6/59 - 2.33 [0.96, 5.66] Hu 2002 5/42 0/30 - 7.93 [0.46, 138.20] Huang 2002 0/40 0/40 0.0 [0.0, 0.0] | Study or subgroup SSRI Control Risk Ratio M- H,Random,95% Risk Ratio M- H,Random,95% Risk Ratio M- H,Random,95% 1 Fluoxetine 14/59 6/59 - 2.33 [0.96, 5.66] Hu 2002 5/42 0/30 - 7.93 [0.46, 138.20] Huang 2002 0/40 0/40 0.0 [0.0, 0.0] | 3/30 | 0/30 | | 7.00 [0.38, 129.93] |
| Study or subgroup SSRI Control Risk Ratio M- H,Random,95% Risk Ratio M- Cl Risk Ratio M- Cl | Study or subgroup SSRI Control Risk Ratio M- H,Random,95% Risk Ratio M- Cl Risk Ratio M- Cl | 4/42 | 4/2 | | 0.50 [0.14, 1.80] |
| Study or subgroup SSRI Control Risk Ratio M- M- H,Random,95% H,Random,95% I Fluoxetine Chollet 2011 14/59 6/59 2.33 [0,96, 5.66] | Study or subgroup SSRI Control Risk Ratio M- M- H,Random,95% H,Random,95% I Fluoxetine Chollet 2011 14/59 6/59 2.33 [0,96, 5.66] | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Study or subgroup SSRI Control Risk Ratio Risk Ratio M- H,Random,95% H,Random,95% N/N n/N CI CI | Study or subgroup SSRI Control Risk Ratio Risk Ratio M- H,Random,95% H,Random,95% N/N n/N CI CI | 5/42 | 0/30 | | 7.93 [0.46, 38.20] |
| Study or subgroup SSRI Control Risk Ratio Risk Ratio M- M- H,Random,95% H,Random,9 n/N n/N Cl Cl | Study or subgroup SSRI Control Risk Ratio Risk Ratio M- M- H,Random,95% H,Random,9 n/N n/N Cl Cl | 14/59 | 6/59 | | 2.33 [0.96, 5.66] |
| Study or subgroup SSRI Control Risk Ratio Risk Ratio M- | Study or subgroup SSRI Control Risk Ratio Risk Ratio M- M- | n/N | n/N | | H,Random,95 Cl |
| Outcome: 11 Gastrointestinal side effects | Outcome: 11 Gastrointestinal side effects | SSRI | Control | | M- |
| | | | | | |
| | | ľ | trol at end of treatmen ide effects SSRI n/N 14/59 5/42 0/40 4/42 3/30 1/16 | ide effects SSRI Control <u>n/N n/N</u> 14/59 6/59 5/42 0/30 0/40 0/40 4/42 4/21 3/30 0/30 1/16 3/16 | trol at end of treatment, incomplete outcome data: low risk of bias ide effects SSRI Control Risk Ratio H,Random,95% Cl I4/59 6/59 Cl I4/59 6/59 Cl I4/52 0/30 Cl I4/42 4/21 Control Risk Ratio II I4/59 6/59 Cl II II II II II II II II II |

| Study or subgroup | SSRI | Control | Risk Ratio | (Continued) Risk Ratio |
|---|---------------------|-----------------------------|------------------------------|----------------------------|
| | | | M- H,Random,95% | M- H,Random,95 |
| | n/N | n/N | Cl | Cl |
| Total events: 27 (SSRI), 13 (Control) | | NON 12 | | |
| Heterogeneity: Tau ² = 0.75; Chi ² = 8. | | 19); 1² =51% | | |
| Test for overall effect: $Z = 0.63$ (P = 0. | .53) | | | |
| 2 Sertraline | 0/14 | | | |
| Burns 1999 | 0/14 | 1/14 | | 0.33 [0.01, 7.55] |
| Subtotal (95% CI) | 14 | 14 | | 0.33 [0.01, 7.55] |
| Total events: 0 (SSRI), 1 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.69$ (P = 0. | .49) | | | |
| 3 Citalopram | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 4 Paroxetine | | | | |
| He 2005 | 9/27 | 0/27 | _ | 19.00 [1.16, 310.94] |
| Subtotal (95% CI) | 27 | 27 | | 19.00 [1.16, 310.94] |
| Total events: 9 (SSRI), 0 (Control) | _/ | -/ | | 1,000 [1110, 5100, 1] |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 2.06$ (P = 0. | 039) | | | |
| 5 Escitalopram | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | Ũ | Ũ | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 6 Sertraline and paroxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | Ũ | Ū | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| Total (95% CI) | 270 | 237 | - | 1.67 [0.56, 4.97] |
| Total events: 36 (SSRI), 14 (Control) | | | | |
| Heterogeneity: Tau ² = 1.00; Chi ² = 12 | 2.75. df = 6 (P = 0 | .05): I ² =53% | | |
| Test for overall effect: $Z = 0.92$ (P = 0. | | | | |
| Test for subgroup differences: $Chi^2 = 4$ | | $ 4\rangle$, $ ^2 = 50\%$ | | |
| | | ,, | | |
| | | | 0.01 0.1 10 100 | |
| | | | Favours SSRI Favours control | |
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Analysis 9.12. Comparison 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias, Outcome 12 Bleeding.

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

Comparison: 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias

Outcome: 12 Bleeding

| Study or subgroup | SSRI | Control | Risk Ratio M- | Weight | Risk Ratic M- |
|--|------------|---------|------------------------------|---------|------------------------|
| | n/N | n/N | H,Random,95% Cl | | H,Random,S C |
| I Fluoxetine | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | le | | | | |
| 2 Sertraline | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | le | | | | |
| 3 Citalopram | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | le | | | | |
| 4 Paroxetine | | | | | |
| He 2005 | 9/27 | 0/27 | | 100.0 % | 19.00 [1.16, 310.94] |
| Subtotal (95% CI) | 27 | 27 | | 100.0 % | 19.00 [1.16, 310.94] |
| Total events: 9 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 2.06$ (P | = 0.039) | | | | |
| 5 Escitalopram | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | le | | | | |
| 6 Sertraline or fluoxetine | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | le | | | | |
| Total (95% CI) | 27 | 27 | | 100.0 % | 19.00 [1.16, 310.94] |
| Total events: 9 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.06 (P | = 0.039) | | | | |
| Test for subgroup differences: Not | applicable | | | | |
| | | | | | |
| | | | 0.01 0.1 1 10 100 | | |
| | | | Favours SSRI Favours control | | |
Analysis 9.14. Comparison 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias, Outcome 14 Change in cognition between baseline and end of treatment.

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

Comparison: 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias

Outcome: 14 Change in cognition between baseline and end of treatment

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|--|-----------------------|------------|--------------|-----------|--|----------------|--|
| l Sertraline Almeida 2006 | 48 | 2.6 (3.04) | 51 | 2.6 (3.9) | - | 100.0 % | 0.0 [-0.39, 0.39] |
| Total (95% CI) Heterogeneity: not app | 48 blicable | | 51 | | + | 100.0 % | 0.0 [-0.39, 0.39] |
| Test for overall effect: Z Test for subgroup differ | | | | | | | |
| | | | | | -2 -1 0 1 2 | | |
| | | | | | Favours SSRI Favours contr | lo | |
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Analysis 9.15. Comparison 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias, Outcome 15 Leaving the trial before the end of scheduled follow-up.

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

Comparison: 9 SSRI versus control at end of treatment, incomplete outcome data: low risk of bias

Outcome: 15 Leaving the trial before the end of scheduled follow-up

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|---|---------------------------|------------------------|---|----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,9 Cl |
| I Fluoxetine | | | | |
| Brown 1998 | 1/10 | 0/10 | | 3.00 [0.14, 65.90] |
| Chollet 2011 | 2/59 | 3/59 | | 0.67 [0.12, 3.85] |
| Hu 2002 | 0/42 | 0/30 | | 0.0 [0.0, 0.0] |
| Huang 2002 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Ji 2000 | 0/20 | 0/20 | | 0.0 [0.0, 0.0] |
| Li 2004a | 0/33 | 0/34 | | 0.0 [0.0, 0.0] |
| Liang 2003 | 0/42 | 0/21 | | 0.0 [0.0, 0.0] |
| Liu 2004 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Robinson 2000a | 9/23 | 4/17 | | 1.66 [0.61, 4.51] |
| Robinson 2000b | 4/17 | 1/16 | | 3.76 [0.47, 30.20] |
| Wen 2006 | 0/42 | 0/42 | | 0.0 [0.0, 0.0] |
| Wiart 2000 | 0/16 | 0/15 | | 0.0 [0.0, 0.0] |
| Zhou 2008 | 0/36 | 0/40 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 410 | 374 | - | 1.62 [0.75, 3.51] |
| Total events: 16 (SSRI), 8 (Contro Heterogeneity: Tau ² = 0.0; Chi ² = Test for overall effect: Z = 1.22 (f 2 Sertraline | = 1.77, df = 3 (P = 0.62) | ; l ² =0.0% | | |
| Almeida 2006 | 11/55 | 6/56 | + | 1.87 [0.74, 4.70] |
| Burns 1999 | 0/14 | 0/14 | | 0.0 [0.0, 0.0] |
| Guo 2009 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Murray 2005 | 24/62 | 11/61 | | 2.15 [1.15, 3.99] |
| Rasmussen 2003 | 35/70 | 35/67 | + | 0.96 [0.69, 1.33] |
| Xie 2005 | 0/65 | 0/65 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 306 | 303 | • | 1.46 [0.79, 2.72] |
| | | | 0.01 0.1 10 100 Favours SSRI Favours control | |

Tavours com

(Continued . . .)

| Study or subgroup | SSRI n/N | Control n/N | Risk Ratio M- H,Random,95% | (Continued Risk Ratio M- H,Random,2 |
|--|-----------------------|---------------------------|----------------------------------|---|
| Total events: 70 (SSRI), 52 (Control) | n/in | n/in | CI | C |
| Heterogeneity: Tau ² = 0.20; Chi ² = 6. | 53, df = 2 (P = 0.04 |); I ² =69% | | |
| Test for overall effect: $Z = 1.20$ (P = 0 | .23) | | | |
| 3 Citalopram | | | | |
| Andersen 1994 | 6/33 | 1/33 | | 6.00 [0.76, 47.14] |
| Liu 2006 | 0/30 | 0/30 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 63 | 63 | | 6.00 [0.76, 47.14] |
| Total events: 6 (SSRI), 1 (Control) | | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = 0.0, | df = 0 (P = 1.00); | ² =0.0% | | |
| Test for overall effect: $Z = 1.70$ (P = 0 | | | | |
| 4 Paroxetine | | | | |
| Chen T 2005 | 0/40 | 0/38 | | 0.0 [0.0, 0.0] |
| He 2005 | 0/27 | 0/27 | | 0.0 [0.0, 0.0] |
| Lai 2006 | 0/40 | 0/40 | | 0.0 [0.0, 0.0] |
| Li 2002 | 0/46 | 0/46 | | 0.0 [0.0, 0.0] |
| Li 2005 | 0/74 | 0/74 | | 0.0 [0.0, 0.0 |
| Yang 2011 | 0/20 | 0/22 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 247 | 247 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = 0.0, | df = 0 (P<0.00001 |); I ² =0.0% | | |
| Test for overall effect: $Z = 0.0$ (P < 0.0 | | | | |
| 5 Sertraline or fluoxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 6 Escitalopram | | | | |
| Robinson 2008 | 7/59 | 5/58 | | 1.38 [0.46, 4.09 |
| Subtotal (95% CI) | 59 | 58 | - | 1.38 [0.46, 4.09] |
| Total events: 7 (SSRI), 5 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.57$ (P = 0 | .57) | | | |
| Total (95% CI) | 1085 | 1045 | ◆ | 1.51 [1.02, 2.23] |
| Total events: 99 (SSRI), 66 (Control) | | | | |
| Heterogeneity: Tau ² = 0.09; Chi ² = 11 | .46, df = 8 (P = 0.1 | 8); I ² =30% | | |
| Test for overall effect: $Z = 2.07$ (P = 0 | .038) | | | |
| Test for subgroup differences: $Chi^2 =$ | 1.73, df = 3 (P = 0.6 | 53), I ² =0.0% | | |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |

Analysis 10.1. Comparison 10 SSRI versus control at end of treatment, selective reporting: low risk, Outcome I Dependent on modified Rankin score (mRS 3 to 5).

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

Comparison: 10 SSRI versus control at end of treatment, selective reporting: low risk

Outcome: I Dependent on modified Rankin score (mRS 3 to 5)

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|---|-----------------------------|---------|--------------------|---------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95% Cl |
| I Fluoxetine | | | | |
| Chollet 2011 | 42/57 | 50/55 | - | 0.81 [0.68, 0.97] |
| Subtotal (95% CI) | 57 | 55 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Contr | ol) | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 2.34$ (P | = 0.019) | | | |
| 2 Sertraline | | | | |
| Almeida 2006 | 0/55 | 0/56 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 55 | 56 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.0$ (P · | < 0.00001) | | | |
| Total (95% CI) | 112 | 111 | • | 0.81 [0.68, 0.97] |
| Total events: 42 (SSRI), 50 (Contr | ol) | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = | = 0.0, df = 0 (P = 1.00); I | 2 =0.0% | | |
| Test for overall effect: $Z = 2.34$ (P | = 0.019) | | | |
| Test for subgroup differences: Not | t applicable | | | |
| | | | <u> </u> | |
| | | | 0.01 0.1 1 10 100 | |

0.01 0.1 I Favours SSRI

Favours control

Analysis 10.2. Comparison 10 SSRI versus control at end of treatment, selective reporting: low risk, Outcome 2 Disability.

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

Comparison: 10 SSRI versus control at end of treatment, selective reporting: low risk

Outcome: 2 Disability

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|---|-------------|-------------|-------------------------|-------------|--|---------|--|
| l Fluoxetine | | | | | | | |
| Dam 1996 | 16 | 61.9 (13) | 16 | 54.1 (21.1) | | 26.8 % | 0.43 [-0.27, 1.14] |
| Robinson 2000a | 14 | 59.2 (11.6) | 13 | 56.2 (7.8) | _ | 22.9 % | 0.29 [-0.47, 1.05] |
| Robinson 2000b | 13 | 60.5 (10.8) | 15 | 63.1 (8.2) | | 23.7 % | -0.27 [-1.01, 0.48] |
| | | | | | | | |
| Wiart 2000 | 16 | 87.4 (22.8) | 15 | 88.7 (25.3) | l | 26.6 % | -0.05 [-0.76, 0.65] |
| Subtotal (95% CI) | 59 | | 59 | | • | 100.0 % | 0.11 [-0.26, 0.47] |
| Heterogeneity: $Tau^2 = 0.0;$ | | |); I ² =0.0% | | | | |
| Test for overall effect: $Z = 0$ | 0.57 (P = 0 |).57) | | | | | |
| 2 Sertraline | 0 | | 0 | | | 0.0.0/ | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat Test for overall effect: not a | | | | | | | |
| 3 Citalopram | аррисаріе | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | | | U U | | | 010 /0 | |
| Test for overall effect: not a | | | | | | | |
| 4 Paroxetine | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | ole | | | | | | |
| Test for overall effect: not a | applicable | | | | | | |
| 5 Escitalopram | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | ole | | | | | | |
| Test for overall effect: not a | applicable | | | | | | |
| 6 Sertraline or fluoxetine | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | | | | | | | |
| Test for overall effect: not a | | | - | | | | |
| Total (95% CI) | 59 | | 59 | | - | 100.0 % | 0.11 [-0.26, 0.47] |
| Heterogeneity: $Tau^2 = 0.0$; | | |); I ² =0.0% | | | | |
| Test for overall effect: $Z = 0$ | ` | , | | | | | |
| Test for subgroup difference | es: inot ap | piicadie | | | | | |
| | | | | | -2 -1 0 1 2 | | |
| | | | | | Favours control Favours SSRI | | |
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Analysis 10.3. Comparison 10 SSRI versus control at end of treatment, selective reporting: low risk, Outcome 3 Neurological deficit score.

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

Comparison: 10 SSRI versus control at end of treatment, selective reporting: low risk

Outcome: 3 Neurological deficit score

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|---|-----------------------|------------------------|--------------------------|--------------|--|----------|--|
| Fluoxetine Chollet 2011 | 57 | | | (0 (4 4) | | 65.1 % | |
| | 57 | 5.8 (3.7) | 55 | 6.9 (4.4) | - | | -0.27 [-0.64, 0.10] |
| Dam 1996 | 16 | 44.1 (9.4) | 16 | 46.8 (9.9) | | 18.6 % | -0.27 [-0.97, 0.42] |
| Subtotal (95% CI) | 73 | | 71 | | • | 83.6 % | -0.27 [-0.60, 0.06] |
| Heterogeneity: $Tau^2 = 0.0$; | $Chi^2 = 0.0$ | 00, df = 1 (P = 0.99 | 9); I ² =0.0% | | | | |
| Test for overall effect: $Z =$ | 1.61 (P = | 0.11) | | | | | |
| 2 Sertraline | | | | | | | |
| Burns 1999 | 14 | -29.7 (14.7) | 14 | -32.2 (13.4) | | 16.4 % | 0.17 [-0.57, 0.91] |
| Subtotal (95% CI) | 14 | | 14 | | | 16.4 % | 0.17 [-0.57, 0.91] |
| Heterogeneity: not applicat | ole | | | | | | |
| Test for overall effect: $Z =$ | 0.46 (P = | 0.65) | | | | | |
| 3 Citalopram | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | ole | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | |
| 4 Paroxetine | - | | | | | / | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | | | | | | | |
| Test for overall effect: not a | pplicable | | | | | | |
| 5 Fluoxetine or sertraline | 0 | | 0 | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | | | | | | | |
| Test for overall effect: not a Total (95% CI) | арнсаріе 87 | | 85 | | • | 100.0 % | -0.20 [-0.50, 0.10] |
| Heterogeneity: $Tau^2 = 0.0$; | | 14 df = 2 (P = 0.57) | - | | | 100.0 /0 | -0.20 [-0.90, 0.10] |
| Test for overall effect: $Z =$ | | |), 1 -0.078 | | | | |
| Test for subgroup difference | ` | , | $(29) ^2 = ^2$ | % | | | |
| | | | | | | I. | |
| | | | | | -2 -1 0 1 | 2 | |
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Analysis 10.4. Comparison 10 SSRI versus control at end of treatment, selective reporting: low risk, Outcome 4 Depression (continuous data).

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

Comparison: 10 SSRI versus control at end of treatment, selective reporting: low risk

Outcome: 4 Depression (continuous data)

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|---|--|------------|--|------------|--|-----------------|--|
| I Fluoxetine | | | | | | | |
| Chollet 2011 | 56 | 5.4 (4.9) | 54 | 8.4 (7.9) | | 22.4 % | -0.46 [-0.83, -0.08] |
| Dam 1996 | 16 | 8.8 (5.6) | 16 | 9.4 (5.6) | | 15.4 % | -0.10 [-0.80, 0.59] |
| Robinson 2000a | 14 | 18.5 (7.6) | 13 | 12.2 (4.7) | | 13.4 % | 0.96 [0.15, 1.76] |
| Robinson 2000b | 13 | 5.9 (3.8) | 15 | 6.2 (4.6) | | 14.4 % | -0.07 [-0.81, 0.67] |
| Wiart 2000 | 16 | 11.8 (6.7) | 15 | 18.7 (10) | ←■ | 14.6 % | -0.79 [-1.53, -0.06] |
| Subtotal (95% CI) Heterogeneity: Tau ² = 0.2 Test for overall effect: Z = | | | 113 0.02); I ² =67% | 6 | | 80.2 % | -0.13 [-0.64, 0.37] |
| 2 Sertraline Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: not | | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| 3 Citalopram Andersen 1994 | 33 | .4 (5.) | 33 | 4. (4.7) | • e | 19.8 % | -0.54 [-1.04, -0.05] |
| Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: Z = | 33 ble | | 33 | () | | 19.8 % | -0.54 [-1.04, -0.05] |
| 4 Paroxetine Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: not | 0 ble | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| 5 Fluoxetine or sertraline Subtotal (95% CI) Heterogeneity: not applica | | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Test for overall effect: not Total (95% CI) Heterogeneity: $Tau^2 = 0.1$ Test for overall effect: $Z =$ | 148 6; Chi ² = 13 | | 146 0.02); I ² =63% | 6 | | 1 00.0 % | -0.22 [-0.63, 0.18] |
| Test for subgroup difference | ` | , | 0.26), I ² =23% | 6 | | | |
| | | | | | -1 -0.5 0 0.5 I Favours SSRI Favours contr | | |

Analysis 10.5. Comparison 10 SSRI versus control at end of treatment, selective reporting: low risk, Outcome 5 Depression (dichotomous data).

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

Comparison: 10 SSRI versus control at end of treatment, selective reporting: low risk

Outcome: 5 Depression (dichotomous data)

| Study or subgroup | SSRI | Control | Risk Ratio M- | Weight | Risk Ratio M- |
|--|-------------------|-------------------------------|--------------------|---------|---------------------|
| | n/N | n/N | H,Random,95% Cl | | H,Random,S CI |
| l Fluoxetine Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | v | Ū | | 0.0 /0 | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | e | | | | |
| 2 Sertraline | | | | | |
| Almeida 2006 | 8/48 | 11/51 | | 46.2 % | 0.77 [0.34, 1.76] |
| Rasmussen 2003 | 3/35 | 8/32 | | 20.4 % | 0.34 [0.10, 1.18] |
| Subtotal (95% CI) | 83 | 83 | • | 66.6 % | 0.59 [0.28, 1.25] |
| Total events: 11 (SSRI), 19 (Contro | , | | | | |
| Heterogeneity: Tau ² = 0.05; Chi ² = | = 1.16, df = 1 (f | $P = 0.28$); $ ^2 = 4\%$ | | | |
| Test for overall effect: $Z = 1.37$ (P | = 0.17) | | | | |
| 3 Citalopram | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | e | | | | |
| 4 Paroxetine | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | e | | | | |
| 5 Escitalopram | | | _ | | |
| Robinson 2008 | 5/59 | 13/58 | | 33.4 % | 0.38 [0.14, 0.99] |
| Subtotal (95% CI) | 59 | 58 | - | 33.4 % | 0.38 [0.14, 0.99] |
| Total events: 5 (SSRI), 13 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 1.97$ (P | , | | | | |
| Total (95% CI) | 142 | 141 | • | 100.0 % | 0.52 [0.30, 0.90] |
| Total events: 16 (SSRI), 32 (Contro | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 =$ | | = 0.41); 1 ² =0.0% | | | |
| Test for overall effect: $Z = 2.32$ (P | , | | | | |
| Test for subgroup differences: Chi ² | = 0.5 I, df = 1 | $(P = 0.48), ^2 = 0.0\%$ | | | |
| | | | | | |
| | | 0. | 01 0.1 1 10 100 | | |

Analysis 10.6. Comparison 10 SSRI versus control at end of treatment, selective reporting: low risk, Outcome 6 Anxiety (continuous data).

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

Comparison: 10 SSRI versus control at end of treatment, selective reporting: low risk

Outcome: 6 Anxiety (continuous data)

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | | Std. Mean erence om,95% Cl | Weight | Std. Mean Difference IV,Random,95% CI |
|---|-----------------|--------------------|--------------------------|-----------|---------------|-------------------------------------|---------|--|
| l Fluoxetine | | | 10 | 00 (T I) | | | 10.1.07 | |
| Robinson 2000a | 14 | 9.8 (4.8) | 13 | 9.9 (5.1) | | | 49.4 % | -0.02 [-0.77, 0.74] |
| Robinson 2000b | 13 | 4.7 (3.8) | 15 | 5.5 (2.9) | | | 50.6 % | -0.23 [-0.98, 0.51] |
| Subtotal (95% CI) | 27 | | 28 | | | | 100.0 % | -0.13 [-0.66, 0.40] |
| Heterogeneity: $Tau^2 = 0.0$; Test for overall effect: $Z = 2$ Sertraline | | , | 9); I ² =0.0% | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applical Test for overall effect: not a 3 Citalopram | | | | | | | | |
| Subtotal (95% CI) Heterogeneity: not applicat | | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Test for overall effect: not a 4 Paroxetine Subtotal (95% CI) | applicable 0 | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applical Test for overall effect: not a | | | | | | | | |
| 5 Escitalopram Subtotal (95% CI) | 0 | | 0 | | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applical Test for overall effect: not a | | | | | | | | |
| Total (95% CI) | 27 | | 28 | | | | 100.0 % | -0.13 [-0.66, 0.40] |
| Heterogeneity: $Tau^2 = 0.0$; | $Chi^2 = 0.1$ | 5, df = 1 (P = 0.6 | 9); I ² =0.0% | | | | | |
| Test for overall effect: Z = | 0.47 (P = 0 |).64) | | | | | | |
| Test for subgroup difference | es: Not app | olicable | | | | | | |
| | | | | | -1 -0.5 0 | 0.5 1 | | |
| | | | | | Favours SSRI | Favours contr | | |
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Analysis 10.8. Comparison 10 SSRI versus control at end of treatment, selective reporting: low risk, Outcome 8 Cognition (continuous scores end of treatment).

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

Comparison: 10 SSRI versus control at end of treatment, selective reporting: low risk

Outcome: 8 Cognition (continuous scores end of treatment)

| Study or subgroup | SSRI | | Control | | Std. Mean Difference | Weight | Std Mean Difference |
|--|-------------------------|------------|--------------------------|------------|---|---------|---------------------------|
| | Ν | Mean(SD) | Ν | Mean(SD) | IV,Random,95% CI | | IV,Random,95% C |
| I Fluoxetine | | | | | | | |
| Robinson 2000a | 14 | 25.9 (7.5) | 13 | 24.5 (6.8) | | 31.6 % | 0.19 [-0.57, 0.95 |
| Robinson 2000b | 13 | 26.1 (7.5) | 15 | 26.8 (2.4) | | 32.7 % | -0.13 [-0.87, 0.62 |
| Wiart 2000 | 16 | 24.8 (3.9) | 15 | 26.2 (3) | | 35.7 % | -0.39 [-1.10, 0.32 |
| Subtotal (95% CI) | 43 | | 43 | | - | 100.0 % | -0.12 [-0.55, 0.30 |
| Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0 2 Sertraline | | | 5); I ² =0.0% | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat Test for overall effect: not a 3 Citalopram | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 % | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicat | | | | | | | |
| Test for overall effect: not a Total (95% CI) | applicable 43 | | 43 | | | 100.0 % | -0.12 [-0.55, 0.30 |
| Heterogeneity: $Tau^2 = 0.0$; Test for overall effect: $Z = 0$ | | | 5); I ² =0.0% | | | | |
| Test for subgroup difference | es: Not app | olicable | | | | | |
| Test for subgroup difference | es: Not app | olicable | | | | | |
| Test for subgroup difference | es: Not app | blicable | | -: | | | |
| Test for subgroup differenc | es: Not app | olicable | | | 2 -I 0 I 2 ours control Favours SSRI | | |
| Test for subgroup differenc | es: Not app | blicable | | | | | |
| Test for subgroup difference | es: Not app | blicable | | | | | |
| Test for subgroup differenc | es: Not apj | blicable | | | | | |
| Test for subgroup differenc | es: Not app | blicable | | | | | |
| Test for subgroup differenc | es: Not apj | blicable | | | | | |
| Test for subgroup difference | es: Not apj | blicable | | | | | |
| Test for subgroup difference | es: Not apj | blicable | | | | | |
| Test for subgroup differenc | es: Not apj | blicable | | | | | |
| Test for subgroup differenc | es: Not apj | blicable | | | | | |
| Test for subgroup difference | es: Not apj | blicable | | | | | |
| Test for subgroup difference | es: Not apj | blicable | | | | | |
| Test for subgroup differenc | es: Not apj | blicable | | | | | |
| Test for subgroup difference | es: Not apj | blicable | | | | | |
| Test for subgroup difference | es: Not apj | blicable | | | | | |
| Test for subgroup differenc | es: Not apj | blicable | | | | | |

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Analysis 10.9. Comparison 10 SSRI versus control at end of treatment, selective reporting: low risk, Outcome 9 Death.

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

Comparison: 10 SSRI versus control at end of treatment, selective reporting: low risk

Outcome: 9 Death

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|-----------|--|---|-----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,955 Cl |
| I Fluoxetine | | | | |
| Chollet 2011 | 1/59 | 1/59 | | 1.00 [0.06, 15.61] |
| Dam 1996 | 0/18 | 0/17 | | 0.0 [0.0, 0.0] |
| Robinson 2000a | 0/23 | 1/17 | | 0.25 [0.01, 5.79] |
| Robinson 2000b | 0/17 | 0/16 | | 0.0 [0.0, 0.0] |
| Wiart 2000 | 0/16 | 0/15 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 133 | 124 | | 0.55 [0.07, 4.34] |
| Total events: 1 (SSRI), 2 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0.4 Test for overall effect: Z = 0.57 (P = 0 2 Sertraline | |); I ² =0.0% | | |
| Almeida 2006 | 2/48 | 1/52 | | 2.17 [0.20, 23.14] |
| Burns 1999 | 1/14 | 1/14 | _ | 1.00 [0.07, 14.45] |
| Subtotal (95% CI) Total events: 3 (SSRI), 2 (Control) Heterogeneity: Tau ² = 0.0; Chi ² = 0.18 Test for overall effect: $Z = 0.48$ (P = 0 3 Citalopram | | 66 ''); I ² =0.0% | | 1.54 [0.26, 9.07] |
| Andersen 1994 | 2/33 | 2/33 | _ | 1.00 [0.15, 6.68] |
| Subtotal (95% CI) Total events: 2 (SSRI), 2 (Control) Heterogeneity: not applicable Test for overall effect: $Z = 0.0$ (P = 1.0 4 Paroxetine | 33 | 33 | | 1.00 [0.15, 6.68] |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable 5 Escitalopram | 0 | 0 | | 0.0 [0.0, 0.0] |
| Robinson 2008 | 2/59 | 0/58 | • | 4.92 [0.24, 100.25] |
| Subtotal (95% CI) | 59 | 58 | | 4.92 [0.24, 100.25] |
| | | | 0.01 0.1 10 100 Favours SSRI Favours control | |
| | | | | (Continued) |

| Study or subgroup | SSRI | Control | Risk Rati M- | | (Continued) Risk Ratio M- |
|--|---------------------|---------------------------|-------------------|--------------|----------------------------------|
| | n/N | n/N | H,Random,95 Cl | | H,Random,9 Cl |
| otal events: 2 (SSRI), 0 (Control) | | | | | |
| leterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 1.04$ (P = 0. | 30) | | | | |
| Sertraline or fluoxetine | | | | | |
| Subtotal (95% CI) | 0 | 0 | | | 0.0 [0.0, 0.0] |
| otal events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| est for overall effect: not applicable | | | | | |
| Total (95% CI) | 287 | 281 | • | | 1.20 [0.43, 3.37] |
| otal events: 8 (SSRI), 6 (Control) | | | | | |
| Heterogeneity: Tau ² = 0.0; Chi ² = 2.11 | , df = 5 (P = 0.83) | ; l ² =0.0% | | | |
| test for overall effect: $Z = 0.35$ (P = 0. | 73) | | | | |
| est for subgroup differences: $Chi^2 = I$ | | 68), I ² =0.0% | | | |
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Analysis 10.10. Comparison 10 SSRI versus control at end of treatment, selective reporting: low risk, Outcome 10 Seizures.

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

Comparison: 10 SSRI versus control at end of treatment, selective reporting: low risk

Outcome: 10 Seizures

| I Fluoxetine Chollet 2011 Dam 1996 | n/N 1/59 2/18 1/16 93 | n/N 0/59 0/17 1/15 91 | H,Random,95% Cl | 21.4 % 24.5 % | H,Random,95 Cl 3.00 [0.12, 72.18] |
|---|--|--|---|------------------|---|
| Chollet 2011 Dam 1996 2 Wiart 2000 1 | 2/18 | 0/17 1/15 | | | |
| Dam 1996 2 Wiart 2000 | 2/18 | 0/17 1/15 | | | |
| Wiart 2000 | 1/16 | 1/15 | | 24.5 % | 474500400073 |
| | | | | | 4.74 [0.24, 92.07] |
| Subtotal (95% CI) | 93 | 91 | | 30.1 % | 0.94 [0.06, 3.68] |
| | | | - | 76.0 % | 2.19 [0.41, 11.85] |
| Total events: 4 (SSRI), 1 (Control) Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.69$ Test for overall effect: $Z = 0.91$ (P = 0. 2 Sertraline | , | P = 0.71); I ² =0.0% | | | |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| 3 Citalopram Andersen 1994 | 2/33 | 0/33 | _ | 24.0 % | 5.00 [0.25, 100.32] |
| Subtotal (95% CI) | 33 | 33 | | 24.0 % | 5.00 [0.25, 100.32] |
| Total events: 2 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: Z = 1.05 (P = 0. 4 Paroxetine | .29) | | | | |
| Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneit <i>y</i> : not applicable Test for overall effect: not applicable | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| 5 Escitalopram Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable Test for overall effect: not applicable | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| 6 Sertraline or fluoxetine Subtotal (95% CI) Total events: 0 (SSRI), 0 (Control) Heterogeneity: not applicable | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| | | | 0.01 0.1 10 100 Favours SSRI Favours control | | (Continued) |



Analysis 10.11. Comparison 10 SSRI versus control at end of treatment, selective reporting: low risk, Outcome 11 Gastrointestinal side effects.

| rol) | | | | |
|------------|--|---|---|---|
| 14 | 14 | | 11.8 % | 0.33 [0.01, 7.55] |
| 0/14 | / 4 | | 11.8 % | 0.33 [0.01, 7.55] |
| (1 - 0.17) | | | | |
| , | $P = 0.21$); $I^2 = 35\%$ | | | |
| trol) | | | | |
| 93 | 92 | | 88.2 % | 1.60 [0.44, 5.77] |
| 1/16 | 3/16 | | 21.2 % | 0.33 [0.04, 2.87] |
| 2/18 | 0/17 | | 12.8 % | 4.74 [0.24, 92.07] |
| 14/59 | 6/59 | | 54.2 % | 2.33 [0.96, 5.66] |
| | | | | |
| n/N | n/N | H,Random,95% Cl | | H,Random,95 Cl |
| SSRI | Control | M- | Weight | Risk Ratio M- |
| | 14/59 2/18 1/16 93 trol) $i^2 = 3.08, df = 2 (i)$ (P = 0.47) 0/14 14 | n/N n/N 14/59 6/59 2/18 0/17 1/16 3/16 93 92 trol) $1^2 = 3.08$, df = 2 (P = 0.21); $1^2 = 35\%$ (P = 0.47) 0/14 14 14 | $\begin{array}{c ccccccccccccccccccccccccccccccccccc$ | $\begin{array}{c ccccccccccccccccccccccccccccccccccc$ |

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

Comparison: 10 SSRI versus control at end of treatment, selective reporting: low risk

| Study or subgroup | SSRI n/N | Control n/N | Risk Ratio M- H,Random,95% Cl | Weight | (Continued) Risk Ratio M- H,Random,95% Cl |
|---|----------------|---|--|---------|--|
| Test for overall effect: $Z = 0.69$ (P | = 0.49) | | | | |
| 3 Citalopram | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable Test for overall effect: not applicabl | L. | | | | |
| 4 Paroxetine | le | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | v | Ŭ | | 0.0 /0 | 0.0 [0.0, 0.0] |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | le | | | | |
| 5 Escitalopram | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | le | | | | |
| 6 Sertraline and paroxetine | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 % | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicabl | | | _ | | |
| Total (95% CI) | 107 | 106 | | 100.0 % | 1.35 [0.42, 4.29] |
| Total events: 17 (SSRI), 10 (Contro | , | | | | |
| Heterogeneity: $Tau^2 = 0.44$; Chi ² = | | ² = 0.24); l ² =29% | | | |
| Test for overall effect: $Z = 0.50$ (P | | (D - 0.2()) 12 - 0.09 | | | |
| Test for subgroup differences: Chi ² | — 0.83, dī — 1 | (P – 0.36), P –0.0% | | | |
| | | | | | |
| | | | 0.01 0.1 1 10 100 | | |
| | | | Favours SSRI Favours control | | |
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Analysis 10.14. Comparison 10 SSRI versus control at end of treatment, selective reporting: low risk, Outcome 14 Change in cognition between baseline and end of treatment.

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

Comparison: 10 SSRI versus control at end of treatment, selective reporting: low risk

Outcome: 14 Change in cognition between baseline and end of treatment

| Study or subgroup | ssri N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% CI | Weight | Std. Mean Difference IV,Random,95% CI |
|--|-----------|------------|--------------|-----------|--|---------|--|
| I Sertraline Almeida 2006 | 48 | 2 ((2 04) | EI | 2.6 (3.9) | | 100.0 % | 0.0 [-0.39, 0.39] |
| | | 2.6 (3.04) | 51 | 2.6 (3.9) | | | |
| Total (95% CI) Heterogeneity: not app | | | 51 | | • | 100.0 % | 0.0 [-0.39, 0.39] |
| Test for overall effect: Z Test for subgroup differ | | | | | | | |
| | | | | | -2 -1 0 1 2 Favours SSRI Favours control | | |
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Analysis 10.15. Comparison 10 SSRI versus control at end of treatment, selective reporting: low risk, Outcome 15 Leaving the trial before the end of scheduled follow-up.

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

Comparison: 10 SSRI versus control at end of treatment, selective reporting: low risk

Outcome: 15 Leaving the trial before the end of scheduled follow-up

| Study or subgroup | SSRI | Control | Risk Ratio M- | Risk Ratio M- |
|--|-------------------------|-------------------------|------------------------------|----------------------|
| | n/N | n/N | H,Random,95% Cl | H,Random,95 Cl |
| l Fluoxetine | | | | |
| Chollet 2011 | 2/59 | 3/59 | | 0.67 [0.12, 3.85] |
| Dam 1996 | 0/16 | 0/17 | | 0.0 [0.0, 0.0] |
| Robinson 2000a | 9/23 | 4/17 | | 1.66 [0.61, 4.51] |
| Robinson 2000b | 4/17 | 1/16 | | 3.76 [0.47, 30.20] |
| Wiart 2000 | 0/16 | 0/15 | | 0.0 [0.0, 0.0] |
| Subtotal (95% CI) | 131 | 124 | - | 1.55 [0.70, 3.45] |
| otal events: 15 (SSRI), 8 (Control) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; Chi ² = | I.6I, df = 2 (P = 0.45) | ; 12 =0.0% | | |
| Test for overall effect: Z = 1.07 (P = | = 0.28) | | | |
| 2 Sertraline | | | | |
| Almeida 2006 | 11/55 | 6/56 | + | 1.87 [0.74, 4.70] |
| Burns 1999 | 0/14 | 0/14 | | 0.0 [0.0, 0.0] |
| Rasmussen 2003 | 35/70 | 35/67 | - | 0.96 [0.69, 1.33] |
| Subtotal (95% CI) | 139 | 137 | + | 1.17 [0.63, 2.16] |
| Total events: 46 (SSRI), 41 (Control |) | | | |
| Heterogeneity: Tau ² = 0.11; Chi ² = | 1.90, df = 1 (P = 0.17 | 7); I ² =47% | | |
| Test for overall effect: Z = 0.49 (P = | = 0.62) | | | |
| 3 Citalopram | | | | |
| Andersen 1994 | 6/33 | 1/33 | | 6.00 [0.76, 47.14] |
| Subtotal (95% CI) | 33 | 33 | | 6.00 [0.76, 47.14] |
| Total events: 6 (SSRI), 1 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 1.70$ (P = | = 0.088) | | | |
| 4 Paroxetine | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 5 Sertraline or fluoxetine | | | | |
| | | | 0.01 0.1 1 10 100 | |
| | | | Favours SSRI Favours control | |
| | | | | (Continued) |

| | | | | (Continued) |
|--|--------------------------|---------------------------|--------------------|---------------------|
| Study or subgroup | SSRI | Control | Risk Ratio | Risk Ratio |
| | | | M- H,Random,95% | M- H,Random,95% |
| | n/N | n/N | Cl | CI |
| Subtotal (95% CI) | 0 | 0 | | 0.0 [0.0, 0.0] |
| Total events: 0 (SSRI), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicab | le | | | |
| 6 Escitalopram | | | | |
| Robinson 2008 | 7/59 | 5/58 | | 1.38 [0.46, 4.09] |
| Subtotal (95% CI) | 59 | 58 | - | 1.38 [0.46, 4.09] |
| Total events: 7 (SSRI), 5 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: $Z = 0.57$ (P | = 0.57) | | | |
| Total (95% CI) | 362 | 352 | • | 1.32 [0.87, 1.99] |
| Total events: 74 (SSRI), 55 (Contro | ol) | | | |
| Heterogeneity: $Tau^2 = 0.07$; Chi ² = | = 7.61, df = 6 (P = 0.27 | 7); I ² =21% | | |
| Test for overall effect: Z = 1.32 (P | = 0.19) | | | |
| Test for subgroup differences: Chi ² | = 2.32, df = 3 (P = 0.5 | 51), I ² =0.0% | | |
| | | | | |
| | | | 0.01 0.1 1 10 100 | |
| | | | 0.01 0.1 10 100 | |

Favours SSRI

Favours control

APPENDICES

Appendix I. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1. MeSH descriptor Cerebrovascular Disorders explode all trees

#2. (stroke in Title, Abstract or Keywords or poststroke in Title, Abstract or Keywords or post-stroke in Title, Abstract or Keywords or cerebrovasc* in Title, Abstract or Keywords or (brain in Title, Abstract or Keywords and vasc* in Title, Abstract or Keywords) or (cerebral in Title, Abstract or Keywords and vasc* in Title, Abstract or Keywords or apoplex* in Title, Abstract or Keywords or SAH in Title, Abstract or Keywords)

#3. ((brain* in Title, Abstract or Keywords or cerebr* in Title, Abstract or Keywords or cerebell* in Title, Abstract or Keywords or intracran* in Title, Abstract or Keywords or intracreabral in Title, Abstract or Keywords) and (ischemi* in Title, Abstract or Keywords or ischaemi* in Title, Abstract or Keywords or infarct* in Title, Abstract or Keywords or thrombo* in Title, Abstract or Keywords or emboli* in Title, Abstract or Keywords or occlus* in Title, Abstract or Keywords))

#4. ((brain* in Title, Abstract or Keywords or cerebr* in Title, Abstract or Keywords or cerebell* in Title, Abstract or Keywords or intracerebral in Title, Abstract or Keywords or intracerebral in Title, Abstract or Keywords or subarachnoid in Title, Abstract or Keywords) and (haemorrhage* in Title, Abstract or Keywords or hemorrhage* in Title, Abstract or Keywords or hemorrhage* in Title, Abstract or Keywords or bleed* in Title, Abstract or Keywords))

#5. MeSH descriptor hemiplegia this term only

#6. MeSH descriptor paresis explode all trees

#7. MeSH descriptor Gait Disorders, Neurologic explode all trees

#8. (hemipleg* in Title, Abstract or Keywords or hemipar* in Title, Abstract or Keywords or paresis in Title, Abstract or Keywords)

#9. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)

#10. MeSH descriptor Serotonin Uptake Inhibitors explode all trees

#11. (serotonin in Title, Abstract or Keywords or 5-HT in Title, Abstract or Keywords or "5 HT" in Title, Abstract or Keywords or 5-hydroxytryptamine in Title, Abstract or Keywords or "5 hydroxytryptamine" in Title, Abstract or Keywords)

#12. (uptake in Title, Abstract or Keywords or reuptake in Title, Abstract or Keywords or re-uptake in Title, Abstract or Keywords)

#13. inhib* in Title, Abstract or Keywords

#14. (#11 and #12 and #13)

#15. SSRI* in Title, Abstract or Keywords

#16. (alaproclat* in Title, Abstract or Keywords or cericlamin* in Title, Abstract or Keywords or citalopram in Title, Abstract or Keywords or dapoxetin* in Title, Abstract or Keywords or escitalopram in Title, Abstract or Keywords or femoxetin* in Title, Abstract or Keywords or fluoxetin* in Title, Abstract or Keywords or fluoxetin* in Title, Abstract or Keywords or fluoxetin* in Title, Abstract or Keywords or trazodone in Title, Abstract or Keywords or vilazodone in Title, Abstract or Keywords or vilazodone in Title, Abstract or Keywords or sertralin* in Title, Abstract or Keywords or trazodone in Title, Abstract or Keywords or vilazodone in Title, Abstract or Keywords or sertralin* in Title, Abstract or Keywords)

#17. (Celexa in Title, Abstract or Keywords or Cipramil in Title, Abstract or Keywords or Cipram in Title, Abstract or Keywords or Seropram in Title, Abstract or Keywords or Seropram in Title, Abstract or Keywords or Seropram in Title, Abstract or Keywords or Cipralex in Title, Abstract or Keywords or Priligy in Title, Abstract or Keywords or Lexapro in Title, Abstract or Keywords or Cipralex in Title, Abstract or Keywords or Seroplex in Title, Abstract or Keywords or Fluctin in Title, Abstract or Keywords or fluox in Title, Abstract or Keywords or Fluox in Title, Abstract or Keywords or Fluox in Title, Abstract or Keywords or Seroplex in Title, Abstract or Keywords or Seroplex in Title, Abstract or Keywords or Seroplex in Title, Abstract or Keywords or Fluox in Title, Abstract or Keywords or Seroplex in Title, Abstract or Keywords or Seroplex in Title, Abstract or Keywords or Seroplex in Title, Abstract or Keywords or Sero

#18. (#10 or #14 or #15 or #16 or #17) #19. (#9 and #18)

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 cerebel\$ 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) adj5 inhib\$).tw.

11. SSRI\$1.tw.

12. (alaproclat\$ or cericlamin\$ or citalopram or dapoxetin\$ or escitalopram or femoxetin\$ or fluoxetin\$ or fluoxamin\$ 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 Faveril or Movox or Paxil or Seroxat or Seroupin 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 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 cerebel\$ or intracran\$ or intracerebral) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$)).tw.

5. ((brain\$ or cerebr\$ or cerebr\$ 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) adj5 inhib\$).tw.

11. SSRI\$1.tw.

12. (alaproclat\$ or cericlamin\$ or citalopram or dapoxetin\$ or escitalopram or femoxetin\$ or fluoxetin\$ or fluoxamin\$ 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 Favoril 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 Seroupin 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 Seroupin 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 fluoxamin* 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 fluoxamin* 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 re-uptake) OR AB (uptake 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)

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 post-stroke or cerebrovasc* or brain vasc* or cerebral vasc or cva or apoplex or SAH) or AB (stroke 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 cerebr\$ 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 fluoxamin\$ 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 Faveril 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 cerebel\$ or intracran\$ or intracerebral) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$)).tw.

4. ((brain\$ or cerebr\$ or cerebel\$ 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 fluoxetin\$ or fluoxetin\$ 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 Seroupin 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

WHAT'S NEW

Last assessed as up-to-date: 10 July 2012.

| Date | Event | Description |
|----------------|---------|---|
| 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; (3) disability data for Acler 2009 had been entered incorrectly; this has now been corrected |

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

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CONTRIBUTIONS OF AUTHORS

Dr Mead, Dr Hackett and Professor Hankey wrote the protocol. Dr Kutlubaev and Dr Lee read the protocol and approved it. All authors contributed to the searches, or selection of trials or data extraction, as indicated in the text. Dr Mead performed the analyses.

DECLARATIONS OF INTEREST

Gillian Mead, Maree Hackett and Graeme Hankey are co-principal investigators on the planned FOCUS trial (Fluoxetine or control under supervision) in the UK and the AFFINITY (Assessment of fluoxetine in stroke recovery) trial in Australia designed to assess the impact of fluoxetine on disability and dependency after stroke. These trials fulfil our inclusion criteria.

SOURCES OF SUPPORT

Internal sources

• None, Not specified.

External sources

• Stroke Research Network, UK.

Stroke Research Network in England provided some financial support to the Cochrane Stroke Group for assistance with the searchesScotland, Not specified.

Scottish Stroke Research Network provided some funding to the Cochrane Stroke group for assistance with the searches

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We had planned to search the Organon and Wyeth pharmaceutical websites, but when the searches were done, these websites no longer existed. We decided to search the Lundbeck website as this company makes citalopram.

We had planned to search www.ClinicalStudyResults.org, but this was removed from the Internet in 2011.

We stated that we would include trials in which patients were recruited within three months of stroke onset. However, when we started our searches, we identified several trials in which patients had been recruited after three months. In order to ensure that our review provides a complete as possible picture about the role of SSRIs for stroke recovery, we decided to include trials in which the mean time since stroke onset was less than one year, and to perform subgroup analyses to explore the effect of time since onset on effect sizes. This decision was made before any data extraction and analysis had been performed.

We stated that two review authors would independently scrutinise the full-text articles retrieved from the searches, but this was not possible for the main MEDLINE and EMBASE searches because of the large number of full texts retrieved; for these searches, one experienced review author (GM) scrutinised the full texts.

We also stated that two review authors would extract data. Several of our included trials had already been included in other Cochrane reviews led by Dr Hackett, one of our review authors. For these trials, only one additional review author extracted data and checked this against the data extraction that had previously been performed for the previous reviews.

We had not anticipated such as large number of Chinese studies. An additional review author joined the team to perform data extraction for these Chinese papers, but we could not find a second independent reviewer who was sufficiently fluent in Chinese to perform data extraction.

We had intended to use random-effects models only if there was evidence of statistical heterogeneity. Following editorial review, we use random-effects models for all our analyses.

We extracted data on sources of funding, and included this as part of risk of bias assessment.

INDEX TERMS

Medical Subject Headings (MeSH)

Anxiety [*drug therapy]; Citalopram [therapeutic use]; Cognition [drug effects]; Depression [*drug therapy]; Fluoxetine [therapeutic use]; Nervous System Diseases [drug therapy]; Paroxetine [therapeutic use]; Randomized Controlled Trials as Topic; Serotonin Uptake Inhibitors [adverse effects; *therapeutic use]; Sertraline [therapeutic use]; Stroke [*drug therapy; psychology; rehabilitation]

MeSH check words

Adult; Humans