Interventions for treating depression after stroke (Review)

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[Intervention Review]

Interventions for treating depression after stroke

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ABSTRACT

Background

Depression is an important consequence of stroke that impacts on recovery yet is often not detected or inadequately treated. This is an update of a Cochrane review first published in 2004.

Objectives

To determine whether pharmaceutical, psychological, or electroconvulsive treatment (ECT) of depression in patients with stroke can improve outcome.

Search methods

We searched the trials registers of the Cochrane Stroke Group (last searched October 2007) and the Cochrane Depression Anxiety and Neurosis Group (last searched February 2008). In addition, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 1, 2008), MEDLINE (1966 to May 2006), EMBASE (1980 to May 2006), CINAHL (1982 to May 2006), PsycINFO (1967 to May 2006) and other databases. We also searched reference lists, clinical trials registers, conference proceedings and dissertation abstracts, and contacted authors, researchers and pharmaceutical companies.

Selection criteria

Randomised controlled trials comparing pharmaceutical agents with placebo, or various forms of psychotherapy or ECT with standard care (or attention control), in patients with stroke, with the intention of treating depression.

Data collection and analysis

Two review authors selected trials for inclusion and assessed methodological quality; three review authors extracted, cross-checked and entered data. Primary analyses were the prevalence of diagnosable depressive disorder at the end of treatment. Secondary outcomes included depression scores on standard scales, physical function, death, recurrent stroke and adverse effects.

Main results

Sixteen trials (17 interventions), with 1655 participants, were included in the review. Data were available for 13 pharmaceutical agents, and four trials of psychotherapy. There were no trials of ECT. The analyses were complicated by the lack of standardised diagnostic and outcome criteria, and differing analytic methods. There was some evidence of benefit of pharmacotherapy in terms of a complete remission of depression and a reduction (improvement) in scores on depression rating scales, but there was also evidence of an associated increase in adverse events. There was no evidence of benefit of psychotherapy.

Authors' conclusions

A small but significant effect of pharmacotherapy (not psychotherapy) on treating depression and reducing depressive symptoms was found, as was a significant increase in adverse events. More research is required before recommendations can be made about the routine use of such treatments.

PLAIN LANGUAGE SUMMARY

Interventions for treating depression after stroke

Antidepressant drugs may be useful in treating depression after stroke, but also cause side effects. Depression is common after stroke and may be treated with antidepressant medication or psychological therapy. This review of 16 trials, including 1655 participants, found that antidepressant drugs may produce recovery or improve depression symptoms. However they also increase side effects. These drugs should be used with caution in people with persistent depressive symptoms after stroke, as little is known about the risks, especially of seizures, falls, and delirium. We found no evidence for the benefit of psychotherapy. Future research should include a broader group of stroke patients.

BACKGROUND

Depressive and anxiety disorders are important sequelae of stroke. These mood disorders occur in at least one third of patients in the first year after onset of stroke, although estimates differ between trials due to varying definitions, populations, exclusion criteria, and the timing of assessments (Hackett 2005a). Inconsistent research findings are also due to the complexity of recognition, assessment and diagnosis of an underlying mood disorder associated with acute stroke, due to cognitive, language and other impairments. In addition, patients with stroke may experience a variety of behavioural syndromes that are more specific to brain injury, including indifference reaction, emotional lability, disinhibition, unawareness of illness (anosognosia) and difficulties with emotional expression (aprosody). In particular, much of the controversy surrounding 'stroke-associated depression' as a specific type of depressive syndrome hinges on concern about whether the tools normally used for the diagnosis of major depression and other depressive illnesses may misattribute features of ischaemic brain injury to depression (House 1987; Johnson 1991). Moreover, results will depend on whether subjects are categorised on the basis of psychiatric interview using standard diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (e.g. DSM-IIIR, DSM-IV) (APA 1987; APA 1994) or psychiatric rating scales such as the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery 1979), or based on self assessment using a rating scale of mood.

Although there is continued controversy about whether this illness is predominantly caused by physical factors (such as stroke lesion location) or by the patients' psychological response to stroke (Carson 2000), evidence suggests that clinically diagnosed stroke-associated depression has a similar frequency and nature to depression among older people with other chronic illnesses (Burvill 1996; Burvill 1997; Sharpe 1990). While it was previously thought that the period of greatest risk appeared to be within the first few months of stroke onset (Burvill 1995a; Herrmann 1998; House 1991) this was not apparent in a systematic review of high-quality observational studies (Hackett 2005a). While some patients recover spontaneously, up to one third of patients have depression that persists during the first year or longer after the onset of stroke (Astrom 1996; Herrmann 1998). Patients with 'anxious depression' and those with more severe symptoms at presentation appear less responsive to treatment and have a worse long-term prognosis (Astrom 1996).

Evidence of a causal relationship between stroke-associated depression and adverse outcomes is complicated by potential confounding factors such as age, gender, social class, physical disability and co-morbid conditions. However, the evidence suggests that abnormal mood may impede rehabilitation (Parikh 1990; Sinyor 1986) by impairing physical and cognitive function (Robinson 1986), and contributing to stress on carers (Anderson 1995a). Furthermore, stroke-associated depression may also be associated with an increased risk of death (House 2001; Morris 1993b) including death by suicide (Stenager 1998). Depressive illness among older people, in general, is associated with greater morbidity and dependency, higher use of drugs and alcohol, increased use of healthcare resources, and poor compliance with treatment of co-morbid conditions (Katona 1995).

Although depression may influence recovery and outcomes following stroke, many, perhaps most, patients do not receive effective treatment because their mood disorder is undiagnosed or inadequately treated. Ebrahim 1987a, for example, found that few patients with stroke-associated depression had been given antidepressants following discharge from hospital, while House et al (House 1989) reported that both general practitioners and hospital doctors had a passive attitude to therapy. While this invariably reflects the problems with the diagnosis of a 'significant' mood state among older people with disability, it may also reflect uncertainty among clinicians as to the balance of benefits and risks (including side effects) of therapies in this setting. Indirect evidence of the effectiveness of pharmacological and psychological treatments for depression (and anxiety) for older people in general, and in those with associated physical illness, are available in several published reviews (Gill 2000; Lima 2001; McCusker 1998; Mittmann 1997; Wilkinson 1997). However, because of the possibility that depression after stroke differs in important ways, it may be inappropriate to extrapolate these data to patients with stroke.

We undertook a systematic review of all randomised controlled trials (RCTs) (published and unpublished) of pharmaceutical agents, psychological therapies or electroconvulsive therapy (ECT) for the treatment of depression associated with stroke.

This is an update of a Cochrane review first published in 2004.

OBJECTIVES

To determine whether treatment of depression in patients with stroke improves outcome in terms of reduction in the proportion of patients with diagnosable depressive disorder. Secondary objectives were to determine whether treatment of depression improves mood scores, physical functioning, and health related quality of life, and reduces dependency either in patients or principle caregivers. We also aimed to determine the safety of and adherence to such treatments.

METHODS

Criteria for considering studies for this review

Types of studies

We restricted the review to all relevant RCTs in patients with a clinical diagnosis of stroke, where a pharmaceutical agent, psychological therapy, or ECT, used for the treatment of depression, was compared with placebo or standard care. We excluded trials using a cross-over design, or in which two or more of the interventions were compared with each other rather than with a placebo or standard care group. There was no restriction on eligibility of RCTs on the basis of language, sample size, duration of follow up, or publication status.

Trials that met all the inclusion criteria, but in which no outcome data were available (either from the report of the trial or from the authors), could not contribute meaningfully to a pooled estimate of effect. These trials were regarded as 'drop outs' rather than ineligible, and are listed in an Additional Table (Table 1), to indicate that they have not been overlooked.

Types of participants

We defined stroke according to clinical criteria. These include cerebral infarction, intracerebral haemorrhage and 'uncertain' pathological subtypes. This review excludes trials of patients with subarachnoid haemorrhage (SAH) only, as this entity has a different natural history and management strategy from other stroke subtypes. However, we did include trials with mixed stroke subtypes, including small numbers of SAH patients. There were no restrictions on the basis of age, sex or other characteristic. Participants were required to have depression (diagnosed by psychiatric interview, mood scale, or treating clinician) on recruitment. We excluded trials with participants who were not depressed at recruitment, but that measured depression as the primary outcome at follow up. These trials were included in a review of interventions for preventing depression after stroke (Hackett 2008).

The diagnostic categories of depression considered were:

(1) depressive disorder, as defined by symptom scores on a standard screening instrument;

(2) major depression, as defined by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-IIIR, DSM-IV; APA 1987; APA 1994) or similar diagnostic criteria;

(3) dysthymia or minor depression, as defined by DSM or other standard diagnostic criteria.

Trials that included mixed populations (such as stroke and head injury or other central nervous system disorders) were excluded unless separate results for the stroke patients could be identified. Patients were excluded if they were being treated primarily for a stroke-associated pain syndrome, even if depression was measured as a secondary outcome.

Types of interventions

We included any trial that attempted to evaluate the following.

(1) A comparison between a pharmacological agent and placebo for the treatment of depression associated with stroke. Specific pharmacological agents included tricyclic antidepressants (for example nortriptyline, imipramine, and clomipramine), selective serotonin reuptake inhibitors (SSRIs) (for example fluvoxamine, fluoxetine, sertraline, citalopram and paroxetine), monoamine oxidase inhibitors (MAOIs) (for example moclobemide), and other

antidepressant medications. Trials of an agent that was being evaluated for other reasons (for example neuroprotection or to facilitate neuro-regeneration) with a mood endpoint were excluded. We found no trials of psychostimulants (for example methylphenidate), mood stabilisers (for example lithium) or benzodiazepines. We found one trial of a combined preparation (Deanxit) which was included but analysed separately.
(2) A comparison between ECT and standard care for the treatment of depression associated with stroke. We found no trials of ECT. Any future trials will be included but analysed separately.
(3) A comparison between a psychological therapy and standard care for the treatment of depression associated with stroke. We included any psychological therapy that involved direct patient-professional interaction. The content of the interaction could vary from counselling to specific psychotherapy provided it was directed at helping patients develop their social problem-solving skills and adjustment to the emotional impact of stroke. All interventions had to have a psychological component - talking, listening, support, advice; be based on a theory of talking therapy; be structured and timetabled as a talking therapy; and be delivered by somebody with some explicitly stated training and supervision in therapies. Exclusions included interventions whose sole purpose was to educate or to provide information, occupational therapy (including leisure therapy and other rehabilitation services), and visits from stroke support workers, unless there was a clearly defined psychological component.

Types of outcome measures

The primary analyses focused on the proportion of patients who could no longer be diagnosed according to diagnostic categories of depression that were applied by the trial authors at the end of the follow-up period (remission). These included:
(1) no longer meeting the criteria for depression or dysthymia as defined by DSM or similar standard diagnostic criteria;
(2) scoring below cut points for depressive disorder, as defined by symptom scores on standard rating scales.
Secondary outcomes were as follows.
(1) Depression, as measured on scales such as the Hamilton Depression Rating Scale (HDRS, Hamilton 1960), Montgomery Åsberg Depression Rating Scale (MADRS, Montgomery 1979), Geriatric Depression Scale (GDS, Gompertz 1993), Beck Depression Inventory (BDI, Beck 1961), and Hospital Anxiety and Depression Scale (HADS Depression sub-scale, Zigmond 1983).
(2) Psychological distress, as measured on composite scales such as the General Health Questionnaire (GHQ, Goldberg 1972).
(3) Anxiety, as measured on scales such as the Hamilton Anxiety Scale, Beck Anxiety Inventory, and the Hospital Anxiety and Depression Scale (HADS Anxiety sub-scale, Zigmond 1983).
(4) Cognition, as measured on scales such as the Mini-Mental State Examination (MMSE, Folstein 1975).
(5) Activities of daily living, as measured on scales such as the Barthel Index (BI, Mahoney 1965).
(6) Disability, as measured on scales such as the Functional Independence Measure (FIM, Deutsch 1997).
(7) Disadvantages of treatment were recorded as adverse events, grouped by death, all, and leaving the study early (including death).
Participants' reason for withdrawal from the trials was examined as a marker of acceptance.
We have identified the following additional endpoints for use in subsequent reviews, if measured.

- General health, as measured on composite scales such as the Nottingham Health Profile (NHP, Hunt 1986).
- Social activities, as measured on scales such as the Frenchay Activities Index (FAI, Wade 1985).
- HRQoL, as measured on scales such as the 36-item short form questionnaire (SF-36, Ware 1993).
- Proportion reporting dependence in self-care ADL on the modified Rankin Scale (mRS, Rankin 1957).
- Principal caregiver HRQoL and stress.

Search methods for identification of studies

See: 'Specialized register' section in Cochrane Stroke Group
We searched the trials registers of the Cochrane Stroke Group (last searched by the Review Group Co-ordinator in October 2007) and the Cochrane Depression Anxiety and Neurosis Group (last searched February 2008). In addition, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 1, 2008), MEDLINE (1966 to May 2006) (Appendix 1), EMBASE (1980 to May 2006), CINAHL (1982 to May 2006), PsycINFO (1967 to May 2006), Applied Science and Technology Plus (1986 to May 2006), Arts and Humanities Index (1991 to September 2002), Biological Abstracts (1969 to September 2002), BIOSIS Previews (2002 to May 2006), General Science Plus (1994 to September 2002), Science Citation Index (1992 to May 2006), Social Sciences Citation Index (1991 to May 2006), SocioFile (1974 to May 2006) and ISI Web of Science (2002 to February 2008). Biological Abstracts has now been superseded by BIOSIS Previews and ISI Web of knowledge includes the Arts and Humanities Index. We have not updated the searches on General Science Plus as this electronic database is not available for the current authors.
(1) We searched Dissertations and Theses (previously called Digital Dissertations), a database of abstracts from doctoral theses from within the United States, Canada, Scandinavia and the United Kingdom (1980 to August 2007).
(2) We searched the proceedings of the European Stroke Conferences (2000 to 2007) and the Stroke Society of Australasia Annual Scientific Meetings (1999 to 2007).
(3) In 2002 we contacted by letter several of the researchers active the area of stroke-associated mood disorders in the previous 10

years. We identified these researchers by scanning author lists of the relevant published trials, reviews and conference proceedings. We asked them to verify that all relevant trials had been identified and also if they had knowledge of any other relevant published or unpublished trials. We have not contacted them for this review update.
(4) In 2002 we contacted major pharmaceutical companies by letter and asked if they knew of any relevant unpublished trials. We did not contact them for this update. However, we searched the online Clinical Trial Results and Clinical Trial Registries for Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Novartis, Organon, Pfizer, Roche, and Wyeth (to August 2007).
(5) We searched the online clinical trials and research registers www.strokecenter.org/trials, www.ClinicalTrials.gov, www.Clinicalstudyresults.org and www.anzctr.org.au (to August 2007). The compulsory registration of clinical trial protocols on these sites before recruitment of the first patient, enabled us to elect not to contact researchers and pharmaceutical companies.
(6) We reviewed chapters in books on the prevention and treatment of depression and management of stroke, including but not limited to, reviews of the management of stroke, books specifically directed at the treatment or prevention of depression, and those on stroke and old age.

Data collection and analysis

Two review authors (MH and CH) reviewed all citations and discarded those that were irrelevant, based on the title of the publication and its abstract. In the presence of any suggestion that an article was possibly relevant, we retrieved the full-length article for further assessment. MH and CH independently selected the trials for inclusion in the review from the culled citation list. Potentially relevant Chinese articles were translated by JX. We resolved disagreements by discussion, and CA confirmed the final list and adjudicated any persisting differences of opinion.

Data extraction

MH, CH and JX independently extracted, cross checked and entered the data on forms designed for the purpose. We discussed and resolved any discrepancies before we entered the data into the Review Manager software, RevMan 4.2.
We collected data on:

- the report: author, year, and source of publication;
- the study: sample characteristics, social demography, definition and criteria used for depression;
- the patients: stroke sequence (first ever versus recurrent), social situation, time elapsed since stroke onset, prior history of psychiatric illness, current neurological status, current treatment for depression, and a history of coronary artery disease;
- the research design and features: sampling mechanism, treatment assignment mechanism, adherence, non-response, and length of follow up;
- the intervention: type, duration, dose, timing, and mode of delivery;
- the effect size: sample size, nature of outcome, estimate and standard error.

To allow for intention-to-treat (ITT) analysis, we sought the data irrespective of their adherence, and regardless of whether the patients were subsequently deemed ineligible, or otherwise excluded from treatment or follow up.
We checked all the extracted data for agreement between review authors. We obtained missing information from the primary investigators whenever possible. To avoid introducing bias, this unpublished information was obtained in writing, on forms designed for the purpose, and entered into RevMan.

Study characteristics

Although there are a number of scales devised for assessing the quality of RCTs, there is no convincing evidence that complex and time-consuming scales are more effective than simple scales (Verhagen 2001). As we extracted data, we documented specific details about the following five points.
(1) Generation of the randomisation sequence: the method used; was the study described as randomised, and a genuine randomisation process described; was this adequate, inadequate, or unknown? If the randomisation was blocked, was the size of the blocks known to those entering patients. Adequate randomisation = 1, inadequate/unknown randomisation = 0.
(2) Concealment of the random sequence from those entering patients into the trial: the method used; was it one that ensured tamper-free concealment of allocation; was it adequate, inadequate or unknown? Concealed randomisation = A, not concealed/unknown = B, and insecure = C.
(3) Who was blinded and how successful was blinding? Was the patient, health worker treating the patient, or the follow up raters blinded, and were attempts made to check blinding was successful?
(4) How many participants in each treatment group who were initially randomised were not included in the analysis? Was an ITT analysis possible on all participants from the published data (were there any exclusions from the trial after randomisation, or for cross over treatment groups)?
(5) How many patients were withdrawn from the trial, crossed-over treatment groups, or were lost to follow up (including when the proportion of patients who were lost to follow up was less than 20%)?
MH and CA independently assessed the methodological characteristics of each trial using the above checklist. The two review authors then met for a consensus meeting. They resolved disagreements by discussion, and a third review author (AH) resolved any persisting differences of opinion. For each included trial, we de-

scribed features that influenced the degree of bias, as well as differences in baseline prognostic variables that might invalidate the results. One or more of these variables could be used to undertake sensitivity analyses in subsequent reviews.

Statistical analysis

The main outcome of interest was the proportion of participants who met the diagnostic, or scoring, categories for depression at the end of follow up. For all dichotomous outcomes, we calculated odds ratios (OR), with 95% confidence intervals (CI) where appropriate using fixed-effect analyses.

For continuous outcomes, if ordinal scale data appeared to be approximately normally distributed or if the analysis suggested parametric tests were appropriate, we treated the outcome measures as continuous variables. If there were at least two trials that reported the same outcomes, we reviewed the data for appropriateness of pooling. If there was definite evidence of heterogeneity ($I^2 > 50\%$), we explored the potential reasons for the differences by performing subgroup or sensitivity analyses. If the heterogeneity could not be explained, we combined the trials using random-effects analyses with cautious interpretation, or did not combine them at all.

We used the RevMan software (RevMan 4.2) where possible; we used Excel and SAS for other analyses.

Subgroup and sensitivity analyses

If there was definite evidence of heterogeneity, we explored potential reasons for the differences by performing subgroup analyses, sensitivity analyses, and meta-regression (Normand 1999). Where possible, we had planned to perform subgroup analyses to examine the impact of treatment type and duration, and of stroke severity. We were to undertake sensitivity analyses to explore the influence of date of publication, sample size, method of diagnosing depression, duration of follow up, high (greater than 20%) number of drop outs, and blinded versus unblinded outcome assessors. The sensitivity of the combined estimate to individual trials was to be explored by leaving one study out, calculating the combined effect of the remaining trials, and comparing the results with the combined effect based on all the trials. If meta-analyses are undertaken in updates of this review, funnel plots will be used to detect the presence of publication bias and the Trim and fill technique will be used to determine whether our results are sensitive to publication bias (Duval 2000).

These were not completed for the current version of this review.

Additional requested data

We wrote to the authors of all newly included, ongoing and drop-out studies requesting data that were unavailable, or ambiguous in the published articles. We received responses with additional data from authors of two new trials (Lai 2006a; Watkins 2007). In 2004 we received responses with regard to six trials (Andersen 1994; Downes 1995; Fruehwald 2003; Lincoln 2003; Murray 2002; Reding 1986, Towle 1989). We received no response from the remaining authors. We also wrote to all pharmaceutical companies known to produce, or have a licence to produce, antidepressants in 2004. We received nine replies identifying no new trials.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Seven new trials (Jiang 2001a; Lai 2006a; Ponzio 2001; Rampello 2005; Watkins 2007; Yang 2002; Zhao 2004) have been included since the previous published version of this review resulting in 16 included trials (17 interventions), with 1655 participants at entry, for inclusion (Andersen 1994; Fruehwald 2003; Jiang 2001a; Jiang 2001b; Lai 2006a; Lincoln 2003; Lipsey 1984; Murray 2002; Ohtomo 1991; Ponzio 2001; Rampello 2005; Reding 1986; Towle 1989; Watkins 2007; Wiart 2000; Yang 2002; Zhao 2004).

Another eight trials require more information before we decide on inclusion or not. Lincoln 2003 compared an active treatment with an attention-control (the time spent by participants in the treatment group with a trained therapist was controlled in the attention-control group by participants spending an equal amount of time in focused conversation), as well as a control (standard care) group. We combined data from the attention-control and control group, and compared this with data for the treatment group. Jiang 2001a compared two active treatment arms with a placebo arm. We compared data from both treatment arms (Jiang 2001a; Jiang 2001b) with data from half the number of participants in the placebo arm and presented the results as two separate trials. More detailed information is provided in Characteristics of included studies.

We identified nine additional trials (Choi-Kwon 2006; Downes 1995; Graffagnino 2003; Isenberg 2000; Mauri 1988; Meara 1998; Ohtomo 1985; Xie 2003; Zhou 2004) that met the inclusion criteria for this review. However, no outcome data were available (unpublished data only, Downes 1995; Graffagnino 2003; Isenberg 2000; data not presented by treatment group or in a suitable format, Choi-Kwon 2006; Mauri 1988; Meara 1998; requires translation, Ohtomo 1985, or method of assessment of mood unclear Xie 2003; Zhou 2004). These trials are considered 'drop outs' and more detailed information on these trials is provided in Table 1. Another three trials (Graven 2008; Mitchell 2002; Thomas 2007) are currently ongoing.

A total of 167 trials were excluded. In 93 trials there was no placebo (pharmaceutical trials) nor usual care (psychotherapy trials) comparison arms, and in 55 the intervention did not meet the review

criteria. The remaining trials were excluded for the variety of reasons listed.

Participants

Sociodemography

The mean age of participants ranged from 60 to 78 years. Six trials had balanced proportional frequencies of males and females (Lincoln 2003; Lipsey 1984; Ponzio 2001; Rampello 2005; Reding 1986; Watkins 2007); four had more males in the control group (Andersen 1994; Fruehwald 2003; Jiang 2001a; Jiang 2001b), and five had more males in the active treatment group (Murray 2002; Towle 1989; Wiart 2000; Yang 2002; Zhao 2004), with the percentage of males ranging from 30% to 71%. The proportion of males was unknown in two trials (Lai 2006a; Ohtomo 1991).

Stroke details

Six trials included participants with stroke due to intracerebral haemorrhage as well as cerebral infarction, five specified the diagnoses was made on the basis of a combination of standard clinical and CT criteria (Andersen 1994; Fruehwald 2003; Lipsey 1984; Rampello 2005; Wiart 2000), with the frequency of CT reported at 100% (Yang 2002 did not specify the method of diagnosis). Five trials included all stroke subtypes (Lincoln 2003; Murray 2002; Reding 1986; Towle 1989; Watkins 2007) with two reporting a CT rate of 100% (Murray 2002; Watkins 2007), one trial included only cases of cerebral infarction (Ohtomo 1991) and five did not specify stroke details (Jiang 2001a; Jiang 2001b; Lai 2006a; Ponzio 2001; Zhao 2004).

Recruitment time window

The average time from stroke onset to entry into trials ranged from 'within a few days' (Fruehwald 2003) to 25 months (Towle 1989). Six trials included patients within one month of stroke onset (Andersen 1994; Fruehwald 2003; Lipsey 1984; Murray 2002; Watkins 2007; Wiart 2000). The time window from stroke onset to randomisation was wide (several months to more than two years) for seven trials (Andersen 1994; Lincoln 2003; Lipsey 1984; Murray 2002; Rampello 2005; Towle 1989; Yang 2002) and narrow (several days to several weeks) for four trials (Fruehwald 2003; Reding 1986; Watkins 2007; Wiart 2000). One trial (Towle 1989) specifically excluded patients with a stroke onset of less than one year from randomisation. Details of the time window for entry are uncertain for three trials (Lai 2006a; Ohtomo 1991; Ponzio 2001).

Exclusion criteria

Nine trials employed criteria that excluded patients with varying degrees of communication and/or cognitive difficulties and/or other co-existing conditions that would interfere with outcome assessments or participation in the treatment regimens (Andersen 1994; Fruehwald 2003; Lipsey 1984; Murray 2002; Ponzio 2001; Rampello 2005; Watkins 2007; Wiart 2000; Zhao 2004). Other specific reasons for exclusion included: a history of depression in the last year (Andersen 1994) or previous five years (Lincoln 2003); on antidepressant medication (Andersen 1994; Jiang 2001a; Jiang 2001b; Lipsey 1984; Murray 2002) or receiving psychotherapy (Ponzio 2001; Watkins 2007); concurrent psychiatric illness (Murray 2002; Ponzio 2001; Rampello 2005; Wiart 2000); any contraindication to the study treatment (Lipsey 1984; Ponzio 2001; Wiart 2000) or where there was concurrent use of antiarrhythmic medication (Reding 1986); a history of myocardial infarction within the previous month (Murray 2002; Reding 1986); a stroke in the year prior to randomisation (Towle 1989); inability to speak English, blindness or deafness (Lincoln 2003); living outside the specific locality (Lincoln 2003; Watkins 2007); living in a hospital or in residential care (Towle 1989); and substance dependency (Ponzio 2001; Rampello 2005). Details are unclear for three trials (Lai 2006a; Ohtomo 1991; Yang 2002).

Setting

Six trials recruited patients from outpatient clinics or from home after they had been discharged from hospital (Lincoln 2003; Ponzio 2001; Rampello 2005; Towle 1989; Yang 2002; Zhao 2004); six trials recruited only inpatients soon after stroke onset (Fruehwald 2003; Jiang 2001a; Jiang 2001b; Lai 2006a; Reding 1986; Watkins 2007); and three trials used mixed inpatient and outpatient sources of patients (Andersen 1994; Lipsey 1984; Murray 2002). Details are unclear for two trials (Ohtomo 1991; Wiart 2000).

Interventions

Twelve trials assessed 13 pharmacological interventions (Andersen 1994; Fruehwald 2003; Jiang 2001a; Jiang 2001b; Lai 2006a; Lipsey 1984; Murray 2002; Ohtomo 1991; Ponzio 2001; Rampello 2005; Reding 1986; Wiart 2000; Yang 2002), and four assessed psychological interventions (Lincoln 2003; Towle 1989; Watkins 2007; Zhao 2004). Results from these trials are presented and discussed separately.

Pharmacotherapy

Among the trials of pharmacological treatments, seven trials compared an SSRI (citalopram, Andersen 1994; fluoxetine, Fruehwald 2003; Wiart 2000; paroxetine Lai 2006a; Ponzio 2001; Yang 2002; sertraline Murray 2002) against placebo; two trials compared a

tricyclic antidepressant (amitriptyline, Jiang 2001a; nortriptyline, Lipsey 1984) against placebo; and other treatments with antidepressant effects were used in four trials (deanxit Jiang 2001b, aniracetam Ohtomo 1991, reboxetine Rampello 2005, trazodone Reding 1986). Five trials used a flexible dose regimen, with a lower dose in older people and/or dose escalation for persistently elevated mood scores during follow up (Andersen 1994; Fruehwald 2003; Jiang 2001a; Lipsey 1984; Murray 2002; Reding 1986). Six trials (Jiang 2001b; Lai 2006a; Ohtomo 1991; Ponzio 2001; Rampello 2005; Wiart 2000; Yang 2002) used a fixed dose. The duration of treatment was generally short, ranging from four to six weeks (Andersen 1994; Lipsey 1984; Reding 1986; Wiart 2000) to 12 weeks (Fruehwald 2003; Lai 2006a; Ohtomo 1991) to 16 weeks (Rampello 2005; Yang 2002). Murray 2002, Jiang 2001a and Jiang 2001b provided treatment with a target duration of 26 weeks.

Psychotherapy

The forms of psychotherapy included problem-solving therapy with counselling delivered by social workers (Towle 1989), more structured cognitive behavioural therapy (CBT) delivered by nurses (Lincoln 2003), motivational interviewing (MI) delivered by nurses and non-clinical psychologists (Watkins 2007), and a supportive psychological intervention including education delivered by special personnel (Zhao 2004). The frequency and duration of sessions was individually tailored to the needs of the patient in three trials, so that the duration of treatment ranged from daily, less than 30 minute, sessions over four weeks (Zhao 2004), seven to 10 one-hour sessions over three months (Lincoln 2003), to four to six months (Towle 1989). In the most recent trial (Watkins 2007) all patients received up to four individual sessions of 30 to 60 minutes over four weeks (one per week). Three trials used standard care as the control comparison (Towle 1989; Watkins 2007; Zhao 2004) and the other used both a standard care control and an attention-control group (Lincoln 2003).

Depression criteria

A wide variety of criteria and methods were used to diagnose depression in the included trials: eight trials included patients who had high scores only on standard depression scales such as the HDRS (Jiang 2001a; Jiang 2001b; Lai 2006a; Yang 2002; Zhao 2004 with cutpoint scores varying from 6 (Lai 2006a) to 20 (Rampello 2005)), the MADRS (cutpoint of 18 Ponzio 2001) and either the WDI (cutpoint 17) or GHQ-28 (cutpoint 9, Towle 1989), or the GHQ-28 alone (cutpoint 4, Watkins 2007); two trials included patients with depressive illness diagnosed by psychiatric interview using standard psychiatric criteria (Lipsey 1984; Reding 1986); five trials used a combination of psychiatric interview and high scores on a depression scale (Fruehwald 2003, HDRS cutpoint 15; Lincoln 2003, BDI cutpoint 10, WDI cutpoint 18; Murray 2002, MADRS cutpoint 9; Rampello 2005, HDRS cutpoint 20, BDI cutpoint 15; Wiart 2000, MADRS cutpoint 19); and one trial used a transformation of symptom domain scores from a standard depression scale (HDRS) to derive a DSM-III-R diagnosis of depression (Andersen 1994). The remaining trial included patients based on the 'physician's impression' (Ohtomo 1991).

Outcome measures

Depression

Eight assessment scales were used to assess mood or assess change in mood at the end of treatment in nine trials. The most commonly used measure was the HDRS (Andersen 1994; Fruehwald 2003; Jiang 2001a; Jiang 2001b; Lai 2006a; Lipsey 1984; Rampello 2005; Yang 2002; Zhao 2004). Seven trials used two or more scales to assess abnormal mood or depression (Fruehwald 2003; Lincoln 2003; Lipsey 1984; Ponzio 2001; Rampello 2005; Towle 1989; Watkins 2007), one trial determined depression by psychiatric interview and a scale (Reding 1986) and one relied on physician impression (Ohtomo 1991).

Additional outcomes

A wide variety of additional measures were used in the trials (*see* Characteristics of included studies). Most trials only presented selected outcome data. Only six trials presented data from all questionnaires listed as being administered (Jiang 2001a; Jiang 2001b; Ponzio 2001; Towle 1989; Watkins 2007; Wiart 2000). Adverse event data were often not reported or reported poorly.

Risk of bias in included studies

Generation and concealment of randomisation sequence

Six trials used an appropriately generated and clearly concealed randomisation procedure (Andersen 1994; Fruehwald 2003; Lincoln 2003; Murray 2002; Towle 1989; Watkins 2007). The randomisation sequence appeared to be appropriately generated in nine trials (Andersen 1994; Fruehwald 2003; Lincoln 2003; Lipsey 1984; Murray 2002; Rampello 2005; Reding 1986; Towle 1989; Watkins 2007), however, not all trials described adequate concealment of allocation (Jiang 2001a; Jiang 2001b; Lai 2006a; Lipsey 1984; Ohtomo 1991; Ponzio 2001; Rampello 2005; Reding 1986; Wiart 2000; Yang 2002; Zhao 2004).

Blinding of participants and outcome assessors

Four of the pharmacotherapy trials used an unequivocal double-blinded outcome assessment for all patients (Fruehwald 2003; Lipsey 1984; Murray 2002; Reding 1986). Four trials stated a double-blind method but did not state who was blinded (Andersen 1994; Ohtomo 1991; Ponzio 2001; Wiart 2000) and in one trial the outcome assessor was not blinded (Rampello 2005). Three psychotherapy trials used single (assessor) blinded outcome assessment (Lincoln 2003; Towle 1989; Watkins 2007), details were unclear for the remaining trials (Jiang 2001a; Jiang 2001b; Lai 2006a; Yang 2002; Zhao 2004).

Method of analysis

Six trials reported per-protocol analyses (Fruehwald 2003; Jiang 2001a; Jiang 2001b; Lincoln 2003; Lipsey 1984; Towle 1989), four provided ITT analyses (Ponzio 2001; Reding 1986; Watkins 2007; Wiart 2000), and two used ITT in addition to per-protocol analyses (Andersen 1994; Murray 2002). The method of analysis was unclear in five trials (Lai 2006a; Ohtomo 1991; Rampello 2005; Yang 2002; Zhao 2004).

Trial size and participants leaving the trial early

The pharmacotherapy trials ranged in size from 17 (Reding 1986) to 285 (Ohtomo 1991) participants, with the drop-out rate ranging from 0% (Jiang 2001a; Jiang 2001b; Ponzio 2001; Rampello 2005; Reding 1986) to 44% (Murray 2002). In the four psychotherapy trials, the number of participants ranged from 44 (Towle 1989) to 254 (Watkins 2007), with drop-out rates ranging from 2% (Towle 1989) to 6% (Lincoln 2003).

Effects of interventions

Overall, 1655 participants were included in this review. In view of the large number and heterogeneous nature of the outcome measures and the reporting of results, we considered it inappropriate to pool outcome data for many endpoints.

Pharmacotherapy

Outcome data were available for 12 antidepressant interventions including 1121 participants (Andersen 1994; Fruehwald 2003; Jiang 2001a; Lai 2006a; Lipsey 1984; Murray 2002; Ohtomo 1991; Ponzio 2001; Rampello 2005; Reding 1986; Wiart 2000; Yang 2002). There was evidence of a benefit of pharmacotherapy in treating depression (remission) with a pooled OR of 0.47 (95% CI 0.22 to 0.98, Analysis 1.1) in the binary outcome measures the trial authors used, however there was substantial heterogeneity across individual studies. There was also evidence of a beneficial effect of pharmacotherapy in reducing (improving) scores on mood rating scales (response), however, because of the multiple scales used to assess mood in several individual trials (Andersen 1994; Fruehwald 2003; Lipsey 1984; Rampello 2005), we did not perform a meta-analysis (Analysis 1.2 and Analysis 1.3). Benefit of pharmacotherapy was also seen in the proportion of participants reporting a 50% or greater reduction in mood scores (OR 0.22, 95% CI 0.09 to 0.52, Analysis 1.4), however, confidence intervals were wide for this endpoint and for average mood scores at the end of treatment which included significant effects both in favour of treatment and in favour of control. There was no evidence of benefit of pharmacotherapy in improving cognitive function. One trial showed a significant benefit on pharmacotherapy on anxiety (OR 0.48, 95% CI 0.26 to 0.88, Analysis 1.5) (Ohtomo 1991). There was no evidence of benefit of pharmacotherapy in improving activities of daily living, or reducing disability, as demonstrated by heterogeneous results with wide confidence intervals. Significant evidence of harm was demonstrated in adverse events (*see* Analysis 1.14), in particular central nervous system OR 1.96 (95% CI 1.19 to 3.24), gastrointestinal OR 2.37 (95% CI 1.38 to 4.06) and other less specific adverse events OR 1.51 (95% CI 0.91 to 2.34). Outcome data were available for one combination preparation (Deanxit, a combination of flupentixol and melitracen) that included 45 people (Jiang 2001b). There was evidence of a benefit of pharmacotherapy in improving mood scores (secondary outcome, mean difference -8.09 (95% CI -12.57 to -3.61, Analysis 2.1) and in neurological function (crude difference between mean scores at the end of treatment -2.19 (95% CI -4.01 to -0.37, Analysis 2.4).

Psychotherapy

Depression data were available for three trials including 445 participants (Lincoln 2003; Watkins 2007; Zhao 2004) with some additional adverse event data available from one trial (Towle 1989). No treatment effect was demonstrated on any of the endpoints measured.

DISCUSSION

Seven new trials, four of pharmacotherapy (five interventions, Jiang 2001a; Lai 2006a; Ponzio 2001; Rampello 2005; Yang 2002) and two of psychotherapy (Watkins 2007; Zhao 2004), meeting our review criteria have become available since this review was first published in 2004. The addition of the new pharmacotherapy trials altered the results of the previous review and while there is now some evidence to support the use of pharmacotherapy to treat depression after stroke there is also stronger evidence of more adverse events for those receiving antidepressants. The results of this meta-analysis should also be considered in light of the recent meta-analysis showing a small benefit of SSRIs only in those with severe depression, with that benefit possibly being explained by fewer in this group responding to placebo (Kirsch 2008). The addition of the psychotherapy trials (Watkins 2007; Zhao 2004) did

not change the previous review finding that there is no evidence of the effectiveness of psychotherapy for the treatment of depression after stroke.

Unfortunately, the results of the trials in this review did not allow for pooling of some key endpoints, so we have provided a predominantly narrative review of the evidence. However, this evidence of benefit must be considered alongside several basic methodological limitations of many of these trials, including the short duration of many interventions, variation in the types of trial participants recruited and the methods used to diagnose depression, lack of an a priori measurable endpoint, and the generally poor design, outcome assessment, analysis and interpretation of results. Of particular concern is the evidence of harm (more adverse events) given the small number of trials that systematically recorded and reported adverse events, making reliable the assessment of the benefits and risks of treatments impossible.

For pharmacotherapy trials, a key requirement is to achieve a therapeutic dose of the medication for an adequate period of time. The guidelines for the American College of Physicians suggest that antidepressants should be continued for at least four months beyond initial recovery, and that treatment should be changed if no response has been shown by six weeks (Snow 2000). In this review, the interventions in most pharmacotherapy trials were probably not given for an adequate length of time to show a maximal or sustained response. Therefore, we are unable to comment on the long-term effects of antidepressant therapy, or provide information on the most appropriate duration or dose of treatment, if one group of antidepressants is more efficacious, or provide stopping rules for antidepressant therapy in this group.

For psychotherapy trials, there is also good evidence that efficacy is linked to delivery of an adequate exposure to the intervention. This means that therapists should be trained and supervised in the therapy they are delivering, and use a standardised, pre-specified, framework for therapy. To achieve this in psychotherapy trials, the therapy is determined using a manual and the research therapists are trained and supervised in the use of the manual. Success in brief therapy is linked to adherence to the therapeutic model as well as to the therapists' characteristics. Future stroke psychotherapy trials should also adhere to these standard psychotherapy research guidelines if there is to be any probability of demonstrating consistency and response.

The trials in this review included participants with depression occurring several days to more than two years following stroke. However, depression occurring in the early phase of stroke is likely to be different from that occurring several months or years after the event. Survivors in the first weeks following stroke are coping with the consequences of experiencing a potentially life-threatening event, as well as recovering from the disabling effects of the stroke itself. In the medium to long-term, survivors of stroke are more likely to be adjusting to the prospects of permanent disability and changes in social and financial circumstances. It is difficult to summarise the evidence from such mixed populations, and even in doing so, whether it could be considered meaningful, especially given the high risk of relapse of depression in the first few months of recovery, which declines over time (Snow 2000).

In contrast to the wide range in the length of time between stroke onset and entry into the trial, many trials included patients with narrow demographic and clinical characteristics, in particular, they excluded patients with communication problems, cognitive loss, or previous psychiatric illness. This reinforces a common criticism of depression research, that the trial participants are not representative of those requiring treatment in the 'real world' (Zimmerman 2002). It would appear that this criticism is also applicable to trials of depression following stroke, where up to half of survivors may be excluded using such criteria (Turner-Stokes 2003). Given the high age of most patients with stroke, and the frequent presence of neurological impairments, aphasia and co-morbid medical conditions, the fact that up to half of all survivors of stroke are excluded limits the external validity (generalisability) of the results. The use of a large list of exclusions means that the results are applicable to only a small proportion of stroke survivors who have a narrow range of co-morbidities and other characteristics. Such exclusions may be justifiable for trials of psychotherapy, where participants are required to actively participate in therapy by talking, but seem inappropriate for the pharmacotherapy trials. Ideally, patients should be heterogeneous with regard to stroke diagnosis, which requires the use of standard diagnostic criteria and neuroimaging in a high proportion of cases. Given differences in the natural history and management of SAH it could be argued that this form of stroke should be examined separately.

The lack of a consistent method to diagnose depression, both for entry and outcome, in the included trials is a concern and a reflection of the general lack of a standard definition for a 'healthy state' among people with mood disorders (Keller 2003). Few trials stated whether the primary goal of therapy was remission (no longer meeting the baseline criteria for depression), response (a 50% reduction in mood scores from baseline), or simply a greater reduction in mood scores (or difference in scores) in one of the randomised groups. The complete remission of symptoms is arguably the most meaningful endpoint for the patient, whereas the significance of a small reduction in mood scores on a continuous scale is generally difficult to interpret for the patient and the treating physician. These problems with outcome assessment were further confounded by the frequent use of multiple scales both between and within trials. Because multiple scales were used in each trial, selective reporting of findings was also common. Any one scale was used across only eight trials at most, and significantly different cut-points were used to determine depression at entry and trial end. Given the practical difficulties and high cost of conducting psychiatric interviews in clinical trials it seems appropriate to adopt a pragmatic approach to determine depression

on the basis of a validated mood questionnaire or semi-structured interview. Hopefully the compulsory registration of trial protocols on publicly available databases will reduce, if not eliminate, the opportunity for selective reporting of results. It has been suggested that more than one third of efficacy outcomes and half of harm outcomes are inadequately reported (Chan 2004).

Several other methodological deficiencies in trials further limit the conclusions that can be drawn from this review. Many trials were small, less than half reported adequate concealment of the randomisation sequence, and drop-out rates were high in several trials. One trial (Andersen 1994) excluded patients randomised before 28 days from their analyses, co-incidentally this group of patients experienced large responses in the placebo group. Additionally, blinding of investigators and outcome assessors was seldom stated. Reporting and analysis of results varied, with most (eight) trials presenting per-protocol analyses only or not specifying whether analyses were per protocol or ITT. For trials with high drop-out rates, ITT analysis of the data is very important. Researchers need to specify how missing data are handled (Hollis 1999). If ITT (giving missing data both the best possible and worst possible outcome) and per-protocol analysis indicate similar trends, the findings are likely to be interpreted as being clinically more robust. It continues to seem pertinent to recommend that researchers consult the ICH Harmonised Tripartite Guidelines for statistical principles for clinical trials (ICH 1999) and the revised CONSORT guidelines (Moher 2003) when designing, and reporting findings of, future trials.

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence from trials in stroke patients to tentatively support the use of prescription antidepressants to treat depression but this must be considered in light of the evidence of an associated increase in harm and of a lack of efficacy of SSRIs generally except in those with severe depression. Antidepressants may produce a remission or a response in terms of lower scores on mood rating scales, but also increase adverse events. It is recommended that these agents are used with caution in those with a persistent depressive disorder after stroke, as little is known about the risks, especially of seizures, falls and delirium, especially in older people and those on concomitant medication. We found no evidence for the benefit of psychotherapy.

Implications for research

We recommend the need for further research in this area. Future trials investigating the effect of pharmacotherapy and psychotherapy in the treatment of depression in people after stroke should address the following:

- review and refine the methods for trials of psychological endpoints in people with physical illness;
- recruit an adequate number of participants so that variables such as time passed between stroke and recruitment, and inclusion of patients with dysphasia, and SAH can be controlled, and modest but clinically important effects can be detected;
- recruit a representative 'real world' sample of patients to enable results to be generalised to the majority of stroke survivors;
- provide treatment for a sufficient duration and follow up, so that rates of relapse or maintenance of remission can be assessed;
- psychotherapy interventions need to be carefully specified and monitored;
- include careful, prospective assessment and complete reporting of adverse events;
- define a priori an unambiguous, measurable, primary endpoint;
- limit the number of secondary outcomes to three or four and report results for all outcomes.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Andersen 1994

Methods	Parallel design Method of randomisation: blocks of 4 used Method of 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 due to AE (6 treatment, 1 control), all excluded from analysis
Participants	Location: Denmark Setting: mixed Treatment: 33 (36% male, mean age 68 years, SD 4) Control: 33 (66% male, mean age 66 years, SD 9) Stroke criteria: ischaemic stroke and primary intracerebral haemorrhage; diagnosis via clinical signs and CT (100%); stroke 2 to 52 weeks prior to randomisation (average time 12 weeks) Depression criteria: HDRS score > 12 (score transformed to appropriate DSM-III-R criteria) Other entry criteria: none stated Comparability of treatment groups: balanced
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
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 Adverse events 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Fruehwald 2003

Methods	Parallel design Method of randomisation: permuted block design Method of concealment: centralised Blinding: double blind Participants: yes Relatives: yes Clinical examiners: yes Nursing staff: yes Analysis: per protocol: death (1 treatment), withdrawn due to AE (1 treatment, 2 control), all excluded from analysis
Participants	Location: Austria Setting: inpatients Treatment: 28 (46% male, mean age 65 years, SD 14) Control: 26 (71% male, mean age 64 years, SD 14) Stroke criteria: ischaemic stroke and primary intracerebral haemorrhage; diagnosis via clinical signs and CT (100%); stroke on average 11 days prior to randomisation Depression criteria: psychiatric interview, HDRS score > 15 Other entry criteria: none stated Comparability of treatment groups: non-significant trend towards more females and right-sided lesion strokes in treatment group
Interventions	Treatment: fluoxetine 20 mg, daily; dose escalation at 4 weeks if HDRS score > 13 Control: matched placebo Duration: treatment continued for 12 weeks
Outcomes	Depression: change in scores from baseline to end of treatment on HDRS, BDI and Clinical Global Impression Scale (Item 1) Proportion of responders (< 13 HDRS) Additional: Scandinavian Stroke Scale Death Adverse events (selected data) Unable to use: RS, BI, MMSE (data not presented at follow up) Adverse events data on dizziness, nausea and cephalalgia (data not presented by group)
Notes	Exclusion criteria: MMSE < 20, more than mild communication deficit, diseases of the CNS and previous degenerative or expansive neurological disorders

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Jiang 2001a

Methods	Parallel design Method of randomisation: randomised stated, method unclear Method of concealment: unclear Blinding: single blind reported Participants: yes Investigators: no Outcome assessors: unclear Analysis: ITT (no drop outs)
Participants	Location: China Setting: inpatient Treatment: 30 (57% male, mean age 62 years, SD 14) Control: 15 (60% male, mean age 63 years, SD 15) Stroke criteria: unclear, diagnosis via CT or MRI (100%); stroke 0 to 7 days prior to randomisation Depression criteria: HDRS > 8 Other entry criteria: Chinese stroke scale score > 8, can independently complete assessment scale, aged < 80 years, no severe negative life events in past year, first stroke, no previous psychosis or antidepressant medication Comparability of treatment groups: intervention group younger, higher HDRS score and lower CSS score
Interventions	Treatment: amitriptyline 50 mg increasing by 25 mg per day to 200 mg daily Control**: placebo (not matched) two tablets per day Duration: treatment continued for 6 months
Outcomes	Depression: change in scores from baseline to end of treatment on HDRS Additional: adverse events, CSS
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Jiang 2001b

Methods	Parallel design Method of randomisation: randomised stated, method unclear Method of concealment: unclear Blinding: single blind reported Participants: yes Investigators: no Outcome assessors: unclear Analysis: ITT
Participants	Location: China Setting: inpatient Treatment: 30 (58% male, mean age 62 years, SD 14)

Jiang 2001b (*Continued*)

	Control: 15 (60% male, mean age 63 years, SD 15) Stroke criteria: unclear, diagnosis via CT or MRI (100%); stroke 0 to 7 days prior to randomisation Depression criteria: HDRS > 8 Other entry criteria: Chinese stroke scale score > 8, can independently complete assessment scale, aged < 80 years, no severe negative life events in past year, first stroke, no previous psychosis or antidepressant medication Comparability of treatment groups: intervention group younger, higher HDRS score and lower CSS score
Interventions	Treatment: Deanxit 2 tablets daily Control**: placebo (not matched but frequency matched) Duration: treatment continued for 6 months
Outcomes	Depression: change in scores from baseline to end of treatment on HDRS Additional: adverse events, CSS
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Lai 2006a

Methods	Parallel design Method of randomisation: randomised stated, method unclear Method of concealment: unclear Blinding: unclear Analysis: unclear
Participants	Location: China Setting: inpatients Treatment: 40 Control: 40 (Total 54% male, mean age 60 years, SD 14) Stroke criteria: unclear; diagnosis via CT; time from stroke to randomisation unclear Depression criteria: HDRS score > 6 Other entry criteria: none stated Comparability of treatment groups: unclear
Interventions	Treatment: paroxetine 20 mg daily Control: placebo Duration: treatment continued for 2 months
Outcomes	Depression: differences in mean scores on HDRS at end of treatment, 50% reduction in scores on HDRS Additional: Scandinavian Stroke Scale Death Adverse events (selected data)

Lai 2006a (*Continued*)

	Unable to use: RS, BI, MMSE (data not presented at follow up) Adverse events data on dizziness, nausea and cephalalgia (data not presented by group)
Notes	Exclusion criteria: unclear

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Lincoln 2003

Methods	Parallel design Method of randomisation: computer-generated random number sequence Method of concealment: opaque consecutively numbered sealed envelopes held by independent researcher Blinding: single blind Participants: no Investigators: yes Outcome assessors: yes Analysis: per protocol: death (2 control), withdrew consent (1 control, 1 attention control, 1 treatment), all excluded from analysis
Participants	Location: UK Setting: outpatients Treatment: 39 (51% male, mean age 67 years, SD 13) Attention control^: 41 (51% male, mean age 66 years, SD 13) Control^: 41 (51% male, mean age 65 years, SD 15) Stroke criteria: all subtypes; diagnosis via clinical signs and symptoms and CT (percentage not reported); stroke 1 to 6 months prior to randomisation Depression criteria: psychiatric interview (SCAN), BDI score > 10, WDI score > 18 Other entry criteria: none stated Comparability of treatment groups: significantly more participants with an ICD-10 diagnosis of depression in the treatment group
Interventions	Treatment: cognitive behavioural therapy, including modification of unhelpful thoughts and beliefs (10 x 1 hour sessions over 13 weeks) Attention control: no formal therapeutic intervention; conversation focused on day-to-day occurrences and discussion regarding the physical effects of stroke and life changes (10 x 1 hour visits over 13 weeks) Control: standard care (no contact) Delivered by: community psychiatric nurse
Outcomes	Depression: change in scores from baseline to end of treatment and end of follow up on BDI, WDI, GHQ 28* Additional: Leaving the study early Death Extended ADL Unable to use: adverse events (data not presented)

Lincoln 2003 (*Continued*)

	London Handicap Scale (no mean or SD presented)
Notes	Exclusion criteria: blindness, deafness, participant did not speak English, dementia documented in medical records, treated for depression in previous 5 years, lived outside specified locality, participant could not complete questionnaire unaided Additional unpublished data provided by author

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Lipsey 1984

Methods	Parallel design Method of randomisation: random number table Method of concealment: unclear Blinding: double blind Participants: yes Families: yes Clinical examiners: yes Nursing staff: yes Analysis: per protocol: withdrawn due to AE (3 treatment, 1 control), withdrew consent (1 control), all excluded from analysis; After at least one week of treatment: withdrew due to AE (3 treatment, 1 control), death (2 control), lost to follow-up (2 control), included in analyses using last observation carried forward
Participants	Location: USA Setting: mixed Treatment: 17 (64% male, mean age 62 years, SD 9) Control: 22 (65% male, mean age 60 years, SD 12) Stroke criteria: ischaemic stroke and primary intracerebral haemorrhage; diagnosis via clinical signs and CT (100%); stroke on average 262 +/- 437 days (treatment group) and 128 +/- 190 days (control group) prior to randomisation Depression criteria: psychiatric interview (PSE, DSM-III) Other entry criteria: included outpatients who requested treatment for poststroke depressive disorder Comparability of treatment groups: balanced
Interventions	Treatment: nortriptyline 20 to 100 mg daily; 2 treatment regimens combined; dose escalation over treatment period to 100 mg Control: matched placebo Duration: treatment continued for 4 to 6 weeks
Outcomes	Depression: change in scores from baseline to end of treatment on HDRS and ZDS*,^,† Proportion no longer meeting entry criteria (DSM-III) Additional: Leaving the study early Death Adverse events

Lipsey 1984 (*Continued*)

	Unable to use: PSE (modified by authors), MMSE, John Hopkins Functioning Inventory, Social Ties Checklist (data not presented)
Notes	Exclusion criteria: current treatment for depression, severe comprehension deficit, medical contraindication to nortriptyline

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Murray 2002

Methods	Parallel design Method of randomisation: block Method of 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 due to AE (8 treatment, 5 control), withdrew consent (1 control), all excluded from analysis
Participants	Location: Sweden Setting: mixed Treatment: 62 (52% male, mean age 71 years, SD 10) Control: 61 (44% male, mean age 71 years, SD 10) Stroke criteria: all subtypes, diagnosis via clinical signs 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 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: matched placebo Duration: treatment continued for 26 weeks
Outcomes	Depression: change in scores from baseline to end of treatment on MADRS Additional: Leaving the study early Death Unable to use: Scandinavian Stroke Scale, BI, Stroke Unit Mental Status, Examination social performance, treatment costs, mortality, relative's situation, neuropsychological performance, neurological recovery (data not presented) Adverse events (selected data presented)

Murray 2002 (*Continued*)

Notes	Exclusion criteria: under 18 years of age, severely impaired communication, apparent difficulties in adhering to study protocol, acute myocardial infarction, other psychiatric illness other than depression, significant risk of suicide, antidepressants during the month before 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Ohtomo 1991

Methods	Parallel design Method of randomisation: randomised stated, method unclear Method of concealment: unclear Blinding: double blind reported, those blinded not stated Analysis: unclear
Participants	Location: Japan Setting: unclear Treatment: 150 (details unclear) Control: 135 (details unclear) Stroke criteria: ischaemic stroke; method of diagnosis unclear; time from stroke to randomisation unclear Depression criteria: based on physician's impression, no scale was used for evaluation Other entry criteria: none stated Comparability of treatment groups: unclear
Interventions	Treatment: aniracetam 600 mg twice daily Control: matched placebo Duration: treatment continued for 12 weeks
Outcomes	Depression: physician assessment of change in depression from baseline to end of treatment Additional: physician assessment of change in anxiety Unable to use: Leaving the study early (data not presented) Death (data not presented) Adverse events (data not presented)
Notes	Exclusion criteria: unclear

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ponzio 2001

Methods	Parallel design Method of randomisation: randomised stated, method unclear Method of concealment: unclear Blinding: double blind reported, those blinded not stated Analysis: ITT
Participants	Location: Italy Setting: outpatient Treatment: 112 (54% male, mean age 64 years, SD 11) Control: 117 (55% male, mean age 66 years, SD 11) Stroke criteria: unclear; method of diagnosis unclear; time from stroke to randomisation unclear Depression criteria: MADRS > 18 Other entry criteria: 18 to 85 years of age, MMSE score > 23 Comparability of treatment groups: balanced
Interventions	Treatment: paroxetine 20 to 40 mg daily Control: matched placebo Duration: treatment continued for 8 weeks
Outcomes	Depression: change in scores from baseline to end of treatment on MADRS, CGI Additional: Proportion scoring < 7 on MADRS and responders on CGI Change in Rankin and BI scores from baseline to end of treatment Adverse events
Notes	Exclusion criteria: concurrent predominant psychiatric disorders, psychotropic pharmacotherapy, substance abuse/dependence, participation in other clinical trials, suicide risk, concomitant medication, intolerance to paroxetine

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Rampello 2005

Methods	Parallel design Method of randomisation: computer generated code number Method of concealment: code disclosed on box. Blinding: double blind Participants: yes Investigators: yes (had potential for being unblinded) Outcome assessor: no Analysis: unclear; no-one withdrew from the study
Participants	Location: Italy Setting: outpatient Treatment: 16 (44% male, mean age 78 years, SD 4) Control: 15 (46% male, mean age 77 years, SD 4)

Rampello 2005 (*Continued*)

	Stroke criteria: single ischaemic or hemorrhagic stroke; diagnosis via CT and MRI; stroke less than 12 months prior to randomisation Depresion criteria: psychiatric interview, HDRS > 20, BDI > 15 Other entry criteria: presence of major or minor depression, presence of retarded depression, lack of treatment with antidepressants 2 weeks prior to randomisation, absence of treatment with neuroleptic drugs during 3 months before enrolment, informed consent Comparability of treatment groups: balanced
Interventions	Treatment: reboxetine 4 mg twice daily Control: matched placebo Duration: treatment continued for 16 weeks
Outcomes	Depression: change in scores from baseline to end of treatment on HDRS* and BDI* Additional: Adverse events Unable to use: adverse event (data presented in a suitable format for this review)
Notes	Exclusion criteria: previous degenerative or expansive neurologic disease, tumours, multiple sclerosis, amyotrophic sclerosis, hydrocephalus, SAH, Binswanger's disease, history of psychiatric illness (other than depression), severe aphasia, severe cognitive deficit, chronic alcoholism

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

Reding 1986

Methods	Parallel design Method of randomisation: random number table Method of concealment: unclear Blinding: double blind Participants: yes Treating physician: yes Analysis: ITT (no drop-outs apparent)
Participants	Location: USA Setting: inpatients Treatment: 11 (66% male, mean age 68 years, SE 2) Control: 6 (73% male, mean age 68 years, SE 3) Stroke criteria: all subtypes; diagnosis via clinical signs and CT (% not reported); stroke on average 45 +/ - 5 days (treatment group) and 48 +/- 13 days (control group) prior to randomisation Depression criteria: psychiatric interview (DSM-III, major and minor) Other entry criteria: none stated Comparability of treatment groups: unclear

Reding 1986 (*Continued*)

Interventions	Treatment: trazodone-HCl 50 mg daily; dose escalation every 3 days to target dose of 200 mg Control: matched placebo Duration: treatment continued for 32 +/- 6 days (treatment group) and 24 +/- 4 days (control group)
Outcomes	Depression: clinical diagnosis of depression Additional: BI Unable to use: clinical diagnosis of depression, ZDS, death (data not presented) Leaving the study early Adverse events (data not presented by group)
Notes	Exclusion criteria: myocardial infarction within previous month, antiarrhythmic medication

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Towle 1989

Methods	Parallel design Method of randomisation: random number tables Method of concealment: sealed envelopes held by secretary Blinding: single blind Participants: no Investigators: no Outcome assessor: yes Analysis: per protocol: withdrew consent (1 control), excluded from analysis
Participants	Location: UK Setting: outpatients Treatment: 21 (43% male, mean age 70 years, SD 9) Control: 23 (30% male, mean age 69 years, SD 7) Stroke criteria: all subtypes; diagnosis via clinical signs; stroke on average 25 +/- 7 months (treatment group) and 25 +/- 6 months (control group) prior to randomisation Depression criteria: WDI score > 17 or GHQ-28 score > 9 Other entry criteria: able to complete questionnaires unaided Comparability of treatment groups: demographically balanced, treatment group reported more social dysfunction on GHQ-28
Interventions	Treatment: pragmatic approach dealing with problems identified by social worker and the patients; included counselling the patient and caregiver, giving opportunity to reflect upon their situation and express their feelings (duration: 2 to11 visits over 16 weeks, mean number visits 6.8 +/- 2.8) Control: custom designed information booklet, 1 visit, no ongoing visits Delivered by: social worker

Towle 1989 (*Continued*)

Outcomes	Depression: change in scores from baseline to end of treatment on WDI, GHQ-28, proportion no longer meeting entry criteria Additional: Leaving the study early Unable to use: WDI, GHQ-28, Extended ADL, FAI, services questionnaire, Life Satisfaction Index, Nottingham Health Profile (data presented as median and range) Death Adverse events (data not presented)
Notes	Exclusion criteria: stroke < 1 year prior to randomisation, residence in hospital or residential care

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Watkins 2007

Methods	Parallel design Method of randomisation: computer package minimizing for age, sex, baseline BI score, stay on acute stroke unit; therapist assignment by opaque envelope Method of concealment: computer program for initial randomisation, opaque envelope for therapist Blinding: open trial Analysis: ITT (hot deck imputation), death (3 treatment, 8 control)
Participants	Location: UK Setting: inpatient Treatment: 127 (52% male, mean age 68 years, SD 12) Control: 127 (53% male, mean age 68 years, SD 12) Stroke criteria: all subtypes; diagnosis via clinical signs and CT (100%); stroke 5 to 28 days prior to randomisation Depression criteria: GHQ score > 4 Other entry criteria: over 18 years Comparability of treatment groups: balanced
Interventions	Treatment: motivational interviewing, up to 4 sessions, 1 per week, with same therapist Control: usual care Delivered by: nurses and non-clinical psychologists
Outcomes	Depression: no longer meeting study criteria for depression on GHQ-28, change in scores from baseline to end of treatment on GHQ-28 Additional: Yale, BI, Stroke Expectations Questionnaire
Notes	Exclusion criteria: severe cognitive and communication problems, moving out of the area after discharge, already receiving psychiatric or clinical psychology intervention Additional unpublished data provided by authors

Watkins 2007 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Wiart 2000

Methods	Parallel design Method of randomisation: randomised stated, method unclear Method of concealment: unclear Blinding: double blind reported, those blinded not stated Analysis: ITT (last observation carried forward), withdrawn due to AE (1 treatment), protocol violation (1 treatment)
Participants	Location: France Setting: unclear Treatment: 16 (56% male, mean age 66 years, SD 7) Control: 15 (40% male, mean age 69 years, SD 12) Stroke criteria: ischaemic stroke and primary intracerebral haemorrhage; diagnosis via clinical signs and CT (100%); stroke on average 47 +/- 22 days (treatment group) and 48 +/- 20 days (control group) prior to randomisation 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: treatment continued for 45 days
Outcomes	Depression: change in scores from baseline to end of treatment on MADRS, 50% reduction in MADRS score Additional: Functional Independence Measure MMSE Motoricity Index Leaving the study early Death Adverse events
Notes	Exclusion criteria: severe psychiatric problems which required hospitalisation, severe cognitive impairment, chronic alcoholism, chronic associated handicapping pathology, contraindication to fluoxetine

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Yang 2002

Methods	Parallel design Method of randomisation: randomised stated, method unclear Method of concealment: unclear Blinding: unclear Analysis: unclear, withdrawn due to AE (4 treatment, 7 control)
Participants	Location: China Setting: outpatient Treatment: 64 (63% male, mean age 64 years, SD 3) Control: 57 (56% male, mean age 63 years, SD 5) Stroke criteria: ischaemic and haemorrhagic stroke; diagnosis unclear; stroke range 1.5 to 6 months prior to randomisation Depression criteria: HDRS score > 7 Other entry criteria: unclear Comparability of treatment groups: balanced
Interventions	Treatment: paroxetine 20 mg daily Control: matched placebo Duration: treatment continued for 4 months
Outcomes	Depression: 50% reduction in scores from baseline to end of treatment on HDRS Additional: cured: defined as scoring < 7 in 2 consecutive weeks (unable to use as timing of these 2 weeks not stated)
Notes	Exclusion criteria: unclear

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Zhao 2004

Methods	Parallel design Method of randomisation: randomised stated, method unclear, but stratified by age, sex and stroke subtype Method of concealment: unclear Blinding: unclear Analysis: unclear
Participants	Location: China Setting: inpatient Treatment: 35 (57% male, mean age 65 years, SD 13) Control: 35 (51% male, mean age 61 years, SD 14) Stroke criteria: unclear; diagnosis via CT or MRI (100%); stroke range to randomisation, unclear Depression criteria: HDRS score > 17 Other entry criteria: cognitively competent, no acute medical problems Comparability of treatment groups: balanced

Zhao 2004 (*Continued*)

Interventions	Treatment: psycho-education, daily, less than 30 minutes Control: usual care Duration: treatment continued for 4 weeks Delivered by: special personnel	
Outcomes	Depression: reduction in scores from baseline to end of treatment on HDRS*	
Notes	Exclusion criteria: unclear	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

*: Change scores calculated by review authors from available data
** Results for control group halved
^: Results for attention-control and control group pooled
^^: Standard deviation of mean scores calculated from standard errors by review authors
†: Mean and standard deviation scores extrapolated from figures in paper
ADL: activities of daily living
AE: adverse event(s)
BDI: Beck Depression Inventory
CSS: Chinese Stroke Scale
CT: computed tomography
BI: Barthel Index
DSM: Diagnostic Scientific Manual
FAI: Frenchay Activities Index
FAST: Frenchay Aphasia Screening Test
GDS: Geriatric Depression Scale
GHQ: General Health Questionnaire
HARS: Hamilton Anxiety Rating Scale
HDRS: Hamilton Depression Rating Scale
HRQoL: Health Related Quality of Life
ICD: International Classification of Diseases
ITT: intention to treat
MADRS: Montgomery Asberg Depression Rating Scale
MMSE: Mini-Mental State Examination
PSE: Present State Examination
RS: Rankin Scale
SD: standard deviation
SE: standard error
WDI: Wakefield Depression Inventory
ZDS: Zung Depression Scale

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

Study	Reason for exclusion
Agnoli 1985	Allocation: randomised Participants: chronic cerebrovascular disease: unable to isolate stroke patients
Aizawa 1986	Allocation: randomised Participants: cerebrovascular disorders Interventions: no placebo comparison
Balunov 1990	Allocation: randomised Participants: poststroke depression Interventions: no placebo comparison
Bao 2001	Allocation: nnclear Participants: post stroke Interventions: some patients in the intervention group received antidepressants, no one in the control group did
Battaglia 1999	Allocation: randomised Participants: post stroke Interventions: Nno placebo comparison
Battaglia 2001	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Bautz-Holter 2002	Allocation: randomised Participants: post stroke Interventions: early supported discharge, did not meet review criteria, not structured or timetabled as a talking therapy
Berrol 1997	Allocation: random Participants: post stroke Intervention: dance/movement therapy, did not meet review criteria
Casella 1960	Allocation: quasi randomised Participants: hemiplegia, unable to isolate stroke Interventions: iproniazid Outcome: depression not primary endpoint
Chen 2001	Allocation: randomised Participants: post stroke Interventions: fluoxetine, no placebo control (routine care)
Chen 2002	Allocation: randomised Participants: post stroke Interventions: fluoxetine, doxepine, vitamin B6, no placebo control

(*Continued*)

Chen 2005	Allocation: randomised Participants: post stroke Interventions: citalopram or fluoxetine, no placebo control (activating blood circulation and rehabilitation)
Chen 2005a	Allocation: randomised Participants: post stroke Interventions: repetitive transcranial magnetic stimulation not meeting review criteria
Cheng 2003	Allocation: randomised Participants: post stroke Interventions: fluoxetine, no placebo control arm (routine care)
Cheng 2003a	Allocation: unclear Participants: post stroke Interventions: fluoxetine, no placebo control (routine care)
Choi-Kwon 2006	Allocation: randomised Participants: post stroke Interventions: fluoxetine, treatment trial for depression, emotionalism and anger Outcome: data not available in depressed and not depressed with proportions, mean scores and standard deviations
Christie 1984	Allocation: randomised Participants: post stroke Interventions: social work, did not meet review criteria, not structured or timetabled as a talking therapy
Corr 1995	Allocation: randomised Participants: post stroke Interventions: rehabilitation, did not meet review criteria, not structured or timetabled as a talking therapy
Corr 2004	Allocation: randomised Participants: post stroke Interventions: cross-over study design. No drug or psychological intervention involved
Cui 2001	Allocation: not randomised Participants: post stroke Intervention: no placebo comparison
Cullum 2007	Allocation: randomised Participants: older medical patients including stroke Intervention: liaison psychiatric nurse + care plan including psychotherapy and/or antidepressents, not meet review criteria
Davis 1997	Allocation: randomised Participants: post stroke Interventions: life review therapy Outcome: therapy did not develop social problem solving skills or adjustment to stroke, did not meet review criteria

(*Continued*)

Dennis 1997	Allocation: randomised Participants: post stroke Interventions: stroke family careworker, did not meet review criteria, not structured or timetabled as a talking therapy
Dennis 2000	Allocation: randomised Participants: post stroke Interventions: stroke family careworker, did not meet review criteria, not structured or timetabled as a talking therapy
Desrosiers 2007	Allocation: unclear Participants: post stroke Intervention: leisure education programme, did not meet review criteria
Dong 2007	Allocation: randomised Participants: post stroke Intervention: electroacupuncture, western medicine, did not meet review criteria
Downes 1995	Allocation: tandomised Participants: post stroke Interventions: Egan's problem solving therapy Outcome: data not currently available
Drummond 1995	Allocation: randomised Participants: post stroke Interventions: leisure rehabilitation, did not meet review criteria, not structured or timetabled as a talking therapy
Du 2005	Allocation: randomised Participants: post stroke Interventions: repetitive transcranial magnetic stimulation not meeting review criteria
Evans 1997	Allocation: randomised Participants: acute geriatric medical inpatients with depression, unable to isolate any chronic stroke patients No acute stroke patients included in sample
Feng 2004	Allocation: random Participants: post stroke Intervention: fluoxetine, jieyu huoxue decoction, no placebo control
Feng 2005	Allocation: randomised Participants: post stroke Intervention: psychotherapy intervenion inlcudes exercise therapy which wasn't included in the control group
Fengqi 2003	Allocation: randomised Participants: post stroke Interventions: yukangning - traditional Chinese medicine, no placebo comparison

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FX Project 1976	Allocation: randomised Participants: cerebrovascular diseases, those with stroke unable to be isolated
Gekht 2002	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Gekht 2003	Allocation: not randomised, 'divided' Participants: post stroke Interventions: no placebo comparison
Goh 2001	Allocation: randomised Participants: post stroke Interventions: music therapy, did not meet review criteria, not structured or timetabled as a talking therapy
Gonzalez-T 1995	Allocation: quasi randomised Participants: depressed post stroke Interventions: no placebo comparison
Graffagnino 2003	Allocation: randomised Participants: post stroke Interventions: sertraline with matched placebo Outcomes: data not currently available
Green 2002	Allocation: randomised Participants: post stroke Interventions: physiotherapy, did not meet review criteria, not structured or timetabled as a talking therapy
Guan 2003	Allocation: randomised Participants: post stroke Interventions: fluoxetine, levodopa, no placebo control
Guan 2004	Allocation: random Participants: post stroke Interventions: patients in the intervention group received fluoxetine, no one in the control group did
He 2001	Allocation: randomised Participants: post stroke Interventions: combined Chinese antidepressants and psychotherapy with no placebo control
He 2003	Allocation: random Participants: post stroke Interventions: combined psychotherapy with amitriptyline, no placebo control
He 2004	Allocation: quasi randomised Participants: post stroke Interventions: fluoxetine, no placebo control

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He 2005	Allocation: randomised Participants: post stroke Interventions: paroxetine and psychotherapy, no placebo control, only a usual care arm
Hindle 2007	Allocation: randomised Participants: post stroke Interventions: sertraline Outcomes: trial not completed
Hogg 1985	Allocation: randomised Participants: post stroke Interventions: acupressure versus therapeutic touch, no placebo control, intervention not meet review criteria
Hong 2004	Allocation: randomised Participants: post stroke Interventions: yuxingchangzhi tang and fluoxetine, no placebo control
House 2005	Allocation: randomised Participants: post stroke Intervention: SSRI Trial not completed due to recruitment problems
Hu 2002	Allocation: randomised Participants: post stroke Intervention: fluoxetine, no placebo control
Hu 2005	Allocation: randomised Participants: post stroke Interventions: psychotherapy combined with fluoxetine, no placebo control
Huang 2001	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Huang 2004	Allocation: random Participants: post stroke Interventions: acupuncture, amitriptyline, no placebo comparison
Hui 1995	Allocation: randomised Participants: post stroke Interventions: medical management, did not meet criteria, not structured or timetabled as a talking therapy
Isenberg 2000	Allocation: unclear Participants: post stroke Interventions: nefiracetam Outcomes: dta not currently available

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Ji 2000	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Jia 2005	Allocation: random Participants: post stroke Interventions: fluoxetine, no placebo control
Johnson 2000	Allocation: randomised Participants: post stroke Interventions: group/class education, did not meet review criteria, not structured or timetabled as a talking therapy
Jongbloed 1991	Allocation: randomised Participants: post stroke Interventions: occupational leisure therapy, did not meet review criteria, not structured or timetabled as a talking therapy
Jorge 2004	Allocation: randomised Participants: post stroke Interventions: transcranial magnetic stimulation, did not meet review criteria
Joubert 2006	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Juby 1996	Allocation: randomised Participants: post stroke Interventions: medical management, did not meet review criteria, not structured or timetabled as a talking therapy
Kendall 2007	Allocation: randomised Participants: post stroke Interventions: primarily education and not delivered by somebody with explicitly stated training and supervision in therapies
Kwon 2003	Allocation: quasi randomised Participants: post stroke Interventions: taping/physiological, did not meet review criteria
Lai 2006b	Allocation: randomised Participants: post stroke Interventions: physical exercise program - did not meet review criteria
Laska 2005	Allocation: randomised Participants: acute stroke with aphasia Interventions: moclobemide Outcome: aphasia

(*Continued*)

Lauritzen 1994	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Lee 2005	Allocation: unclear Participants: post stroke Interventions: repetitive transcranial magnetic stimulation, does not meet review criteria
Lehmann 2001	Allocation: randomised Participants: post stroke Interventions: imipramine, piracetam,versus usual care, no placebo comparison
Leijon 1989	Allocation: randomised Participants: post stroke Interventions: amitriptyline and carbamazepine Outcome: pain
Li 1994	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Li 1999	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Li 2000	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Li 2002	Allocation: randomised Participants: post stroke Interventions: no placebo comparison (paroxetine versus traditional Chinese medicine)
Li 2004	Allocation: randomised Participants: post stroke Interventions: fluoxetine versus usual care, no placebo comparison
Li 2004a	Allocation: random Participants: post stroke Interventions: antidepressant + activities of daily living training + psychotherapy + early rehabilitation, does not meet review criteria
Li 2004b	Allocation: random Participants: post stroke Interventions: psychotherapy + antidepressant (unspecified) versus usual care, no placebo comparison

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Li 2004c	Allocation: random Participants: post stroke Interventions: antidepressants (unspecified) versus usual care, no placebo comparison
Li 2004d	Allocation: unclear Participants: post stroke Interventions: patients in the intervention group received antidepressants, no one in the control group did
Li 2005	Allocation: randomised Participants: post stroke Interventions: doxepin hydrochloride no placebo control
Liang 2003	Allocation: randomised Participants: post stroke Interventions: fluoxetine, no placebo comparison
Liang 2005	Allocation: randomised Participants: post stroke Interventions: no placebo control
Liborio 2002	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Lin 2005	Allocation: randomised Participants: post stroke Interventions: psychotherapy and/or antidepressant care, no placebo control
Lincoln 1985	Allocation: randomised Participants: post stroke Interventions: speech therapy, did not meet review criteria, not structured or timetabled as a talking therapy
Liu 2003	Allocation: unclear Participants: silent stroke (not meet review criteria) Interventions: antidepressant + psychological intervention (not meet review criteria)
Liu 2003a	Allocation: unclear Participants: post stroke Interventions: fastigial nucleus electrical stimulation + antidepressant therapy (not meet review criteria) versus routine drug (unspecified) versus control, no placebo control group
Liu 2006	Allocation: randomised Participants: post stroke Interventions: yu le shu, fluoxetine, no placebo control
Liu 2006a	Allocation: randomised Participants: post stroke Interventions: fluoxetine and acup-moxibustion, no placebo comparison

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Liu 2006b	Allocation: randomised Participants: post stroke Interventions: citalopram versus amitriptyline, no placebo comaprison
Lu 2005	Allocation: randomised Participants: diabetic patients post stroke Interventions: cognitive therapy + electromyographic feedback + medication (not meet criteria) versus usual care
Mant 1998	Allocation: randomised Participants: post stroke Interventions: information pack, did not meet review criteria, not structured or timetabled as a talking therapy
Mant 2000	Allocation: randomised Participants: post stroke Interventions: family support, did not meet review criteria, not structured or timetabled as a talking therapy
Martucci 1986	Allocation: randomised Participants: unable to isolate people with stroke
Mauri 1988	Allocation: randomised Participants: post stroke Interventions: mianserin vs placebo Outcomes: not available in a format appropriate for this review
Meara 1998	Allocation: randomised Participants: post stroke Interventions: sertraline with matched placebo for 6 weeks Outcome: data not currently available
Meng 1996	Allocation: unclear Participants: post stroke Interventions: mi-an-she-lin versus amitriptyline, no placebo control
Miao 2004	Allocation: random Participants: post stroke Interventions: citalopram versus usual care, no placebo control
Min 2002	Allocation: randomised Participants: post stroke Interventions: no placebo control (control group received physcological rehabilitation therapy)
Min 2002a	Allocation: randomised Participants: post stroke Interventions: antidepressant versus psychological therapy, no placebo or usual care comparison

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Miyai 1998	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Niedermaier 2004	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Nir 2004	Allocation: randomised Participants: post stroke Interventions: not talking therapy or sufficient training or supervision of 'therapists'
Nour 2002	Allocation: randomised Participants: post stroke Interventions: home leisure educational programme, not meet review criteria, not structured or timetabled as a talking therapy
Ohtomo 1985	Allocation: randomised Participants: post stroke Interventions: tiapride with matched placebo for 6 weeks Outcome: data not currently available
Ostwald 2006	Allocation: randomised Participants: post stroke patients and carers Interventions: no usual care comparison
Rampello 2004	Allocation: randomised Participants: post stroke Interventions: citalopram or reboxetine, no placebo control
Ricauda 2004	Allocation: unclear Participants: post stroke Interventions: home hospitalisation service, does not meet review criteria
Roberts 1995	Allocation: randomised Participants: chronic illness Interventions: no placebo comparison
Rodgers 1999	Allocation: randomised Participants: post stroke Interventions: stroke education, did not meet review criteria, not structured or timetabled as a talking therapy
Rudd 1997	Allocation: randomised Participants: post stroke Interventions: early hospital discharge, did not meet review criteria, not structured or timetabled as a talking therapy

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Rønning 1998	Allocation: randomised Participants: post stroke Interventions: subacute rehabilitation, did not meet review criteria, not structured or timetabled as a talking therapy
Sandberg 2001	Allocation: randomised Participants: post stroke Interventions: cPAP, did not meet review criteria
Seliger 1990	Allocation: not randomised Participants: post stroke and multiple sclerosis Interventions: no placebo comparison
Shan 2001	Allocation: randomised Participants: post stroke Interventions: fluoxetine versus acetamidepyrrolidone, no placebo control
Sivenius 2001	Allocation: randomised Participants: acute post stroke Interventions: did not meet review criteria (acute treatment) Outcome: depression not primary endpoint
Smedley 1986	Allocation: randomised Participants: post stroke Interventions: slot machines, did not meet review criteria
Smith 2004	Allocation: randomised Participants: post stroke (combined depressed and not depressed) Intervention: education, did not meet review criteria
Song 1999	Allocation: randomised Participants: post stroke Interventions: scalp acupuncture, did not meet review criteria
Su 2004	Allocation: randomised Participants: post stroke Interventions: rehabilitation plus psychotherapy versus rehabilitation but rehabilitation includes fluoxetine
Sulch 2000	Allocation: randomised Participants: post stroke Interventions: integrated managed care pathway, did not meet review criteria, not structured or timetabled as a talking therapy
Sulch 2002	Allocation: randomised Participants: post stroke Interventions: integrated managed care pathway, did not meet review criteria, not structured or timetabled as a talking therapy

(*Continued*)

Suskin 2006	Allocation: randomised Participants: post stroke or transient ischaemic attack Interventions: cardiac rehabilitation, not meet review criteria
Suzuki 2001	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Tan 2004	Allocation: unclear Participants: post stroke Interventions: provide comfortable environment, nutrition and medication instruction, rehabilitation training and education, did not meet review criteria
Taragano 2001	Allocation: randomised Participants: post stroke Interventions: no placebo comparison (both groups received fluoxetine, half received additional nimodipine, half additional placebo)
Wade 1992	Allocation: randomised Participants: post stroke Interventions: physiotherapy, did not meet review criteria, not structured or timetabled as a talking therapy
Walker-Batson 1995	Allocation: randomised Participants: post stroke Interventions: dextroamphetamine versus placebo paired with physical therapy Outcome: not depression
Walsh 1999	Allocation: unclear Participants: post stroke Interventions: relaxation versus aromatherapy versus reflexology versus aromatherapy + reflexology, not meet review criteria
Wang 2002	Allocation: random Participants: post stroke Interventions: yukangning versus usual care, no placebo control
Wang 2003	Allocation: unclear Participants: post stroke Interventions: prozac versus amitriptyline versus usual care, no placebo comparison
Wang 2004	Allocation: randomised Participants: post stroke Interventions: paroxetine, no placebo control
Wang 2007	Allocation: randomised Participants: post stroke Interventions: yiyu, routine care + neurstan, no placebo control

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Werner 1996	Allocation: randomised Participants: post stroke Interventions: outpatient rehabilitation, did not meet review criteria, not structured or timetabled as a talking therapy
Wheeler 2003	Allocation: unclear Participants: post stroke Interventions: music therapy, not meet review criteria
Wiart 1997	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Williams 2002	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Wolfe 2000	Allocation: randomised Participants: post stroke Interventions: community based rehabilitation, did not meet review criteria, not structured or timetabled as a talking therapy
Wu 2002	Allocation: random Participants: post stroke Interventions: fluoxetine plus usual care versus usual care, no placebo comparison
Xia 2003	Allocation: random Participants: post stroke Interventions: some patients in the intervention group received antidepressants, no one in the control group did
Xiaoying 2001	Allocation: randomised Participants: post stroke Interventions: no placebo comparison for antidepressants
Xie 2003	Allocation: unclear Participants: post stroke but unclear whether includes only depressed, or mixed patients Interventions: psychological intervention: feeling support therapy, recognition therapy, collective therapy, social support and skills training
Xie 2005	Allocation: randomised Participants: post stroke Interventions: sertraline, no placebo control
Xing 1999	Allocation: random Participants: post stroke Interventions: fluoxetine plus routine drug therapy and rehabilitation versus routine drug therapy and rehabilitation, no placebo

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Xu 2001	Allocation: random Participants: post stroke Interventions: fluoxetine, rehabilitation, neurological drugs and psychotherapy versus rehabilitation, neurological drugs and psychotherapy, no placebo control
Ye 2004	Allocation: random Participants: post stroke Interventions: paroxetine versus imipramine versus usual care, no placebo comparison
Yi 1990	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Yokokawa 1991	Allocation: randomised Participants: post stroke Interventions: physical activity, did not meet review criteria, not structured or timetabled as a talking therapy
Yoneyama 1993	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
You 2002	Allocation: randomised Participants: post stroke Interventions: rehabilitation plus antidepressant versus rehabilitation versus drug therapy alone, no placebo control
Young 1992	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Yu 1991	Allocation: unclear Participants: post stroke (some) Interventions: prompted toileting + social reinforcement versus control, not meet review criteria
Zhang 2000	Allocation: unclear Participants: post stroke Interventions: psychological therapy plus paroxetine versus psychological therapy
Zhang 2002	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Zhang 2002a	Allocation: randomised Participants: post stroke Interventions: no placebo comparison

(*Continued*)

Zhang 2002b	Allocation: randomised Participants: post stroke Interventions: fluoxetine plus usual care versus usual care, no placebo comparison
Zhang 2005	Allocation: random Participants: post stroke Interventions: buspirone hydrocholride versus usual care, no placebo comparison
Zhang 2005a	Allocation: randomised Participants: post stroke Interventions: acupuncture versus fluoxetine, no placebo comparison
Zhao 1999	Allocation: randomised Participants: post stroke Interventions: no placebo comparison
Zhao 2005	Allocation: random Participants: post stroke Interventions: citalopram versus venlafaxing, no placebo comparison
Zhao 2005a	Allocation: randomised Participants: post stroke Interventions: citalopram versus amitriptyline, no placebo comparison
Zhou 2003	Allocation: unclear Participants: post stroke Interventions: fluoxetine and rehabilitation training, no placebo comparison
Zhou 2004	Allocation: random Participants: post stroke Interventions: therapist (not defined, no training or supervision stated) led strategy involving lots of people including family and a buddy system
Zhu 2002	Allocation: random Participants: post stroke Interventions: fluoxetine plus usual care versus usual care, no placebo comparison
Zifko 2002	Allocation: not randomised Participants: post stroke Interventions: no placebo comparison

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

Graven 2008

Trial name or title	Parallel design Method of randomisation: computer generated randomisation table Method of concealment: sealed opaque envelopes Blinding Participants: yes Outcome assessors: yes Statisticians: yes
Methods	
Participants	Location: Australia Setting: unclear Stroke criteria: ischaemic and haemorrhagic stroke Other entry criteria: unclear
Interventions	Treatment: rehabilitation, goal setting, problem solving, facilitated referral to services, promotion of health lifestyle, self efficacy and self reliance Control: active control, usual care plus phone contact with allied health professional three times for support and encouragement Duration: treatment duration: minimum of 4, maximum of 12
Outcomes	Depression: Geriatric Depression Scale
Starting date	2008
Contact information	Christine Graven Physiotherapy Department St. Vincent's Health Melbourne PO Box 2900 Fitzroy 3065 Victoria Tel: +61 3 9288 3927 Christine.GRAVEN@svhm.org.au
Notes	Exclusion criteria: unclear

Mitchell 2002

Trial name or title	Parallel design Method of randomisation: unclear Method of concealment: unclear Blinding: single blind
Methods	

Mitchell 2002 (*Continued*)

Participants	Location: USA Setting: unclear Stroke criteria: ischaemic stroke Other entry criteria: stroke within 4 months, 21 years of age and above
Interventions	Treatment: cognitive behavioral therapy plus problem-solving Control: active control, standard antidepressant treatment and written material Duration: treatment duration: 9 sessions over 7 weeks
Outcomes	Depression: HDRS
Starting date	March 2002
Contact information	Pamela H Mitchell University of Washington Seattle Washington 98195-7266 USA
Notes	Exclusion criteria: subarachnoid or intracranial hemorrhagic stroke, global aphasia, reduced level of consciousness (GCS < 15) NCT00194454

Thomas 2007

Trial name or title	Parallel design Method of randomisation: unclear Method of concealment: unclear Blinding: unclear
Methods	
Participants	Location: UK Setting: unclear Stroke criteria: unclear
Interventions	Treatment 1: behavioural psychotherapy Control 1: attention control Control 2: no intervention Duration: unclear
Outcomes	Depression: unclear
Starting date	April 2005
Contact information	Miss Shirley Thomas Research Associate Division of Rehabilitation and Ageing

Thomas 2007 (*Continued*)

	B Floor Medical School Queens Medical Centre Nottingham NG7 2UH UK shirley.thomas@nottingham.ac.uk
Notes	Exclusion criteria: unclear

HDRS: Hamilton Depression Rating Scale

DATA AND ANALYSES

Comparison 1. Pharmaceutical interventions versus placebo (antidepressants)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Depression: 1. Meeting study criteria for depression	7	789	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.22, 0.98]
1.1 Clinician interview/impression (number improved)	1	206	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.27, 0.83]
1.2 DSM-III	1	26	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.22, 5.00]
1.3 HDRS	3	209	Odds Ratio (M-H, Random, 95% CI)	0.21 [0.03, 1.40]
1.4 MADRS	2	348	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.27, 2.62]
2 Depression: 2. Average change in scores between baseline and end of treatment	8		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 BDI (high score = more depressed)	2		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 CGI (low score = improvement / high score = deterioration)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.3 HDRS (high score = more depressed)	5		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.4 MADRS (high score = more depressed)	3		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.5 Melancholia scale (high score = more depressed)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.6 Zung (high score = more depressed)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Depression: 3. Mean scores at end of treatment	8		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 BDI (high score = more depressed)	2		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 CGI (low score = improvement / high score = deterioration)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.3 HDRS (high score = more depressed)	6		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.4 MADRS (high score = more depressed)	2		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.5 Melancholia scale (high score = more depressed)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.6 Zung (high score = more depressed)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Depression: 4. Less than 50% reduction in scale scores	5	414	Odds Ratio (M-H, Random, 95% CI)	0.22 [0.09, 0.52]
4.1 HDRS	3	260	Odds Ratio (M-H, Random, 95% CI)	0.13 [0.06, 0.30]

4.2 MADRS	2	154	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.27, 1.00]
5 Anxiety: 1. Meeting study criteria for anxiety	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Clinician interview/impression	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Cognitive functioning: 1. Average change in scores between baseline and end of treatment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 MMSE (low score = cognitive impairment)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
7 Cognitive functioning: 2. Mean scores at end of treatment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 MMSE (low score = cognitive impairment)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
8 Activities of daily living: 1. Average change in scores between baseline and end of treatment	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Barthel (high score = more dependent)	2		Mean Difference (IV, Fixed, 95% CI)	Not estimable
9 Disability: 1. Average change in scores between baseline and end of treatment	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Functional Independence Measure (low score = dependence)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
9.2 Motoricity Index (low score = more motor impairment)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
9.3 Scandinavian Stroke Scale (low score = more neurological deficit)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
9.4 Rankin Scale (high score = more disability)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
10 Disability: 2. Mean scores at end of treatment	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Functional Independence Measure (low score = dependence)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
10.2 Motoricity Index (low score = more motor impairment)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
10.3 Scandinavian Stroke Scale (low score = more neurological deficit)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
11 Neurological function: 1. Average change in scores between baseline and end of treatment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

11.1 Chinese Stroke Scale (high score = more impairment)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
12 Neurological function: 2. Mean scores at end of treatment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Chinese Stroke Scale (high score = more impairment)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
13 Adverse events: 1. Death	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 At end of treatment	6	537	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.15, 2.15]
14 Adverse events: 2. All	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Central nervous system events (e.g. confusion, sedation, tremor)	5	488	Odds Ratio (M-H, Fixed, 95% CI)	1.96 [1.19, 3.24]
14.2 Gastrointestinal effects (e.g. constipation, diarrhoea)	3	383	Odds Ratio (M-H, Fixed, 95% CI)	2.37 [1.38, 4.06]
14.3 Other events - not listed above (e.g. dysuria, eye discomfort)	6	544	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.97, 2.34]
14.4 Protocol violation (e.g. refused treatment, withdrew consent)	3	136	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.20, 3.66]
14.5 Psychiatric events (e.g. anxiety, increased depression)	2	89	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.03, 3.47]
14.6 Recurrent stroke	2	105	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.15, 8.60]
14.7 Vascular events - not stroke (e.g. dizziness, palpitation)	7	583	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [0.93, 2.73]
15 Adverse events: 3. Leaving the study early (including death)	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 all drop outs and withdrawals	6	542	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.69, 1.59]

Comparison 2. Pharmaceutical interventions versus placebo (combination therapy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Depression: 1. Average change in scores between baseline and end of treatment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 HDRS (high score = more depressed)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2 Depression: 2. Mean scores at end of treatment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 HDRS (high score = more depressed)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Neurological function: 1. Average change in scores between baseline and end of treatment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

3.1 Chinese Stroke Scale (high score = more impairment)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Neurological function: 2. Mean scores at end of treatment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Chinese Stroke Scale (high score = more impairment)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Adverse events: 1. All	1	90	Odds Ratio (M-H, Fixed, 95% CI)	2.14 [0.23, 19.95]
5.1 Other events (GPT elevation)	1	45	Odds Ratio (M-H, Fixed, 95% CI)	2.72 [0.12, 60.29]
5.2 Vascular events - not stroke (e.g. ECG changes)	1	45	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [0.06, 41.03]

Comparison 3. Psychological interventions versus standard care and/or attention control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Depression: Meeting study criteria for depression at end of treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 GHQ-28 (high score = greater psychological distress)	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Depression: 1. Average change in scores between baseline and end of treatment	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 BDI (high score = more depressed)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 WDI (high score = more depressed)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.3 HDRS (high score = more depressed)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Depression: 2. Mean scores at end of treatment	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 BDI (high score = more depressed)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 WDI (high score = more depressed)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.3 HDRS (high score = more depressed)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Psychological distress: 1. Average change in scores between baseline and end of treatment	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 GHQ-28 (high score = greater psychological distress)	2		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Psychological distress: 2. Mean scores at end of treatment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 GHQ-28 (high score = greater psychological distress)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

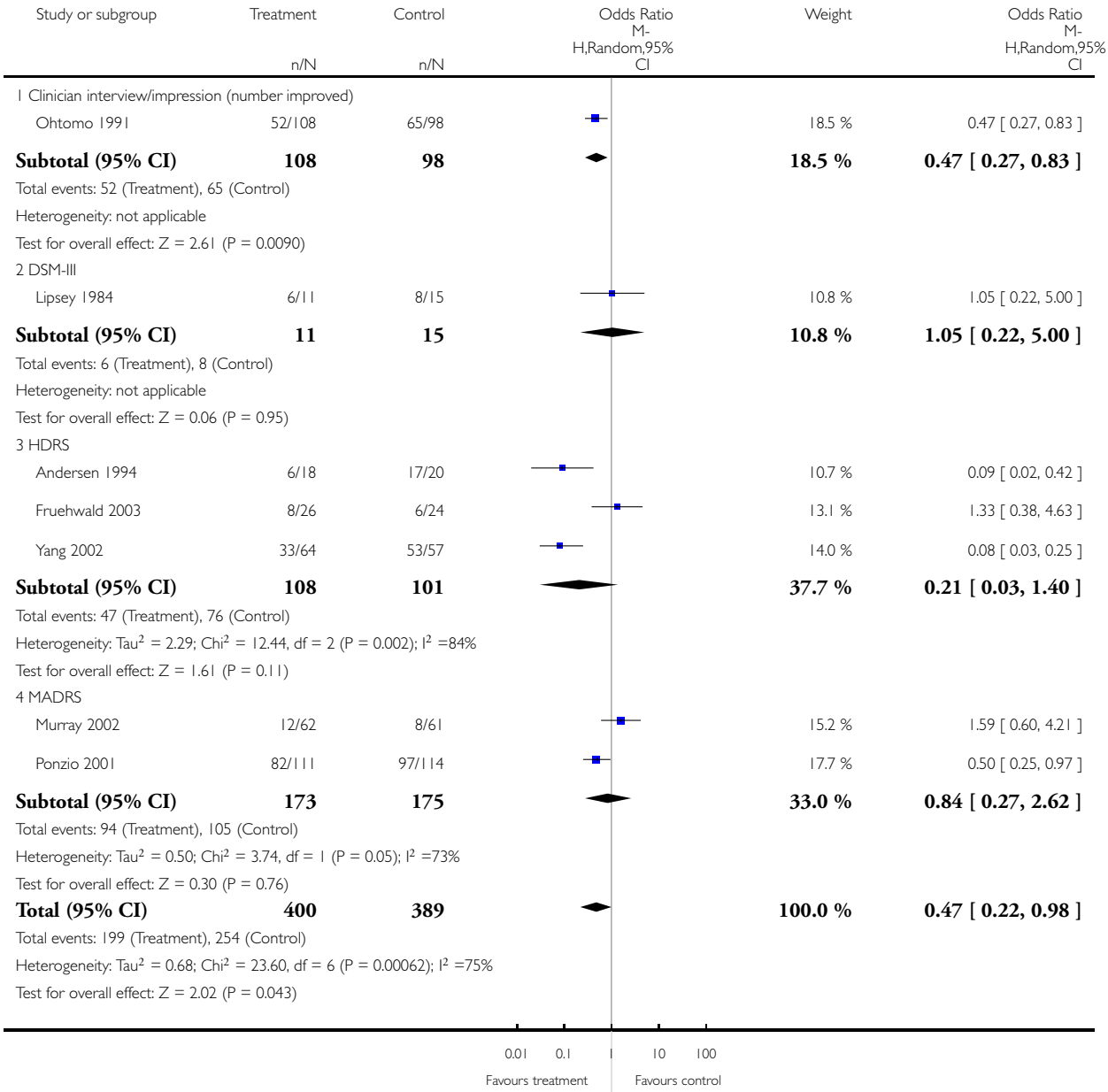
6 Activities of daily living: 1. Average change in scores from baseline to end of treatment	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 EADL (high score = more dependent)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
6.2 Barthel (high score = more dependent)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
7 Activities of daily living: 2. Mean scores at end of treatment	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 EADL (high score = more dependent)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
7.2 Barthel (high score = more dependent)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
8 Adverse events: 1. Death	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 At end of treatment	3	421	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.11, 1.28]
9 Adverse events: 2. All	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Protocol violation (e.g. refused treatment, withdrew consent)	1	43	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.65]
9.2 Recurrent stroke	1	254	Odds Ratio (M-H, Fixed, 95% CI)	5.08 [0.24, 106.87]
9.3 Vascular events - not stroke (e.g. transient ischaemic attack)	1	254	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.22, 2.27]
10 Adverse events: 3. Leaving the study early (including death)	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 All drop outs and withdrawals	3	421	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.13, 1.17]

Analysis 1.1. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 1 Depression: 1. Meeting study criteria for depression.

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 1 Depression: 1. Meeting study criteria for depression



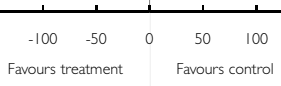
Analysis 1.2. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 2 Depression: 2. Average change in scores between baseline and end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 2 Depression: 2. Average change in scores between baseline and end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 BDI (high score = more depressed)						
Fruehwald 2003	26	-6.1 (5.6)	24	-4.1 (6.48)		-2.00 [-5.37, 1.37]
Rampello 2005	16	-12.5 (11.62)	15	-1.47 (9.35)		-11.03 [-18.43, -3.63]
2 CGI (low score = improvement / high score = deterioration)						
Fruehwald 2003	26	-2.7 (1.16)	24	-2.1 (1.36)		-0.60 [-1.30, 0.10]
3 HDRS (high score = more depressed)						
Andersen 1994	33	-8 (4.22)	33	-4.8 (3.87)		-3.20 [-5.15, -1.25]
Fruehwald 2003	26	-23.3 (12)	24	-19.1 (15.1)		-4.20 [-11.80, 3.40]
Jiang 2001a	30	-20.13 (6.82)	15	-11.85 (7.5)		-8.28 [-12.79, -3.77]
Lipsey 1984	11	-11 (4.62)	15	-6.4 (7.94)		-4.60 [-9.46, 0.26]
Rampello 2005	16	-14.8 (4.9)	15	-1.27 (5.29)		-13.53 [-17.13, -9.93]
4 MADRS (high score = more depressed)						
Murray 2002	62	-8.5 (8.9)	61	-7.6 (9.3)		-0.90 [-4.12, 2.32]
Ponzio 2001	112	-12 (9.52)	114	-9.9 (7.47)		-2.10 [-4.33, 0.13]
Wiart 2000	16	-16.7 (7.22)	15	-8.5 (8.36)		-8.20 [-13.71, -2.69]
5 Melancholia scale (high score = more depressed)						
Andersen 1994	33	-7.2 (4.22)	33	-4.3 (3.67)		-2.90 [-4.81, -0.99]
6 Zung (high score = more depressed)						
Lipsey 1984	11	-23 (7.28)	15	-12 (13.98)		-11.00 [-19.28, -2.72]



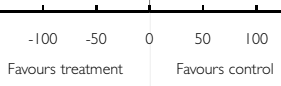
Analysis 1.3. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 3 Depression: 3. Mean scores at end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 3 Depression: 3. Mean scores at end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 BDI (high score = more depressed)						
Fruehwald 2003	26	6.1 (5.6)	24	6.8 (7.4)		-0.70 [-4.36, 2.96]
Rampello 2005	16	8.06 (3.43)	15	18.4 (3.33)		-10.34 [-12.72, -7.96]
2 CGI (low score = improvement / high score = deterioration)						
Fruehwald 2003	26	3.1 (1.3)	24	3.4 (1.7)		-0.30 [-1.14, 0.54]
3 HDRS (high score = more depressed)						
Andersen 1994	33	11.4 (5.1)	33	14.1 (4.7)		-2.70 [-5.07, -0.33]
Fruehwald 2003	26	9.5 (7.9)	24	11.2 (12.4)		-1.70 [-7.52, 4.12]
Jiang 2001a	30	5.12 (3.11)	15	13.21 (5.56)		-8.09 [-11.12, -5.06]
Lai 2006a	40	12.5 (8.4)	40	21.5 (4.3)		-9.00 [-11.92, -6.08]
Lipsey 1984	11	2.8 (2.65)	15	10 (8.13)		-7.20 [-11.60, -2.80]
Rampello 2005	16	9.26 (2.15)	15	22.73 (2.4)		-13.47 [-15.08, -11.86]
4 MADRS (high score = more depressed)						
Murray 2002	62	10.5 (9.6)	61	12 (8.5)		-1.50 [-4.70, 1.70]
Wiart 2000	16	11.8 (6.7)	15	18.7 (10)		-6.90 [-12.93, -0.87]
5 Melancholia scale (high score = more depressed)						
Andersen 1994	33	10.5 (5.1)	33	12.9 (4.5)		-2.40 [-4.72, -0.08]
6 Zung (high score = more depressed)						
Lipsey 1984	11	31 (9.95)	15	42 (15.49)		-11.00 [-20.80, -1.20]

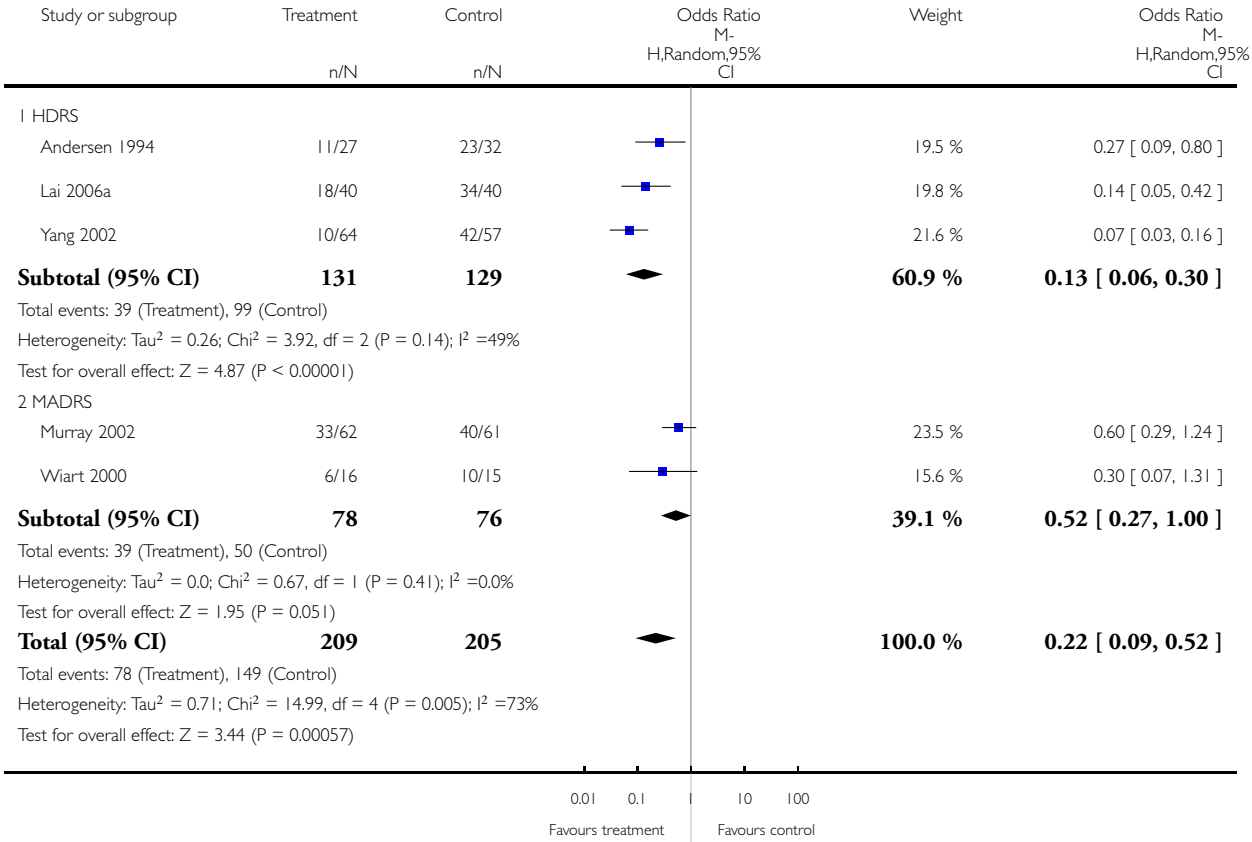


Analysis 1.4. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 4 Depression: 4. Less than 50% reduction in scale scores.

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 4 Depression: 4. Less than 50% reduction in scale scores



Analysis 1.5. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 5 Anxiety: 1. Meeting study criteria for anxiety.

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 5 Anxiety: 1. Meeting study criteria for anxiety

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Clinician interview/impression				
Ohtomo 1991	46/93	57/85		0.48 [0.26, 0.88]

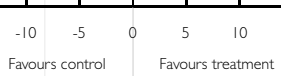
Analysis 1.6. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 6 Cognitive functioning: 1. Average change in scores between baseline and end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 6 Cognitive functioning: 1. Average change in scores between baseline and end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 MMSE (low score = cognitive impairment)						
Wiart 2000	16	1.3 (3.71)	15	2.1 (2.95)		-0.80 [-3.15, 1.55]



Analysis 1.7. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 7 Cognitive functioning: 2. Mean scores at end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 7 Cognitive functioning: 2. Mean scores at end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 MMSE (low score = cognitive impairment)						
Wiart 2000	16	24.8 (3.9)	15	26.2 (3)		-1.40 [-3.84, 1.04]

Analysis 1.8. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 8 Activities of daily living: 1. Average change in scores between baseline and end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 8 Activities of daily living: 1. Average change in scores between baseline and end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Barthel (high score = more dependent)						
Ponzio 2001	102	1.7 (0)	102	1.8 (0)		0.0 [0.0, 0.0]
Reding 1986	11	-28 (23.22)	6	-20 (17.5)		-8.00 [-27.61, 11.61]

Analysis 1.9. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 9 Disability: 1. Average change in scores between baseline and end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 9 Disability: 1. Average change in scores between baseline and end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Functional Independence Measure (low score = dependence)						
Wiart 2000	16	24.7 (20.37)	15	16.4 (23.2)		8.30 [-7.11, 23.71]
2 Motoricity Index (low score = more motor impairment)						
Wiart 2000	18	18.9 (23.81)	15	11.9 (26)		7.00 [-10.15, 24.15]
3 Scandinavian Stroke Scale (low score = more neurological deficit)						
Fruehwald 2003	26	13.55 (7.4)	24	15.4 (9.24)		-1.85 [-6.51, 2.81]
4 Rankin Scale (high score = more disability)						
Ponzio 2001	102	-0.4 (0)	103	-0.4 (0)		0.0 [0.0, 0.0]

Analysis 1.10. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 10 Disability: 2. Mean scores at end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 10 Disability: 2. Mean scores at end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Functional Independence Measure (low score = dependence)						
Wiart 2000	16	87.4 (22.8)	15	88.7 (25.3)		-1.30 [-18.29, 15.69]
2 Motoricity Index (low score = more motor impairment)						
Wiart 2000	16	48.5 (24.6)	15	55.3 (26.5)		-6.80 [-24.83, 11.23]
3 Scandinavian Stroke Scale (low score = more neurological deficit)						
Fruehwald 2003	26	53.5 (4.8)	24	52.8 (5.4)		0.70 [-2.14, 3.54]

Analysis 1.11. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 11 Neurological function: 1. Average change in scores between baseline and end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 11 Neurological function: 1. Average change in scores between baseline and end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Chinese Stroke Scale (high score = more impairment)						
Jiang 2001a	30	-14.81 (6.39)	15	-13.06 (6.78)		-1.75 [-5.87, 2.37]

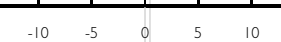
Analysis 1.12. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 12 Neurological function: 2. Mean scores at end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 12 Neurological function: 2. Mean scores at end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Chinese Stroke Scale (high score = more impairment)						
Jiang 2001a	30	3.23 (2.37)	15	5.2 (3.27)		-1.97 [-3.83, -0.11]

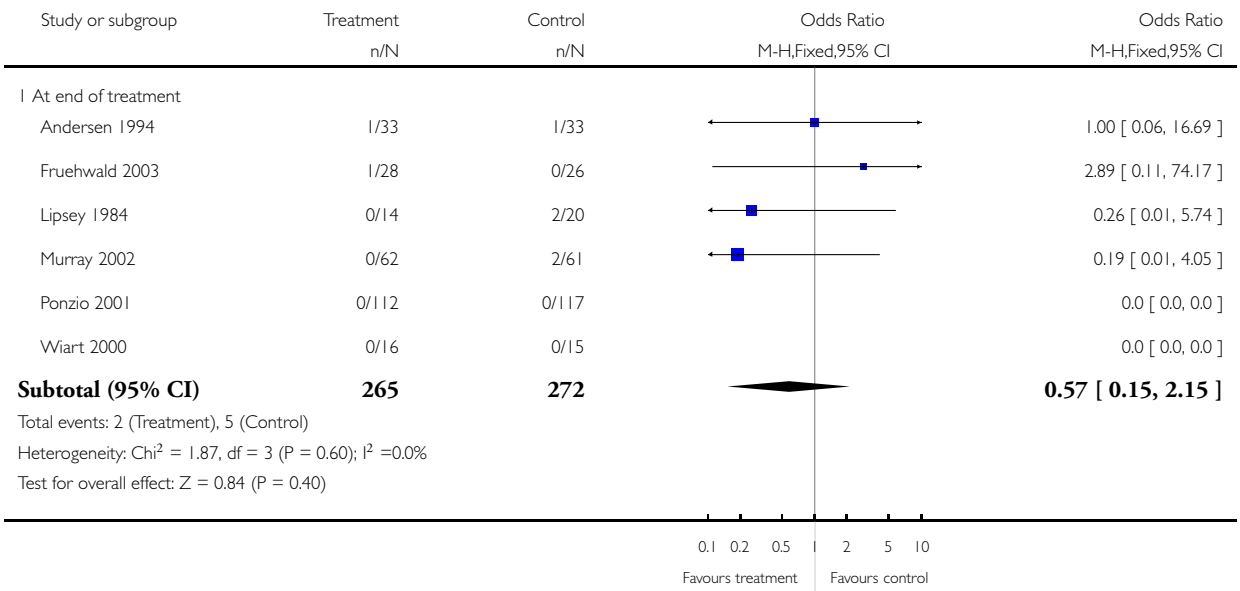


Analysis 1.13. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 13 Adverse events: 1. Death.

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 13 Adverse events: 1. Death

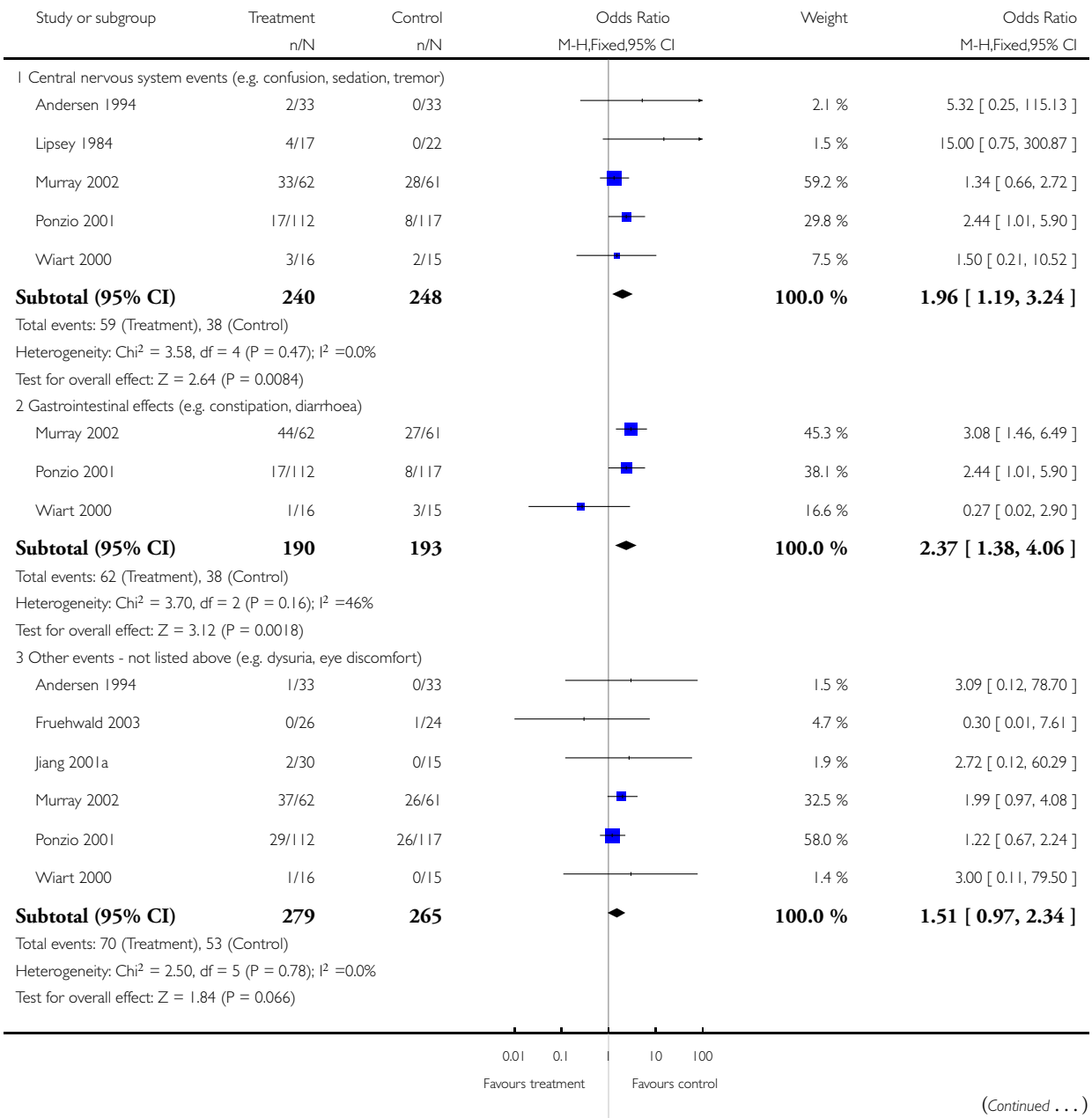


Analysis 1.14. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 14 Adverse events: 2. All.

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 14 Adverse events: 2. All



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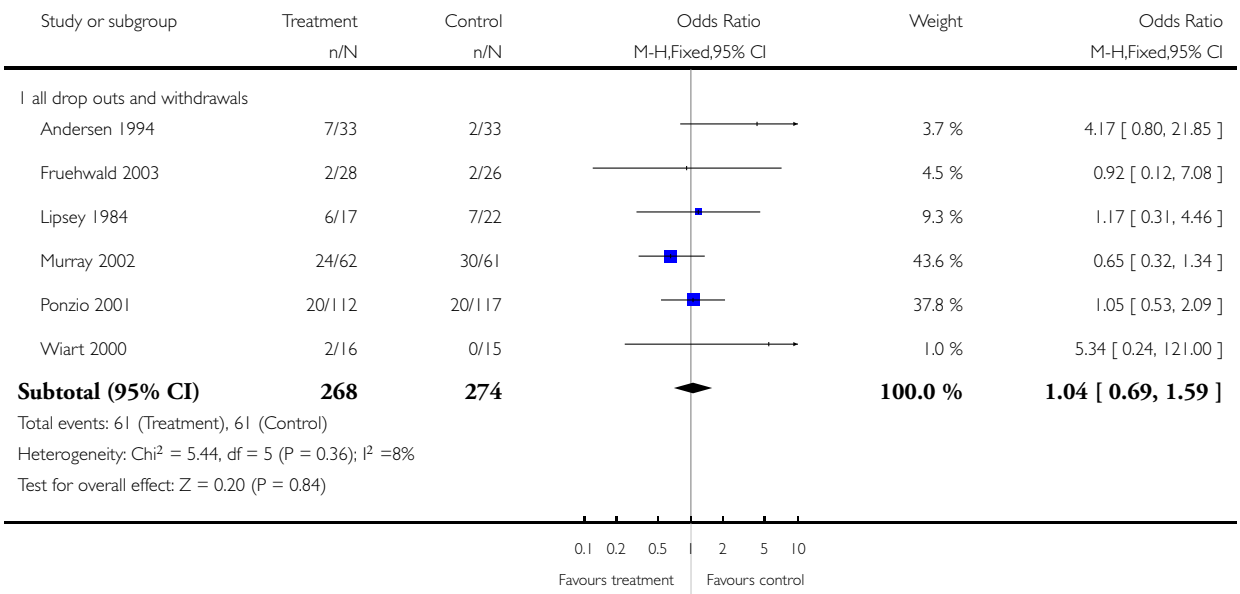
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
4 Protocol violation (e.g. refused treatment, withdrew consent)					
Andersen 1994	1/33	0/33		12.1 %	3.09 [0.12, 78.70]
Lipsey 1984	0/17	3/22		75.9 %	0.16 [0.01, 3.30]
Wiart 2000	1/16	0/15		11.9 %	3.00 [0.11, 79.50]
Subtotal (95% CI)	**66**	**70**		**100.0 %**	**0.85 [0.20, 3.66]**
Total events: 2 (Treatment), 3 (Control)					
Heterogeneity: Chi² = 2.35, df = 2 (P = 0.31); I² =15%					
Test for overall effect: Z = 0.21 (P = 0.83)					
5 Psychiatric events (e.g. anxiety, increased depression)					
Fruehwald 2003	0/26	1/24		54.4 %	0.30 [0.01, 7.61]
Lipsey 1984	0/17	1/22		45.6 %	0.41 [0.02, 10.69]
Subtotal (95% CI)	**43**	**46**		**100.0 %**	**0.35 [0.03, 3.47]**
Total events: 0 (Treatment), 2 (Control)					
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² =0.0%					
Test for overall effect: Z = 0.90 (P = 0.37)					
6 Recurrent stroke					
Andersen 1994	1/33	0/33		27.2 %	3.09 [0.12, 78.70]
Lipsey 1984	0/17	1/22		72.8 %	0.41 [0.02, 10.69]
Subtotal (95% CI)	**50**	**55**		**100.0 %**	**1.14 [0.15, 8.60]**
Total events: 1 (Treatment), 1 (Control)					
Heterogeneity: Chi² = 0.74, df = 1 (P = 0.39); I² =0.0%					
Test for overall effect: Z = 0.13 (P = 0.90)					
7 Vascular events - not stroke (e.g. dizziness, palpitation)					
Andersen 1994	1/33	1/33		4.5 %	1.00 [0.06, 16.69]
Fruehwald 2003	1/26	0/24		2.3 %	2.88 [0.11, 74.21]
Jiang 2001a	7/30	0/15		2.3 %	9.89 [0.53, 185.97]
Lipsey 1984	2/17	1/22		3.6 %	2.80 [0.23, 33.78]
Murray 2002	22/62	18/61		54.9 %	1.31 [0.62, 2.80]
Ponzio 2001	9/112	6/117		25.3 %	1.62 [0.56, 4.70]
Wiart 2000	0/16	1/15		7.0 %	0.29 [0.01, 7.76]
Subtotal (95% CI)	**296**	**287**		**100.0 %**	**1.60 [0.93, 2.73]**
Total events: 42 (Treatment), 27 (Control)					
Heterogeneity: Chi² = 3.20, df = 6 (P = 0.78); I² =0.0%					
Test for overall effect: Z = 1.70 (P = 0.089)					

Analysis 1.15. Comparison 1 Pharmaceutical interventions versus placebo (antidepressants), Outcome 15 Adverse events: 3. Leaving the study early (including death).

Review: Interventions for treating depression after stroke

Comparison: 1 Pharmaceutical interventions versus placebo (antidepressants)

Outcome: 15 Adverse events: 3. Leaving the study early (including death)

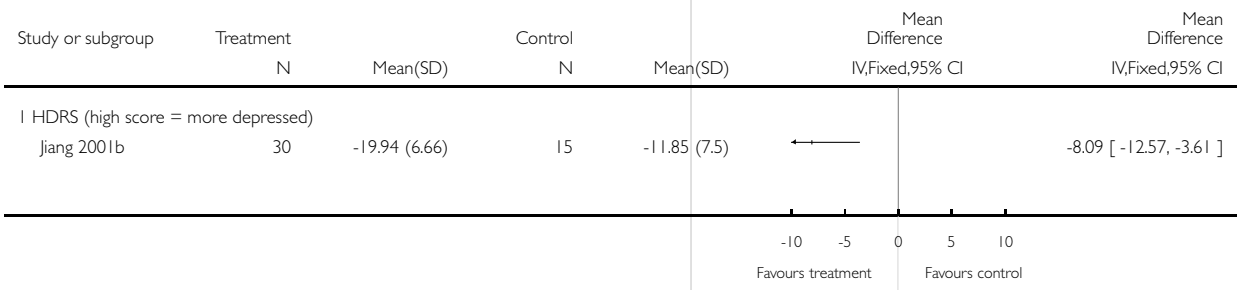


Analysis 2.1. Comparison 2 Pharmaceutical interventions versus placebo (combination therapy), Outcome 1 Depression: 1. Average change in scores between baseline and end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 2 Pharmaceutical interventions versus placebo (combination therapy)

Outcome: 1 Depression: 1. Average change in scores between baseline and end of treatment



Analysis 2.2. Comparison 2 Pharmaceutical interventions versus placebo (combination therapy), Outcome 2 Depression: 2. Mean scores at end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 2 Pharmaceutical interventions versus placebo (combination therapy)

Outcome: 2 Depression: 2. Mean scores at end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 HDRS (high score = more depressed)						
Jiang 2001b	30	4.9 (2.96)	15	13.21 (5.56)		-8.31 [-11.32, -5.30]

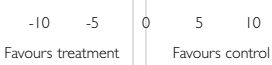
Analysis 2.3. Comparison 2 Pharmaceutical interventions versus placebo (combination therapy), Outcome 3 Neurological function: 1. Average change in scores between baseline and end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 2 Pharmaceutical interventions versus placebo (combination therapy)

Outcome: 3 Neurological function: 1. Average change in scores between baseline and end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Chinese Stroke Scale (high score = more impairment)						
Jiang 2001b	30	-14.85 (6.25)	15	-13.06 (6.78)		-1.79 [-5.89, 2.31]



Analysis 2.4. Comparison 2 Pharmaceutical interventions versus placebo (combination therapy), Outcome 4 Neurological function: 2. Mean scores at end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 2 Pharmaceutical interventions versus placebo (combination therapy)

Outcome: 4 Neurological function: 2. Mean scores at end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Chinese Stroke Scale (high score = more impairment)						
Jiang 2001b	30	3.01 (2.12)	15	5.2 (3.27)		-2.19 [-4.01, -0.37]

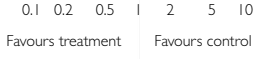
Analysis 2.5. Comparison 2 Pharmaceutical interventions versus placebo (combination therapy), Outcome 5 Adverse events: 1. All.

Review: Interventions for treating depression after stroke

Comparison: 2 Pharmaceutical interventions versus placebo (combination therapy)

Outcome: 5 Adverse events: 1. All

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Other events (GPT elevation)					
Jiang 2001b	2/30	0/15		49.1 %	2.72 [0.12, 60.29]
Subtotal (95% CI)	**30**	**15**		**49.1 %**	**2.72 [0.12, 60.29]**
Total events: 2 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					
2 Vascular events - not stroke (e.g. ECG changes)					
Jiang 2001b	1/30	0/15		50.9 %	1.58 [0.06, 41.03]
Subtotal (95% CI)	**30**	**15**		**50.9 %**	**1.58 [0.06, 41.03]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.27 (P = 0.78)					
Total (95% CI)	**60**	**30**		**100.0 %**	**2.14 [0.23, 19.95]**



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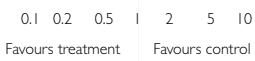
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Total events: 3 (Treatment), 0 (Control)					
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² =0.0%					
Test for overall effect: Z = 0.67 (P = 0.50)					



Analysis 3.1. Comparison 3 Psychological interventions versus standard care and/or attention control, Outcome 1 Depression: Meeting study criteria for depression at end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 3 Psychological interventions versus standard care and/or attention control

Outcome: 1 Depression: Meeting study criteria for depression at end of treatment

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 GHQ-28 (high score = greater psychological distress)				
Watkins 2007	85/127	95/127		0.68 [0.40, 1.18]

Analysis 3.2. Comparison 3 Psychological interventions versus standard care and/or attention control, Outcome 2 Depression: 1. Average change in scores between baseline and end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 3 Psychological interventions versus standard care and/or attention control

Outcome: 2 Depression: 1. Average change in scores between baseline and end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 BDI (high score = more depressed)						
Lincoln 2003	38	-3 (8.99)	80	-3 (8.12)		0.0 [-3.37, 3.37]
2 WDI (high score = more depressed)						
Lincoln 2003	38	-3.77 (6.84)	80	-3 (6.36)		-0.77 [-3.35, 1.81]
3 HDRS (high score = more depressed)						
Zhao 2004	35	-13.11 (15.79)	35	-7.07 (15.79)		-6.04 [-13.44, 1.36]

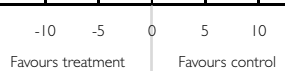
Analysis 3.3. Comparison 3 Psychological interventions versus standard care and/or attention control, Outcome 3 Depression: 2. Mean scores at end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 3 Psychological interventions versus standard care and/or attention control

Outcome: 3 Depression: 2. Mean scores at end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 BDI (high score = more depressed)						
Lincoln 2003	38	15.21 (10.1)	80	15 (8.41)		0.21 [-3.49, 3.91]
2 WDI (high score = more depressed)						
Lincoln 2003	38	18.97 (8.34)	80	19 (7.14)		-0.03 [-3.11, 3.05]
3 HDRS (high score = more depressed)						
Zhao 2004	35	14.35 (3.12)	35	21.07 (2.5)		-6.72 [-8.04, -5.40]



Analysis 3.4. Comparison 3 Psychological interventions versus standard care and/or attention control, Outcome 4 Psychological distress: 1. Average change in scores between baseline and end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 3 Psychological interventions versus standard care and/or attention control

Outcome: 4 Psychological distress: 1. Average change in scores between baseline and end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 GHQ-28 (high score = greater psychological distress)						
Lincoln 2003	38	-6.18 (15.31)	81	-7 (15.3)		0.82 [-5.08, 6.72]
Watkins 2007	127	-1.3 (7.1)	127	-1 (7.2)		-0.30 [-2.06, 1.46]

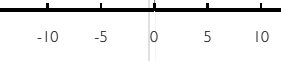
Analysis 3.5. Comparison 3 Psychological interventions versus standard care and/or attention control, Outcome 5 Psychological distress: 2. Mean scores at end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 3 Psychological interventions versus standard care and/or attention control

Outcome: 5 Psychological distress: 2. Mean scores at end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 GHQ-28 (high score = greater psychological distress)						
Lincoln 2003	38	28.79 (16.71)	81	27 (15.17)		1.79 [-4.47, 8.05]



Analysis 3.6. Comparison 3 Psychological interventions versus standard care and/or attention control, Outcome 6 Activities of daily living: 1. Average change in scores from baseline to end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 3 Psychological interventions versus standard care and/or attention control

Outcome: 6 Activities of daily living: 1. Average change in scores from baseline to end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 EADL (high score = more dependent)						
Lincoln 2003	38	-5.4 (13.31)	81	-4 (14.69)		-1.40 [-6.71, 3.91]
2 Barthel (high score = more dependent)						
Watkins 2007	124	-1.4 (3.9)	119	-1.4 (4.4)		0.0 [-1.05, 1.05]

Analysis 3.7. Comparison 3 Psychological interventions versus standard care and/or attention control, Outcome 7 Activities of daily living: 2. Mean scores at end of treatment.

Review: Interventions for treating depression after stroke

Comparison: 3 Psychological interventions versus standard care and/or attention control

Outcome: 7 Activities of daily living: 2. Mean scores at end of treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 EADL (high score = more dependent)						
Lincoln 2003	38	30.29 (12.78)	81	32 (15.75)		-1.71 [-7.03, 3.61]
2 Barthel (high score = more dependent)						
Watkins 2007	124	16.2 (4.3)	119	16.8 (3.8)		-0.60 [-1.62, 0.42]

Analysis 3.8. Comparison 3 Psychological interventions versus standard care and/or attention control, Outcome 8 Adverse events: 1. Death.

Review: Interventions for treating depression after stroke

Comparison: 3 Psychological interventions versus standard care and/or attention control

Outcome: 8 Adverse events: 1. Death

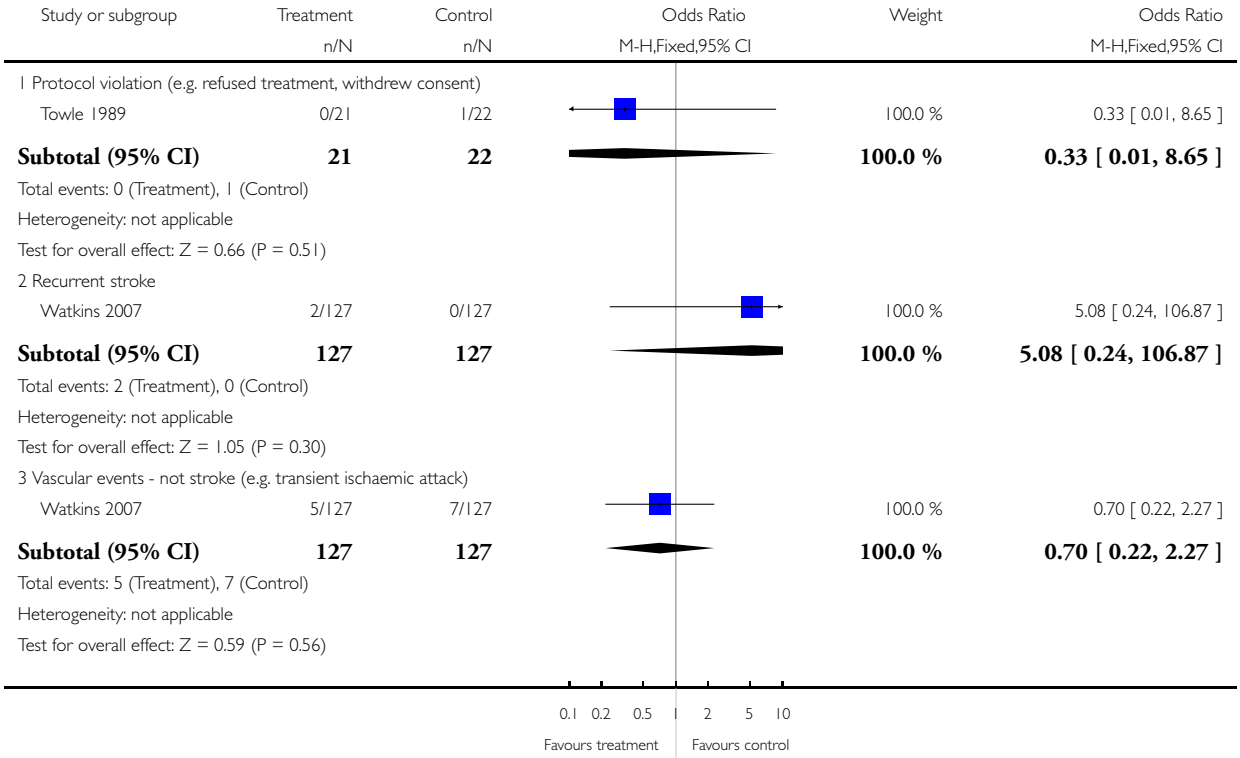
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 At end of treatment				
Lincoln 2003	0/39	2/84		0.42 [0.02, 8.91]
Towle 1989	0/21	0/23		0.0 [0.0, 0.0]
Watkins 2007	3/127	8/127		0.36 [0.09, 1.39]
Subtotal (95% CI)	**187**	**234**		**0.37 [0.11, 1.28]**
Total events: 3 (Treatment), 10 (Control)				
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%				
Test for overall effect: Z = 1.57 (P = 0.12)				

Analysis 3.9. Comparison 3 Psychological interventions versus standard care and/or attention control, Outcome 9 Adverse events: 2. All.

Review: Interventions for treating depression after stroke

Comparison: 3 Psychological interventions versus standard care and/or attention control

Outcome: 9 Adverse events: 2. All

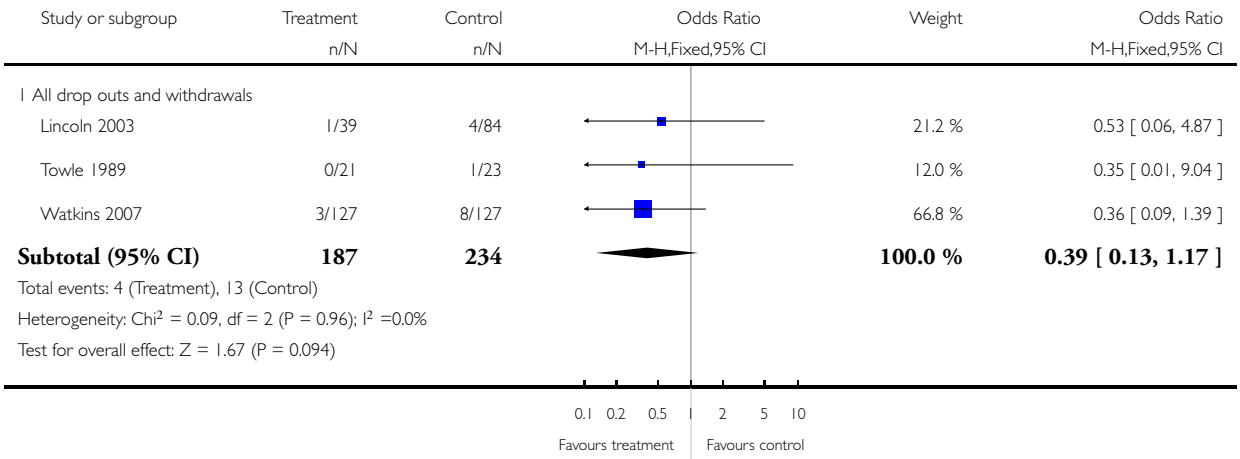


Analysis 3.10. Comparison 3 Psychological interventions versus standard care and/or attention control, Outcome 10 Adverse events: 3. Leaving the study early (including death).

Review: Interventions for treating depression after stroke

Comparison: 3 Psychological interventions versus standard care and/or attention control

Outcome: 10 Adverse events: 3. Leaving the study early (including death)



ADDITIONAL TABLES

Table 1. Characteristics of 'drop-out' studies

Study ID	Methods	Participants	Interventions	Outcomes	Notes	Allocation
Choi-Kwon 2006	Parallel design Method of randomisation: computer-generated list of treatment numbers Method of concealment: unclear Blinding: double blind Particiapnts: yes Investigators: yes Relatives: yes Outcome assessors: no	Location: Seoul Setting: outpatients Treatment: 76 (75% male, mean age 58 years, SD 9) Control: 76 (79% male, mean age 58 years, SD 9) Stroke criteria: ischaemic stroke; diagnosis via CT and MRI scans; interview performed on average of 14 months	Treatment: fluoxetine 20 mg daily Control: matched placebo Duration: treatment continued for 3 months	Depression: change in scores from baseline to end of treatment and end of follow up on BDI Additional: leaving the study early, adverse events Unable to use: outcome data not presented in a format suitable for this review	Exclusion criteria: did not undergo imaging (CT/MRI) studies, SAH, had TIA without progression to stroke, severe communication problems (aphasia, dementia, or dysarthria, scored < 23 on MMSE, history of depression or psychiatric ill-	A

Table 1. Characteristics of 'drop-out' studies (*Continued*)

	Analysis: ITT: 27 withdrew before completing 3-month treatment protocol, withdrew due to protocol violation (4 treatment, 6 control), withdrew due to AE (10 treatment, 2 control), withdrawn due to readmission into hospital because of other diseases (1 treatment, 2 control), withdrew due to believing treatment was not effective (2 control)	after stroke Depression criteria: psychiatric interview, BDI score > 13 Other entry criteria: none stated Comparability of treatment groups: non-significant trend towards right-sided lesion strokes in control group and left-sided lesion strokes in treatment group			ness before onset of stroke, already treated with psychiatric regimens, lived alone	
Downes 1995	Parallel design Method of randomisation: random number sequence stratified by Rankin score Method of concealment: randomised by one of the authors Blinding: single blind Participants: no Investigators: no Outcome assessors: yes Analysis: per protocol: 105 participants randomised, 87 available at 6 months, 18 lost to follow up	Location: UK Setting: outpatient Treatment 1: 22 (50% male, age not reported) Treatment 2: 22 (55% male, age not reported) Control: 18 (44% male, age not reported) Stroke criteria: unclear; no criteria defined in study for time from stroke to randomisation Other entry criteria: lived at home, had an informal carer, stroke in-	Treatment 1: information plus counselling. Egan's problem solving approach, individual is helped to explore concerns, clarify problems, set goal and take appropriate action. Protocol discussed first and formulated into a counsellor/client contract. Information pack containing information on physical, cognitive,	Depression: change in scores from baseline to end of treatment on HADS Additional: HADS anxiety score Unable to use: all data presented combines both depressed and non-depressed participants at baseline	Exclusion criteria: not living at home, not having an informal carer, having no increase in disability or change in lifestyle/ dependency	B

Table 1. Characteristics of 'drop-out' studies (*Continued*)

	(no reason given), 25 not assessed (no reason given), 43 excluded from analysis	crease mRS, post-stroke mRS score of 2 to 5 Comparability of treatment groups: balanced	behavioural and emotional effects of stroke, carer well-being, and local services. Treatment 2: information only: information pack containing information on physical, cognitive, behavioural and emotional effects of stroke, carer well-being, and local services. Control: standard care, no visit(s) or information pack provided Duration: information session consisted of 1 visit and provision of the information pack Counselling consisted of up to 8 counselling sessions over 4 to 6 months Delivered by: nurse counsellor			
Graffagnino 2003	Parallel design Method of randomisation: unclear Method of concealment: unclear Blinding: unclear Analysis: unclear	Location: unclear Setting: unclear Treatment: unclear Control: unclear Stroke criteria: unclear Depression criteria: unclear Other entry criteria: unclear Comparabil-	Treatment: sertraline Control: matched placebo Duration: unclear	Depression: unclear Additional: unclear Unable to use: no data presented	Exclusion criteria: unclear	B

Table 1. Characteristics of 'drop-out' studies (*Continued*)

		ity of treatment groups: unclear				
Isenberg 2000	Parallel design Method of randomisation: unclear Method of concealment: unclear Blinding: double blind	Location: unclear Setting: unclear Treatment: nefiracetam Control: unclear Stroke criteria: unclear Depression criteria: unclear Other entry criteria: participants must be at least 3 months poststroke Comparability of treatment groups: unclear	Treatment: nefiracetam Control: matched placebo Duration: unclear	Depression: unclear Additional: unclear Unable to use: no results available	Exclusion criteria: unclear	B
Mauri 1988	Parallel design Method of randomisation: unclear Method of concealment: unclear Blinding: unclear Analysis: unclear	Location: Spain Setting: unclear Treatment: mianserin, 6 weeks, dose unclear Control: placebo Stroke criteria: ischaemic stroke, diagnosis unclear; stroke 6 months prior to randomisation Depression criteria: GDS (15 item) score > 4 Other entry criteria: none stated Comparability of treatment groups: unclear	Treatment: mianserin Control: placebo Duration: treatment continued for 6 weeks	Depression: unclear Additional: unclear Unable to use: results not available in format suitable for this review	Exclusion criteria: unclear	B
Meara 1998	Parallel design Method of randomisation: unclear	Location: Wales, UK Setting: inpatient	Treatment: sertraline, 50 mg, daily Dose esca-	Depression: change in scores from baseline to end of treatment	Exclusion criteria: moderate to severe dementia, severe aphasia,	B

Table 1. Characteristics of 'drop-out' studies (*Continued*)

	Method of concealment: unclear Blinding: double blind reported, those blinded not stated Analysis: unclear	Treatment: unclear Control: unclear Stroke criteria: ischaemic stroke, diagnosis unclear; stroke > 11 weeks prior to randomisation Depression criteria: GDS (15 item) score > 4 Other entry criteria: none stated Comparability of treatment groups: balanced	lation to 100 mg for non-responders at 2 weeks Control: matched placebo Duration: treatment continued for 6 weeks	on GDS Unable to use: GDS, BI, MMSE, FAI, FAST, leaving the study early, death (data not presented) Adverse events (data not presented by treatment group, 9 patients developed side effects, generally mild and transient)	communication difficulties, poorly controlled epilepsy	
Ohtomo 1985	Parallel design Method of randomisation: unclear Method of concealment: unclear Blinding: double bind reported, those blinded not stated Analysis: per protocol: protocol violation (1 control), excluded from analysis	Location: Japan Setting: unclear Treatment: 141 (54% male, age details unclear) Control: 147 (61% male, age details unclear) Stroke criteria: all subtypes; diagnosis via clinical signs and CT (% not reported); time from stroke to randomisation not reported Other entry criteria: > 40 years of age, high blood pressure (> 160/90 mmHg) and hypertensive changes on fundoscopy changes, stable Neuroleptic, minor tranquilliser, antidepressant,	Treatment: tiapride, 75 mg daily for 1 week, dose escalation to 150 to 225 mg daily for 5 weeks according to clinical response Control: matched placebo Duration: treatment continued for 6 weeks	Depression: unclear Unable to use: no data presented by 'not depressed at baseline'	Exclusion criteria: severe aphasia, severe dementia, drug dependence, inadequate conditions for the study	B

Table 1. Characteristics of 'drop-out' studies (*Continued*)

		brain metabolic activators, cerebro-vasodilators washed out for 3 to 7 days prior to randomisation Comparability of treatment groups: balanced				
Xie 2003	Parallel design Method of randomisation: unclear, 'paired' Method of concealment: unclear Blinding: unclear Analysis: unclear	Location: China Setting: unclear Treatment: 41 (% male unclear, mean age 64 years SD 7) Control: 41 (% male unclear, mean age 62 years SD 5) Stroke criteria: infarction and cerebral haemorrhage; time from stroke to randomisation not reported Other entry criteria: hemiplegia, admitted during January 1988 to July 2002 Comparability of treatment groups: balanced	Treatment: psychological intervention: feeling support therapy, recognition therapy, collective therapy, social support and skills training, plus routine drug treatment and rehabilitation training Control: routine drug treatment and rehabilitation training Duration: unclear Delivered by: unclear	Depression: endpoint but method of assessment unclear Additional: panic, anxiety, stubborn, hostility Unable to use: Method of assessment not clear, SCL-90 stated but outcomes reported are different	Exclusion criteria: unclear	B
Zhou 2004	Parallel design Method of randomisation: unclear, 'equally randomised' Method of concealment: unclear Blinding: unclear Analysis: unclear	Location: China Setting: unclear Treatment: 50 (56% male, mean age 63.8 years) Control: 50 (60% male, mean age 65.4 years) Stroke criteria: unclear; time	Treatment: rehabilitation therapy plus psychological nursing strategy involving many people including carers and a buddy system Control: rehabilitation therapy	Depression: multimodal approach to diagnosis, Beck Depression Inventory, HDRS Additional: physical function	Exclusion criteria: unclear	B

Table 1. Characteristics of 'drop-out' studies (*Continued*)

		from stroke to randomisation not reported Other entry criteria: unclear Comparability of treatment groups: unclear	Duration: 6 weeks Delivered by: unclear			

AE: adverse event(s)
BDI: Beck Depression Inventory
CT: computed tomography
BI: Barthel Index
FAI: Frenchay Activities Index
FAST: Frenchay Aphasia Screening Test
GDS: Geriatric Depression Scale
HADS: Hospital Anxiety and Depression Scale
HDRS: Hamilton Depression Rating Scale
ITT: intention to treat
MMSE: Mini-Mental State Examination
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
SAH: subarachnoid haemorrhage
TIA: transient ischaemic attack

APPENDICES

Appendix 1. MEDLINE search strategy

We used the following search strategy using a combination of controlled vocabulary and free text terms for MEDLINE and CINAHL (Ovid), and modified it to suit the other databases.
1 exp cerebrovascular disorders/
2 (stroke$ or poststroke$ or cva$).tw.
3 (cerebrovascular$ or cerebral vascular).tw.
4 (cerebral or cerebellar or brain$ or vertebrobasilar).tw.
5 (infarct$ or isch?emi$ or thrombo$ or emboli$ or apoplexy).tw.
6 (cerebral or intracerebral or intracranial or brain$).tw.
7 (haemorrhage or hemorrhage or bleed$).tw.
8 4 and 5
9 6 and 7
10 1 or 2 or 3 or 8 or 9
11 Depression/
12 Depression, involutional/ or Depressive disorder/ or Dysthymic disorder/
13 (depress$ or dysthymi$).tw.
14 11 or 12 or 13

15 10 and 14
16 randomized controlled trial.pt.
17 randomized controlled trials/
18 controlled clinical trial.pt.
19 controlled clinical trials/
20 random allocation/
21 double-blind method/
22 single-blind method/
23 clinical trial.pt.
24 exp clinical trials/
25 (clin$ adj25 trial$).tw.
26 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).tw.
27 placebos/
28 placebo$.tw.
29 random$.tw.
30 research design/
31 clinical trial phase ii.pt.
32 clinical trial phase iii.pt.
33 clinical trial phase iv.pt.
34 meta analysis.pt.
35 multicenter study.pt.
36 intervention studies/
37 cross-over studies/
38 meta-analysis/
39 control$.tw.
40 alternate treatment.tw.
41 "comparative study"/
42 exp evaluation studies/
43 Follow-up studies/
44 Prospective studies/
45 prospective.tw.
46 (versus or sham or intervention group or comparative stud$).tw.
47 or/16-46
48 15 and 47
49 limit 48 to human

WHAT'S NEW

Last assessed as up-to-date: 25 May 2008.

Date	Event	Description
28 March 2008	Amended	Converted to new review format.
14 March 2008	New search has been performed	The searches for the review were completed to February 2008. Seven new trials have been added: six pharmacological interventions making a total of 13, and two psychological interventions making a total of four comparisons. There are now 16 included trials with 1655 participants

(*Continued*)

		Eight trials require more information before they can be assessed for inclusion in the review (down from 14 in the previous version). Nine trials appear to meet the review inclusion criteria but information is not available in a format suitable for pooling. Three studies are ongoing (up from 0 in the previous version)
14 March 2008	New citation required and conclusions have changed	This version of the review found a small but significant effect of pharmacotherapy (not psychotherapy) on treating depression and reducing depressive symptoms in stroke patients There has also been a change of authorship.

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 3, 2004

CONTRIBUTIONS OF AUTHORS

The first three review authors had equal input into the development, writing, and editing of the protocol and undertook the work necessary to complete the review. JX assisted with obtaining and translating and extracting data from Chinese studies for the updated review. The update was completed by MH.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- The George Institute for International Health, Australia.

External sources

- Stroke Society of Australasia, Overseas Study Scholarship, Australia.
- The Academic Unit of Psychiatry, The University of Leeds, UK.
- The Department of Clinical Neurosciences, The University of Edinburgh, UK.
- The Clinical Trials Research Unit, The University of Auckland, New Zealand.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [adverse effects; therapeutic use]; Anxiety [chemically induced]; Depression [*therapy]; Psychotherapy; Randomized Controlled Trials as Topic; Stroke [*psychology]

MeSH check words

Humans